IASLC

2025 World Conference on Lung Cancer

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ABSTRACT BOOK

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TABLE OF CONTENTS

Plenary Sessions ---- 01

Oral Abstract Sessions ---- 15

Mini Oral Abstract Sessions ---- 91

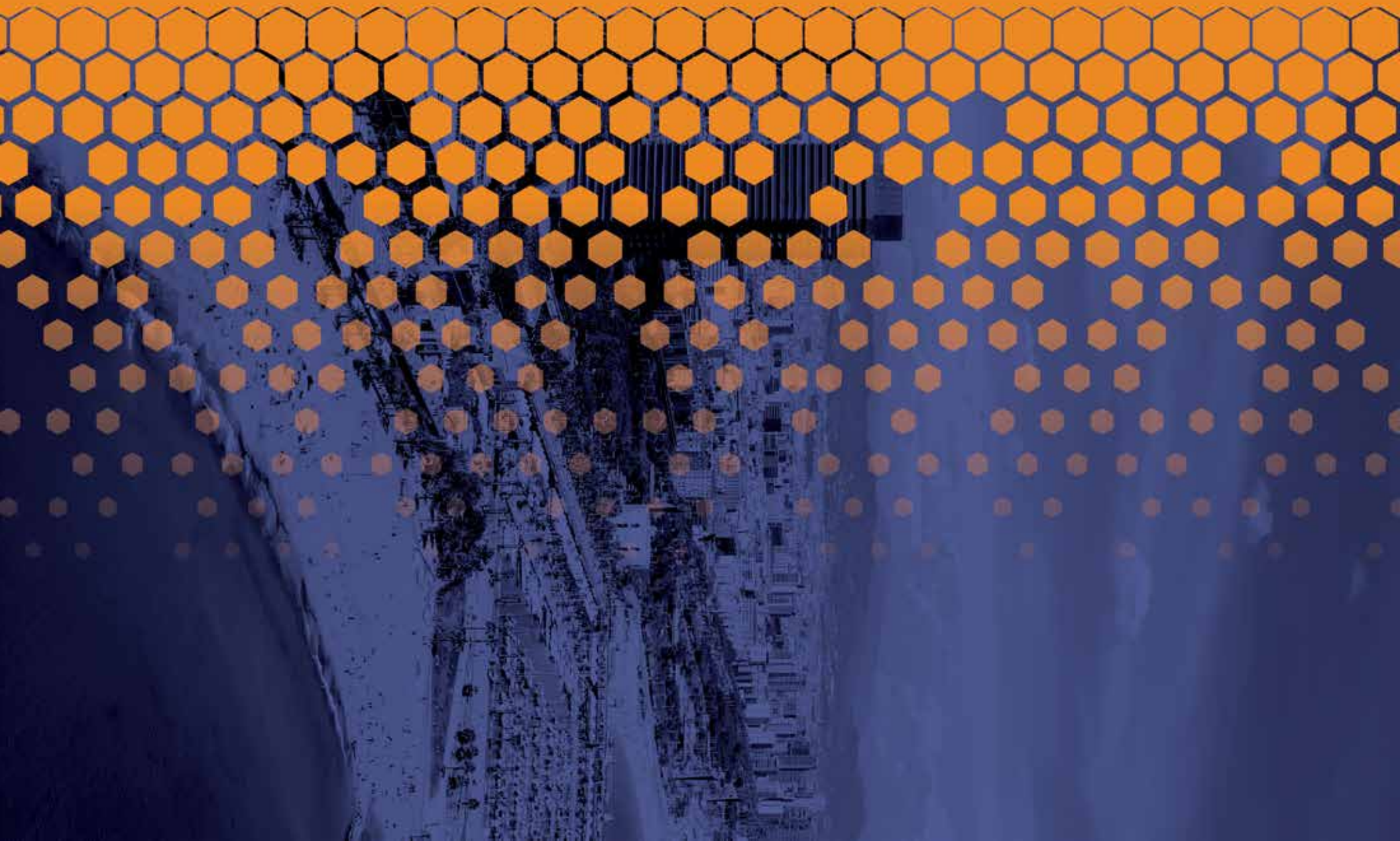
Poster Tour ---- 197

Poster Presentations ---- 283

ePosters Listings ---- 1310

Author Index ---- 1917

10 | PLENARY SESSIONS



PL02 PRESIDENTIAL SYMPOSIUM 1 WITH LECTURESHIP AWARD PRESENTATIONS (LIVESTREAMED)
SUNDAY, SEPTEMBER 7, 2025 - 8:15 - 10:30

PL02.06 First-Line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival

D. Planchard[1],[2], P.A. Jänne[3], K. Kobayashi[4], J.C-H. Yang[5], Y. Liu[6], N. Valdiviezo[7], T.M. Kim[8], L. Jiang[9], H. Kagamu[10], N. Yanagitani[11], J. Wang[12], B. Biswas[13], A. Poltoratskiy[14], Y. Neron[15], C. Rojas[16], L. Koubkova[17], C. Escriu[18], D.A. Ezeife[19], K. Barrett[20], M. Albayaty[21], H. Jiang[22], C.K. Lee[23]
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PL02.09 Aumolertinib plus Chemotherapy for NSCLC with EGFR and Concomitant Tumor Suppressor Genes (ACROSS 2): Phase III study

J. Wang[1], Z-J. Wang[1], J. Zhong[1], W-H. Zhao[2], L. Wu[3], Q. Chu[4], Q-B. Song[5], D-X. Zhu[6], Q-S. Guo[7], Y. Yu[8], X-Y. Liu[9], J. Zhao[10], L. Nei[11], S. Li[12], J. Lin[13], X-D. Peng[14], L-H. Li[15], Y-F. Chen[16], J. Zhou[17], Z-X. Zhan[18], D-S. Zhong[19]
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PL02.12 Ivonescimab vs Placebo Plus Chemo, Phase 3 in Patients with EGFR+ NSCLC Progressed with 3rd gen EGFR-TKI Treatment: HARMONi

J.W. Goldman[1], A. Passaro[2], J. Laskin[3], D. Rodrigues-Abreu[4], A. Calles[5], L. Bazhenova[6], G. Lo Russo[7], N. Leighl[8], F. Cappuzzo[9], N. Girard[10], S. Popat[11], W. Fang[12], Y. Luo[13], R. Yang[14], W. Li[15], J. Li[16], L. Styles[16], B. Thompson[16], L. Zhang[12], X. Le[17]
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PL02.15 Pivotal ARROS-1 Efficacy and Safety Data: Zidesamtinib in TKI Pre-treated Patients with Advanced/Metastatic ROS1+ NSCLC

A.E. Drilon[1], B.C. Cho[2], J.J. Lin[3], B.J. Solomon[4], C-C. Lin[5], A.J. de Langen[6], E. Felip[7], J.W. Neal[8], S.V. Liu[9], R.A. Soo[10], S. Kao[11], J. Wolf[12], G. Liu[13], C.S. Baik[14], C. Dooms[15], M. Nagasaka[16], A.J. van der Wekken[17], D.R. Camidge[18], T. Yoshida[19], C-C. Lin[20], G-C. Chang[21], M-J. Ahn[22], J.R. Bauman[23], S. Gadgeel[24], A. Calles[25], E. Pons-Tostivint[26], D.S.W. Tan[27], M. Johnson[28], C. Bennati[29], G. Spitaleri[30], S. Waqar[31], S. Popat[32], H. Hayashi[33], D. Haggstrom[34], M. Samant[35], J. Shen[35], V.A. Upadhyay[35], B. Besse[36]
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PL02.18 Phase 3 Trial of Crizotinib vs Observation for Surgically Resected Early-Stage ALK+ NSCLC

D.E. Gerber[1,2], Y. Wang[3,4], C.J. Langer[5], O.V. Khullar[6], D.E. Kozono[4], L.A. Cornelius[7], P.M. Forde[8,9], M.O. Nwaneri[10], J.W. Neal[11], A. Talsania[12], T.A. Leal[6], M. Patel[13], K.R. Donthireddy[2], S.N. Waqar[14], J.E. Chaft[15], R. Govindan[14], J.M. Sands[4], S. Malik[16], T. Li[17], T. Stinchcombe[18], E.E. Vokes[19], S.J. Mandrekar[20], G.R. Oxnard[4], D.P. Carbone[21], S.S. Ramalingam[6]
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PL03 PRESIDENTIAL SYMPOSIUM 2 WITH LECTURESHIP AWARD PRESENTATIONS (LIVESTREAMED)
MONDAY, SEPTEMBER 8, 2025 - 8:15 - 10:30

PL03.06 EA5181: Phase 3 Trial of Concurrent and Consolidative Durvalumab vs Consolidation Durva Alone for Unresectable Stage 3 NSCLC

J.M. Varlotto[1], Y. Xie[2], N. Pennell[3], K. Oettel[4], C.M. Lovly[5], V. Anagnostou[6], G. Srkalovic[7], N.J. Mackler[8], B.A. Faller[9], P.T. Dyk[10], A.A. Chowdhary[11], G.M.M. Videtic[11], Y. Chen[12], P.O. Thieme[13], S.K. Jabbour[14], M. Haigentz[14], D. Almquist[15], S.R. Nurkic[16], A.A. Onitilo[17], P.E. Lammers[18], O. Ogbeide[18], U.K. Iheagwara[19], D.C. Weksberg[20], H.J. Ross[21], M.M. Harkenrider[22], G.A. Masters[23], H. Borghaei[24], J. Brahmer[6], S.S. Ramalingam[25]
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PL03 PRESIDENTIAL SYMPOSIUM 2 WITH LECTURESHIP AWARD PRESENTATIONS (LIVESTREAMED)
MONDAY, SEPTEMBER 8, 2025 - 8:15 - 10:30

PL03.07 Hypofractionated vs Conventional Fractionated Radiotherapy With Concurrent Chemotherapy for LS-SCLC: A Multi-Center Phase III Trial

N. Bi[1], T. Zhang[1], X. Hu[2], L. Zhang[3], J. Zhang[4], J. Cao[5], M. E[6], H. Ge[7], X. Zhu[8], L. Zhao[9], W. Jiang[10], D. Qian[11], W. Shen[12], Y. Wang[13], J. Ran[14], T. Zhang[15], H. Chen[16], M. Chen[17], L. Wang[10]
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PL03.10 Adjuvant Chemotherapy (CT) vs CT-immunotherapy for R0 Stage IB-IIIA NSCLC Patients (NADIM ADJUVANT): a Randomized, Phase 3 Trial

M. Provencio[1,2], R. Bernabé[2,3], E. Nadal[2,4], A. Martínez-Marti[2,5], E. Carcereny[2,6], A.L. Ortega[2,7], B. Campos[2,8], M. Dómine[2,9], B. Massuti[2,10], M. Martínez Aguillo[2,11], I. Sullivan[2,12], A. Padilla[2,13], J.L. González-Larriba[2,14], R. García Campelo[2,15], J. Bosch-Barrera[2,16], S. Sandiego[2,17], O. Juan-Vidal[2,18], D. Rodriguez[2,19], A. Blasco[2,20], L. Vilà[2,21], P. Martín-Martorell[2,22], R. Marsé[2,23], X. Mielgo[2,24], J. de Castro[2,25], J.M. Mane[2,26], J. Aires Machado[2,27], M.A. Sala[2,28], M. Lázaro-Quintela[2,29], R. Palmero[2,4], V. Calvo[1,2]
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PL03 PRESIDENTIAL SYMPOSIUM 2 WITH LECTURESHIP AWARD PRESENTATIONS (LIVESTREAMED)
MONDAY, SEPTEMBER 8, 2025 - 8:15 - 10:30

PL03.13 Survival Outcome of VATS Compared to Open Lobectomy for Lung Cancer: An Individual Patient Data Meta-analysis of Randomised Trials

J.J. Law[1], R. Harris[2], H. Long[3], D. Situ[3], F.A. Dittberner[4], M. Bendixen[4], P. Licht[4], C. Rogers[2], E. Lim[1]
[1]Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London/GB ,[2]Bristol Trials Centre, Bristol Medical School, University of Bristol, Bristol/GB ,[3]Sun Yat-Sen University Cancer Centre, Guangzhou/CN ,[4]Odense University Hospital, Odense/DK

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PL03 PRESIDENTIAL SYMPOSIUM 2 WITH LECTURESHIP AWARD PRESENTATIONS (LIVESTREAMED)
MONDAY, SEPTEMBER 8, 2025 - 8:15 - 10:30

PL03.16 Spread Through Airspaces (STAS) and Prognosis in the Phase III JCOG0802/WJOG4607L Trial of Segmentectomy vs Lobectomy in NSCLC

Y. Yatabe[1], M.B. Beasley[2], M-S. Tsao[3], A. Borczuk[4], S. Berezowska[5], L. Bubendorf[6], W-C. Chang[7], T-Y. Chou[7], W.A. Cooper[8], S. Dacic[9], Y. Han[10], T. Hayashi[11], P. Hofman[12], D.M. Hwang[13], D. Jain[14], P. Joubert[15], K.M. Kerr[16], T-J. Kim[17], S. Kishikawa[18], J. Le Quesne[19], D. Lin[20], F. Lopez-Rios[21], Y. Minami[22], M. Mino-Kenudson[23], A.G. Nicholson[24], M. Papotti[25], A.C. Roden[26], A. Saqi[27], H.S. Shim[28], F. Tavora[29], J.H. von der Thüsen[30], A. Yoshizawa[31], M. Wakabayashi[18], S-I. Watanabe[18], H. Asamura[32]
[1]National Cancer Center, Tokyo/JP ,[2]Mount Sinai Medical Center, New York City/NY/USA ,[3]Princess Margaret Cancer Centre, Toronto/ON/CA ,[4]Northwell Health, Greenvale/NY/USA ,[5]Lausanne University Hospital and University of Lausanne, Lausanne/CH ,[6]University of Basel, Basel/CH ,[7]Taipei Medical University Hospital and Taipei Medical University, Taipei/TW ,[8]Royal Prince Alfred Hospital, NSW Health Pathology, Camperdown/AU ,[9]Yale School of Medicine, New Haven/CT/USA ,[10]Shanghai Chest Hospital, Jiaotong University, Shanghai/CN ,[11]Juntendo University Faculty of Medicine, Tokyo/JP ,[12]Centre Hospitalier Universitaire de Nice, Hôpital Pasteur, Nice/FR ,[13]Sunnybrook Health Sciences Centre, Odette Cancer Centre, Ontario/ON/CA ,[14]All India Institute of Medical Sciences, New Delhi/IN ,[15]Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Université Laval,, Quebec City/QC/CA ,[16]Aberdeen University School of Medicine and Aberdeen Royal Infirmary, Aberdeen/GB ,[17]Yeouido St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul/KR ,[18]National Cancer Center Hospital, Tokyo/JP ,[19]University of Glasgow, NHS Greater Glasgow and Clyde Glasgow, Glasgow/GB ,[20]Peking University Cancer Hospital & Institute, Beijing/CN ,[21]Hospital Universitario [12] de Octubre, Madrid/ES ,[22]National Hospital Organization Ibarakihigashi National Hospital, Tokai-Naka/JP ,[23]Massachusetts General Hospital & Harvard Medical School, Boston/MA/USA ,[24]National Heart and Lung Institute, Imperial College, London/GB ,[25]University of Turin, Torino/IT ,[26]Mayo Clinic, Rochester/MN/USA ,[27]Columbia University Medical Center, New York/NY/USA ,[28]Yonsei University College of Medicine, Seoul/KR ,[29]Federal University of Ceara, Fortaleza/BR ,[30]Erasmus MC, Rotterdam/NL ,[31]Nara Medical University, Nara/JP ,[32]Keio University School of Medicine, Tokyo/JP

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PL03.19 Comparing 74 vs 80 as the Upper Age Limit for Lung Cancer Screening: A Multi-Centre Cohort Study

P. Goodley[1,2], H. Balata[1,2], S. Ahmad[3], R. Gabe[4], P.A. Crosbie[1,2], M.E. Callister[3,5]
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010 | ORAL ABSTRACT SESSIONS

OA01 SMOKING AND BEYOND: NAVIGATING RISK FACTORS IN LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA01.01 Genetic and Air Pollution Scores Identify Individuals at Elevated Risk in a Lung Cancer Screening Cohort

L. Trap[1], R. Büyükcelik[1], N.J.C. Antonissen[2], G.A. Sidorenkov[3], R. Ruiter[1], J. Van Heemst[1], B. Sedaghati-Khayat[1], B.S. Stikker[1], D.W. Dumoulin[1], H. Gietema[4], M. Heuvelmans[3,5,6], F. Mohamed Hoesein[7], P. De Jong[7], A.G. Uitterlinden[1], G. Brusselle[1,8], C. Jacobs[2], J.G.J.V. Aerts[1], R.C.H. Vermeulen[9], G.H. De Bock[3], H.J.M. Groen[3], R. Vliegenthart[3], G.S. Downward[7,9], R. Stadhouders[1], J.G.J. Van Rooij[1]
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Introduction: Low-dose CT screening is effective in reducing lung cancer mortality in high-risk populations. Ongoing research is focused at increasing cost effectiveness and improving risk stratification for screening. Genetic variation and exposure to ambient air pollution (AAP) are known risk factors for the development of lung cancer. However, their value in the context of risk stratification for screening remains poorly explored. In >18,000 Dutch study participants, we here assess the value of polygenic risk scores (PRSs), derived from genetic variation previously linked to lung cancer, and AAP exposure for predicting lung cancer, mortality, and actionable screening outcomes.

Methods: We evaluated the association and discriminative ability of PRSs and AAP exposure with lung cancer in a Dutch prospective population cohort, the Rotterdam Study (RS) (N=11,493, age: ≥45yrs.) and a Dutch-Belgian lung cancer screening cohort, the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) (N=7,394, age: 50-74yrs., persons with a history of heavy smoking). For PRS construction, we selected genome-wide association studies (GWAS) analyzing >10,000 lung cancer cases of European ancestry. We generated two weighted, restricted PRSs: PRS-McKay and PRS-Byun, consisting of 48 and 36 independent genetic variants, respectively. For the NELSON participants, we extracted annual AAP exposures to NO2, ozone, particulate matter 10 (PM10), PM2.5, and ultra-fine particles (UFP) at their residential ZIP code. All predictors were analyzed as continuous (z-standardized) and categorical variables (top and bottom deciles vs. the 40th-60th percentile). Additionally, we evaluated the relationship of the continuous PRSs and PM2.5 with screening outcomes in NELSON, i.e. lung cancer-specific and all-cause mortality, and positive/indeterminate screening-test results.

Results: PRS-Byun was associated with lung cancer and showed discrimination in RS and in NELSON (odds ratio (OR) per SD [95% CI]: 1.19 [1.07-1.32] and 1.28 [1.13-1.44], area under the curve (AUC) [95% CI]: 0.541 [0.510-0.572] and 0.569 [0.533-0.604], respectively). Moreover, we observed an association for the top decile of PRS-Byun in NELSON (OR [95% CI]: 2.35 [1.54-3.58]). PRS-McKay and only PM2.5 out of all interrogated AAP exposures also predicted lung cancer in NELSON (OR [95% CI]: 1.22 [1.08-1.37] and 1.11 [1.01-1.22], AUC [95% CI]: 0.560 [0.525-0.596] and 0.530 [0.503-0.557], respectively). In a baseline lung cancer model containing age, sex, and pack-year history, PRS-Byun and PM2.5 added 0.012 (AUC [95% CI]: 0.656 [0.620-0.691]) and 0.002 (AUC [95% CI]: 0.646 [0.610-0.682], respectively) to its discriminative power in NELSON. Both PRSs were associated with lung cancer mortality (OR PRS-McKay [95% CI]: 1.24 [1.05-1.47] and OR PRS-Byun [95% CI]: 1.24 [1.05-1.47]), but not with all-cause mortality. Only PRS-McKay was significantly associated with a positive/indeterminate screening-test result in NELSON (OR [95% CI]: 1.08 [1.02-1.15]). This association remained significant when the analysis was stratified to participants who did not develop lung cancer.

Conclusions: Our findings suggest a potential role for PRS and AAP — more specifically PM2.5 exposure — for risk stratification in lung cancer screening. PRS-Byun and PM2.5 exposure were associated with a true lung cancer diagnosis, but not with a positive/indeterminate screening-test result, highlighting that these predictors could help limit unnecessary follow-up in screening programs.

Keywords: risk stratification, lung cancer screening, polygenic risk score

OA01 SMOKING AND BEYOND: NAVIGATING RISK FACTORS IN LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA01.02 The Mirror Study: Tumor Microenvironment (TME) in Patients With Non-Small Cell Lung Cancer Exposed to Indoor Radon +/- Tobacco Smoke

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Introduction: Indoor radon (iRn) is a leading cause of lung cancer (LC) in non-smokers, and the second in smokers due to synergistic effects. Preclinical data suggest alpha radiation can influence the immune system and modulate the TME. However, the immune TME associated with iRn, with or without tobacco-smoking remains unknown. In this study, we aimed to morphologically characterize the immune-TME of NSCLC according to the exposure to iRn alone or combined with tobacco-smoking.

Methods: Prospective cross-sectional study of patients with NSCLC enrolled across 15 Spanish hospitals from Jan/21 to date. iRn was measured using alpha-track detectors. Demographics, home characteristics, and additional exposure data were collected via a detailed questionnaire. Clinical/Tumor data were prospectively recorded in an electronic case report form. Tissue blocks were optionally collected for translational research. We morphologically characterized the TME phenotype and density of tumor-infiltrating lymphocytes (TILs), assessed by LC pathologists. High-TILs was defined as >10%, and the TME classified as inflamed, desert or excluded. Immunohistochemistry (IHC) was performed in cases with available tissue.

Results: Out of 750 patients enrolled, with 357 H&E slides and tissue-blocks collected. We report here the first analysis of 298, with available clinical/tumor/exposure data. Among them 59% were male, 76% smokers, with a median age of 65. One-third had advanced-stage and adenocarcinoma was the predominant histology (61%). A total of 41% had NSCLC harbouring driver alterations, and 30% had ≥50%PD-L1 expression. Median iRn was 29 Bq/m3 (10-710). A total of 36 pts was exposed to ≥150 Bq/m^3, including 14 non-smokers and 22 smokers. Additionally, 175 pts (59%) were exposed only to tobacco-smoking, and 87 (33%) were not exposed to either iRn or tobacco-smoking. TIL-density was evaluable in 256 patients. High-TILs were observed in 121 (47%) with a median of 10% (0-85), significantly higher in smokers (15% vs. 7% in non-smokers, p=0.02) and in squamous histology (17% vs. 9% in non-squamous, p=0.021). TME was evaluable in 221 patients: 46% showed an inflamed-TME, 33% had a desert-TME, and 21% an excluded-TME. High-TILs were observed in 45% (5/11) of iRn-exposed patients vs 51% (55/108) of smoking-group, and 44% (23/52) of non-exposed group (p=0.06). This proportion increased significantly to 56% (10/18) in the combined-group (iRn+smoking) vs. others (p=0.019). TME was significantly associated with exposure. In the iRn-exposed group, an inflamed-phenotype was identified in 56% (5/11) vs. 27% with a desert-TME vs. 9% with an excluded-TME (p=0.019). An inflamed TME was also predominant in the smoking-group, 51% (52/101) vs. 27% (11/41) in the non-exposed group. In the combined-group, the inflamed-TME was present in 50% (9/18), followed by 39% as dessert and 11% excluded. Among the 5 iRn-exposed cases with inflamed-TME, IHC (4) showed highCD8$^+$/PD1$^+$expression, and CD4$^+$/FOXP3$^+$expression. In the combined-exposure group, IHC (6) showed highCD8$^+$/PD1$^+$ and CD4$^+$expression, with low-FOXP3$^+$expression.

Conclusions: In this study, we observed that exposure to radon, especially combined with tobacco-smoking, was associated with increased TIL-density and a predominance of inflamed-TME in NSCLC, suggesting a potential immunomodulatory effect. Further in-depth characterization of the TME is needed to better understand the clinical implications of radon in NSCLC.

Keywords: Radon, smoking, TILs

OA01 SMOKING AND BEYOND: NAVIGATING RISK FACTORS IN LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA01.03 Lung Cancer Among People Who Never Smoked: Global Epidemiology and Initial Identification of Early Detection Biomarkers

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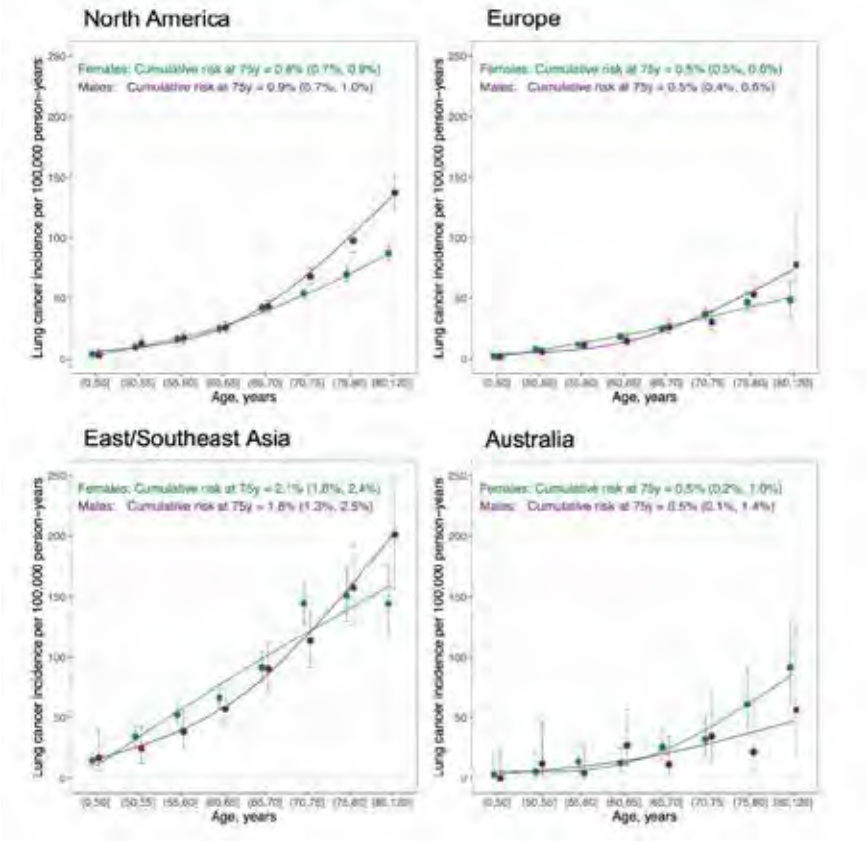
Introduction: In some contexts, low-dose CT (LDCT) screening is being offered to people who never smoked (PWNS), though with evidence of overdiagnosis. We aimed to understand how rates of lung cancer among PWNS vary by geographical region and sex, and to identify novel biomarkers to identify PWNS at elevated risk of lung cancer.

Methods: We analyzed lung cancer risk among 1.47 million PWNS from 24 population cohorts from Europe, North America, Asia, and Australia in the Lung Cancer Cohort Consortium (LC3). Lung cancer in LC3 cohorts is typically diagnosed symptomatically, rather than by screening. We further used Olink Proteomics assays to measure 2,943 proteins in blood from 180 PWNS who developed lung cancer within 5 years after blood draw and 180 PWNS controls matched on study, age, and date of blood draw.

Results: Compared with cohort participants from North America, lung cancer incidence among PWNS was higher in those from East/Southeast Asia (HR=2.20, 95%CI=2.08-2.33) and lower in those from Europe (HR=0.64, 95%CI 0.60-0.68) and Australia (HR=0.65, 95%CI=0.55-0.77). Lifetime risk of lung cancer among PWNS to age 75 years was similar between males and females in each region, including among East/Southeast Asian PWNS (East/Southeast Asian females=2.1%, 95%CI=1.8-2.4%, East/Southeast Asian males=1.8%, 95%CI=1.3%-2.5%, with lifetime risks in North America, Europe, and Australia ranging from 0.5%-0.9%). Among PWNS in the USA, compared with Whites, lung cancer risk was higher among Black PWNS (HR=1.23, 95%CI 1.08-1.41) and Asian-American PWNS (HR=1.34, 95%CI=1.12-1.61) but similar among Hispanic PWNS (HR=0.94, 95%CI=0.74-1.18). We identified 2 proteins associated with future lung cancer risk among PWNS after correcting for multiple comparisons: CEACAM5 (OR=1.65 for a 1-SD increase, 95%CI=1.31-2.09) and CEACAM6 (OR=1.72, 95%CI=1.33-2.22). These associations replicated successfully among participants from UK Biobank.

Conclusions: Risk of lung cancer among people who never smoked is higher among East/Southeast Asians compared with other world regions but appears similar between males and females across 4 continents. Planned research in the LC3 will increase the sample size for protein biomarker discovery and validation for lung cancer in PWNS.

Figure 1. Incidence and lifetime risk of lung cancer among 1.4 million Lung Cancer Cohort Consortium participants who never smoked, by world region.



Keywords: People who never smoked, Biomarkers, Global epidemiology

OA01 SMOKING AND BEYOND: NAVIGATING RISK FACTORS IN LUNG CANCER
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OA01.04 Investigating the Association Between Procedure Duration of Coronary Angiography and Intervention and Postoperative Cancer Risk

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Introduction: Coronary angiography (CAG) and percutaneous coronary intervention (PCI) have long been cornerstones in treating coronary artery disease. These procedures are well-established in improving both clinical outcomes and quality of life. However, with their increasing use, especially under prolonged exposure settings, questions have emerged regarding the long-term oncologic risks potentially tied to cumulative low-dose ionizing radiation during such interventions.This study investigates whether the length of CAG/PCI procedures correlates with the incidence of post-interventional cancer, aiming to inform future strategies for oncologic risk assessment in patients undergoing coronary interventions.

Methods: We conducted a retrospective analysis of 1,079 patients who underwent their first CAG or PCI at our institution between January 2012 and March 2022. Using a 35-minute threshold—based on the median duration—we stratified patients into two groups: longer (≥35 min) and shorter (<35 min) procedure times. To control for baseline imbalances, propensity score matching (PSM) was implemented. Following PSM, we applied a suite of variable selection methods, including univariate logistic regression, stepwise regression, LASSO, ridge regression, and elastic net models. Significant predictors were included in a multivariable logistic regression framework. Cancer-free survival was examined via Kaplan-Meier curves, and subgroup analyses were conducted by cancer type. Sensitivity analyses before and after matching further supported model robustness.

Results: Post-matching, both groups contained 470 individuals with well-balanced covariates (SMD <0.1, all p-values >0.05). The multivariable model identified age ≥66 years (OR=2.40, p=0.003), tobacco use history (OR=2.58, p=0.040), hypertension (OR=2.64, p<0.001), elevated systemic immune-inflammation index (SII ≥460, OR=2.22, p=0.006), reduced left ventricular ejection fraction (LVEF <54%, OR=1.96, p=0.019), and prolonged procedure time (OR=2.32, p=0.004) as independent predictors of cancer development. No substantial multicollinearity was observed (VIFs <5). Survival analysis revealed shorter cancer-free intervals in the longer-duration group (log-rank p=0.006), a finding further supported by adjusted Cox regression. Notably, subgroup analysis highlighted a specific association between longer procedure time and increased lung cancer risk (OR=2.90, p=0.029), whereas other cancer types showed no significant relationships.

Conclusions: Longer durations of CAG or PCI (≥35 minutes) appear to independently increase the risk of developing cancer after the procedure, with lung cancer showing the strongest association. These findings suggest that procedure time could serve as a practical indicator in post-interventional oncology risk models. For high-risk populations, more rigorous follow-up and tailored cancer surveillance may be warranted. Prospective, large-scale investigations will be essential to confirm these results and clarify the biological underpinnings linking procedural exposure to oncogenesis.

Keywords: Percutaneous coronary intervention, Ionizing radiation exposure, Oncologic risk

OA02 LATEST DIAGNOSTIC AND MANAGEMENT OPTIONS TO IMPROVE SURVIVAL OUTCOMES IN EARLY-STAGE RESECTABLE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA02.01 SKYSCRAPER-05: Phase II Study of Perioperative Tiragolumab + Atezolizumab ±Chemotherapy in Locally Advanced Resectable NSCLC

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Introduction: The SKYSCRAPER-05, phase II, open-label, multicenter study (NCT04832854) assessed neoadjuvant and adjuvant treatment with tiragolumab, an anti-TIGIT antibody, plus atezolizumab with/without platinum-based chemotherapy, in locally advanced resectable NSCLC.

Methods: Eligible patients (previously untreated; Stage II-IIIB [AJCC V8], locally advanced resectable NSCLC) were enrolled in Cohort A (PD-L1 ≥50%; per SP263 assay) or Cohort B (PD-L1 any). Cohort A received neoadjuvant tiragolumab (600mg IV) plus atezolizumab (1200mg IV) Q3W (4 cycles), followed by surgery and investigator's choice of adjuvant tiragolumab plus atezolizumab Q3W (16 cycles) or adjuvant platinum-based chemotherapy (4 cycles). Cohort B received neoadjuvant tiragolumab (600mg IV) plus atezolizumab (1200mg IV) Q3W plus chemotherapy (4 cycles), followed by surgery and adjuvant tiragolumab plus atezolizumab Q3W (16 cycles). Primary endpoints: major pathological response (MPR), surgical feasibility and safety. Secondary endpoints: pathological complete response (pCR) and event-free survival (EFS).

Results: At clinical cut-off (14 Feb 2024), 50 patients were enrolled (Cohort A, n=8; Cohort B, n=42). Most patients were male (70%) and white (66%); in Cohort B, 57%, 24% and 19% of patients had tumors that were PD-L1 <1%, 1-49% and ≥50%, respectively. The efficacy and safety evaluable populations comprised 48 patients who received ≥1 dose of study treatment (Cohort A, n=7; Cohort B, n=41; median follow-up 9.5 months). Cohort A was terminated early due to the evolving treatment landscape. Overall, 96% of patients received a resection, of whom 4% had a pneumonectomy and 90% a lobectomy/bilobectomy; 96% of patients had an R0 resection. In Cohort B, the MPR rate was 51% (95% CI: 35-67) and the pCR rate was 29% (95% CI: 17-46); patients achieved MPR and pCR across all PD-L1 subgroups (Table). EFS was immature. In Cohort B, two patients (5%) experienced surgical delays due to adverse events (AEs), and two patients (5%) did not undergo surgery due to progressive disease (Table). Grade 3-5 treatment-related AEs occurred in two (29%) and 17 (41%) patients in Cohorts A and B, respectively; Grade 3-5 surgery-related AEs occurred in one (14%) and two (5%) patients, respectively (Table). Nine patients (22%) in Cohort B (zero in Cohort A) experienced AEs leading to treatment withdrawal.

Conclusions: In the SKYSCRAPER-05 study in locally advanced resectable NSCLC, neoadjuvant and adjuvant tiragolumab plus atezolizumab with/without chemotherapy was surgically feasible, and demonstrated a safety profile consistent with expectations and MPR rates across PD-L1 subgroups similar to other perioperative immunotherapy plus chemotherapy regimens.

	Cohort A PD-L1 high (N=7)	Cohort B PD-L1 any (N=41)
Efficacy endpoints, n (%) [95% CI]		
MPR (per local testing)	5 (71) [30.3–94.9]	21 (51) [35.4–66.9]*
PD-L1 <1%	n=0 –	n=23 10 (43) [23.9–65.1]
PD-L1 1–49%	n=0 –	n=10 6 (60) [27.4–86.3]
PD-L1 ≥50%	n=7 5 (71) [30.3–94.9]	n=8 5 (63) [25.9–89.8]
pCR (per local testing)	2 (29) [5.1–69.7]	12 (29) [16.7–45.7]*
PD-L1 <1%	n=0 –	n=23 5 (22) [8.3–44.2]
PD-L1 1–49%	n=0 –	n=10 2 (20) [3.5–55.8]
PD-L1 ≥50%	n=7 2 (29) [5.1–69.7]	n=8 5 (63) [25.9–89.8]
Surgical feasibility, n (%)		
Surgery performed	7 (100)	39 (95)
Pneumonectomy	0	2 (5)
Bilobectomy	0	3 (8)
Lobectomy	7 (100)	32 (82)
R0 resection	7 (100)	37 (95)
Surgery not performed	0	2 (5)†
Surgery delayed	0	4 (10)
Due to AE	0	2 (5)‡
Patients with post-operative complications	2 (29)§	7 (17)¶
Safety, n (%)		
Any grade AE	7 (100)	41 (100)
Grade 3–4	3 (43)	18 (44)
Grade 5	0	3 (7)‖#
Treatment-related AE	7 (100)	39 (95)
Grade 3–4	2 (29)	15 (37)
Grade 5	0	2 (5)‖
AEs of special interest	6 (86)	33 (80)
Surgery-related AEs within 30 days after surgery	n=7 4 (57)	n=39 15 (38)
Grade 3–4	1 (14)	1 (3)
Grade 5	0	1 (3)**
AE leading to treatment withdrawal		
Any treatment	0	9 (22)
Tiragolumab plus atezolizumab	0	9 (22)
Chemotherapy	0	1 (2)
AE leading to dose modification/interruption		
Any treatment	3 (43)	19 (46)
Tiragolumab plus atezolizumab	3 (43)	13 (32)
Chemotherapy	0	12 (29)

*Two patients did not undergo surgery and were counted as non-MPR/non-pCR

†Due to progressive disease (n=2)

‡Thrombocytopenia (n=1) and dyspnea (n=1)

§Pneumonia (n=1), added instrumentation (n=1)

¶Added instrumentation (n=4), pneumonia (n=2), bronchopleural fistula (n=1), initial ventilator support >48 hours (n=1), reintubation (n=1), tracheostomy (n=1)

‖Infectious pleura effusion (n=1; related to chemotherapy), unexplained death (n=1; related to tiragolumab + atezolizumab)

#Respiratory distress (n=1)

AE, adverse event; CI, confidence interval; MPR, major pathological response; pCR, pathological complete response

keywords: neoadjuvant, tiragolumab plus atezolizumab, locally advanced resectable NSCLC

OA02 LATEST DIAGNOSTIC AND MANAGEMENT OPTIONS TO IMPROVE SURVIVAL OUTCOMES IN EARLY-STAGE RESECTABLE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA02.02 Molecular Residual Disease (MRD) Analysis from NeoADAURA: Neoadjuvant Osimertinib ± Chemotherapy in Resectable EGFRm NSCLC

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Introduction: Neoadjuvant osimertinib±chemotherapy demonstrated statistically significant improvements in major pathological response (MPR) rates vs placebo+chemotherapy in patients with resectable EGFRm stage II-IIIB NSCLC in the Phase 3 NeoADAURA study (NCT04351555). We report results from a pre-planned exploratory analysis using an ultra-sensitive circulating tumour (ct)DNA-based molecular residual disease (MRD) assay to predict outcomes in NeoADAURA.

Methods: Adult patients with resectable EGFRm (Ex19del/L858R) stage II-IIIB NSCLC and WHO PS ≤1 were randomised 1:1:1 to neoadjuvant osimertinib 80 mg QD (≥9 weeks) + chemotherapy (cisplatin/carboplatin+pemetrexed; 3 cycles, Q3W), osimertinib monotherapy 80 mg QD (≥9 weeks), or placebo QD (≥9 weeks) + chemotherapy (3 cycles, Q3W), followed by surgery. Baseline (cycle 1 day 1 of neoadjuvant treatment) and pre-surgical plasma samples were tested for detection of ctDNA (MRD+/MRD-) using personalised tumour-informed MRD panels (NeXT Personal®, Personalis®). Baseline and pre-surgical MRD status were compared with MPR and event-free survival (EFS). MRD clearance was defined as a 10-fold decrease in ctDNA or MRD- in the presurgical sample after baseline MRD+.

Results: Of 358 patients randomised, 210 had samples for MRD panels; 189 had evaluable MRD panels (90%; osimertinib+chemotherapy n=61, osimertinib n=64, placebo+chemotherapy n=64). At baseline, 71% of the 189 patient samples were MRD+ whereas 30% had COBAS-detected plasma EGFRm. Patients with baseline MRD- vs MRD+ had less extensive disease (stage II 81% vs 39%, stage III 19% vs 61%; median tumour size 4.1mm vs 4.3mm; mean number of positive lymph nodes 0.60 vs 1.3) and improved EFS (HR for MRD- vs MRD+, 0.24, 95% CI 0.07, 0.80). Treatment with osimertinib-containing regimens led to decreased pre-surgical vs baseline MRD+ rates (osimertinib+chemotherapy 23% vs 77%, osimertinib 23% vs 72%, placebo+chemotherapy 53% vs 68%; Table) and higher MRD clearance rates vs placebo+chemotherapy (osimertinib+chemotherapy 83%, osimertinib 84%, placebo+chemotherapy 58%; Table). Across arms, more patients with pre-surgical MRD- vs MRD+ (20% vs 9%; Table) and with MRD clearance vs non-clearance (24% vs 6%; Table) had an MPR.

Conclusions: The tumour-informed, ctDNA-based MRD assay had a greater tumour detection rate vs single EGFR gene mutation testing. Baseline MRD status was prognostic for clinical outcomes. Osimertinib-containing regimens improved pre-surgical MRD clearance vs placebo+CT; pre-surgical MRD- and clearance were associated with MPR. These findings support the potential utility of neoadjuvant osimertinib-containing regimens in patients with resectable EGFRm stage II-III NSCLC; longer follow-up will determine how MRD status may guide treatment decisions in this setting.

Keywords: Molecular residual disease (MRD), EGFR-tyrosine kinase inhibitor, Resectable EGFR-mutated NSCLC

OA02 LATEST DIAGNOSTIC AND MANAGEMENT OPTIONS TO IMPROVE SURVIVAL OUTCOMES IN EARLY-STAGE RESECTABLE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

OA02.03 Overall Survival (OS) with Neoadjuvant Nivolumab Plus Chemotherapy by Surgical Outcomes in the Phase 3 CheckMate 816 Study

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Introduction: Neoadjuvant nivolumab pluschemotherapy demonstrated statistically significant and clinically meaningfulimprovements in the primary endpoints of event-free survival (EFS) andpathologic complete response (pCR) inthe phase 3 CheckMate 816 study and is the sole neoadjuvant-onlyregimen to demonstrate statistically significant overall survival (OS) benefitin a phase 3 study of chemoimmunotherapy for resectable solid tumors. Here, we report final, 5-year OS by surgical outcomes fromCheckMate 816, the longest follow-up among studies evaluating neoadjuvant/perioperativechemoimmunotherapy in resectable NSCLC.

Methods: Adultswith stage IB-IIIA (per AJCC v7) resectable NSCLC, ECOG PS ≤1, and no known EGFR/ALKalterations were randomized 1:1 to receive nivolumab plus chemotherapy Q3W orchemotherapy Q3W for 3 cycles, followed by surgery within 6 weeks aftertreatment. EFS and pCR (both per blinded independent review) were primaryendpoints. OS was a key prespecified, statistically powered, hierarchicallytested secondary endpoint. Exploratory analyses included OS by definitivesurgery status, and OS and patient-reported outcomes (PROs; per the EQ-5D-3L utilityindex) by surgical approach, extent of resection, and completeness ofresection.

Results: With a median follow-up of 68.4 months (range, 59.9-85.2; database lock, January 23, 2025), continued OS benefit was seen with neoadjuvant nivolumab plus chemotherapy (n=149) versus chemotherapy (n=135) in patients with definitive surgery (median [95% CI], not reached [NR] vs 76.8 months [73.7-NR]; HR [95% CI], 0.69 [0.46-1.03]; 5-year OS rates, 74% versus 63%). Median OS (95% CI) was 32.9 months (11.0-44.1) with nivolumab plus chemotherapy (n=30) versus 22.0 months (15.6-38.3) with chemotherapy (n=44) in patients without definitive surgery (HR [95% CI], 1.04 [0.60-1.79]). OS was improved with nivolumab plus chemotherapy versus chemotherapy, regardless of surgical approach and extent of resection, and in patients with R0 resection (Table). Any-grade and grade 3-4 surgery-related adverse events occurred in 45% and 11% of patients, respectively, treated with nivolumab plus chemotherapy and in 49% and 15% of patients treated with chemotherapy. PROs by surgical approach and extent of resection will be presented.

Conclusions: In this final 5-year analysis from CheckMate 816, neoadjuvant nivolumab plus chemotherapy demonstrated long-term survival benefit versus chemotherapy in patients with resectable NSCLC who received definitive surgery, regardless of surgical approach or extent of resection and including patients with R0 resection. These findings, along with previously reported results demonstrating statistically significant OS benefit with nivolumab plus chemotherapy, further affirm the use of this regimen as a standard neoadjuvant treatment in patients with resectable NSCLC.

Table. OS by surgical outcomes in patients with definitive surgery

	Nivolumab plus chemotherapy versus chemotherapy				
	Surgical approach		Extent of resection[a]		Completeness of resection
	Minimally invasive[b]	Thoracotomy or conversion[c]	Lobectomy	Pneumonectomy	R0
n	44 vs 29	105 vs 106	115 vs 82	25 vs 34	124 vs 105
HR (95% CI)	Not calculated[d]	0.81 (0.53–1.26)	0.79 (0.48–1.31)	Not calculated[d]	0.65 (0.41–1.01)
5-year OS rate, %	89 vs 68	67 vs 62	74 vs 67	80 vs 53	75 vs 62

[a]Patients may have had ≥ 1 surgery type.
[b]Includes minimally invasive-thoracoscopic/robotic approaches.
[c]Defined as conversion from minimally invasive surgery to thoracotomy.
[d]HR was not calculated due to an insufficient number of events (< 10 per arm).

Keywords: Immunotherapy, Neoadjuvant, Nivolumab

OA03 UNRAVELLING TUMOR EVOLUTION AND BOOSTING IMMUNOTHERAPY EFFICACY
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA03.01 Multiomic Single Cell Profiling Reveals Novel Evolutionary Trajectories in Lung Carcinogenesis

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Introduction: Multiple early-stage lung cancer (MPLC) is increasingly being detected owing to the advancements in low-dose CT screening. However, the underlying molecular mechanism driving tumorigenesis remains poorly understood. This study aims to elucidate tumor evolution trajectories, focusing on the functional plasticity in histologically normal tissue, representing the earliest changes in carcinogenesis.

Methods: We performed single cell transcriptomic profiling in 88 paired paratumor and tumor samples from 16 solitary primary lung cancer (SPLC) and 18 MPLC using a multiregion sampling strategy. To delineate the field of injury, we performed single cell DNA sequencing (scDNA) to characterize tumor-associated mutation profiles in histologically normal tissue.

Results: The SPLC cohort comprised patients with single pathologically confirmed lung adenocarcinoma nodule, while the MPLC cohort included patients with 2-80 suspicious nodules with a median number of 15. We distinguished malignant cells from normal epithelial cells based on copy number variation (CNV) patterns. Normal epithelial cells were subclassified into type 1 pneumocytes (AT1), type 2 pneumocytes (AT2), intermediate cells (IC), club cells, basal cells and Epi_CXCL14 cells as well based on marker gene expressions. Intermediate cells, characterized by co-expression of AT1 and AT2 markers, were further subclassified into IC1 (IC1_NAPSA), IC2 (IC2_PLAUR) and IC3 (IC3_SPP1). Notably, IC3 cells that displayed elevated SPP1, APOC and GPNMB expression were specifically enriched in histologically normal lung tissue from MPLC patients, which is more pronounced in patients with more than 10 tumors. Intriguingly, we identified two distinct tumor development routes including a stochastic pathway and an inflammatory associated pathway. In the stochastic trajectory, AT2 cells differentiated into IC1 and could further develop into either malignant cells or AT1. In the inflammatory trajectory, AT2 cells developed into IC1, followed by IC3, and finally progressed to tumor formation, which was exclusively observed in MPLC. Functional characterization revealed an increased cellular plasticity in both IC1 and IC3, with both cells upregulating genes related to cell structure regulation. Specifically, IC3 demonstrated upregulated leukocyte mediated immunity, regulation of mitotic cell cycle and MAPK pathway activation compared to other epithelial subtypes, suggesting close association between IC3 and immune cells. Moreover, malignant cells derived from the inflammatory trajectory demonstrated elevated cytokine production, cell proliferation and myeloid migration, consistent with the charcteristics of IC3. scDNA profiling of histologically normal lung tissue revealed a prevalent clonal expansion of tumor related mutation, including GNA11, ERBB4, RET and EGFR, which is related to cell proliferation and MAPK pathway. We found an increased frequency of single-nucleotide variants and small insertions/deletions within the normal lung tissue of MPLC patients, compared to those of SPLC patients.

Conclusions: We identified two distinct evolutionary trajectories in lung carcinogenesis. The inflammation-associated trajectory mediated by IC3_SPP1 promotes MPLC development. Our findings collectively demonstrate that inflammatory remodeling facilitates tumor evolution, providing novel insights into the pathogenesis of multiple primary lung cancers and potential targets for early intervention strategies.

Keywords: Multiple primary lung cancer, Carcinogenesis, Multiomic

OA03 UNRAVELLING TUMOR EVOLUTION AND BOOSTING IMMUNOTHERAPY EFFICACY
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA03.02 Deciphering Genomic Evolution of Metastatic Organotropism With Large-Scale Paired Primary Lung Cancers and Metastases

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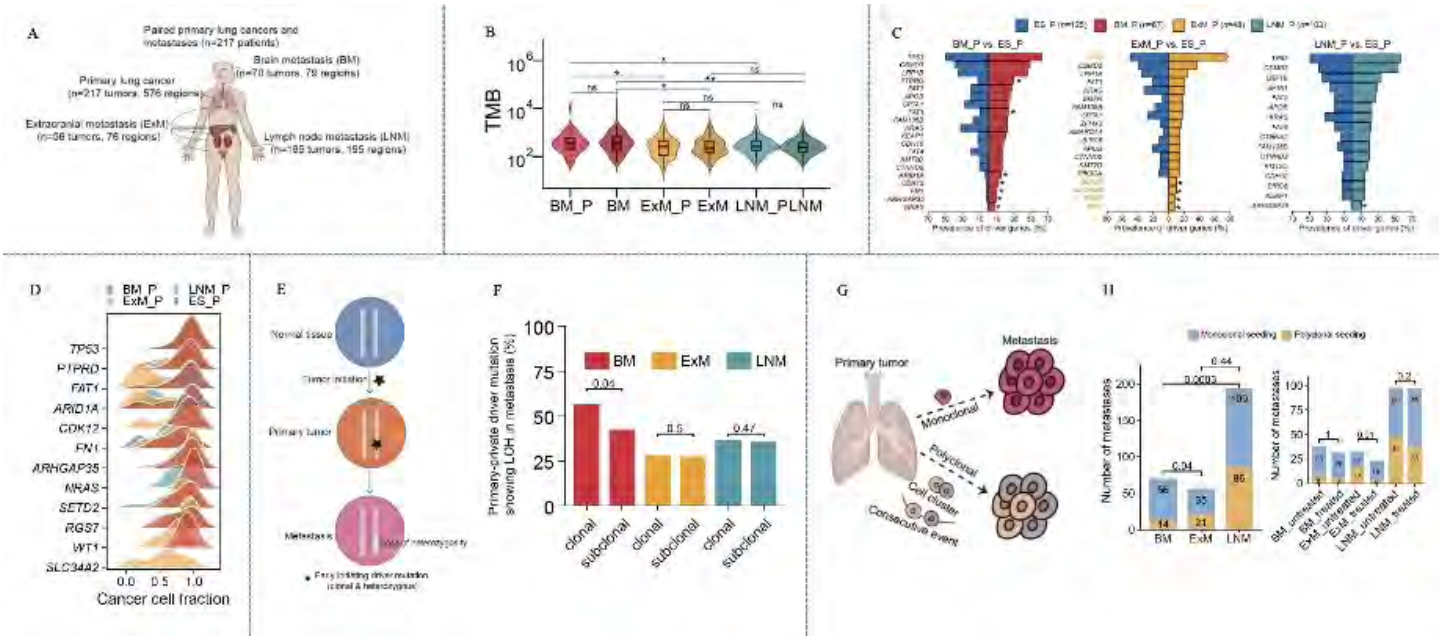
Introduction: Metastasis is the primary cause of death in lung cancer patients, yet our understanding of the genomic determinants and evolution across different metastatic sites remains limited.

Methods: We comprehensively analyzed whole-exome sequencing data from 538 paired primary and metastatic tumors from 217 non-small cell lung cancer (NSCLC) patients, including brain (BM, n=70), distant extracranial (ExM, n=56) and lymph node (LNM, n=195) metastases (Figure A). Furthermore, we retrieved 128 patients from the TRACERx 421 cohort who developed early-stage lung cancer as the non-metastatic control group (ES_P). Genomic drivers and evolutionary trajectories between different metastatic sites were explored.

Results: Overall, BMs harbored higher mutation burden than ExM (P=0.014) and LNM cohort (P=0.0016), while the mutation burden between ExM and LNM cohort were comparable. Similar patterns were observed in the corresponding paired primary tumors (Figure B). Despite the high concordance in driver genomic alterations between paired primary tumors and metastases, several driver genes (including PTPRD, FAT1, ARID1A and CDK12) were more frequently mutated in the brain-metastatic primary tumors as compared to the primary tumors of early-stage and with extracranial and lymph node metastases (Figure C). Notably, these genes were under strong positive selection in primary tumors (Figure D). Unexpectedly, we found BM experienced frequent losses of early driver mutations through specific loss of heterozygosity (LOH) (Figure E-F). This suggested that a higher level of purifying selection was also operating during the initiation of BM. Furthermore, polyclonal seeding was common in LNM (44.1%, 86 out of 195) and in ExM cohort (37.5%, 21 out of 56), but relatively rarer in BM (20%, 14 out 70), which suggested that brain metastasis underwent more stringent selection (Figure G-H).

Conclusions: Our systematic analysis revealed distinct evolutionary trajectories between BM and ExM/LNM in lung cancer, demonstrating that drivers of brain metastatic tropism were already presented in primary tumors rather than being acquired during metastatic spread. Furthermore, this study provides a compendium of candidate brain-tropism metastatic drivers for potential early prediction and intervention of this lethal disease condition.



Keywords: Evolution, Organotropism, Lung cancer metastasis

OA03 UNRAVELLING TUMOR EVOLUTION AND BOOSTING IMMUNOTHERAPY EFFICACY
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA03.03 Rilvegostomig Enhances Ex Vivo Immune Activation in Patient-Resected NSCLC Tumors Over PDx or PDX/aTIGIT Combination Therapy

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Introduction: Rilvegostomig is a monovalent, bispecific humanized IgG1 monoclonal antibody that binds to human TIGIT and PD-1 with high affinity. Rilvegostomig was engineered with a triple-mutation in its fragment crystallizable (Fc)-domain to prevent NK/macrophage-mediated depletion of TIGIT-expressing effector cells. Rilvegostomig has shown promising anti-tumor activity in NSCLC patients in a Phase I/II clinical trial (NCT04995523) and is under investigation in multiple Phase III clinical trials (BTC: NCT06109779, NCT06467357; GC: NCT06764875; NSCLC: NCT06357533, NCT06564844, NCT06627647, NCT06692738). Here, we report the enhanced anti-tumor immune activity of rilvegostomig compared to clinically approved anti-PD-(L)1 drugs and the combinations of anti-PD-1 + anti-TIGIT mono/bivalent antibodies with Fc-active or Fc-reduced domains in a nonclinical human tumor explant model.

Methods: NSCLC tumor fragments from 68 patients were evaluated. These fragments retain the tumor cell composition and immunosuppressive factors of the tumor microenvironment (TME) to provide a physiologically relevant nonclinical model to evaluate dynamic changes in the TME after ex vivo addition of IO therapy. A portion of the tumor fragments was immediately collected post fragmentation for 'baseline' evaluation by IHC and flow cytometry. Remaining tumor fragments were cultured in medium containing therapeutic agents. After 96 hours, IFN-γ levels were quantified as a marker of ex vivo immune activity. The frequency of tumors with statistically significant changes in IFN-γ was defined in comparison with untreated controls (fold change > 1.5, $p<0.05$ determined by Wilcoxon Rank Sum Test).

Results: In a cohort of 68 NSCLC resected tumors, 46% (31/68) of the tumors demonstrated increased IFN-γ when treated with rilvegostomig, whereas, clinically approved anti-PD-1 or anti-PD-L1 monotherapies only elicited increased IFN-γ in 34% (23/68) and 7% (2/29) of the tumors, respectively. Rilvegostomig's activity was observed across PD-L1 expression levels, histological subtypes, disease stages, smoking status, and levels of CD8 immune infiltration. To evaluate the effect of the bispecific format, a subset of the tumors was treated with a combination of rilvegostomig's parental monovalent mAbs. This combination elicited IFN-γ in 41% (14/34) of the sampled tumors. Furthermore, to understand the contribution of Fc-biology in mediating an anti-TIGIT effect, a subset of the tumors was tested with clinical grade anti-PD1 plus Fc-active or Fc-reduced bivalent anti-TIGIT mAbs, yielding 28% (7/25) and 40% (10/25) IFN-γ response. The role of Fc format in modulating rilvegostomig's functionality was confirmed by testing rilvegostomig on different Fc backbones. Engineering rilvegostomig on a Fc-active or afucosylated format diminished IFN-γ response, with activity observed in 40% (6/15) and 30% (7/23) of the tumors, respectively.

Conclusions: Within our ex vivo model we observed that rilvegostomig promotes greater immune cell activation compared to clinical grade anti-PD1 and combinations of anti-PD1 + anti-TIGIT monoclonal antibodies, especially in the context of Fc-active anti-TIGIT mAbs. This suggests that the monovalent bispecific format of rilvegostomig enables greater anti-tumor activity due to its synchronized and localized inhibition of PD-1 and TIGIT. Additionally, rilvegostomig's Fc-reduced design prevents the depletion of PD-1+/TIGIT+ effector cells required for an optimal anti-tumor response. Ongoing analyses are dissecting the mechanisms driving the enhanced activity of rilvegostomig.

Keywords: Tumor explant, TIGIT, NSCLC

OA03 UNRAVELLING TUMOR EVOLUTION AND BOOSTING IMMUNOTHERAPY EFFICACY
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA03.04 TNFSF8-Targeting CpG Peptide Vaccine Reduces ICB Pneumonitis While Boosting Cancer Immunotherapy Efficacy

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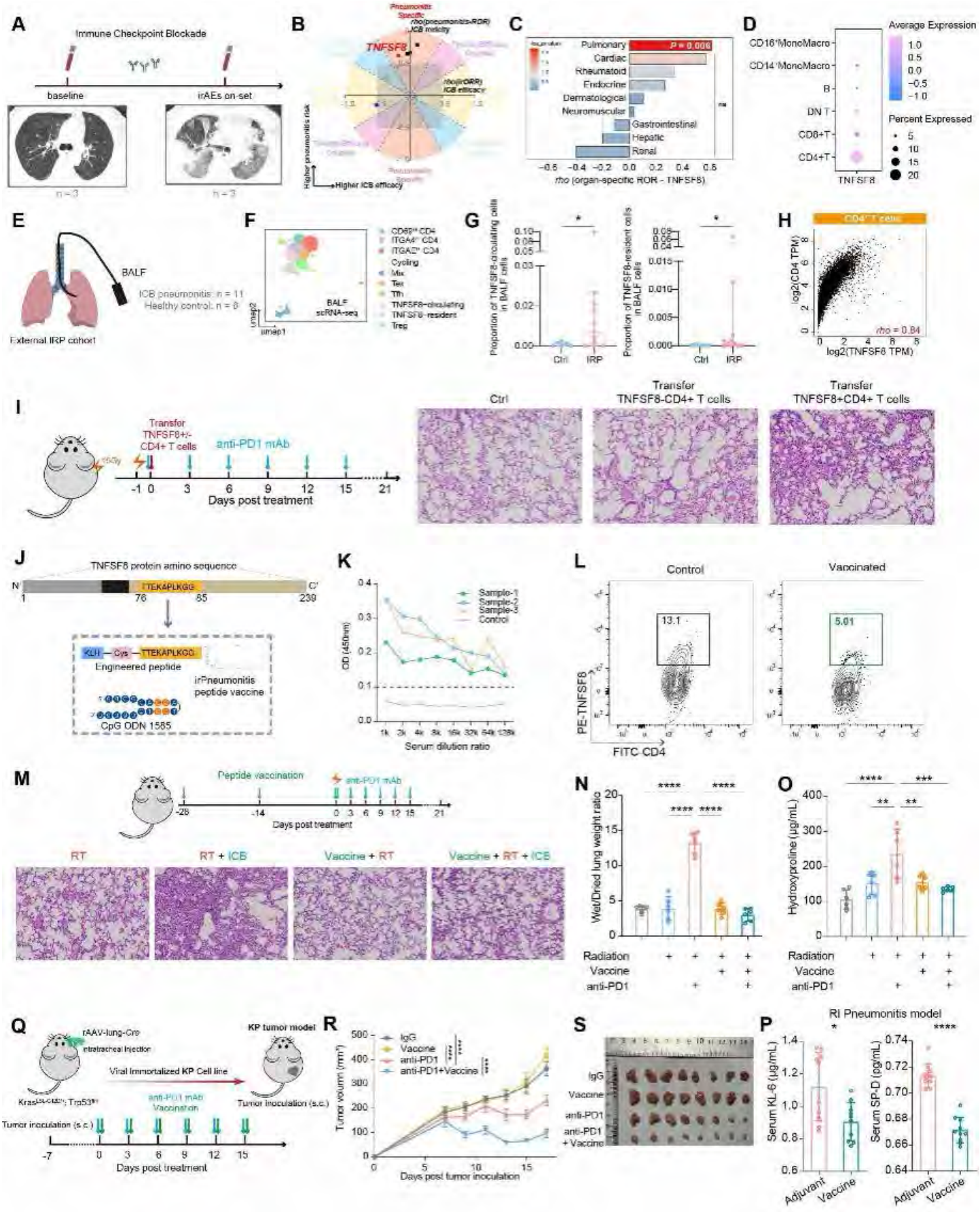
Introduction: Non-small cell lung cancer (NSCLC) patients undergoing immune checkpoint blockade (ICB) face elevated risks of immune-related pneumonitis (irPneumonitis). Emerging evidence challenges prior assumptions by demonstrating that pneumonitis development adversely impacts survival outcomes, while corticosteroid interventions compromise antitumor efficacy. These dual clinical dilemmas underscore the urgent need for precision strategies that mitigate irPneumonitis and enhancing ICB therapeutic benefits.

Methods: Multi-modal analyses integrated real-world pharmacovigilance data (FAERS database), pan-cancer transcriptomics, and single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage fluid (BALF) from irPneumonitis cohorts. An ICB pneumonitis model was established via lung irradiation plus ICB treatment. An adoptive transfer model was used to confirm the pathogenic cell subsets. We engineered a peptide vaccine targeting TNFSF8 extracellular domains, adjuvanted with CpG ODN 1585 - a Th1-polarizing DNA oligonucleotide selected for its safety profile and antitumor synergy. Vaccine efficacy was quantified via ELISA and flow cytometry. Lung injury was assessed through wet/dry weight ratios (edema), hydroxyproline quantification (fibrosis), serum KL-6/SP-D biomarkers, and histopathology (H&E). A KrasLSL-G12D/+ Trp53flox/flox lung adenocarcinoma syngeneic tumor model induced by rAAV-Cre and immortalization was employed to evaluate the efficacy of combination therapy.

Results: Comparative single-cell analysis revealed TNFSF8+CD4+ T cells as hallmark effectors in irPneumonitis patients, showing significant enrichment in irPneumonitis PBMCs and BALF compared to controls. Adoptive transfer of these cells intensified ICB-induced lung pathology, with characteristic increases in alveolar wall thickening, immune cell infiltration, and parenchymal damage. A rationally designed TNFSF8 peptide vaccine adjuvanted with CpG ODN 1585 was produced. The engineered TNFSF8 peptide vaccine demonstrated effective induction of TNFSF8-specific antibodies confirmed by ELISA. Selective reduction of circulating TNFSF8+CD4+ T cells was evaluated via flow cytometry. Moreover, histopathological analysis demonstrated preserved alveolar architecture with diminished inflammatory infiltrates in vaccinated mice receiving ICB. Vaccination mitigated ICB-induced pulmonary edema (decreased wet/dry lung weight) and fibrotic progression (decreased hydroxyproline content). Serum pulmonary biomarkers (KL-6/SP-D) also reflected reduced lung injury in vaccinated mice receiving ICB. Crucially, vaccination synergized with anti-PD1 therapy to suppress tumor growth in Kras/Trp53-driven models without exacerbating pulmonary toxicity.

Conclusions: TNFSF8+CD4+ T cells constitute a pathogenic axis in ICB-associated pneumonitis. Our TNFSF8-targeted vaccine platform coupled with Th1-skewing CpG adjuvant demonstrates dual therapeutic advantages: mitigating irPneumonitis severity while enhancing antitumor immunity. This precision immunomodulatory approach addresses the critical need for toxicity-sparing and efficacy-enhancing strategies in ICB-treated NSCLC populations.



Keywords: ICB Pneumonitis, Peptide Vaccine, TNFSF8

OA04 FROM AI TO PSYCHOSOCIAL SUPPORT: NEW FRONTIERS IN LUNG CANCER MULTIDISCIPLINARY CARE
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA04.01 Perceptions of Dyspnea and Quality of Life Before and After Lung-Sparing Surgery: A Pilot Mixed Methods Study

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Introduction: Pleural mesothelioma (PM) is a rare, incurable cancer associated with asbestos exposure. Lung-sparing surgery aims to improve survival. Despite being deemed fit for surgery, some patients do not return to their baseline physical function and continue to experience many of their initial debilitating symptoms. By gaining a better understanding of the impact lung-sparing surgery has on a patient's breathing capacity, physical function, symptom burden and quality of life (QOL), surgical teams will be better able to prepare patients for surgery, support them through their recovery and improve their QOL and palliate their symptom burden.

Methods: This prospective convergent parallel mixed methods study aimed to compare qualitatively derived themes that influenced the experience of living with PM and the perception of dyspnea with QOL and dyspnea measures, before and three months after lung-sparing surgery. Qualitative and quantitative data were collected concurrently and analyzed independently before being merged to provide a comprehensive understanding of the lived experiences of dyspnea and QOL. Interpretive phenomenological analysis of the qualitative data was conducted. Descriptive statistics were used to characterize the participants and summarize the Dyspnea-12 and McGill Quality of Life-Extended (MQoL-E) questionnaire outcomes. Correlations and mixed model linear regressions were used to analyze pre-operative and post-operative measures. The group experiential themes were compared to the MQoL-E score, the eight individual QOL domains and the Dyspnea-12 scores. Analysis and interpretations were made to determine if the results were convergent or divergent.

Results: The mixed methods analysis revealed a general convergence between the quantitative quality of life and dyspnea data and the qualitative themes derived from participant interviews (Table 1). Participants who expressed significant physical or psychological distress in their interviews often had lower scores in corresponding quantitative measures. Divergence was observed, particularly in the psychological domain, after surgery. Quantitative data showed an overall improvement in psychological scores post-operatively, but interviews revealed that some participants continued to struggle with the mental aspects of dyspnea, even as their psychological domain scores improved.

Conclusions: These results provide valuable insight into patient experience before and after surgery and identify a complex interplay between QOL and dyspnea. While surgery may improve psychological and existential well-being, it exacerbates respiratory symptoms, highlighting the need for multidimensional perioperative care. The mixed methods approach allowed for a deeper understanding of the existential impact of living with mesothelioma and undergoing surgery, revealing the complex interplay between physical symptoms, emotional well-being and existential concerns.

Group Experiential Themes	Personal Experiential Themes	Quantitative Data	Convergence / Divergence
		Before Surgery	
Psychological *Mind supports body in the world*	>Emotional impact of a new reality, >Interplay of the mind-body experience, >Physical and psychological symptom experience, >Redefining normalcy and identity, >Mental strength to accept the diagnosis of mesothelioma.	Pre-operative psychological domain scores range: 9–40 (mean 28.25, SD 14.4)	**Convergence:** Some deeply impacted, others unaffected.
		After Surgery	
	>Redefining normalcy and identity, >Interplay of the mind-body experience.	Post-operative scores remained the same or increased, range 33–40 (mean 37.67, SD 2.58)	**Convergence:** Mental relief and mind-body connection
	>Dyspnea experience and psychological distress.	Moderate negative correlation between post-operative psychological domain and Dyspnea-12 scores (r = -0.490, N = 6, p = 0.324)	**Divergence:** Strong connection in interviews despite the moderate correlation
		Before Surgery	
Physical *Body fighting, enduring, adjusting and adapting in the world*	>Preserving life and guarding against disruption, >Symptom awareness disconnects, >Managing the symptom experience, >Fighting the impact on daily routine. >Multidimensional dyspnea experience.	Pre-operative physical domain scores range: 6–30 (mean 22.75, SD = 9.13)	**Convergence:** Varying levels of symptoms and life
		After Surgery	
	>Physical endurance and commitment to the future, >Resilience through adaptation, >Appreciation of regaining life while facing mortality, >Physical impact of recovery.	Post-operative scores remained the same or increased for 4/6 participants, range 16–30 (mean = 25.67, SD 5.279)	**Divergence:** Some continued limitations, others resumed pre-operative normality.
		Before Surgery	
Social *Others sharing and supporting body in the world*	>Balancing needing help and giving help, >Not being alone in the experience, >Navigating complex family experiences, >Importance of family support and protection.	Pre-operative social domain scores range: 19–30 (mean = 26.88 SD 3.94)	**Convergence:** Varying levels of perceived social support.
		After Surgery	
	>Gaining strength from support of others, >Importance of family support, >Not going it alone.	Post-operative scores remained the same or increased for 4/6 participants, range 26–30 (mean = 28.5 SD 1.76)	**Convergence:** Recognition of the importance of social support.
		Before Surgery	
Experiential *Facing an uncertain future of body living in the world*	>Balancing hope and reality; >Spiritual strength, >Peace and resilience; >Self-determination in the face of a life-threatening illness; >Focus on the future and life priorities; >Moving forward with knowledge and confidence.	Pre-operative existential domain scores range: 21–40 (mean 32.5 SD 6.18)	**Convergence:** Varying levels of existential impact.
		After Surgery	
	>Balancing hope and reality, spiritual strength, >Peace and resilience.	Post-operative scores remained the same or increased for all participants: range 27–40 (mean 35.67 SD 4.84)	**Convergence:** Sense of relief and renewed hope.

Keywords: pleural mesothelioma, quality of life, dyspnea

OA04 FROM AI TO PSYCHOSOCIAL SUPPORT: NEW FRONTIERS IN LUNG CANCER MULTIDISCIPLINARY CARE
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA04.02 Implementation of Large Language Model and GraphRAG-Assisted Decision Support for Multidisciplinary Team Cancer Care

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Introduction: Lung cancer remains a leading cause of morbidity and mortality worldwide, with late diagnosis and misdiagnosis significantly impacting survival rates. Current multidisciplinary team (MDT) workflows are hindered by data fragmentation, inconsistent interpretation of guidelines, and limited integration of trial results. While traditional AI-powered Clinical Decision Support Systems (CDSS) have improved diagnostic accuracy and personalized treatment options, they still face limitations in data retrieval, contextual reasoning, and decision traceability. To address these challenges, we evaluated a novel approach combining large language models (LLMs) with GraphRAG technology.

Methods: We selected DeepSeek-R1, a reinforcement learning enhanced large language model, as foundation model for contextual reasoning and treatment option matching. We then developed a comprehensive knowledge graph integrating patient data from multiple sources, where nodes represented clinical entities (e.g., gene mutations, treatment types) and edges defined relationships between them. Publicly available clinical guidelines and evidences (e.g., NCCN, CSCO, industry consensus, abstracts from WCLC) were incorporated as reference nodes linked to patient-specific nodes to provide management recommendations.We retrospectively analyzed 283 MDT cases from January 2021 to February 2025 for model training and prospectively validated the performance of this approach in 8 real-world MDT cases through an Investigator-Initiated Trial (IIT). The LLM and GraphRAG-assisted recommendations were compared against MDT expert consensus decisions in our hospital. The primary outcome was agreement rate with MDT expert consensus. Exploratory outcomes included time to diagnosis and accuracy of decision traceability.

Results: The LLM and GraphRAG-assisted approach achieved an alignment rate of 88.9% (16/18) with MDT expert consensus. Misalignment occurred due to failure in clinical entity extraction for a patient undergoing multiple treatment lines and uncollected innovative clinical findings (e.g., LAURA trial data) during graph construction. For exploratory endpoints, the average response generation time was 3.2 minutes, significantly faster than the traditional expert-consensus mode (5.6 minutes). The model demonstrated 100% traceability for recommended treatment options, including their sources and source links.

Conclusions: The LLM and GraphRAG-assisted approach represents an innovative AI tool that enhances the accuracy and efficiency of lung cancer MDT discussions. Future development should focus on prospective validation across diverse patient populations and integration with existing clinical systems to maximize adoption and improve patient outcomes.

Keywords: multidisciplinary team (MDT), GraphRAG technology, decision traceability

OA04 FROM AI TO PSYCHOSOCIAL SUPPORT: NEW FRONTIERS IN LUNG CANCER MULTIDISCIPLINARY CARE
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA04.03 Association of Pre- and Postdiagnosis Physical Activity, Promotion, and Maintenance With Lung Cancer Survival: A Nationwide Cohort Study

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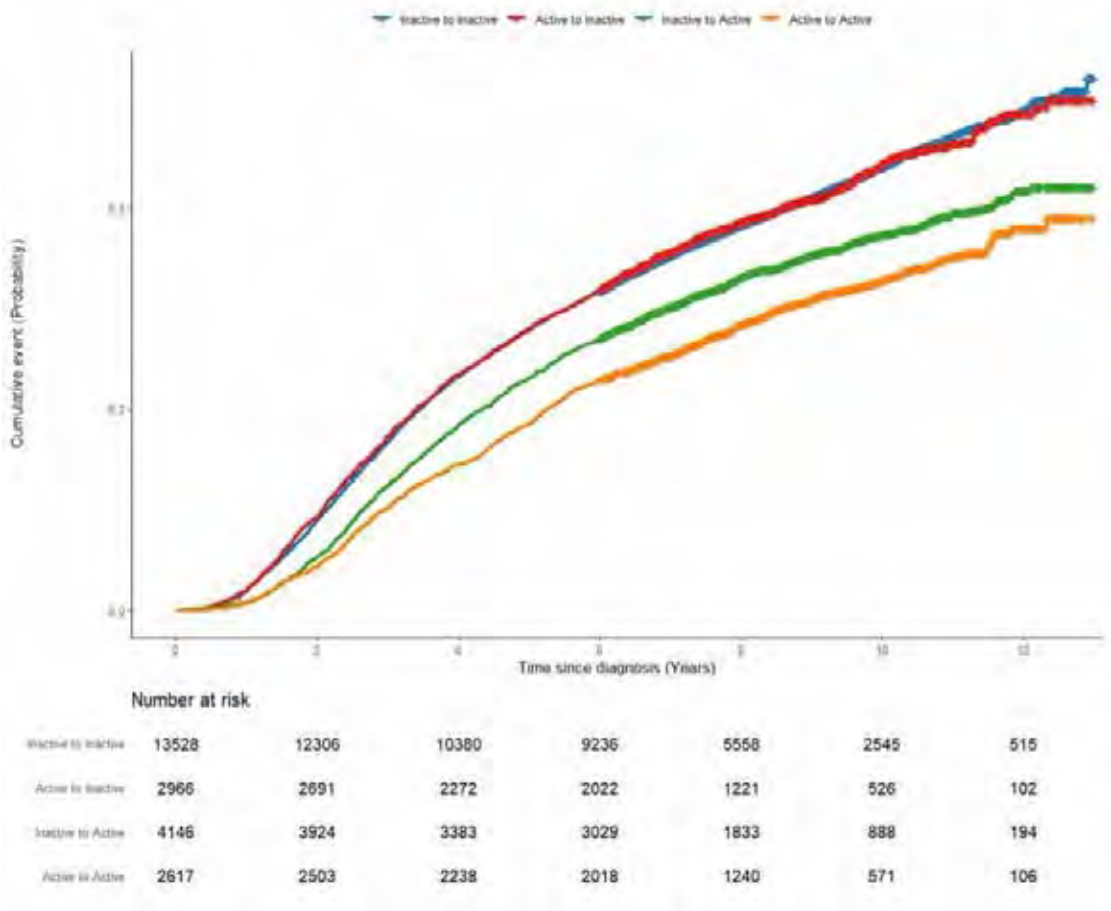
Introduction: Physical activity (PA) is important for improving life expectancy and is suggested as a prognostic factor for certain cancer types. However, the association between PA and mortality outcomes in survivors of lung cancer remains unclear.

Methods: We conducted a nationwide cohort study involving 23,257 individuals diagnosed with lung cancer between January 1, 2010, and December 31, 2016, who attended the National Health Screening Program within 2 years before and after diagnosis. Pre- and postdiagnosis PA levels and changes in PA levels before and after diagnosis were measured. All participants were followed up from the date of diagnosis to December 31, 2022 for the outcome of mortality.

Results: During the follow-up period of 165,344.0 person-years, 9,094 deaths occurred (6,633 lung cancer-specific and 2,461 non-lung cancer deaths). Multivariable analyses revealed that prediagnosis PA was associated with significantly reduced risk of all-cause (adjusted hazard ratio [aHR]=0.89, 95% confidence interval [CI]=0.85-0.94) and lung cancer-specific (aHR=0.90, 95% CI=0.85-0.95) mortality compared with inactivity. Similarly, post-diagnosis PA was associated with a significantly reduced risk of mortality outcomes (aHR=0.82, 95% CI=0.78-0.86 for all-cause and aHR=0.85, 95% CI=0.81-0.90 for lung cancer-specific mortality). When stratified by the total amount of PA (in MET-min/week), a significant dose-response relationship was observed between both pre- and postdiagnosis PA levels and mortality risk reduction. Compared with individuals who were consistently inactive before and after diagnosis, significant mortality risk reduction was seen in those who maintained PA (aHR=0.72, 95% CI=0.67-0.78 for all-cause and aHR=0.76, 95% CI=0.69-0.82 for lung cancer-specific mortality) and those who promoted PA after lung cancer diagnosis (aHR=0.89, 95% CI=0.84-0.94 for all-cause and aHR=0.92, 95% CI=0.86-0.98 for lung cancer-specific mortality). However, individuals who were active before diagnosis but became inactive after diagnosis showed no significant difference in survival outcomes compared with those who were consistently inactive.

Conclusions: Both pre- and postdiagnosis PA are associated with reduced mortality in survivors of lung cancer in a dose-response manner. Maintenance and promotion of PA after diagnosis are key to achieving optimal benefits in overall survival.



Keywords: physical activity, lung cancer, survivorship

OA04 FROM AI TO PSYCHOSOCIAL SUPPORT: NEW FRONTIERS IN LUNG CANCER MULTIDISCIPLINARY CARE
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

OA04.04 Resiliency Among Older Adults Receiving Lung Cancer Treatment (ROAR-LCT): A Phase II - RCT Supportive Care Intervention

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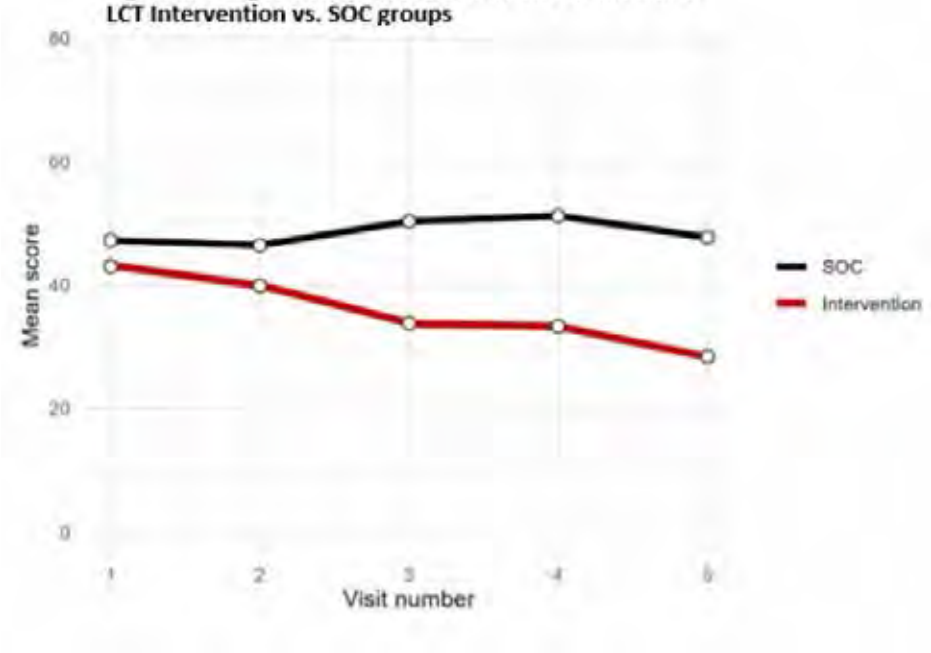
Introduction: Older adults with advanced thoracic cancers experience several unmet supportive care needs. Poor physical function and negative mood are risk factors for functional decline among patients receiving cancer treatment. This study reports planned interim analyses from a Phase II randomized control trial (RCT) examining novel virtual health physical therapy (PT) plus progressive muscle relaxation (R) supportive care interventions delivered to older adults with advanced thoracic cancer.

Methods: This prospective RCT (NCT05339022) accrued older adults ≥ 60 years of age with an advanced thoracic cancer (NSCLC, mesothelioma, or SCLC). Participants in the intervention group were evaluated by PT, given an exercise peddler, resistance bands, and completed 12 weekly PT and R sessions. Patients were provided a R recording for between-session practice. PTs evaluated participants in-person at the start and end of the 12-session intervention with the remainder of sessions conducted via virtual health. Relative perceived effort using the Borg Rating Scale was used to evaluate level of physical activity intensity. Participants in the standard of care (SOC) group received a referral to physical therapy and were provided the R instructions + recording. Patient-reported outcomes were conducted at baseline, weeks 4, 7, 10, and end of study (EoS) with the Short Physical Performance Battery (SPPB) and PROMIS Fatigue conducted at baseline, week 7, and EoS.

Results: To date, 100 participants consented to the ROAR study (intervention, n=50; SOC, n=50), 90% of which began the study (intervention, n=42; SOC, n=48). Nine patients withdrew prior to study start with one participant pending intervention start. Thus far, 60 participants have completed the study (intervention, n=26; SOC, n=34), with 6 participants still actively participating (intervention, n=1; SOC, n=5). 26 participants (29%) dropped out prior to study completion for the following reasons: death n=5, hospice transition n=5, became ineligible n=2, withdrew n=8, and LTFU n=4. Planned interim analyses demonstrate fatigue significantly decreased among the intervention group pre-post intervention compared to the SOC group (Cohen's D: 0.85 (95% CI: 0.18, 1.5), p=.02, Figure 1). SPPB scores improved a full point pre-post in the intervention group but not in the SOC group.

Conclusions: The ROAR-LCT intervention is the first study in the U.S. to demonstrate feasibility and preliminary efficacy among older adults with advanced thoracic cancer. Significant improvements in fatigue can improve physical and functional resiliency in this high-risk, vulnerable patient population. This trial in progress will be presented in full at the meeting.

Figure 1: Fatigue Score Differences Between the ROAR-LCT Intervention vs. SOC groups



Keywords: Older Adults, Thoracic Cancer, Rehabilitation

OA05 IMMUNOTHERAPY FOR SPECIAL POPULATIONS
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA05.01 ASTRUM-002: First-Line Serplulimab Plus Chemotherapy With or Without HLX04 in Advanced Nonsquamous Non-Small Cell Lung Cancer

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Introduction: IMpower130 study demonstrated efficacy of atezolizumab plus chemotherapy (chemo) over chemo alone. IMpower150 study demonstrated efficacy of atezolizumab plus chemo with bevacizumab over bevacizumab plus chemo in nonsquamous non-small cell lung cancer (nsNSCLC) as first-line treatment. PD-1 inhibitors plus chemo have also demonstrated efficacy over chemo. However, whether the combination of a PD-1 inhibitor plus bevacizumab and chemo can provide further survival benefits, especially when comparing to PD-1 inhibitor plus chemo is still unknown. This study, for the first time, evaluated serplulimab (anti-PD-1 antibody) plus HLX04 (bevacizumab biosimilar) and chemo (pemetrexed plus carboplatin) versus serplulimab plus chemo in nsNSCLC.

Methods: This was a three-arm, randomized, double-blind, multicenter, phase 3 study. Patients with locally advanced or metastatic nsNSCLC without EGFR sensitizing mutations or ALK/ROS1 rearrangements and no prior systemic therapy were randomized 1:1:1 to receive serplulimab + HLX04 + chemo (group A), serplulimab + chemo (group B), or chemo (group C). Serplulimab and HLX04 were given every 3 weeks. The primary endpoint was the IRRC-assessed progression-free survival (PFS) per the RECIST version 1.1. Secondary endpoints included other efficacy endpoints and safety.

Results: From November 25, 2019 to June 15, 2023 (data cutoff date), 636 patients were randomized to group A (n=212), B (n=214), or C (n=210). The median follow-up duration was 23.4 (95% CI, 21.6-24.9), 23.1 (95% CI, 21.4-25.6), and 23.0 (95% CI, 20.7-25.6) months for the respective groups. Median PFS was significantly prolonged in group B than in group C (11.0 months vs. 5.6 months; stratified HR = 0.55, 95% CI 0.43-0.69, P < 0.0001), meeting the superiority criterion specified in the protocol. A numerical benefit in PFS was observed for group A compared to group B (12.6 months vs. 11.0 months, HR = 0.86, 95% CI 0.67-1.11, P=0.2529). Overall survival was not mature. Other efficacy results are listed in Table 1. Treatment-related adverse events leading to death occurred in 10 (4.7%), 5 (2.3%), and 7 (3.3%) patients in the respective groups.

Table 1. IRRC-assessed efficacy in ASTRUM-002.

Parameter	Group A (n=212)	Group B (n=214)	Group C (n=210)
Median PFS, months (95% CI)	12.6 (8.7, 14.0)	11.0 (8.4, 12.7)	5.6 (4.8, 6.8)
Stratified HR (95% CI)*	0.86 (0.67, 1.11)	0.55 (0.43, 0.69)	
p-value*	0.2529	<0.0001	
Brain metastases			
Yes	9.7 (7.4, 22.1)	8.1 (6.4, 11.0)	4.1 (3.0, 5.7)
Stratified HR (95% CI)*	0.65 (0.36, 1.14)	0.51 (0.30, 0.87)	
No	13.3 (8.5, 15.0)	11.2 (9.0, 15.1)	6.2 (5.0, 7.1)
Stratified HR (95% CI)*	0.93 (0.70, 1.22)	0.56 (0.43, 0.73)	
Confirmed objective response rate, n (%)	116 (54.7)	113 (52.8)	58 (27.6)
95% CI	47.8, 61.6	45.9, 59.7	21.7, 34.2
Confirmed median duration of response, months (95% CI)	18.3 (11.2, 29.1)	15.4 (11.0, 21.2)	9.7 (5.5, 13.9)

* Statistical comparison: group A versus B, group B versus C.

Conclusions: The addition of serplulimab to chemo provided significantly longer PFS compared to chemo alone in patients with locally advanced or metastatic nsNSCLC, while the combination of serpluliamb, bevacizumab and chemo provided numerical improvements in PFS when compared to serplulimab and chemo. Both treatment regimens had manageable safety profiles.

Keywords: nonsquamous NSCLC, serplulimab, HLX04

OA05 IMMUNOTHERAPY FOR SPECIAL POPULATIONS
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA05.02 First-Line Atezolizumab Plus Chemotherapy in Elderly Patients With Advanced NSCLC, IFCT-1805 Elderly: A Randomized, Multicenter, Phase 3 Trial

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Introduction: For advanced non-small cell lung cancer (NSCLC), the combination of chemotherapy (CT) with an immune checkpoint inhibitor (ICI) in first-line treatment is now the standard of care. The benefit of adding immunotherapy (IO) to CT was not investigated by dedicated studies for elderly people. The IFCT-1805 ELDERLY trial assessed the addition of atezolizumab (ATZ), an ICI targeting the human programmed death-ligand 1 (PD-L1), to the current standard of care by monthly carboplatin with weekly paclitaxel CT (E Quoix et al, Lancet 2011) in elderly patients with advanced NSCLC.

Methods: We conducted a multicenter phase III randomized (2:1) trial in patients aged 70-89 years, with metastatic or locally advanced non-irradiable NSCLC (with neither EGFR mutation nor ALK rearrangement) naïve of treatment, to compare monthly carboplatin and weekly paclitaxel with (CT+IO arm) and without ATZ (CT arm). The patients were required to have a performance status (PS) 0-1 and mini-mental score ≥ 24. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), best response rate (ORR), duration of response (DOR) and safety.

Results: In total, 510 patients were randomized: 340 in the CT+IO arm and 170 in the CT arm, with a median age of 77 (range 70 - 89), male/female in 73%/27% cases, PS 0/1 in 27%/73% and 87% of current and ex-smokers. The main histologies were adenocarcinoma in 69% and squamous in 23%, with 49% and 51% of PD-L1 - and + (≥1%) tumours, respectively. Stage IV represented 94% of the patients. The median follow-up time was 38 months (ms). The median OS was 18.6 ms (95% CI 15.5-22.4) for CT+IO arm vs 15.0 ms (95% CI 11.8-17.5) for the CT arm with no statistically significant difference (HR 0.87 [0.70-1.08], p=0.20). The PFS was significantly improved by IO with a median PFS of 7.4 ms (95% CI 6.0-7.8) vs 5.7 ms (95% CI 5.4-5.8), respectively (HR 0.56 [0.46-0.69], p<0.0001). The ORR were 51.2% and 41.8% (p=0.04) and the median DOR were 6.7 ms vs 3.8 (p<0.0001), respectively. Second-line treatment was IO in 9.6 % and 55.5%, respectively. PD-L1 expression had borderline prognostic value (HR 0.81 [0.66-1.00], p=0.05), but no predictive value (p interaction=0.14). The safety analyses showed grade ≥3 treatment-related adverse events (TRAE) in 71.4% vs 61.9% (p=0.03) and grade ≥3 serious TRAE 16.3% vs 7.7% (p=0.008), in the CT+IO and CT arms respectively, with 5 grade 5 TRAE in the CT+IO arm (2 CT- and 3 IO-related) and 0 in the CT arm.

Conclusions: In the IFCT-1805 ELDERLY trial, despite a numerically longer OS when adding ATZ to the current standard of care CT for first line therapy of elderly patients with NSCLC, the gain was not statistically significant. However, the addition of ATZ to CT significantly improved the PFS, the ORR and the DOR regardless of PD-L1 expression.

Keywords: Elderly patients, Immunotherapy, NSCLC

OA05 IMMUNOTHERAPY FOR SPECIAL POPULATIONS
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA05.03 NIVIPI-Brain: Phase 2 Study of Nivolumab + Ipilimumab Combined With Chemotherapy in NSCLC With Synchronous Brain Metastases

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Introduction: Chemotherapy plus immunotherapy is effective and safe in patients with advanced non-small cell lung cancer (NSCLC) with untreated brain metastases (BM). Dual immunotherapy plus a short chemotherapy course achieved high intracranial efficacy in patients with previously treated BM. This combination was investigated in patients with untreated BM in the NIVIPI-BRAIN trial (NCT05012254).

Methods: This open-label phase 2 study evaluated the efficacy and safety of two cycles of platinum-based chemotherapy (according to the histological type) combined with nivolumab 360mg Q3W plus ipilimumab 1mg/kg Q6W. Treatment was maintained until tumor progression, unacceptable toxicity, or up to 2 years. Patients with multiple, untreated and measurable BM, ECOG PS 0-1, EGFR/ALK/ROS1 negative, were assigned to 2 cohorts: (A) Asymptomatic BM without systemic corticosteroids; (B) Olygosymptomatic BM causing neurologic signs and symptoms controlled with ≤ 4mg qd of dexamethasone. Primary endpoint: to determine the 6 and 5 months (m) intracranial PFS rate by RANO-BM criteria for cohort A and B, respectively.

Results: 66 patients were included and 65 patients were finally treated (39 in cohort A and 26 in cohort B). Median age was 64 years and most patients were males (73%), ever smokers (89%) and had lung adenocarcinoma (77%). The median number of cycles of nivolumab and ipilimumab were 5 and 3, respectively, and 8 patients (12%) completed 2 years of treatment. Treatment discontinuation was mainly due to progression (55%) and toxicity (20%). Systemic and intracranial ORR was 41.5% (27 PR for systemic and 6 CR / 21 PR for intracranial). The 6m intracranial PFS rate was 41% (95% CI 28.2-59.8) for cohort A and 5m intracranial PFS rate was 46.2% (95% CI 30.5-69.9) for cohort B, both below the expected 50%. The median intracranial PFS was shorter than systemic PFS (4.9 vs 6.7 months). With a median follow-up of 25 months, the median OS was 10.6 months and the 2-year OS rate was 29.4% in the whole cohort. Most neurological adverse events (AEs) were G1-2, and 7 patients had G3 (1 seizure, 1 cognitive impairment, 1 headache, 1 limbs weakness, 1 polyneuropathy, 1 disorientation, 1 stroke) and 1 patient had a G4 seizure. Treatment-related AEs (TRAEs) with immunotherapy were observed in 78.5% of patients. No G5 TRAEs were reported.

Conclusions: The combination of nivolumab plus ipilimumab and two cycles of chemotherapy did not reach the expected intracranial efficacy in patients with advanced NSCLC with untreated BM.

Table 1. Efficacy outcomes in the NIVIPI-BRAIN clinical trial.

	Cohort A (n=39)	Cohort B (n=26)	Total (n=65)
Systemic ORR/DCR (%)	43.6 / 84.6	38.5 / 69.3	41.5 / 78.4
Intracranial ORR/DCR (%)	41 / 69.2	42.3 / 80.8	41.5 / 73.8
Median syst. PFS, months (95% CI)	6.8 (4.6-11.4)	5.8 (3.3-NR)	6.7 (4.3-11)
Median ic. PFS, months (95% CI)	5 (3.6-8.4)	4 (3.5-14)	4.9 (3.7-8.3)
6 months syst. PFS rate (%)	53.8	46.2	50.8
6 months ic. PFS rate (%)	41.0	42.3	41.5
Median OS, months (95% CI)	10.6 (5.8-21.9)	10.2 (6.7-NR)	10.6 (7.5-21.9)
1 year OS rate (%)	39.9	46.2	42.6

Keywords: Nivipi-Brain, NSCLC, brain metastases

OA05 IMMUNOTHERAPY FOR SPECIAL POPULATIONS
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA05.04 A Randomized Phase 3 Study of Niraparib Plus Pembrolizumab as Maintenance Therapy for Advanced/Metastatic NSCLC: ZEAL-1L

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Introduction: Niraparib, a poly(ADP-ribose) polymerase inhibitor, has demonstrated efficacy in ovarian cancer. The ZEAL-1L study was designed to assess the combination of niraparib plus pembrolizumab in patients with advanced or metastatic non-small cell lung cancer (NSCLC) in the maintenance-therapy setting.

Methods: In ZEAL-1L, a multicenter, randomized, double-blind, placebo-controlled phase 3 study, niraparib plus pembrolizumab was compared with placebo plus pembrolizumab as maintenance therapy in patients with advanced/metastatic stage IIIB/IIIC and stage IV NSCLC presenting with stable disease, partial response (PR), or complete response (CR) per investigator's assessment after 4-6 cycles of first-line standard-of-care platinum-doublet chemotherapy plus pembrolizumab. Patients were randomized 1:1 to receive niraparib (300 mg for baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL; 200 mg for baseline body weight <77 kg and/or baseline platelet count <150,000/µL) or matched placebo once daily plus maintenance pembrolizumab every 3 weeks until radiographic progression, unacceptable toxicity, or death. Primary and key secondary endpoints are shown in Table 1.

Table 1. Efficacy endpoints

Endpoint	Niraparib plus pembrolizumab (n=331)[a]	Placebo plus pembrolizumab (n=335)[a]
Primary endpoint		
PFS by BICR in patients with a best response of PR or CR, median (95% CI), mo	n=200	n=201
	5.6 (4.14–8.28)	5.6 (4.21–7.16)
	HR, 1.00 (95% CI, 0.79–1.27) 1-sided P=0.502	
Key secondary endpoints		
PFS by BICR in the ITT population, median (95% CI), mo	4.4 (95% CI, 4.17–5.52)	4.4 (95% CI, 4.14–5.52)
	HR, 0.99 (95% CI, 0.82–1.19)	
OS in patients with a PR or CR, median (95% CI), mo	n=200	n=201
	24.8 (20.11–31.44)	32.5 (24.67–NE)
	HR, 1.20 (95% CI, 0.92–1.56)	
OS in the ITT population, median (95% CI), mo	21.4 (18.23–23.23)	25.3 (21.22–28.71)
	HR, 1.16 (95% CI, 0.96–1.41)	
TTP-CNS by BICR using RANO-BM criteria in the ITT population, cumulative incidence competing risk analysis	Subdistribution HR, 0.98 (95% CI, 0.63–1.52)	

[a]Reflects ITT population for each arm.
BICR, blinded independent central review; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PFS, progression-free survival; RANO-BM, response assessment in neuro-oncology brain metastases; TTP-CNS, time to progression in the central nervous system.

Results: Overall, 331 patients were randomized to niraparib plus pembrolizumab, and 335 to placebo plus pembrolizumab; 194 (29%) had squamous histology, and 472 (71%) had nonsquamous histology by randomization stratification factor. At data cutoff (26Feb2025), median follow-up time for OS was 34.30 months for patients in the niraparib-plus-pembrolizumab arm and 33.45 months for patients in the placebo-plus-pembrolizumab arm, and 443 patients (67%) had discontinued from the study (n=373 [56%] died). Primary and key secondary efficacy endpoint data are shown in Table 1. Safety was consistent with the known safety profiles of niraparib and pembrolizumab (Table 2). There were 4 treatment-related TEAE deaths (niraparib-plus-pembrolizumab arm: sudden death [n=1], pneumonitis and pulmonary embolism [n=1]; placebo-plus-pembrolizumab arm: colitis [n=1], pneumonia [n=1]).

Conclusion: Niraparib failed to improve BICR-assessed PFS in the CR/PR population; no efficacy benefit was detected in key secondary endpoints.

Keywords: Niraparib, PARPi, PD-1

OA06 NOVEL ADCS IN SCLC
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA06.01 A First-In-Human Phase 1 Study of SHR-4849 (IDE849), a DLL3-Directed Antibody-Drug Conjugate, in Relapsed SCLC

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OA06 NOVEL ADCS IN SCLC
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA06.02 Safety and Efficacy of QLC5508 in Previously Treated Patients with Small Cell Lung Cancer: Updated Data from a Phase 1 Study

C. Zhou[1,2], Y. Yu[3], X. Yu[4], Y. Sun[5], X. Meng[5], Y. Ji[6], F. Ning[7], Y. Jia[8], Y. Ji[9], H. Yang[10], Y. Luo[11], R. Yang[12], Z. Zhang[13], Y. Zhao[14], Z. Zhang[15], Q. Wen[16], M. Sun[16], L. Shen[17], L. Han[18], Z. Zhang[19], O. Jiang[20], G. Wu[21], X. Wang[21], L. Wan[22], G. Cao[23], H. Li[24], W. Cheng[24], X. Qiu[24], X. Kang[24]
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Introduction: QLC5508 (MHB088C), a novel B7-H3-targeted antibody-drug conjugate with high cell-binding activity and internalization rate, contains SuperTopoiTM payload which is 5 to 10 times more potent than Dxd. The preliminary data of a phase 1 study indicated the promising anti-tumor activity and tolerability of QLC5508 in patients with solid tumors, including extensive-stage small cell lung cancer (ES-SCLC). Here we report the updated results of survival and safety in patients with ES-SCLC.

Methods: This multi-center phase 1 trial consisted of dose-escalation stage and dose-expansion stage. In dose-escalation stage, QLC5508 was administered via intravenous infusion at dosage ranging from 0.8 mg/kg to 4.0 mg/kg every two (Q2W) or three weeks (Q3W). In dose-expansion stage, patients with ES-SCLC who failed platinum-based systematic chemotherapy±PD-1/PD-L1 and had no more than three lines of prior treatment or intolerable to standard treatment were recruited. Dose levels of 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W were selected for dose-expansion stage. The primary endpoints were safety and tolerability.

As of Jun 13, 2025, a total of 106 patients were included in 1.6 mg/kg Q2W (n=30), 2.0 mg/kg Q2W (n=46), and 2.4 mg/kg Q3W (n=30) dose levels. Most of the patients (90.6%) had stage IV disease. There were 28 patients (26.4%), 15 patients (14.2%), and seven patients (6.6%) who had previously received 2, 3, >3 lines of treatment, respectively. Over half of the patients (58.5%) had received immunotherapy. Eleven (10.4%) patients had prior treatment of irinotecan. Treatment-related adverse events (TRAEs) of ≥grade 3 occurred in 15 (50.0%), 16 (34.8%), and 13 (43.3%) patients in 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W cohorts, respectively. The most common TRAEs of ≥grade 3 with incidence of ≥10% were neutrophil count decreased (17.0%) and white blood cell count decreased (10.4%). Two (4.3%) patients discontinued the treatment due to TRAEs of interstitial lung disease, both were in the 2.0 mg/kg Q2W cohort. One patient (3.3%) died due to treatment-related cachexia in the 1.6 mg/kg cohort. In the efficacy set (n=103), median progression-free survival was 5.55 (95% confidence interval [CI], 3.65-6.31), 5.95 (95% CI, 4.63-8.15), and 5.52 (95% CI, 3.81-7.06) months in 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W cohorts, respectively. The overall survival in the three cohorts were 11.50 (95% CI, 7.00-13.34), 11.73 (95% CI, 8.77-not evaluable [NE]), and 11.50 (95% CI, 7.59-NE) months, respectively. In conclusion, QLC5508 showed prolonged survival as well as manageable and tolerable safety profile in previously treated patients with ES-SCLC. QLC5508 2.0 mg/kg Q2W is being evaluated in an ongoing phase 3 study.

Keywords: B7H3 ADC, SCLC

OA06 NOVEL ADCS IN SCLC
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA06.03 Ifinatamab Deruxtecan (I-DXd) in Extensive-Stage Small Cell Lung Cancer: Primary Analysis of the Phase 2 IDeate-Lung01 Study

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OA06 NOVEL ADCS IN SCLC
SUNDAY, SEPTEMBER 7, 2025 - 16:45 - 18:00

OA06.04 Safety and Efficacy of ABBV-706, a Seizure-related Homolog Protein 6-targeting Antibody-drug Conjugate, in R/R SCLC

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Introduction: Seizure-related homolog protein 6 (SEZ6) is highly expressed in small cell lung cancer (SCLC). ABBV-706, an antibody-drug conjugate (ADC) comprising a SEZ6-targeting antibody with a topoisomerase 1 inhibitor (Top1i) payload, was evaluated in a phase 1 study (NCT05599984). Preliminary results from dose escalation (1.3 to 3.5 mg/kg Q3W) showed encouraging antitumor activity and manageable safety of ABBV-706 monotherapy in patients with advanced solid tumors (JCO 2024;42:suppl16;abstr 3001). We present updated safety and efficacy results for patients with SCLC in the dose optimization cohorts.

Methods: Patients (≥18 years) with relapsed/refractory (R/R) SCLC were randomized to receive ABBV-706 at 1.8 or 2.5 mg/kg Q3W until disease progression/unacceptable toxicity. SEZ6 expression was assessed retrospectively. Patients with prior treated or untreated stable brain metastases were eligible. Prior exposure to SEZ6-targeted ADCs or ADCs with Top1i payload was not permitted. Primary objectives were to assess efficacy, safety, pharmacokinetics, and determine the recommended phase 2 dose (RP2D) in SCLC.

Results: In total, 80 patients with SCLC were enrolled: 1.8 mg/kg, n=41; 2.5 mg/kg, n=39. Median number of prior therapies was 2 (range: 1-6); median treatment duration was 5.8 months (range: 0.7-11.3). SEZ6 expression and patient characteristics were balanced between the dose cohorts. ABBV-706 showed similar ORR at both doses, with longer DOR and PFS at 1.8 mg/kg (see Table). ORR was higher in patients who were Top1i naive and/or receiving ABBV-706 in second line (62.1% and 81.3% at 1.8 mg/kg). The 1.8-mg/kg dose had improved safety vs 2.5 mg/kg. Relative dose intensity was 99% and 85% at 1.8 mg/kg and 2.5 mg/kg. Any-grade (G) treatment-related adverse events (TRAEs) in the 1.8-mg/kg and 2.5-mg/kg cohorts occurred in 85% and 95% of patients; most common were anemia (51% vs 74%) and fatigue (34% vs 39%). G≥3 TRAEs in the 1.8-mg/kg and 2.5-mg/kg cohorts occurred in 49% and 77% of patients; anemia (39% vs 62%) and neutrophil count decreased (17% vs 31%) were most common. Serious TRAEs occurred in 17% (1.8 mg/kg) and 10% (2.5 mg/kg) of patients. Overall, TRAEs leading to dose discontinuation, interruption, reduction, and death occurred in 9%, 44%, 28%, and 4% of patients. Adjudicated interstitial lung disease rate was 9%.

Conclusions: ABBV-706 has manageable safety and promising efficacy in patients with R/R SCLC. Based on the totality of the benefit-risk profile, monotherapy RP2D was determined to be 1.8 mg/kg Q3W in SCLC.

Table. Efficacy outcomes in patients with SCLC in the DO cohorts

Outcome	1.8 mg/kg (n=41)	2.5 mg/kg (n=39)	DO Overall (N=80)
Median follow-up, months	9.0	8.3	8.4
ORR[a], n/N (%)	23/41 (56.1)	23/39 (59.0)	46/80 (57.5)
1 prior LOT	13/16 (81.3)	10/14 (71.4)	23/30 (76.7)
≥2 prior LOT	10/25 (40.0)	13/25 (52.0)	23/50 (46.0)
Top1i naive	18/29 (62.1)	18/28 (64.3)	36/57 (63.2)
Top1i exposed	5/12 (41.7)	5/11 (45.5)	10/23 (43.5)
Brain metastasis	10/16 (62.5)	6/12 (50.0)	16/28 (57.1)
Median DOR, months [95% CI]	6.2[b] [4.2, NE]	4.4[b] [3.5, 6.9]	5.6[c] [4.2, 6.9]
Median PFS, months [95% CI]	6.8 [4.0, 8.2]	5.6 [4.4, 7.0]	5.7 [4.9, 7.0]
9-month OS, probability [95% CI]	0.6 [0.4, 0.7]	0.6 [0.4, 0.7]	0.6 [0.5, 0.7]

[a]Confirmed responses. [b]n=23. [c]n=46.
CI, confidence interval; DO, dose optimization; DOR, duration of response; LOT; line of therapy; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Keywords: SCLC, ABBV-706, antibody-drug conjugate

OA07 EXPANDING HORIZONS IN ADVANCED NSCLC INTEGRATING LOCAL THERAPY
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA07.01 Final Analysis of Brighstar: LCT With Brigatinib in Tyrosine Kinase Inhibitor-Naïve ALK-Rearranged Metastatic NSCLC

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Introduction: Approximately 95% of patients who have an initial response to ALK-TKIs exhibit an incomplete response, resulting in residual disease that may enable emergence of acquired resistance. Minimizing or eliminating residual disease with local consolidative therapy (LCT) may delay development of resistance and improve clinical outcomes.

Methods: BRIGHTSTAR is a single-center investigator-initiated trial assessing the safety and efficacy of brigatinib with LCT. Eligible patients with TKI-naïve ALK-rearranged advanced NSCLC with oligo- and poly-metastatic disease, were treated for 8 weeks with induction brigatinib followed by LCT with radiation and/or surgery. (ClinicalTrials.gov Identifier: NCT03707938). Baseline and post-brigatinib induction tumor images were comprehensively annotated. Disease burden was defined by overall 3D tumor volume. Individual patient data from a phase 3 trial of brigatinib vs crizotinib (ALTA-1L, NCT02737501) were retrospectively compared. Herein, we present the final analysis of the study.

Results: A total of 34 patients were enrolled, of whom 32 (94%) proceeded to LCT. At study entry, most patients (82%, n=28) had polymetastatic disease (>3 sites) and 41% (n=14) had brain metastases. LCT modalities included radiation (n=27), surgery (n=3), and surgery + radiation (n=2). LCT-related grade ≥3 adverse events included esophagitis (9%), pneumonitis (3%), anemia (3%), adrenal insufficiency (3%), and bronchopulmonary hemorrhage (3%). One patient with grade 3 pneumonitis successfully transitioned to full-dose alectinib after resolution with corticosteroids. The median PFS was 66 months (95%CI: 27.4 months to not reached (NR))., with a 5-year PFS rate of 51% (95%CI: 33 to 69). For comparison, in the ALTA-1L trial, in which patients received brigatinib alone, median PFS was 29.4 months. A post hoc analysis showed that patients who underwent comprehensive consolidation (n = 20) had a median PFS that was not reached, whereas those who received partial consolidation (n = 12) had a median PFS of 26 months (95%CI: 16.4 to 29.0 months, ($p<0.001$). Additionally, among patients with baseline ctDNA positivity (n = 16), median PFS was 28 months (95%CI: 18.2 months to NR), while it was not reached in patients with ctDNA negativity (n = 13). Patients with baseline total tumor volume greater than 55 cm^3 experienced a median PFS of 27.5 months (95% CI: 25.03 months to NR), whereas the median PFS was not reached in those with a baseline total tumor volume of 55 cm^3 or less. Using multivariant analysis incorporating these variables, patients were stratified into high- and low-risk groups, with high-risk group showing significantly worse PFS (HR 11.6, 95% CI:2.51-53.8).

Conclusions: Brigatinib with LCT is safe in patients with ALK-rearranged advanced NSCLC and yielded promising results when compared to historical outcomes from brigatinib alone. Patients who received comprehensive LCT had superior outcomes, and baseline ctDNA status and radiological volumetric measurements may serve as prognostic biomarkers for treatment response.

Keywords: ALK, LCT, ablation

OA07 EXPANDING HORIZONS IN ADVANCED NSCLC INTEGRATING LOCAL THERAPY
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA07.02 Tumor Burden Metrics at Oligoprogression and Survival After SBRT in NSCLC: An Analysis of the Randomized Phase II CURB Trial

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Introduction: The CURB trial (NCT03808662) demonstrated that adding stereotactic body radiotherapy (SBRT) to the standard of care significantly prolonged progression-free survival (PFS) in patients with oligoprogressive non-small cell lung cancer (NSCLC). While tumor burden may have played a role in outcomes, it remains unclear which tumor burden metrics are most impactful in stratifying patient risk. To this end, we performed a secondary analysis of the SBRT-treated NSCLC cohort to assess the correlation of various burden metrics with PFS and overall survival (OS).

Methods: We analyzed clinical and tumor characteristics at the time of oligoprogression in patients with NSCLC randomized to SBRT plus standard of care in the phase II CURB trial. Tumor burden parameters evaluated for association with PFS and OS included: (a) total number of growing lesions (TGL), (b) total number of lesions (TNL), (c) sum of longest diameters (SLD) of all lesions (SLD-AL), (d) SLD of growing lesions (SLD-GL), and (e) SLD of stable and regressing lesions (SLD-SRL). We also examined the impact of patterns of oligoprogression, defined as progression in new vs. known lesions, on outcomes. Survival was analyzed using Kaplan-Meier estimates and log-rank tests; multivariable associations were assessed using Cox regression.

Results: Among 31 NSCLC patients who received SBRT, a lower SLD-GL at the time of oligoprogression was associated with longer PFS: patients with a SLD-GL ≤ 4.0 cm (i.e., the median SLD-GL) had a PFS of 20.0 months vs 4.5 months in those with a SLD-GL > 4.0 cm (p=0.047). A SLD-GL ≤ 4.0 cm was also associated with superior OS compared to a SLD-GL > 4.0 cm (60.5 months vs 10.8 months, p<0.001). Conversely, the SLD-AL and SLD-SRL were not associated with PFS (p=0.943 and p=0.436, respectively) or OS (p=0.112 and p=0.297, respectively). The TNL at oligoprogression (i.e., ≤ 5 vs > 5) was not associated with PFS (p=0.732) or OS (p=0.264). Additionally, TGL at oligoprogression was not associated with PFS (p=0.402); however, having only one TGL at oligoprogression was associated with superior OS compared to having ≥ 2 TGL (median: 52.8 months vs 13.6 months, p=0.028). Having at least one liver metastasis was associated with worse median OS (7.9 months vs 38.2 months, p=0.027) and a trend towards worse median PFS (1.7 months vs 10.1 months, p=0.123). The pattern of oligoprogression was not associated with PFS or OS. Histology, PD-L1 TPS, and targetable alterations were not associated with differential benefit. On multivariable analysis, lower SLD-GL at oligoprogression was associated with a reduced hazard for death and a trend toward reduced hazard for progression.

Conclusions: While "tumor burden" can be assessed with several approaches, in patients receiving SBRT in oligoprogressive NSCLC, the sum of longest diameters of all growing lesions was found to be most correlated with both PFS and OS. Our analysis suggests that this tumor burden metric should be prioritized with respect to treatment options in this context, warranting further exploration.

Keywords: oligoprogressive non-small cell lung cancer, tumor burden, stereotactic body radiotherapy

OA07 EXPANDING HORIZONS IN ADVANCED NSCLC INTEGRATING LOCAL THERAPY
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA07.03 Stereotactic Ablative Radiotherapy in Oligo-Metastatic NSCLC Patients:START NEW ERA#OLIGO Non-Randomised Phase II Trial

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Introduction: Therapeutic advances such as targeted therapies (TT) and immunotherapy (IO) have dramatically improved the prognosis of patients with stage IV non-small-cell lung cancer (NSCLC). However, most patients eventually develop resistance to systemic therapy, with some having limited disease progression (ie, oligoprogression - oligo-P). We aimed to assess whether stereotactic ablative radiotherapy (SAbR) targeting oligo-P sites could improve patient outcomes. Here we report outcomes of the START-NEW-ERA #oligo non-randomized phase II trial (Clinical Trial NCT06207292) on the efficacy and safety of SAbR in oncogene addicted and non-oncogene addicted oligo-P NSCLC.

Methods: Patients with oligo-P (body) NSCLC defined on PET-CT, after having received at least first-line systemic therapy, were enrolled in a single centre non randomised phase II trial of SAbR. The primary endpoints were new systemic therapy-free survival (NST-FS) and safety.

Results: Between May 2015 and February 2025, 80 oligo-P NSCLC patients were enrolled. 66% and 34% were non-oncogene addicted and oncogene addicted, respectively and had ongoing IO (with or without chemotherapy) and TT. The median number of treated oligo-metastases were 4. The main site of oligo-P was the primary tumor followed by hilar-mediastinal nodes, bone and adrenal gland. After a median follow-up of 30 months (95% CI, 20 to 41) range (1-86 months) the median NST-FS was 34 months (95% CI, 21 to 49). The 1, 3, and 5-year NST-FS rates were 73 ± 5%, 48 ± 8% and 39 ± 10%, respectively. 15% have completed the systemic therapy according to natural completion; 11% have permanently suspended systemic therapy due to toxicity (not SAbR related) or poor compliance; 26% discontinued therapy due to poly-progression; 48% are undergoing the same therapy ongoing at the time of enrollment. 40% patients received at least one further cycle of SAbR on newly oligo-P site while maintaining the same ongoing systemic therapy. 21% developed brain oligo-metastases treated by stereotactic radiosurgery. The median PFS was 9 months (95% CI, 5 to 16). The 1-, 3- and 5- year PFS rates were 43 ± 6%, 23 ± 6% and 23 ± 6%, respectively. The median OS was 57 months (95% CI, 35 to 68). The 1, 3, and 5-year OS rates were 82 ± 4%, 60 ± 7% and 40 ± 9%, respectively. Only 9 patients had experienced local recurrence in one of oligo-P sites submitted to SAbR.Only 1 patient had experience ≥G3 lung toxicity.

Conclusions: The START-NEW-ERA #oligo non-randomized phase II trial confirms the safety and effectiveness of SAbR in oncogene addicted and non-oncogene addicted oligo-P NSCLC patients. Local treatment with SAbR extended the ongoing therapy for a median time of 34 months avoiding the switch to new systemic therapy suggesting that SAbR should be the standard of care in oligo-progressive NSCLC patients.

OA07 EXPANDING HORIZONS IN ADVANCED NSCLC INTEGRATING LOCAL THERAPY
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA07.04 Molecular and Early Outcomes of a Randomized Phase II Trial of Primary Tumor Resection Following EGFR TKI in Metastatic NSCLC

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OA08 IMPROVING OUTCOMES IN EGFR AND KRAS MUTANT TUMOURS, MORE IS BETTER?
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA08.01 BMS-986504 in Patients With Homozygous MTAP-Deletion (Del): Clinical Results in Patients With NSCLC Enrolled in CA240-0007

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OA08 IMPROVING OUTCOMES IN EGFR AND KRAS MUTANT TUMOURS, MORE IS BETTER?
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA08.02 Efficacy and Safety of 1L Olomorasib + Chemoimmunotherapy in KRAS G12C-Mutant NSCLC: Results From LOXO-RAS-20001 and SUNRAY-01

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Introduction: Olomorasib, a potent and selective second-generation KRAS G12C inhibitor, demonstrated promising antitumor activity and a manageable safety profile in first-line (1L) KRAS G12C-mutant advanced NSCLC in combination with pembrolizumab plus chemotherapy (chemoimmunotherapy). Here, we report results of an integrated analysis in 1L patient (pts) who received olomorasib plus chemoimmunotherapy in LOXO-RAS-20001 (Phase 1) and the safety lead-in for SUNRAY-01 (Phase 3).

Methods: Pts with advanced KRAS G12C-mutant NSCLC, PD-L1 0-100% (ECOG PS 0-1) were assigned to olomorasib (50 or 100 mg, orally BID) with pembrolizumab plus chemotherapy (per label). One prior cycle of SOC was allowed when timely initiation of treatment was medically indicated. Safety was assessed across all treated pts. ORR was assessed in the efficacy evaluable population, including pts with ≥1 post-baseline response assessment or who discontinued treatment before the first response assessment.

Results: As of 15 January 2025, 78 pts received olomorasib plus chemoimmunotherapy, including 24 pts (31%) who received 1 cycle of SOC prior to enrollment; 35% were PD-L1 <1%, 40% were PD-L1 1-49%, and 22% were PD-L1 ≥50% (4% [3 pts] unknown). With a median follow-up of 5.5 months (IQR: 3.5-6.1), any grade treatment-related adverse events (TRAEs) in ≥20% of pts were nausea (37%), anemia (35%), fatigue (32%), diarrhea (30%), AST increased (27%) and ALT increased (26%). The most common grade ≥3 TRAEs were anemia (14%), neutrophil count decreased (12%), and ALT/AST increased (12%/12%). Cytopenias and hepatic events were overall manageable with dose adjustments and/or corticosteroids. TRAEs led to olomorasib dose reduction in 15% of pts, and discontinuation of all study treatment in 6% of pts. The ORR was 59% in all pts (n=75) regardless of PD-L1 expression, and 64% in pts who received olomorasib 100 mg BID (n=44). Responses were durable, with a median DOR of 10.5 months and median PFS of 11.6 months (Table 1). Updated data will be presented.

Conclusions: In this merged dataset with more than triple the number of 1L pts relative to prior presentations, olomorasib plus chemoimmunotherapy continues to demonstrate a manageable safety profile and promising efficacy across all PD-L1 levels. Moreover, efficacy remains promising in this higher-risk population, largely of pts with PD-L1 0-49%. These updated findings further support the ongoing Phase 3 SUNRAY-01 trial, comparing olomorasib (100 mg BID) plus chemoimmunotherapy versus placebo plus chemoimmunotherapy as 1L treatment in pts with KRAS G12C-mutant NSCLC and any PD-L1 level.

Table. Response and Time-To-Event Endpoints in the Efficacy Evaluable Population

	Olomorasib (50 mg or 100 mg BID) + Pembrolizumab + Pemetrexed + Platinum			
Endpoint	All pts* (PD-L1 0-100%) N = 75	Pts with PD-L1 < 1% N = 24	Pts with PD-L1 1-49% N = 31	Pts with PD-L1 ≥ 50% N = 17
ORR†, % (n/N)	59 (44/75)	58 (14/24)	58 (18/31)	71 (12/17)
BOR, n (%)				
PR†	44 (59)	14 (58)	18 (58)	12 (71)
SD	22 (29)	5 (21)	11 (36)	4 (24)
PD	3 (4)	2 (8)	0 (0)	0 (0)
NE	6 (8)	3 (13)	2 (7)	1 (6)
DCR, % (n/N)	88 (66/75)	79 (19/24)	94 (29/31)	94 (16/17)
mDOR, months (95% CI)	10.5 (4.6-NE)	10.5 (4.1-NE)	10.6 (4.2-NE)	NE (NE-NE)
mPFS, months (95% CI)	11.6 (8.3-11.8)	11.6 (8.3-NE)	11.8 (5.5-NE)	NE (3.3-NE)

†Includes responses confirmed and pending. *PD-L1 status was unknown for 3 pts. One pt did not receive olomorasib treatment simultaneously with pembrolizumab + pemetrexed + platinum

Keywords: KRAS G12C, olomorasib, chemoimmunotherapy

OA08 IMPROVING OUTCOMES IN EGFR AND KRAS MUTANT TUMOURS, MORE IS BETTER?
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA08.03 COMPEL: Osimertinib + Platinum-Based Chemotherapy in Patients With EGFRm Advanced NSCLC and Progression on 1L Osimertinib

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OA08 IMPROVING OUTCOMES IN EGFR AND KRAS MUTANT TUMOURS, MORE IS BETTER?
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

OA08.04 Primary Endpoint Results from SHERLOCK: a Phase 2 trial of Sotorasib, Bevacizumab and Chemotherapy in Advanced KRAS G12C NSCLC

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Introduction: The combination of sotorasib, bevacizumab, and platinum-based chemotherapy may exert synergistic anti-tumor effects enhancing clinical outcomes in patients with NSCLCs harboring KRAS G12C mutations. We conducted a phase 2 trial evaluating the efficacy and safety of this novel first-line regimen in treatment-naïve, newly diagnosed advanced or recurrent NSCLC with KRAS G12C mutations.

Methods: SHERLOCK was an investigator-initiated, multicentre open-label trial across 13 sites in Australia. Study treatment consisted of sotorasib 960mg once daily with 4 cycles of induction carboplatin (AUC5), pemetrexed (500mg/m2) and bevacizumab (15mg/kg) every 3 weeks, followed by maintenance sotorasib, pemetrexed and bevacizumab every 3 weeks until disease progression. CT imaging was performed at baseline and every 8 weeks until disease progression. Plasma samples for ctDNA were obtained at baseline, week 8, week 16 and at progression. The primary endpoint was to determine the objective response rate (ORR) according to RECIST 1.1. Key secondary outcomes included progression-free survival (PFS) and adverse events.

Results: Between August 2022 and June 2025, a total of 52 participants were enrolled. Baseline characteristics were: median age 67 years; 62% female; 40% ECOG 0; 96% were former or current smokers; and 38% had brain metastases. Baseline tumor characteristics showed PD-L1 expression ≥50% in 23% (12/52). In ctDNA evaluable participants, baseline TP53 co-mutation occurred in 51% (19/37), STK11 in 30% (11/37), and KEAP1 in 16% (6/37). With a median follow-up of 20 months, 47 participants were evaluable for the primary endpoint. Unconfirmed ORR was 72% (34/47). Confirmed ORR was 62% (29/47). The median duration of unconfirmed and confirmed response was 9.0 and 7.5 months respectively. In PD-L1 evaluable participants, confirmed ORR according to PD-L1 ≥50%, 1-49%, and <1% was 80% (8/10), 58% (7/12) and 57% (13/23), respectively. Confirmed ORR for participants harboring plasma co-mutations in TP53, STK11, or KEAP1 was 79% (15/19), 64% (7/11) and 50% (3/6), respectively. Intracranial CNS response was documented in non-target lesions in 30% (3/10, none with prior radiotherapy). There were 63% PFS events (33/52) and median PFS was 9.0 months (95% CI 7.9-15). Median PFS according to PD-L1 ≥50%, 1-49%, and <1% was 15.0, 7.9 and 9.0 months respectively. In ctDNA evaluable population (n=37), median PFS according to TP53, STK11 or KEAP1 co-mutation was 11.0, 9.6 and 5.8 months respectively. Plasma KRAS G12C clearance was observed in 84% (27/32) of participants with paired baseline and week 8 samples, and in 85% (23/27) of those with paired baseline and week 16 samples. Among participants with confirmed ORR, 79% (23/29) had detectable plasma KRAS G12C mutations at baseline, and 95% (20/21) achieved clearance by week 8. Adverse events were consistent with the known safety profiles of each individual study drug with no new safety signals identified.

Conclusion: Sotorasib, in combination with bevacizumab and chemotherapy, demonstrated promising anti-tumor activity as a first-line treatment for advanced NSCLC with KRAS G12C mutation. High ORR were observed across all PD-L1 expression levels and molecular subgroups, including those with TP53, STK11, or KEAP1 co-mutations. These findings warrant further evaluation in a randomized phase 3 trial.

Keywords: KRAS G12C, Sotorasib, Non-small cell lung cancer

OA09 NEW ADVANCES IN PATHOLOGY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA09.01 Machine Learning Assessment of Pathologic Response in Lung Resections After Neoadjuvant Therapy - IASLC MPR Project

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Introduction: A study by the International Association for the Study of Lung Cancer (IASLC) on the reproducibility of pathologic response (PR) assessment in surgically resected lung specimens after neoadjuvant therapy showed good interrater agreement between thoracic pathologists, though challenges remain. The aim of this study was to develop machine learning algorithms for quantifying tumor bed (TB) area and residual viable tumor (VT), and to compare these results to previously published assessment by pathologists from the IASLC reproducibility study.

Methods: The study included 72 patients with non-small cell lung carcinoma (NSCLC) from 5 clinical trials [NADIM phase II (NCT03081689), NEOSTAR phase II (NCT03158129), MPDL3280A (NCT02716038), TOP 1501 (NCT02818920) and MEDI4736 (NCT02904954)]. Hematoxylin and eosin (H&E)-stained glass slides were reviewed by five (N=25 patients) or six (N=47 patients) pathologists. Manual pathologist annotations (N=15,564) of regions including TB and VT were collected from whole slide images . Convolutional neural network models were trained using these annotations to classify tissue regions. TB detection was trained using a multi-resolution architecture. A separate Convex Hull algorithm (CHA) was applied to the VT region predictions to predict VT area in a manner more closely aligned with pathologist visual assessments. For both models, digital PR was computed at the case level as the percent of TB area that was VT , weighted by slide-level TB area. For each method (pathologist reads and both models) the PR percentage was calculated as the average PR percentages across slides (unweighted). PR from pathologist reads were averaged (average pathologist read [APR]). Correlation of PR values between the approaches was done with Spearman's correlation coefficient. Rater agreement was assessed with Cohen's Kappa statistic. The major pathologic response (MPR) cutoff for digital PR and CHA was determined by the matching percentile based on the APR percentage at 10%.

Results: There was strong correlation of PR percentages between approaches: APR vs. Digital PR (0.97), APR vs. CHA (0.97), and Digital PR vs. CHA (0.99). The APR was ≤10% (MPR) in 38.9% of the study patients. Digital PR and CHA were in perfect agreement for MPR. The kappa statistic was 0.82 (95% CI: 0.69, 0.96) for APR versus Digital PR/CHA with 6 discordant cases. Agreement was stronger for squamous cell carcinoma (Kappa 0.92, 95% CI: 0.76, 1.0) than for non-squamous carcinoma (Kappa 0.77, 95% CI: 0.59, 0.96). Survival analysis is ongoing.

Conclusions: Our study demonstrated the high concordance of PR assessment between machine learning algorithms and expert pathologists. Despite some discordances, the overall high level of agreement suports the utility of these machine learning approaches in ensuring accurate and standardized evaluations of PR in lung cancer clinical trials.

Keywords: neoadjuvant, pathologic response, machine learning

OA09 NEW ADVANCES IN PATHOLOGY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA09.02 I3LUNG-PDSS: A Multimodal AI-Based Clinical Decision Support System for Predicting Immunotherapy Efficacy in Metastatic NSCLC

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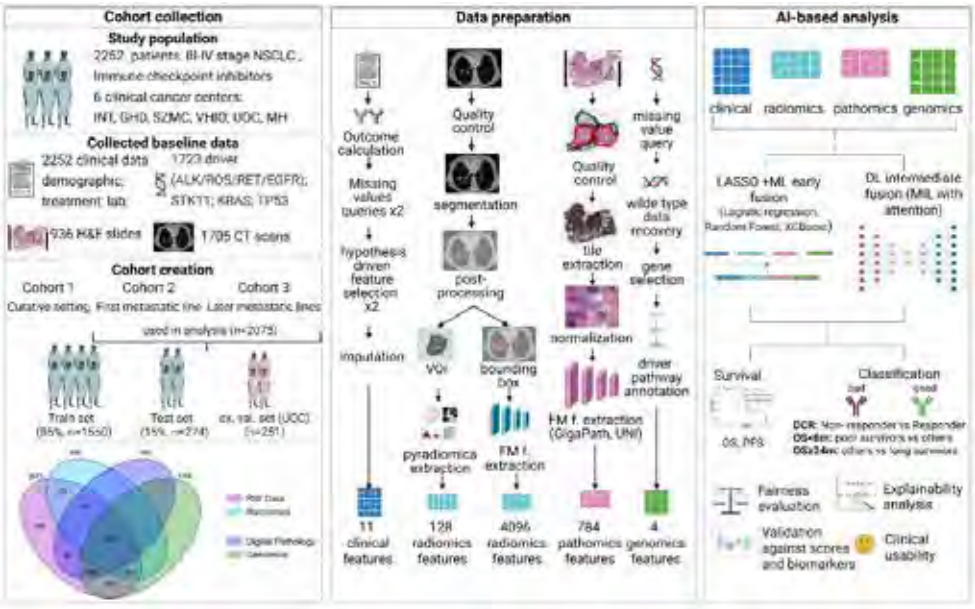
Introduction: Even after 10-years of immunotherapy (IO), treatment selection still depends on subgroup analyses/clinical scores, highlighting the urgent need for robust, validated tools. AI enables integration of Real-world (RWD) and multimodal data for improved treatment selection. To our knowledge, I3LUNG (NCT05537922) is the largest international trial building AI-based Physician Decision Support Systems (PDSSs) to support immunotherapy decisions.

Methods: NSCLC patients across six EU/non-EU centers were divided into C1 (durvalumab, stage III), C2 (First line IO), and C3 (later-line IO). We included: RWD (246 expert-selected features), CT_scans via PyRadiomics and Foundation Models (FMs), histopathology slides via FMs, and genomics (EGFR, ALK, ROS1, RET, STK11, KRAS, TP53). Endpoints were: primary, OS survival, death at OS<6 and ³24 months; secondary: DCR, ORR, PFS, TTF. Combined C2,3 was used for the primary analysis. Models included machine learning early fusion (MLEF) and deep learning intermediate fusion (DLIF), using Leave-One-Center-Out CV. Models were benchmarked against single biomarkers and scores. Fairness, explainability, and clinical usability were assessed.



Results: 2365 advanced NSCLC patients were enrolled; C2,3 (n=2075; C2:1437; C3:638) formed the primary analysis. 2075 had RWD, 1723 genomic, 1634 CT scans, and 936 histopathology slides. 339 patients had data from all four modalities. MLEF in C2,3 achieved AUCs of 0.74±0.08, 0.73±0.06, and 0.75±0.06 for OS24, OS6, and DCR, respectively. DLIF results were in line. MLEF models trained on C2 only showed higher performance than C2,3 (AUC: OS24=0.82±0.07, OS6=0.79±0.07, DCR =0.78±0.06). OS by Cox Regression (Cindex) was 0.66±0.02 for C2,3 and better for C2 (0.70±0.05).

AI-Multimodal approaches outperformed AI-RWD only in PDL1≥50% (among C2,3) with MLEF-submodel, detecting poor survivors with AUC=0.86±0.08, compared to 0.61±0.13 for RWD-only. IO monotherapy multimodal model identified long survivors with AUC=0.86±0.08 versus RWD's 0.54±0.10, and DCR with AUC=0.80±0.07 versus 0.61±0.10, regardless of PDL1 expression. On the testset, MLEF models outperformed single biomarkers across all outcomes: in DCR, AUC=0.71 vs. NLR=0.59 (p<0.01) and AUC=0.72 vs. PDL1=0.53 (p<0.001). Results are in line with OS24 and OS6. Models performed consistently on the test set across outcomes regarding AUC and C-index. Over the external validation set, OS achieved C-index=0.64.

Conclusion: The I3LUNG-PDSS AI tool demonstrates superior performance compared to traditional biomarkers, marking a significant advancement in predicting treatment outcomes for NSCLC patients. In submodels, on specific cohorts, the importance of multimodal data emerges compared to RWD, providing significant insights, despite the reduced sample. A prospective validation is ongoing across current centers, incorporating comprehensive multiomics data assessing PDSS generalizability.

Keywords: Decision Support System, Immunotherapy, Non-small cell lung cancer (NSCLC)

OA09 NEW ADVANCES IN PATHOLOGY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA09.03 Real-World Assessment of TROP2-NMR by Quantitative Continuous Scoring (QCS) in Non-Small Cell Lung Carcinoma (NSCLC)

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Introduction: Trophoblast cell surface antigen 2 (TROP2) has emerged as a therapeutic delivery target in non-small cell lung carcinoma (NSCLC). However, its use as a predictive biomarker by conventional immunohistochemistry (IHC) has proven challenging. Quantitative Continuous Scoring (QCS), a fully-supervised computational pathology algorithm, has demonstrated the ability to predict NSCLC patient response to a TROP2 targeting antibody-drug conjugate (ADC) by quantifying TROP2 protein expression on digitized IHC slides. This global, multi-center study aims to assess the impact of pathologists input on QCS analysis of TROP2 expression in NSCLC and to evaluate its reproducibility across real-world laboratory settings.

Methods: A total of 100 commercial samples of NSCLC were obtained for the study, stained using the research-use-only (RUO) TROP2 (EPR20043) IHC assay using a standard protocol on VENTANA BenchMark ULTRA staining platforms, and qualified using the TROP2 (EPR20043) NSCLC NMR RUO algorithm. 64 cases were selected to be analyzed with the algorithm by 9 global sites and 1 internal Roche laboratory (n=30 pathologists) using Navify digital pathology (Navify DP). Stained slides were scanned on VENTANA DP600 or DP200 slide scanners and images were uploaded into Navify DP. Following algorithm training, pathologists generated normalized membrane ratio (TROP2-NMR) scores using the TROP2 (EPR20043) NSCLC NMR RUO algorithm. To algorithm reproducibility, overall percent agreement (OPA), positive percent agreement (PPA) and negative percent agreement (NPA) were calculated between readers and across sites. An exploratory analysis of raw TROP2-NMR scores and related metrics among pathologists was also performed.

Reproducibility of TROP2 expression assessment using the TROP2 (EPR20043) NSCLC NMR RUO algorithm was high across both sites and readers (TABLE 1). Across all 10 sites, the algorithm demonstrated a PPA of 99.9% and a negative percent NPA of 100.0%, resulting in an OPA of 99.9%. When comparing the Roche laboratory with nine external sites, the PPA was 99.9% and the NPA was 100.0%, with an OPA of 99.9%. Among the 30 participating pathologists, reader-level agreement remained consistently high, with a PPA of 99.9%, an NPA of 100.0%, and an OPA of 99.9%.

Although TROP2 QCS requires pathologist input to accurately evaluate TROP2 expression in NSCLC tumor cells, and such intervention could introduce variability, our data demonstrate that the QCS assessment of TROP2 expression is highly reproducible across pathologists. Despite TROP2-NMR being a fully quantitative score, the consistency observed confirms the robustness of this fully-supervised approach in real-world settings.

Table 1

Between Sites		Case level mode status					
Site	Slide-Level TROP2 Status	Positive	Negative	Total	Measure [a]	% (n/N)	95% CI [b]
Overall (10 sites)	Positive	955	0	955	PPA	99.9 (955/956)	(99.7, 100.0)
	Negative	1	956	957	NPA	100.0 (956/956)	(99.6, 100.0)
	Total	956	956	1912	OPA	99.9 (1911/1912)	(99.8, 100.0)
Between Sites		Roche Laboratory					
Site	Slide-Level TROP2 Status	Positive	Negative	Total	Measure [a]	% (n/N)	95% CI [b]
Overall (9 external sites)	Positive	859	0	859	PPA	99.9 (859/860)	(99.6, 100.0)
	Negative	1	860	861	NPA	100.0 (860/860)	(99.6, 100.0)
	Total	860	860	1720	OPA	99.9 (1719/1720)	(99.8, 100.0)
Between Readers		Case-Level Mode Status					
Site Reader	Slide-Level TROP2 Status	Positive	Negative	Total	Measure [a]	% (n/N)	95% CI [b]
Overall (n=30)	Positive	955	0	955	PPA	99.9 (955/956)	(99.7, 100.0)
	Negative	1	956	957	NPA	100.0 (956/956)	(99.6, 100.0)
	Total	956	956	1912	OPA	99.9 (1911/1912)	(99.8, 100.0)

Keywords: TROP2, Immunohistochemistry, Artificial Intelligence

OA10 OPTIMISING SYSTEMIC THERAPY; BRIDGING NEW AND OLD
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA10.01 Intracranial Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic NSCLC in TROPION-Lung01

E. Pons-Tostivint[1], I. Okamoto[2], M-J. Ahn[3], N. Girard[4], R. Cornelissen[5], M.H. Hong[6], L. Paz-Ares[7], D.V. Baz[8], S. Sugawara[9], M.C. Dols[10], M. Pérol[11], C. Mascaux[12], H. Hayashi[13], A. Lisberg[14], O. Juan-Vidal[15], Y. Zhang[16], M. Chargualaf[16], R. Joseph[16], D. Leung[16], J. Sands[17]
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Introduction: Brain metastases are common in patients with non-small cell lung cancer (NSCLC) and are associated with poor prognosis. We report a retrospective analysis of patients treated with Dato-DXd or docetaxel in the phase 3 TROPION-Lung01 trial (NCT04656652) who had brain metastases at study entry, to assess the intracranial objective response rate (ORR) and intracranial progression-free survival (PFS).

Methods: Patients were randomized 1:1 to Dato-DXd 6 mg/kg or docetaxel 75 mg/m2 once every 3 weeks. All patients were required to undergo baseline brain imaging; those with asymptomatic brain metastases identified by the investigator (treated or newly discovered and stable at screening) were eligible for the study and were required to undergo further imaging assessments every 6 weeks. In this post hoc analysis (data cutoff: August 30, 2024), central nervous system (CNS) disease was retrospectively assessed by blinded independent central review (BICR) per CNS RECIST in the population with baseline brain metastases. Patients were divided into subgroups based on prior receipt of radiation. Those who received prior CNS radiation and subsequently experienced CNS progression before randomization were included in the untreated group. Patients were also further divided based on the presence or absence of measurable disease.

Results: Overall, 127/604 patients (21.0%) in TROPION-Lung01 had baseline brain metastases identified by CNS BICR (Dato-DXd, n=70; docetaxel, n=57). Baseline characteristics were balanced between treatment arms; 17 patients in each arm had EGFR mutations. Sixty-eight patients had untreated brain metastases/progression after radiotherapy (Dato-DXd, n=38; docetaxel, n=30); of these patients, 27 had measurable disease and 41 had non-measurable disease. In patients with untreated and measurable disease (n=27), the confirmed intracranial ORR in the Dato-DXd arm was 37.5% (95% CI, 15.2-64.6, including one complete response; n=6/16) and in the docetaxel arm was 0% (95% CI, 0-28.5; n=0/11). When including those with non-measurable disease, the confirmed intracranial ORR in the Dato-DXd arm was 15.8% (95% CI, 6.0-31.3; n=6/38) versus 0% (95% CI, 0-11.6; n=0/30) with docetaxel. All responses were observed in patients with nonsquamous histology, and outcomes in patients with EGFR-mutated tumors were consistent with the overall population. Median time to intracranial response to Dato-DXd was 1.5 months (range, 1.2-2.6; n=6); there were no responses in the docetaxel arm. Dato-DXd prolonged median intracranial PFS versus docetaxel in the overall population with baseline brain metastases (5.1 vs 4.4 months; hazard ratio [HR] 0.65 [95% CI, 0.39-1.09]; n=127) and in patients with untreated brain metastases/progression after radiotherapy (5.0 vs 3.0 months; HR 0.48 [95% CI, 0.23-0.98]; n=68).

Conclusions: In this retrospective analysis of TROPION-Lung01, Dato-DXd demonstrated intracranial activity and improved clinical benefit versus docetaxel in patients with baseline brain metastases, including those with untreated brain metastases or progression after radiotherapy. These findings were consistent with intracranial activity in the TROPION-Lung05 trial (NCT04484142), supporting the potential of Dato-DXd treatment in patients with NSCLC brain metastases.

Keywords: Brain metastases, NSCLC, Antibody-drug conjugate

OA10 OPTIMISING SYSTEMIC THERAPY; BRIDGING NEW AND OLD
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA10.02 Bevacizumab Plus Chemotherapy Versus Chemotherapy in Untreated Non-Squamous NSCLC With Brain Metastases: A Randomized, Phase 3 Study

M. Li[1], Y. Pan[1], G. Jiang[2], Q. Wang[3], G. Wu[4], W. Feng[5], S. Ma[3], X. Hou[1], L. Chen[1]
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Introduction: There is a lack of prospective randomized controlled trials of antiangiogenic therapy in patients with brain metastases. We conducted this phase 3, randomized, multicenter study (BAP BRAIN) to evaluate the intracranial efficacy and safety of bevacizumab plus chemotherapy versus chemotherapy alone in patients with non-squamous non-small cell lung cancer (NSCLC) and brain metastases, and provide evidence for this previously unexplored subgroup.

Methods: Treatment-naïve, confirmed brain metastases and without sensitizing EGFR or ALK mutations, non-squamous NSCLC patients were screened from 11 centers in China. The eligible patients were randomly assigned (1:1) to receive bevacizumab plus pemetrexed-platinum or pemetrexed-platinum for 4-6 cycles, followed by bevacizumab plus pemetrexed or pemetrexed maintenance until disease progression, unacceptable toxicity or death. The primary endpoint was intracranial progression-free survival (iPFS), secondary endpoints included PFS, overall survival, intracranial objective response rate (iORR), systemic ORR and safety. We assessed efficacy and safety in the intention-to-treat population (all participants who received at least one dose of study treatment).

Results: Total 153 patients were enrolled and randomly assigned to receive bevacizumab plus pemetrexed-platinum (n=79) or pemetrexed-platinum (n=74). After a median follow-up of 16.8 months, the median iPFS was 11.07 months in bevacizumab plus chemotherapy group versus 5.73 months in chemotherapy group (HR=0.439, P<0.001). Similarly, the median systemic PFS was significantly longer in bevacizumab plus pemetrexed-platinum than pemetrexed-platinum alone (8.77 months versus 5.23 months, HR=0.540, P<0.001). Bevacizumab plus chemotherapy group had better iORR (69.6% versus 32.4%) and ORR (58.2% versus 27.0%) than chemotherapy group. The remission of cerebral edema was also higher in bevacizumab plus pemetrexed-platinum group (88.9% vs 34.9%). At the data cutoff, median OS was 28.07 months in bevacizumab plus pemetrexed-platinum group versus 18.53 months in pemetrexed-platinum group (HR=0.752, P=0.162). There was no ≥3 grade intracranial hemorrhage occurred, and most of adverse events were manageable.

Conclusions: This study demonstrated encouraging intracranial efficacy and acceptable safety of bevacizumab plus chemotherapy in patients with non-squamous NSCLC and brain metastases in the first-line setting.

Keywords: Bevacizumab, NSCLC with brain metastases, Randomized phase 3 study

OA10 OPTIMISING SYSTEMIC THERAPY; BRIDGING NEW AND OLD
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA10.03 Phase I/II Study of Iza-Bren (BL-B01D1) as Monotherapy in Patients With Locally Advanced or Metastatic EGFR Mutated NSCLC

w. fang[1], H. Zhao[2], Y. Zhao[2], Y. Ma[2], Y. Huang[2], Y. Yang[2], L. Chen[2], X. Hou[2], Y. Wang[3], S. Xiao[4], H. Zhu[5], Y. Zhu[5], L. Zhang[2]
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This abstract is under embargo until September 6 at 17:45 CET.

OA10 OPTIMISING SYSTEMIC THERAPY; BRIDGING NEW AND OLD
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

OA10.04 Phase II Study of Iza-Bren (BL-B01D1) Combo With Osimertinib in EGFR Mutated Locally Advanced or Metastatic NSCLC Patients

F. Zhou[1], Q. Wang[2], H. Wang[3], Q. Yu[4], X. Li[5], Y. Yu[6], Y. Ji[7], J. Shi[8], B. Jiang[9], L. Sun[10], B. Li[11], Z. He[12], D. Lv[13], G. Zhang[14], S. Xiao[15], H. Zhu[16], Y. Zhu[16], C. Zhou[1]

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This abstract is under embargo until September 6 at 17:45 CET.

OA11 BEYOND TNM - NEW HORIZONS IN PROGNOSTICATION
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA11.01 Impact of Smoking Status on the Prognosis of Lung Cancer in the IASLC Ninth Edition TNM Classification Database

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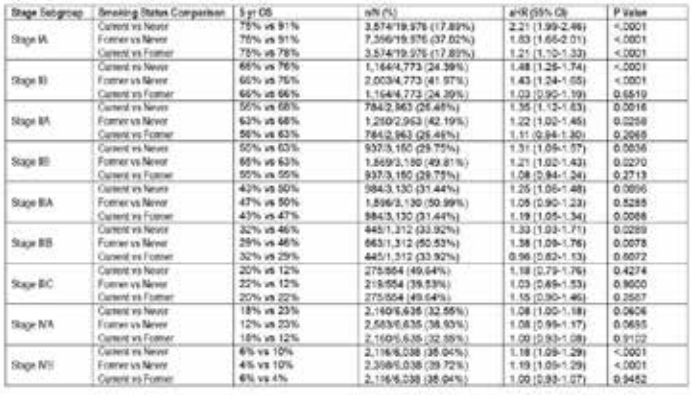
Introduction: Smoking is known to negatively impact lung cancer survival. Incorporating non-anatomical factors, such as the smoking history into staging may improve prognostication. We evaluated the impact of smoking status on the prognosis of patients with lung cancer.

Methods: Using the IASLC 9th edition NSCLC staging database, we evaluated the association between smoking status at diagnosis and overall survival (OS) using Kaplan-Meier curves and multivariable Cox proportional hazard models adjusted for age, region, sex, histological type, performance status and TNM stage. Subgroup analyses evaluated within- and between-stage survival according to smoking status. Recursive partitioning analysis evaluated the impact of smoking status relative to anatomical factors in staging.

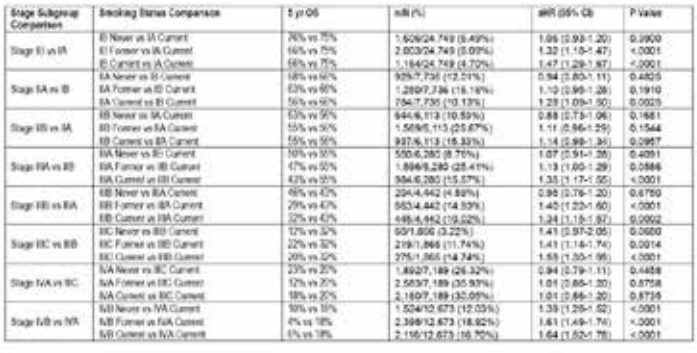
Results: Among 48,531 patients with NSCLC, 26%, 41% and 34% currently, formerly or never smoked, respectively; 75% were diagnosed with adenocarcinoma and 21% with squamous cell carcinoma. Compared to those who never smoked, those who currently (aHR=1.39, 95% CI [1.34-1.46], p<0.0001) and formerly smoked (aHR=1.32, 95% CI [1.27-1.36], p<0.0001) had worse OS. Current smoking was also associated with worse OS (aHR=1.05, 95% [1.02-1.06], p=0.005) compared to former smoking. These associations were consistent within each stage group (Table 1). In pair-wise comparison, those who formerly or currently smoked had similar OS to patients in the next higher adjacent stage group who never smoked (Table 2). In patients with early-stage disease (up to T3N1M0), recursive partitioning analysis demonstrated that smoking status had greater prognostic impact than N0 vs N1 categories, while among patients with locally advanced (T4 or N2+) disease, smoking status still identified unique prognostic subgroups.

Conclusions: Smoking status is an important prognostic factor in this lung cancer staging cohort and may have greater impact on prognosis than some anatomical descriptors. Further exploration of combining smoking status and TNM classification for lung cancer is planned in the 10th edition IASLC staging project.



Stage Subgroup	Smoking Status Comparison	5 yr OS	n/N (%)	aHR (95% CI)	P Value
Stage IA	Current vs Never	75% vs 91%	3,574/19,976 (17.89%)	2.21 (1.99-2.46)	<.0001
	Former vs Never	76% vs 91%	7,396/19,976 (37.02%)	1.83 (1.66-2.01)	<.0001
	Current vs Former	75% vs 76%	3,574/19,976 (17.89%)	1.21 (1.10-1.33)	<.0001
Stage IB	Current vs Never	66% vs 76%	1,164/4,773 (24.39%)	1.48 (1.26-1.74)	<.0001
	Former vs Never	66% vs 76%	2,003/4,773 (41.97%)	1.43 (1.24-1.65)	<.0001
	Current vs Former	66% vs 66%	1,164/4,773 (24.39%)	1.03 (0.90-1.19)	0.6519
Stage IIA	Current vs Never	55% vs 68%	784/2,963 (26.46%)	1.35 (1.12-1.63)	0.0016
	Former vs Never	63% vs 68%	1,250/2,963 (42.19%)	1.22 (1.02-1.45)	0.0288
	Current vs Former	55% vs 63%	784/2,963 (26.46%)	1.11 (0.94-1.30)	0.2065
Stage IIB	Current vs Never	55% vs 63%	937/3,160 (29.75%)	1.31 (1.09-1.57)	0.0036
	Former vs Never	65% vs 63%	1,569/3,160 (49.81%)	1.21 (1.02-1.43)	0.0270
	Current vs Former	55% vs 65%	937/3,160 (29.75%)	1.08 (0.94-1.24)	0.2713
Stage IIIA	Current vs Never	43% vs 50%	984/3,130 (31.44%)	1.25 (1.06-1.48)	0.0096
	Former vs Never	47% vs 50%	1,596/3,130 (50.99%)	1.09 (0.90-1.33)	0.5285
	Current vs Former	43% vs 47%	984/3,130 (31.44%)	1.19 (1.05-1.34)	0.0068
Stage IIIB	Current vs Never	32% vs 46%	445/1,312 (33.92%)	1.33 (1.03-1.71)	0.0289
	Former vs Never	39% vs 46%	663/1,312 (50.53%)	1.38 (1.09-1.76)	0.0078
	Current vs Former	32% vs 39%	445/1,312 (33.92%)	0.96 (0.82-1.13)	0.6072
Stage IIIC	Current vs Never	20% vs 12%	275/554 (49.64%)	1.18 (0.79-1.76)	0.4274
	Former vs Never	22% vs 12%	219/554 (39.53%)	1.03 (0.69-1.53)	0.9000
	Current vs Former	20% vs 22%	275/554 (49.64%)	1.15 (0.90-1.46)	0.2557
Stage IVA	Current vs Never	18% vs 23%	2,140/6,635 (32.56%)	1.08 (1.00-1.18)	0.0626
	Former vs Never	12% vs 23%	2,583/6,635 (38.93%)	1.08 (0.99-1.17)	0.0693
	Current vs Former	18% vs 12%	2,140/6,635 (32.56%)	1.00 (0.93-1.08)	0.9122
Stage IVB	Current vs Never	6% vs 10%	2,116/6,038 (35.04%)	1.18 (1.09-1.29)	<.0001
	Former vs Never	4% vs 10%	2,368/6,038 (39.72%)	1.19 (1.09-1.29)	<.0001
	Current vs Former	6% vs 4%	2,116/6,038 (35.04%)	1.00 (0.93-1.07)	0.9452

Table 1 - Association between smoking status and overall survival in cohort stratified by aggregate stage group.



Stage Subgroup Comparison	Smoking Status Comparison	5 yr OS	n/N (%)	aHR (95% CI)	P Value
Stage IB vs IA	IB Never vs IA Current	76% vs 75%	1,926/24,749 (5.49%)	1.05 (0.93-1.20)	0.3909
	IB Former vs IA Current	66% vs 75%	2,003/24,749 (8.09%)	1.32 (1.18-1.47)	<.0001
	IB Current vs IA Current	66% vs 75%	1,164/24,749 (4.70%)	1.47 (1.29-1.67)	<.0001
Stage IIA vs IB	IIA Never vs IB Current	68% vs 66%	929/7,736 (12.01%)	0.94 (0.80-1.11)	0.4825
	IIA Former vs IB Current	63% vs 66%	1,250/7,736 (16.16%)	1.10 (0.96-1.26)	0.1910
	IIA Current vs IB Current	55% vs 66%	784/7,736 (10.13%)	1.23 (1.09-1.50)	0.0023
Stage IIB vs IIA	IIB Never vs IIA Current	53% vs 55%	644/6,113 (10.53%)	0.88 (0.73-1.06)	0.1681
	IIB Former vs IIA Current	55% vs 55%	1,569/6,113 (25.67%)	1.11 (0.96-1.29)	0.1544
	IIB Current vs IIA Current	55% vs 55%	937/6,113 (15.33%)	1.14 (0.99-1.34)	0.0957
Stage IIIA vs IIB	IIIA Never vs IIB Current	50% vs 55%	550/6,280 (8.76%)	1.07 (0.91-1.26)	0.4091
	IIIA Former vs IIB Current	47% vs 55%	1,596/6,280 (25.41%)	1.13 (1.00-1.29)	0.0586
	IIIA Current vs IIB Current	43% vs 55%	984/6,280 (15.67%)	1.35 (1.17-1.55)	<.0001
Stage IIIB vs IIIA	IIIB Never vs IIIA Current	46% vs 43%	294/4,442 (4.89%)	0.98 (0.78-1.20)	0.8759
	IIIB Former vs IIIA Current	29% vs 43%	663/4,442 (14.93%)	1.45 (1.22-1.60)	<.0001
	IIIB Current vs IIIA Current	32% vs 43%	445/4,442 (10.02%)	1.24 (1.10-1.57)	0.0092
Stage IIIC vs IIIB	IIIC Never vs IIIB Current	12% vs 32%	60/1,866 (3.22%)	1.41 (0.97-2.05)	0.0680
	IIIC Former vs IIIB Current	22% vs 32%	219/1,866 (11.74%)	1.41 (1.14-1.74)	0.0014
	IIIC Current vs IIIB Current	20% vs 32%	275/1,866 (14.74%)	1.53 (1.30-1.80)	<.0001
Stage IVA vs IIIC	IVA Never vs IIIC Current	23% vs 20%	1,892/7,189 (26.32%)	0.94 (0.79-1.11)	0.4458
	IVA Former vs IIIC Current	12% vs 20%	2,583/7,189 (35.93%)	1.01 (0.86-1.20)	0.8758
	IVA Current vs IIIC Current	18% vs 20%	2,140/7,189 (30.05%)	1.01 (0.86-1.20)	0.8739
Stage IVB vs IVA	IVB Never vs IVA Current	10% vs 18%	1,524/12,673 (12.05%)	1.39 (1.29-1.52)	<.0001
	IVB Former vs IVA Current	4% vs 18%	2,368/12,673 (18.92%)	1.61 (1.49-1.74)	<.0001
	IVB Current vs IVA Current	6% vs 18%	2,116/12,673 (16.70%)	1.64 (1.52-1.78)	<.0001

Table 2 - Comparative survival of cohorts in adjacent 9th edition stage groups segregated according to smoking status.

Keywords: Smoking, Staging, Prognosis

OA11 BEYOND TNM - NEW HORIZONS IN PROGNOSTICATION
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA11.02 Molecular Alterations and Survival: Analyses from IASLC 9th Edition Staging Database

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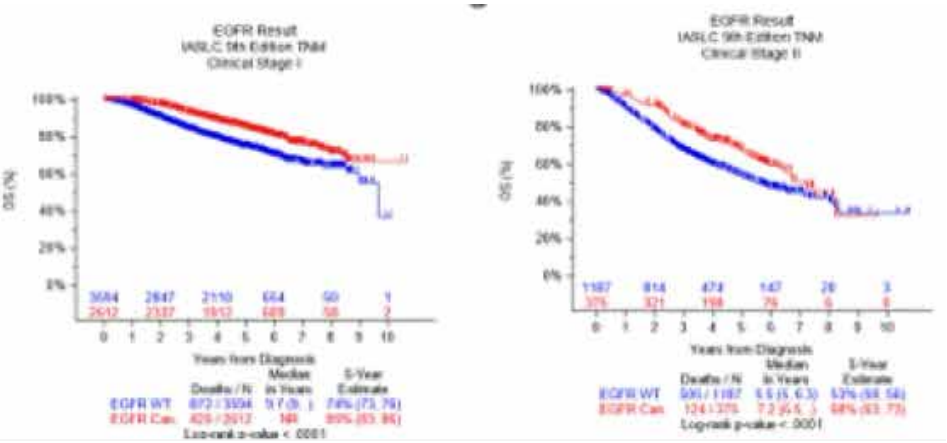
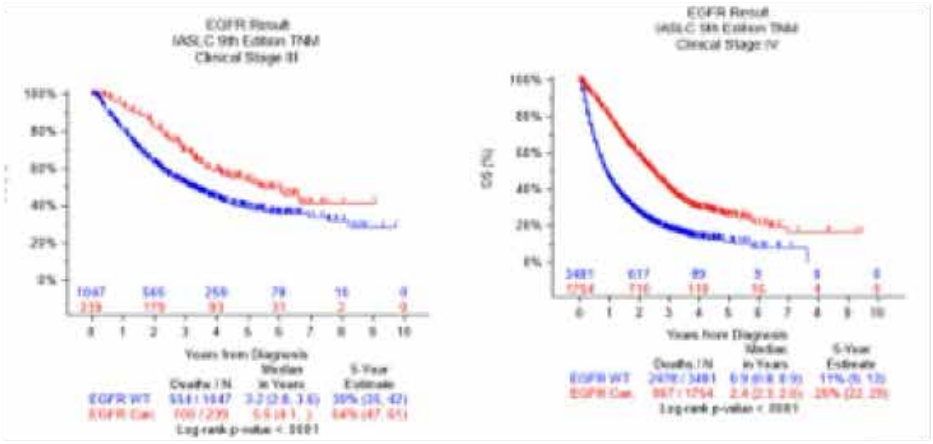
Introduction: TNM staging systems create prognostic categories by anatomic extent of disease. Whether therapeutically important molecular alterations in NSCLC augment the prognostic information of TNM staging is unclear. To study this, we analyzed molecular data from the 9th edition of the lung cancer staging system.

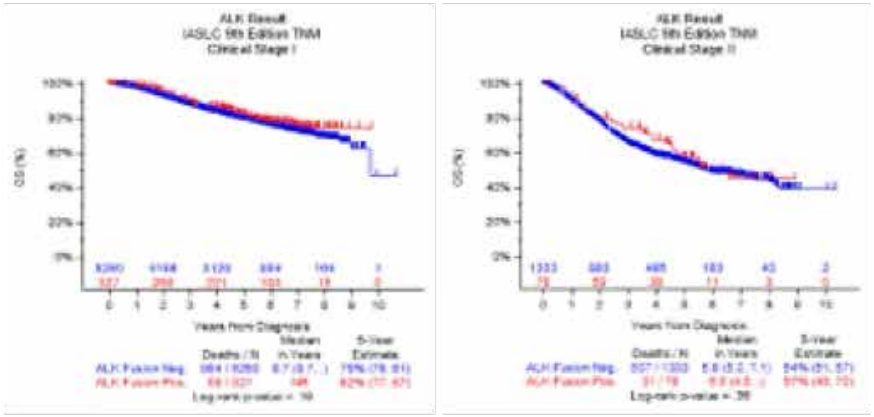
Methods: Eligible patients were diagnosed between 2011-2019. Analysis was restricted to three genes for reliable statistical analyses: EGFR mutations (L858R, exon 19 deletion), ALK fusions, and KRAS mutations (codons 12, 13, or 61). Overall survival (OS) was calculated by the Kaplan-Meier method and differences in OS assessed by Cox proportional hazard regression models.

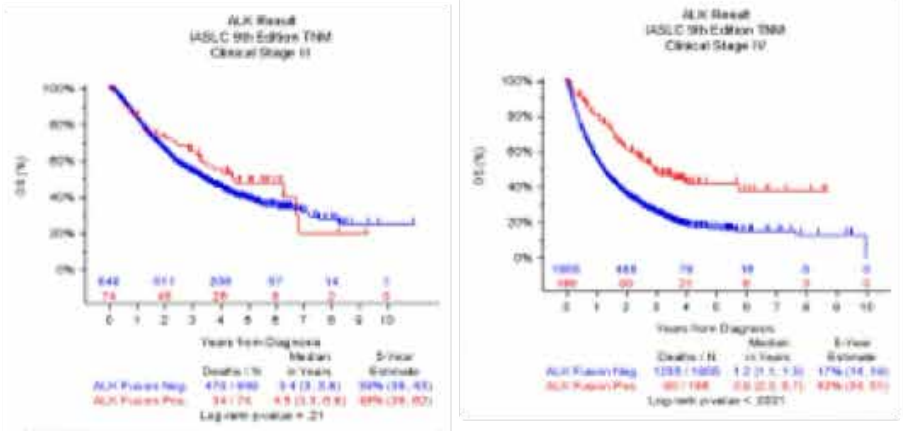
Results: 20,580 patients had tumors with molecular data (EGFR = 16,497, ALK = 11,546, KRAS = 2,909 patients). EGFR mutations were found in 5,428 (32.9%), ALK fusions in 723 (6.3%) and KRAS mutations in 890 (30.6%) tumors. OS was significantly better across all TNM stages among patients with EGFR mutated tumors and patients with Stage IV ALK fusion-positive tumors, while patients with Stage I KRAS mutated tumors had significantly worse OS. Multivariable analyses confirmed the OS associations with EGFR mutated tumors (Stage I HR = 0.79, Stage II HR=0.71, Stage III HR = 0.67, Stage IV HR = 0.49) and stage IV ALK fusion-positive tumors (HR = 0.56).

Conclusions: Patients with EGFR mutated tumors had improved OS regardless of stage while an OS benefit was seen in stage IV patients with ALK positive tumors. In the 10th edition, we will systematically integrate molecular biomarkers and treatment to refine prognostication for molecular subsets of NSCLC.









Keywords: EGFR, ALK, TNM

OA11 BEYOND TNM - NEW HORIZONS IN PROGNOSTICATION
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA11.03 The Survival Impact of Subdividing Clinical and Pathologic N2 Descriptors in a Population-Based Surgical Cohort

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Introduction: The 9th edition lung cancer staging system subdivided the N2 category based on single station (N2a) and multi-station (N2b) ipsilateral lymph node involvement. We assessed the prognostic value of this revision in a population-based US cohort.

Methods: We analyzed patients in the Mid-South Quality of Surgical Resection (MSQSR) cohort from 2009-2024. We retrospectively reclassified N2 descriptors based on single vs multiple station lymph node (LN) involvement. We compared overall survival (OS) with the log-rank test and fit proportional hazards (PH) models with crude and adjusted hazard ratios (aHR). Adjusted models included age, sex, histology, smoking status, comorbidities, and adjuvant therapy.

Results: Of 4363 eligible patients (median follow-up 44 months), the relative proportions of N2 were 120 (78%) cN2a versus 34 (22%) cN2b; and 259 (75%) pN2a versus 83 (25%) pN2b. In both crude and adjusted analysis, OS differed significantly between pN2a and pN2b (aHR: 1.47, p=0.02, Figure 1B) but not for cN2a and cN2b (aHR: 1.35, p=0.19, Figure 1A). Additionally, OS was significantly better in pN1 vs. pN2a (aHR: 1.28, p=0.01), but not for cN1 vs. cN2a (aHR: 1.01, p=0.92). A sensitivity analysis among patients meeting CoC Operative Standard 5.8 found significant differences in OS in pN2a vs. pN2b (aHR: 1.86, p<0.01) but not pN1 vs. pN2a (aHR: 1.39, p=0.06) or cN2a vs. cN2b (aHR:1.02, p=0.96). Sensitivity analyses for patients with PET scans revealed significant associations between pN2a and pN2b in adjusted models (aHR: 1.50, p=0.02) as well as among those with at least 6 LNs sampled (aHR:1.47, p=0.02). Neither sensitivity analysis showed significant results for cN2a vs cN2b (aHR:1.23, p=0.41 for PET and aHR:1.29, p=0.43 for at least 6 LNs sampled).

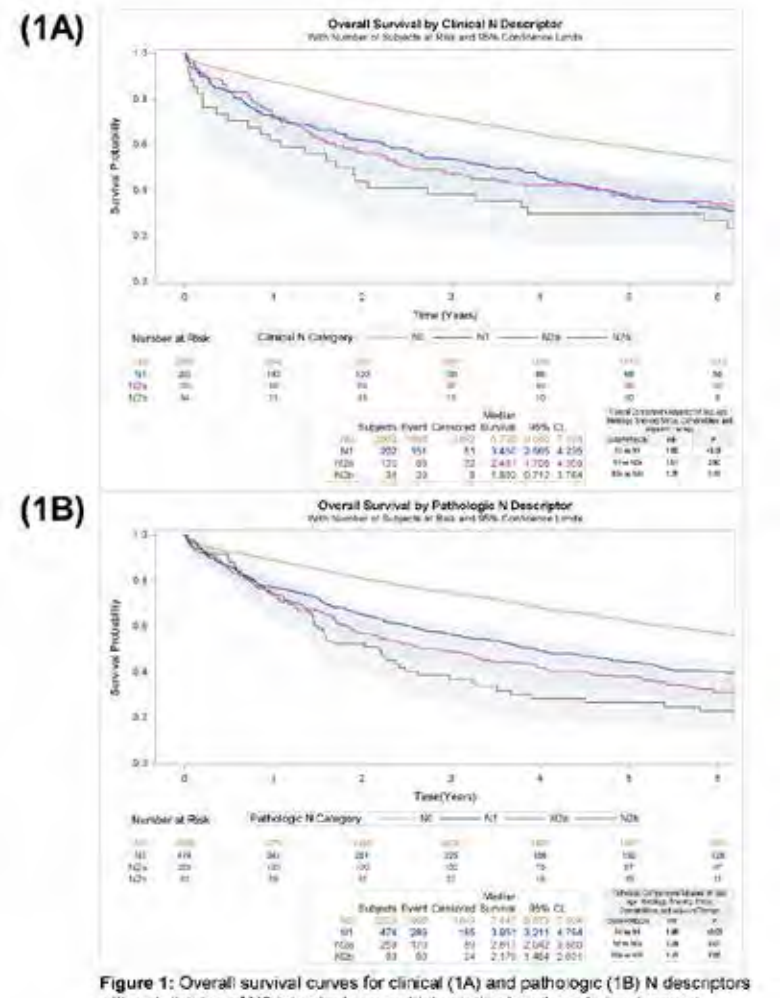

Figure 1: Overall survival curves for clinical (1A) and pathologic (1B) N descriptors with subdivision of N2 into single vs multiple station lymph node involvement.

Conclusions: The pN2, but not the cN2, subdivision was significantly associated with overall survival in this population-based cohort. Our inability to discriminate between cN2a and cN2b could be explained by the relatively small sample size or preoperative staging limitations.

Keywords: TNM Classification, N Descriptor, N Stage

OA11 BEYOND TNM - NEW HORIZONS IN PROGNOSTICATION
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA11.04 Validation and Refinement Proposal of the Ninth Edition n Descriptor for Non-Small Cell Lung Cancer Receiving Neoadjuvant Therapy

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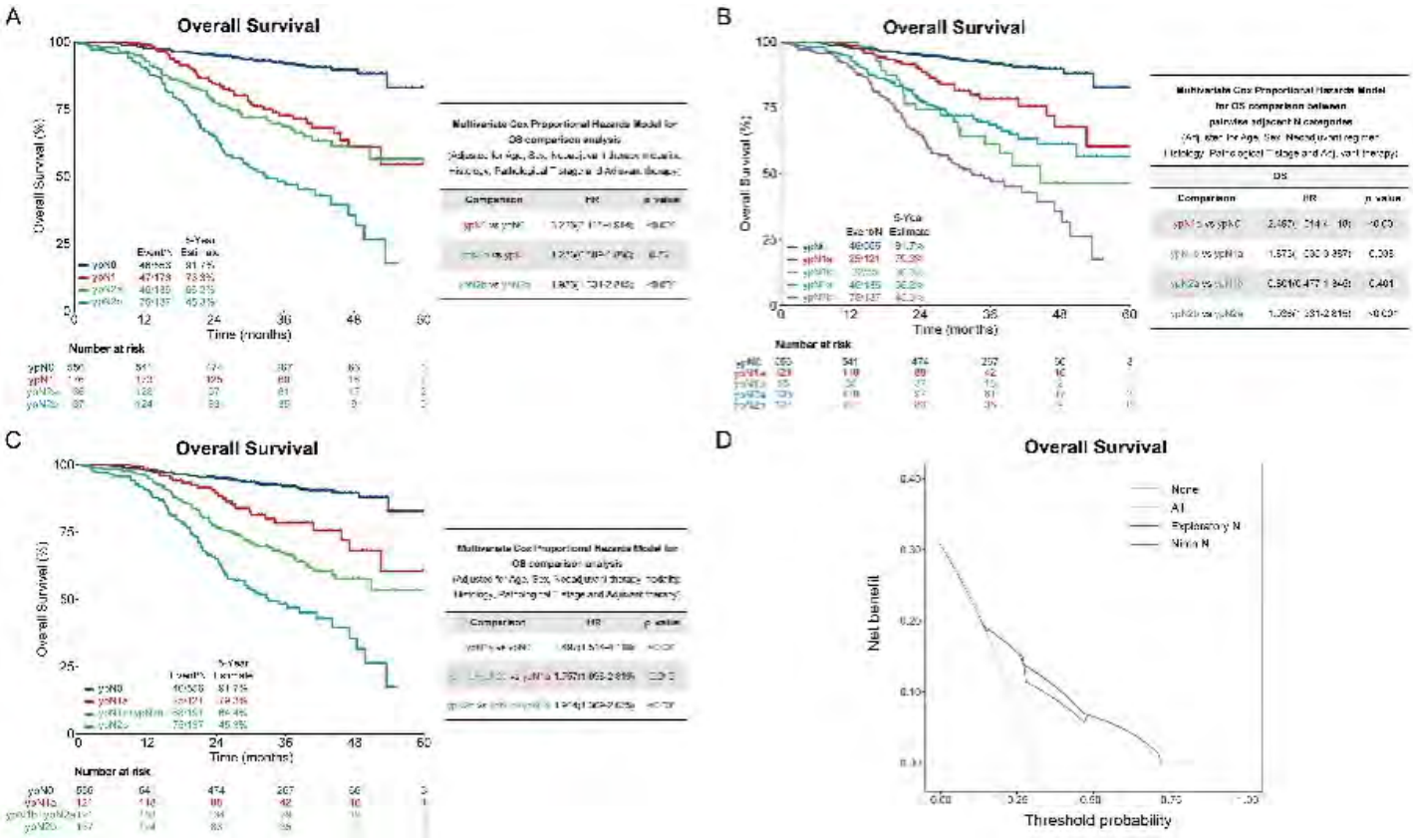
Introduction: Although the ninth edition N descriptors have been validated in upfront surgery populations, evidence supporting their validity and addressing their limitations in prognostic stratification in the neoadjuvant setting remain sparse. The study aimed to validate these newly proposed N descriptors, and explore the prognostic relevance of exploratory quaternary N scheme relative to the ninth edition N classification in postneoadjuvant non-small cell lung cancer (NSCLC).

Methods: We identified 1,005 NSCLC individuals who underwent complete resection following neoadjuvant therapy from four clinical centers between May 2019 and September 2022. Prognostic difference of adjacent N categories' comparison regarding recurrence-free survival (RFS) and overall survival (OS) was estimated by the log-rank test and the Cox proportional hazards model. Decision curve analysis (DCA) was performed to quantify incremental survival prediction benefit.

Results: According to the ninth edition proposal, pathologic N0, N1, N2a, and N2b were associated with a stepwise deterioration in prognosis, except between N1 and N2a (p=0.331 for OS; p=0.508 for RFS, Figure 1A). In exploratory analyses, multiple N1 stations involvement subcategory (N1b) with N2a showed prognostic homogeneity and comparable adjuvant treatment benefit (Figure 1B). With observed homogeneity, integration of N1b and N2a into one single group could significantly distinct from single N1 station involvement (N1a) (p=0.019 for OS; p=0.018 for RFS) as well as from N2b (p<0.001 for both OS and RFS, Figure 1C). Sensitivity analyses stratified by neoadjuvant regimen, histology, and T descriptor revealed that exploratory four-tier N scheme similarly exhibited a graded tendency towards prognostic decline. Further DCA indicated exploratory quaternary descriptors comprising of N0/N1a/N1b+N2a/N2b yielded stronger prognostic relevance than the ninth edition classification (Figure 1D).

Conclusions: The ninth edition N classification was validated to demonstrate moderate prognostic discrimination in neoadjuvant population. Exhibiting superior prognostic stratification, burden-directed and location-supplemented N considerations would provide novel insights into further N refinement.



Keywords: Neoadjuvant therapy, N descriptor, Resectable non-small cell lung cancer

OA12 NOVEL CLINICAL APPROACHES AND TRANSLATIONAL INVESTIGATION IN MESOTHELIOMA
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA12.01 IASLC Mesothelioma Staging Project: Impact of Molecular Alterations on Survival in a Cohort From 9Th Edition Database

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Introduction: The current staging system for pleural mesothelioma (PM) is based on anatomic extent of disease. Whether assessment of molecular alterations adds prognostic information is undefined. We examined the impact of molecular alterations on overall survival (OS) in PM in a 3-institution cohort from IASLC 9th edition Staging Project.

Methods: Biomarker data included PD-L1 IHC (clones E1L3N, 28-8, or 22C3), BAP1 IHC, and somatic NGS. BAP1, CDKN2A, and NF2 genes were categorized as wild-type (WT), pathogenic, or variant of unknown significance (VUS). TP53 mutational status was categorized as WT or pathogenic. OS was calculated from date of diagnosis by Kaplan-Meier method and compared between groups by Cox proportional hazard regression. Hazard ratios for pathogenic alterations were adjusted for age, sex, histology, performance status, curative-intent resection (EPP or EPD), and TNM categories. Models were compared using pseudo-R2 and Harrell's C-statistic.

Results: The cohort included 556 patients: median age=72 years; 72.7% male; 77.5% epithelioid; 69.6% cT1-T3, cM0 stage; 29.3% curative-intent resection; 82.0% treated with systemic therapy. Pathogenic alterations in BAP1 were most common (141/262, 53.8%), followed by CDKN2A (94/262, 35.96%), NF2 (62/262, 23.7%) and TP53 (47/262, 17.9%). Loss of BAP1 by IHC was detected in 58.2% (263/452) of cases. PD-L1 expression by IHC was positive (> 1% membranous staining) in 43.7% (69/158) and 47.6% (20/42) of epithelioid and non-epithelioid PM cases, respectively. Median OS for entire cohort (n=556) was 19.1 months. On univariate analysis, pathogenic alterations in CDKN2A (HR 2.67, CI: 1.93-3.69), NF2 (HR 1.89, CI: 1.34-2.67), and TP53 (HR 1.86, CI: 1.27-2.73) were associated with worse OS (p<0.001), while BAP1 alterations were associated with better OS (NGS HR 0.63, CI: 0.46-0.85, p=0.003; IHC HR 0.60, CI: 0.48-0.75, p<0.001). PD-L1 IHC expression was not associated with OS (p=0.645). Multivariable analyses confirmed OS associations. While the clinical covariates performed better than the set of molecular alterations alone (C-statistic: 0.67 vs 0.65; R2: 25.8 vs 20.2), a model that included BAP1 alterations plus any pathogenic alteration in CDKN2A, NF2, and TP53, along with clinical covariates best predicted survival (C-statistic: 0.70; R2: 37.1).

Conclusions: In this large, clinically well-annotated cohort, alterations in CDKN2A, NF2, and TP53 were associated with worse OS, while BAP1 alterations were associated with better OS in PM independent of clinical variables and histology. Modeling suggests that genomic alterations provide additional prognostic information beyond anatomic TNM and pathologic features. These findings will be studied further in the 10th edition database.

Table. Somatic next generation sequencing results in pleural mesothelioma.

	Total (N=262)
BAP1, n (%)	
Altered: pathogenic	141 (53.8%)
Altered: VUS	6 (2.3%)
Wild type	115 (43.9%)
CDKN2A, n (%)	
Altered: pathogenic	94 (35.9%)
Altered: VUS	1 (0.4%)
Wild type	167 (63.7%)
NF2, n (%)	
Altered: pathogenic	62 (23.7%)
Altered: VUS	3 (1.1%)
Wild type	197 (75.2%)
TP53, n (%)	
Altered: pathogenic	47 (17.9%)
Wild type	215 (82.1%)

Keywords: Mesothelioma, Staging, Molecular

OA12 NOVEL CLINICAL APPROACHES AND TRANSLATIONAL INVESTIGATION IN MESOTHELIOMA
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA12.02 CCTG IND227, a Randomized Trial of Chemotherapy + Pembrolizumab in Advanced Pleural Mesothelioma: Updated Analyses

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Introduction: IND227 was a 3-arm randomised phase 2 trial that was amended to a 2-arm phase 2/3 design. The final phase 2/3 analysis revealed improved overall survival (OS) with the addition of pembrolizumab to standard platinum-pemetrexed chemotherapy in advanced incurable pleural mesothelioma (PM), with a hazard ratio (HR) for OS of 0.79 [95 % CI 0.64-0.98, log-rank p=0.0324]. Herein we present the final, updated OS analysis along with additional exploratory analyses.

Methods: Fit, eligible adult patients with advanced, incurable PM were enrolled at sites in Canada, Italy and France. IND227 was originally designed as a 3-arm phase 2 trial with a primary endpoint of progression-free survival, in which patients were randomized 1:1:1 (stratified by histology) to standard platinum (either cisplatin or carboplatin) and pemetrexed chemotherapy q3weeks for up to six cycles with or without the addition of pembrolizumab 200 mg q3weeks for up to two years, or to pembrolizumab alone [J Thorac Oncol 2023;18:813-819]. At the first planned interim analysis (2017), the CCTG DMSC recommended the pembrolizumab cohort be discontinued. In 2018, the trial was amended to a phase 2/3 trial in which patients were randomized 1:1 to chemotherapy +/- pembrolizumab with a primary endpoint of OS. Patients included in the first interim phase 2 analysis (phase 2 only cohort) were excluded from the final analysis of the phase 2/3.

Results: A total of 440 patients were included in the phase 2/3 final analyses; 222 randomized to chemotherapy+pembrolizumab and 218 to chemotherapy alone. Median age 71 years (range 28-88), 24% female, 78% epithelioid, 47 % PS 0. At the updated phase 2/3 analysis (data cut-off September 30, 2023), with a median follow up of 16.2 months (range 0.03-69.9), an additional 29 deaths had occurred. The HR for OS was 0.79 [0.64-0.97, nominal p = 0.022]. The estimated 3- and 5-year survivals were 24 and 12 % with the addition of pembrolizumab versus 18 and 2 % for chemotherapy alone. For the epithelioid subgroup, the HR for OS was 0.85 [0.67-1.08] and for the non-epithelioid subgroup was 0.65 [0.42-1.00].

Conclusions: The benefit of the addition of pembrolizumab to standard chemotherapy in advanced PM is confirmed with longer follow-up. Additional analyses, including outcomes by biomarkers such as BAP1, and exploratory analyses incorporating additional patients enrolled to the phase 2 component of the trial [phase 2 only cohort; n=80] originally excluded from the OS analysis will be presented at the meeting. Central pathology re-review is also planned.

Keywords: mesothelioma, pembrolizumab, chemotherapy

OA12 NOVEL CLINICAL APPROACHES AND TRANSLATIONAL INVESTIGATION IN MESOTHELIOMA
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA12.03 Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Resectable Diffuse Pleural Mesothelioma

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Introduction: While the role of surgery in limited-stage diffuse pleural mesothelioma (DPM) is controversial, an aggressive tri-modality approach incorporating perioperative chemotherapy (CT), surgery, and radiotherapy (RT) is considered for select patients. Immune checkpoint blockade (ICB) has shown a survival benefit in advanced DPM, but its role in perioperative management of DPM is unclear. This prospective, multi-center, multi-arm clinical trial investigated neoadjuvant nivolumab (nivo) and nivolumab/ipilimumab (nivo/ipi) in patients with resectable DPM (NCT03918252).

Methods: Patients with epithelioid or biphasic DPM deemed resectable by multidisciplinary assessment were enrolled sequentially to receive neoadjuvant nivo 240mg IV every 2 weeks (q2w) for 3 doses (Arm A) or nivo 3mg/kg IV q2w for 3 doses with ipi 1mg/kg given on day 1 only (Arm B). After surgery, patients received optional adjuvant RT and/or CT followed by nivo 480mg IV q4w for 1 year. Co-primary endpoints were safety (frequency of dose-limiting toxicities [DLTs]) and feasibility (proportion of surgeries occurring ≤24 days from the preplanned surgery date), with feasibility defined by a posterior 90% credible interval (pCI) encompassing 80%. Key secondary endpoints included event-free survival (EFS - time from neoadjuvant therapy initiation to progression precluding surgery, recurrence post-surgery, or death) and overall survival (OS - time from neoadjuvant therapy initiation to death).

Results: 30 patients (16 Arm A, 14 Arm B) were enrolled and received neoadjuvant ICB. In Arm A, median age was 64 years, 81.3% (13/16) were male, and 87.5% (14/16) had epithelioid histology (2/16 had biphasic histology). In Arm B, median age was 68 years, 57.1% (8/14) were male, and 78.6% (11/14) had epithelioid histology (3/14 biphasic). In Arms A and B, surgery was performed in 81.3% (13/16) and 78.6% (11/14) of patients, of which 11/13 and 11/11 completed surgery within the predefined feasibility window, respectively. The posterior means and pCIs for feasibility were 67.0% (90% pCI: 47.8-83.4) and 75.0% (90% pCI: 56.0-90.3) in Arms A and B, respectively. One DLT was seen in each arm (pneumonitis - Arm A; elevated ALT - Arm B), neither precluded surgery. Among the 13 patients who completed surgery in Arm A, 9 (69.2%), 7 (53.9%), and 7 (53.9%) received adjuvant CT, RT, and nivo, respectively. Of the 11 patients who completed surgery in Arm B, 5 (45.5%), 5 (45.5%), and 5 (45.5%) received adjuvant CT, RT and nivo, respectively. At median follow-up of 43.2 months in Arm A, the median EFS and OS were 9.6 months (95% confidence interval (CI): 2.5-27.7) and 19.3 months (95% CI: 14.9-34.7), respectively. At median follow-up of 21.5 months in Arm B, the median EFS and OS were 19.8 months (95% CI: 5.5-not reached [NR]) and NR (95% CI: 20.4-NR), respectively.

Conclusions: Incorporation of neoadjuvant ICB into the perioperative treatment of limited-stage DPM was safe and feasible, without delay of resection. Compared to historical data with systemic therapy alone, neoadjuvant nivo/ipi demonstrated favorable long-term clinical efficacy. Planned correlative analyses will explore immunologic, molecular, and pathologic features of response in order to identify patient subsets most likely to benefit from this approach.

Keywords: mesothelioma, neoadjuvant, immunotherapy

OA12 NOVEL CLINICAL APPROACHES AND TRANSLATIONAL INVESTIGATION IN MESOTHELIOMA
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA12.04 Radiation Reprograms CDKN2A/p16 Wild Type Epithelioid Mesothelioma Towards an Immune Responsive Tumor Microenvironment

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Introduction: We developed a new treatment paradigm for pleural mesothelioma using accelerated sub-ablative hemithoracic radiotherapy (hemi-RT) with concomitant boost followed by surgery one week later. This approach demonstrated encouraging results in epithelioid mesothelioma in the SMART trial using hemi-RT dose of 25Gy/5 daily fractions followed by extrapleural pneumonectomy. The safety of hemi-RT before lung-sparing surgery was demonstrated in the SMARTER trial using hemi-RT dose up to 12 Gy/3 alternate daily fractions. In this analysis, we performed correlative studies to define the mechanisms of immune activation after radiation, and to identify potential biomarkers predicting response.

Methods: Tumor samples from patients treated with the SMART (n=48) and SMARTER approach (n=24) were analyzed using single-cell RNA sequencing, CyTOF, transcriptomics (Nanostring), and multiplexed imaging mass cytometry. Luminex was performed in the serum collected before radiation, at the time of surgery (9±2 days post-RT), and during follow-up (6±2 weeks post-surgery) in the SMARTER trial (n=24). Homozygous deletion of CDKN2A/p16 (p16HD) was defined by FISH, and BAP1 loss by immunohistochemistry.

Results: Circulating CXCL10, FLT3L, and IL-5 significantly increased post-RT. Persistent CXCL10 upregulation post-surgery was associated with longer OS, independent of tumor histology, tumor volume, nodal disease, T category, and BAP1 loss in multivariate analysis. CXCL10 upregulation post-RT was detected in CDKN2A/p16 wild type (p16WT) tumors, and inversely correlated with its baseline level (r=-0.53, p=0.006). At baseline, epithelioid p16WT tumor cells were characterized by a type-I interferon (IFN-I) response associated with VSIR (VISTA) upregulation, and an immunosuppressive TME generated by VSIG4+ tumor associated macrophages (TAMs). BAP1 loss was associated with downregulation of the stimulator of IFN genes, TMEM173 (STING), specifically in tumor cells compared to BAP1 WT. p16HD tumor cells were characterized by a cancer-associated fibroblast (CAF)-like phenotype expressing TNFA-signaling, and promoting an inflammatory TME. Radiation induced CDKN1A/p21 in epithelioid p16WT tumor cells, promoting an adaptive immune response with upregulation of CXCL10 and SLAMF7 in TAMs, and reinvigoration of cytotoxic CD8+ T cells. The immune response was predominantly mediated by an IFN response in tumors with BAP1 loss, and TNFA-signaling in BAP1 WT. The potential benefit from sub-ablative hemi-RT and surgery in epithelioid p16WT mesothelioma was retrodicted in the SMART trial with DFS and OS reaching 54% and 60% at 5 years, respectively. The benefit was particularly notable in epithelioid p16WT mesothelioma with BAP1 loss, reaching a DFS of 60% and OS of 70% at 5 years. The best OS correlated with upregulation of SLAMF7 (r=0.81, p=0.0008) and CXCL10 (r=0.73, p=0.004). CDKN1A/p21+ tumor cells interacted with CAFs to promote EMT, and suppress the IFN response in non-epithelioid mesothelioma. Radiation, paradoxically, upregulated IFN-stimulated genes in p16HD tumor cells, and suppressed the TME.

Conclusions: These results demonstrated the potential benefit of radiation in epithelioid p16WT mesothelioma. BAP1 loss was associated with the downregulation of STING in tumor cells, and greater activation of the adaptive immunity after radiation. By deciphering the mechanisms of response to radiation at a molecular level, we identified divergent TME with different responses to therapy, providing a rationale for more personalized therapy in mesothelioma.

Keywords: Mesothelioma, Radiation, Immune

OA13 OPTIMIZING FRONT-LINE TREATMENT IN SCLC
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA13.01 Safety and Survival Update of Tarlatamab with Anti-PD-L1 as 1L Maintenance After Chemo-IO for ES-SCLC: DeLLphi-303 Ph1b Trial

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OA13 OPTIMIZING FRONT-LINE TREATMENT IN SCLC
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA13.02 Global Phase 2 Randomized Trial of BNT327 (Pumitamig; PD-L1 x VEGF-A bsAb) + Chemotherapy for 1L ES-SCLC: Dose Optimization Analysis

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Introduction: BNT327 (pumitamig) is an investigational bispecificantibody targeting PD-L1 and VEGF-A, designed to restore effectorT-cell function through PD-L1 binding while co-localizing VEGF-A neutralizationwithin the tumor microenvironment. Pumitamig+chemotherapyshowed encouraging activity in Phase 2 trials in Chinesepatients with SCLC. Hereinwe present the first pumitamig data from a global population.

Methods: In this global Phase 2, randomized, open-label,parallel group trial (NCT06449209), patients with treatment-naïveES-SCLC received pumitamig+etoposide+carboplatin x 4 cycles followed by pumitamigmaintenance (Cohort 1); patients progressing after 1L or 2L treatment received pumitamig+paclitaxel(Cohort 2) or pumitamig+topotecan (Cohort 3). Patients within each cohort wererandomized to pumitamig 20 or 30 mg/kg IV Q3W for up to 2 years or untildisease progression/unacceptable toxicity. Primary endpoints were efficacy perRECIST 1.1 (ORR per investigator, change in tumor size and early tumorshrinkage) and safety per NCI CTCAE v5.0.FoundationOne®Liquid CDx analysis estimated circulating tumorfraction (TFx) of cell-free DNA (cfDNA). Here wepresent data from Cohort 1 supporting optimal dose finding for Phase 3development.

Results: At cutoff (04 Apr 2025), enrolment wascomplete with 107 patients. In Cohort 1 (N=43median age: 65.0 years [range 45-80], 62.8% ECOG PS 1; median pumitamigtreatment duration: 11.6 weeks), 22 patients received pumitamig 20 mg/kg and 21received 30 mg/kg. Amongst 38 efficacy-evaluable patients, 33 had PR and 5 had SDresulting in 86.8% unconfirmed ORR (uORR) and 100% DCR. The mean bestpercentage change in tumor size was -47.3%with 89.5% of patients achieving early tumor shrinkage. uORR was 95.0%and 77.8% with pumitamig 20 mg/kg and 30 mg/kg, respectively. Among 11 patients with 2 post-baseline tumor assessmentsand >90 days' follow-up, confirmed ORR was 81.8% (9/11) for both dose levels,and 100% (6/6) for 20 mg/kg and 60.0% (3/5) for 30 mg/kg; DoR and PFS were notmature. Updated efficacy, including early DOR and PFS, will bepresented.Baseline circulating tumor DNA (ctDNA) detection ratewas 93.8% (30/32 patients with cfDNA data), with median TFx of 57.0%. At C3D1,all evaluable patients (n=18) had confirmed ctDNA reduction vs baseline, with amedian TFx change of -99.3% and ctDNA clearance rate of 44.4% (8/18). Similarresults were observed between dose levels. Adverseevents (AEs) related to any treatment were reported in 35/43 (81.4%) patientsand were Grade ≥3 in 23 (53.5%) patients. Pumitamig-related Grade ≥3 AEs were reported in 1 patient receiving 20 mg/kg and 5receiving 30 mg/kg (hypertension [n=2], platelet count decreased, hemoptysis,proteinuria, and pulmonary embolism [n=1 each]). Six (14.0%) patients discontinuedpumitamig due to AEs (20 mg/kg n=2, 30 mg/kg n=4). Notreatment-related deaths occurred.

Conclusions: Pumitamig plus etoposide/carboplatinshowed encouraging efficacy and acceptable safety in 1L ES-SCLC. This firstpresentation in a global population of a bispecific antibody targetingcheckpoint inhibition and angiogenesis confirms the encouraging data previouslyreported in the 1L SCLC Chinese study (https://doi.org/10.1016/S1556-0864(25)00494-0).This dose optimization study supportsfurther development of pumitamig in 1L SCLC,currently being evaluated in the ROSETTA Lung-01 Phase 3 trial.

Keywords: PD-L1 x VEGF-A bispecific antibody, BNT327, SCLC

OA13 OPTIMIZING FRONT-LINE TREATMENT IN SCLC
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA13.03 RYZ101 (225Ac-DOTATATE) + Carboplatin + Etoposide + Atezolizumab in Somatostatin Receptor-Expressing Extensive-Stage SCLC

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Introduction: RYZ101 (225Ac-DOTATATE) is a first-in-class, alpha-emitting radiopharmaceutical in development for the treatment of patients with somatostatin receptor-expressing (SSTR2+) solid tumors. Alpha particles (emitted by 225Ac) have a higher linear energy transfer (80-100 keV/µm) and shorter path length (40-100 µm) than beta particles, potentially allowing for improved cancer cell kill rates while limiting off-tumor toxicity. Here we describe preliminary safety data from a single-arm, open-label, phase 1b dose-escalation and dose-expansion trial of RYZ101 in combination with standard of care (SoC) therapy in patients with treatment-naïve SSTR2+ extensive-stage small-cell lung cancer (ES-SCLC; NCT05595460).

Methods: Adult patients with histologically/cytologically confirmed SSTR2+ ES-SCLC, ECOG PS 0-1, life expectancy ≥12w, and sufficient renal, hepatic, and hematologic function are eligible. Patients must have ≥1 SSTR2 PET imaging-positive RECIST v1.1-measurable disease sites; ≥50% of measurable lesions must be SSTR2+. Patients may receive ≤1 cycle of SoC before/during screening. Patients with CNS metastases are permitted but must be asymptomatic, adequately treated, and on stable/decreasing steroid doses. During dose-escalation, patients receive RYZ101 (IV q6w then q4w) starting at dose level 1 (DL1) of 6.5 MBq, with escalation to 8.3 MBq (DL2) and 10.2 MBq (DL3) in the absence of dose-limiting toxicities (DLTs). Patients also receive SoC: atezolizumab (Tecentriq®, 1200 mg IV d1 q21d ≤4 cycles, then 1680 mg IV q28d); carboplatin (AUC 5-6 IV 60min d1 q21d ≤4 cycles); etoposide (80-100 mg/mm2 IV 60min d1-3 q21d ≤4 cycles). Primary endpoints: safety, recommended phase 2 dose. Secondary endpoints: efficacy, pharmacokinetics.

Results: Forty-three patients have been screened and 15 have been dosed with RYZ101 to date. As of September 3, 2024, nine patients (n=4; DL1 and n=5; DL2) had mature safety data. Median age was 67 years (range 49-79), 55.6% were female, and 88.9% were former smokers. All patients received 1 cycle of SoC before/during screening. Median treatment duration of RYZ101 was 2.9 months (range 1.4-11.9); median number of RYZ101 doses was 2.0 (range 1-6). Treatment is ongoing in five patients (DL2). No DLTs were reported. One patient had a G≥3 RYZ101-related AE (DL1; G4 lymphocyte count decreased). Other RYZ101-related AEs occurred in three additional patients: G1 diarrhea, eosinophilia, fatigue, and vomiting (all n=1); and G2 decreased appetite, dehydration, depression, fatigue, influenza-like illness, nausea, neutrophil count decrease, and weight decreased (all n=1). SAEs, all unrelated to RYZ101, were pneumonia (n=2), and infective arthritis, sepsis, pain, back pain, hyponatremia, spinal cord compression, and syncope (all n=1). One patient had G4 neutropenia related to SoC following 3 cycles of SOC and 1 of RYZ101 requiring temporary RYZ101 dose reduction; this recovered with dose delays and supportive care.

Conclusions: There were no DLTs reported at DL1 (6.5 MBq) or DL2 (8.3 MBq) and the RYZ101 dose was escalated to DL3 (10.2 MBq) with six patients dosed to date; the study has completed enrollment for dose escalation and is proceeding to dose expansion. Updated data will be presented.

Keywords: RYZ101, 225Ac-DOTATATE, Radiopharmaceutical

OA13 OPTIMIZING FRONT-LINE TREATMENT IN SCLC
MONDAY, SEPTEMBER 8, 2025 - 17:00 - 18:15

OA13.04 Highly Proliferative (G3) Lung Carcinoids: IASLC Pathology Committee Study With Proposal for Inclusion in WHO Classification

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Introduction: The World Health Organization (WHO) classifies pulmonary carcinoids (well-differentiated neuroendocrine tumors or NETs) as typical carcinoids (grade 1; <2 mitoses per 2 mm2) and atypical carcinoids (grade 2; 2-10 mitoses per 2 mm2 and/or necrosis). Lung tumors with carcinoid/NET morphology but exceeding 10 mitoses per 2 mm2 are rare, and are currently classified in the WHO as large cell neuroendocrine carcinoma (LCNEC); however, this has been a matter of growing debate. To address this, the IASLC Pathology Committee initiated a multi-institutional study to collect and characterize such tumors with the goal of clarifying their clinicopathologic characteristics and optimal classification.

Methods: Members of the Neuroendocrine Working Group within the IASLC Pathology Committee identified resected lung tumors meeting the inclusion criteria (carcinoid morphology with mitotic count of >10/2mm2) from their individual institutions. Digitized whole-slide images were organized and reviewed using PathPresenter, including H&E and immunohistochemistry (IHC) for Ki67, neuroendocrine markers (synaptophysin, chromogranin, INSM1, CD56), pRb, and p53. Detailed clinicopathologic characteristics and clinical outcome data were analyzed. Areas of highest (hot-spot) and lowest (cold-spot) Ki67 proliferation index were assessed by digital image analysis with >500 cells counted in triplicate. Available results of next-generation sequencing (NGS) were reviewed.

Results: A total of 27 cases from 9 institutions in 7 countries were collected that met the criteria of tumors with morphology of carcinoids/NETs (confirmed by central review) and mitoses of >10 per 2 mm2. Patients were 52% female with a mean age of 63, and 40% were never/light (<10 pack-year) smokers. All tumors were strongly and diffusely positive for all neuroendocrine markers. Mitotic counts ranged from 11 to 30 (mean 15 per 2 mm2). In most cases, mitotic counts remained below 20, with only 3 cases exceeding 20 per 2 mm2. Ki67 hot-spot index ranged from 16% to 56% (mean 34%), with 4 cases exceeding 50%. However, in all cases, Ki67 was heterogenous, containing low-proliferative cold-spots where Ki67 index was only <1%-10%. In all evaluable cases (n=25), pRb and p53 showed retained expression or focal labeling, respectively, supporting a wild-type pattern. Cases with NGS (n=6) lacked RB1 and TP53 alterations, and contained MEN1 (n=1) and ATM (n=1) mutations, which are common in carcinoid tumors. For patients with available follow-up (n=21), 62% had post-operative recurrence/metastasis within a median follow-up of 2.7 yrs (range 0.3 -10 yrs).

Conclusions: In this multi-institutional international study, we collected the largest cohort to-date of rare resected pulmonary tumors with carcinoid/NET morphology but proliferation rates exceeding current WHO criteria. We highlight here that while elevated, mitotic and Ki67 rates are generally lower and more heterogenous than typically seen in LCNEC or small cell lung carcinoma (SCLC), and these tumors lack TP53+/-RB1 alterations seen in most SCLC/LCNEC. We propose that such tumors should be classified as highly proliferative, grade 3 (G3) carcinoids/NETs, analogous to G3 NETs recognized in enteropancreatic organs, and that they should be removed from their current grouping as LCNEC to enable clinical management that is more accurately tailored to tumor biology.

Keywords: carcinoid, NET, neuroendocrine

OA14 CANCER EVOLUTION AND DRUG RESISTANCE
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 13:00

OA14.01 Glutamine Metabolic Reprogramming Drives Evolution of Lung Adenocarcinoma

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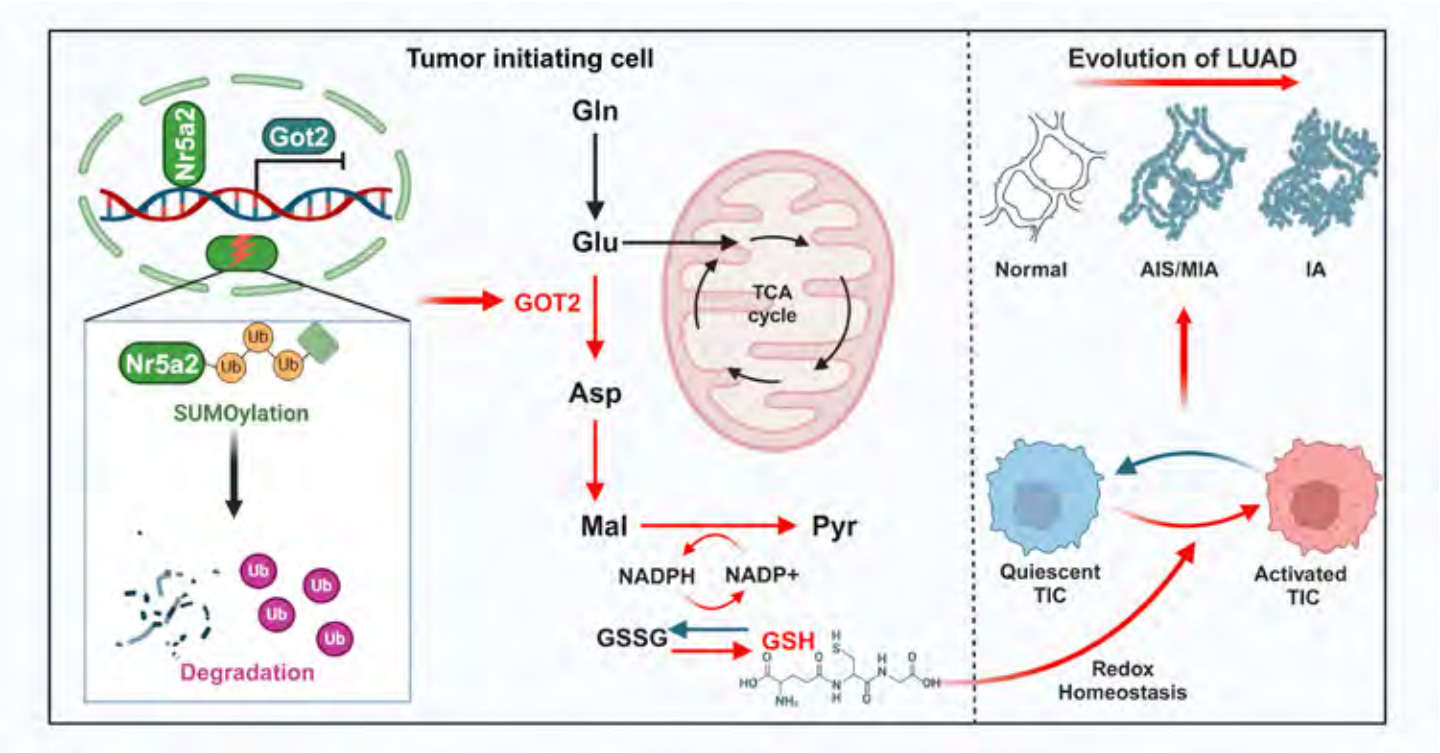
Introduction: Lung adenocarcinoma represents the predominant pathological subtype of lung cancer, progressing from precursor non-invasive lesions to invasive adenocarcinoma (IA). Glutamine (Gln) metabolism reprogramming stands as a significant biological hallmark in lung cancer, yet its exact contribution to LUAD progression remains unclear.

Methods: We performed spatial metabolomics on lung tissue obtained from patients with lung adenocarcinoma (n = 76). We validated these data using immunofluorescence on lung tissue from 24 additional subjects. Organoid, western blotting, quantitative PCR, invasion and migration analysis were applied to assess differentiation, invasion, and migration in vitro and in vivo.

Results: Preliminary spatial metabolomics analysis revealed enhanced Gln extramitochondrial metabolism in the invasive focus of IA. Further studies identified tumor-initiating cells (TICs) as effectors of Gln metabolism, with high expression of glutamic-oxaloacetic transaminase 2 (Got2) promoting extramitochondrial Gln metabolism and glutathione generation, regulating the redox homeostasis within TICs and promoting their invasive differentiation. Mechanically, small ubiquitin-like modifier (SUMO) modification of Nr5a2 promotes Got2 transcription, enhancing extramitochondrial Gln metabolism within TICs, regulating intracellular redox homeostasis, activating invasive differentiation of TICs, and driving the invasive progression of lung adenocarcinoma.

Conclusions: Our study depicts the metabolic landscape of lung adenocarcinoma progression using multi-omics data and elucidates the metabolic mechanisms driving the progression of lung adenocarcinoma in vitro and in vivo, providing new therapeutic targets for this malignancy.



Keywords: lung adenocarcinoma, Glutamine metabolic reprogramming, evolution

OA14 CANCER EVOLUTION AND DRUG RESISTANCE
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 13:00

OA14.02 DCBLD2high Tumor-Derived Retinoic Acid Orchestrates Macrophages to Drive Vascular Immunosuppression and Immunotherapy Resistance

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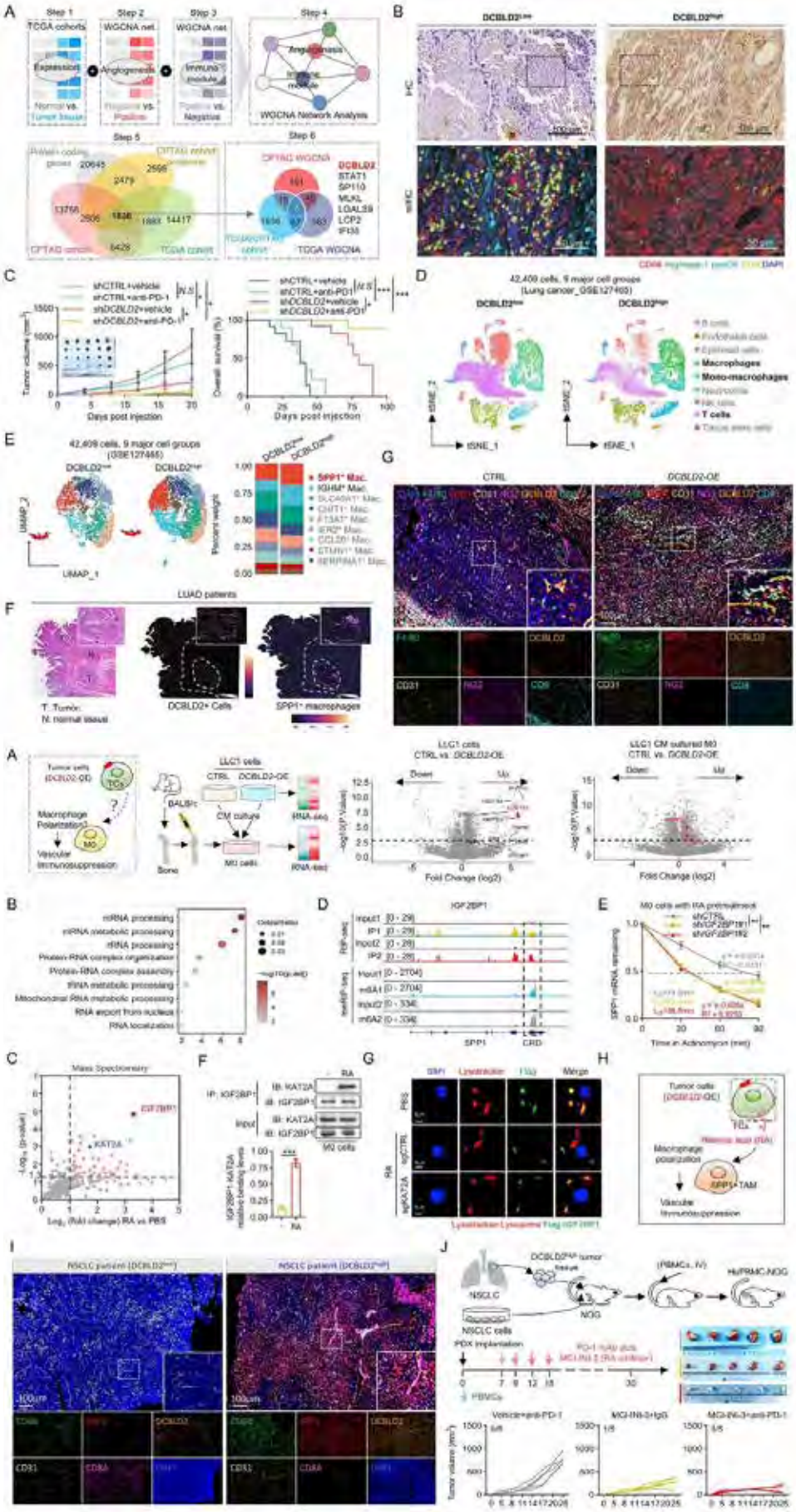
Introduction: Immunotherapy resistance represents a critical challenge in the management of lung cancer. While tumor angiogenesis is increasingly recognized as a driver of immunosuppression in the tumor microenvironment (TME), the molecular mechanisms linking vascular remodeling to immune evasion remain elusive, and targeted therapeutic strategies to disrupt this crosstalk have yet to be clinically implemented.

Methods: To identify master bipotent regulators of angiogenesis and immunosuppression in lung cancer, we performed WGCNA network analysis on CPTAC and TCGA transcriptomic data. Top candidates were validated through multi-omics (Single-cell sequencing, spatial proteomics, and bulk RNA-seq) to define their roles in shaping the immunosuppressive TME. Furthermore, an immune system-tumor double humanized lung cancer patient-derived xenograft (PDX) models were established to recapitulates the human tumor-immune-vascular niche and evaluate the therapeutic potential of targeting this critical signaling axis.

Results: We identified DCBLD2 as a dual regulator of angiogenesis and immunosuppression in lung cancer via WGCNA analysis, with pronounced expression in tumor cells (TCs) and clinical specimens. Genetic ablation of Dcbld2 in TCs significantly attenuated angiogenesis and potentiated immunotherapy response in murine lung cancer xenograft models. Single-cell/spatial profiling revealed SPP1high-TAMs preferentially surrounding DCBLD2+ tumors, induced by tumor-derived retinoic acid (RA). Specifically, RA stabilizes SPP1 mRNA in macrophages by triggering KAT2A-mediated acetylation of IGF2BP1, thereby blocking its proteasomal degradation. This post-translational modification reinforces IGF2BP1-dependent SPP1 transcript stabilization, fostering an immunosuppressive TME characterized by SPP1high-TAM accumulation and CD8+ T-cell exclusion. Therapeutically, pharmacological inhibition of RA signaling markedly reduced tumor progression and synergized with immune checkpoint blockade in both syngeneic murine models and humanized PDX systems, underscoring its translational potential as a combinatorial strategy to overcome immunotherapy resistance.

Conclusions: Targeting DCBLD2-RA signaling disrupts immunosuppressive vascular niches, providing a dual strategy to recondition the TME and restore immunotherapy efficacy in lung cancer.



Keywords: DCBLD2, Retinoic Acid, Immunotherapy Resistance

OA14 CANCER EVOLUTION AND DRUG RESISTANCE
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 13:00

OA14.03 Functional Characterization of Osimertinib-Induced Drug Tolerant Persisters in Lung Adenocarcinoma

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Introduction: Resistance to epidermal growth factor receptor (EGFR)-targeted therapy limits survival in lung adenocarcinoma (LUAD) patients with activating EGFR mutations (EGFRmut). Resistance can stem from drug-tolerant persister cells (DTPs), a rare, slow-growing population of cells that survives tyrosine kinase inhibitor (TKI) treatment, which contributes to minimal residual disease and eventual tumor recurrence. Understanding DTP survival mechanisms in EGFRmut LUAD may uncover therapeutic vulnerabilities that could be targeted to enhance TKI efficacy, but these mechanisms remain poorly characterized. Using EGFRmut LUAD patient-derived xenograft (PDX) models, our lab previously profiled gene expression changes in DTP tumors induced by the first-generation TKI, erlotinib, compared to treatment naïve controls (Moghal et al., J Thoracic Oncol, 2023; 18: 499-515). We identified several genes that were upregulated in DTPs and significantly enriched for pathways associated with NFkB and STAT3 signaling. We hypothesize that inhibiting these signaling pathways in combination with the third-generation TKI, osimertinib (Osi), will abrogate DTP formation and circumvent resistance to Osi in EGFRmut LUAD. This project sought to determine whether inhibiting NFkB and STAT3 signaling via genetic perturbation of the RELA and STAT3 genes increases sensitivity to Osi in LUAD models.

Methods: CRISPR-mediated gene editing was used to engineer the EGFRmut LUAD cell lines PC9 and HCC4006 (both EGFR exon 19 deletion) with RELA and STAT3 LOF. Lentiviral plasmids containing single-guide RNA (sgRNAs) targeting RELA and STAT3, or AAVS1 as a negative control, were transduced into Cas9+ cells. Loss of protein expression was validated in clonally derived lines using immunoblotting. Cell lines were treated with 2 μM Osi for 3 days (d) to assess the effects of gene LOF on apoptosis measured by flow cytometry. The capacity for cells with RELA and STAT3 LOF to form DTPs was evaluated using clonogenic survival assays. Cells were treated for 12d with 2 μM Osi and surviving, drug-tolerant colonies were stained with sulforhodamine B and counted.

Results: To date, we confirmed that RELA was transcriptionally upregulated in PC9 and HCC4006 cells following short- and long-term Osi treatment. However, STAT3 mRNA was downregulated. RELA and STAT3 LOF potentiated apoptosis induced by acute Osi treatment, suggesting that STAT3- and RELA-driven mechanisms mediate response to Osi. Additionally, RELA and STAT3 LOF reduced the clonogenic survival of Osi-treated cells compared to control cells, further implicating these genes in regulating DTP survival.

Conclusions: Upregulation of RELA in PC9 and HCC4006 DTPs further implicates NFkB signaling as a potential DTP survival mechanism. This suggests that activation of NFkB is a generalizable mechanism enabling drug tolerance across cell line and PDX models of EGFRmut LUAD. The increased apoptotic response and reduced clonogenic potential observed upon combining Osi with STAT3 and RELA LOF highlight their promise as targets for abrogating DTP survival. These findings could inform novel interventions for preventing tumor relapse following osimertinib therapy in EGFRmut LUAD patients.

Keywords: Drug Tolerance, Osimertinib, Lung Adenocarcinoma

OA14 CANCER EVOLUTION AND DRUG RESISTANCE
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 13:00

OA14.04 Genetic Inactivation of the Epigenetic Regulator ATF7IP: Functional Impact in Lung Adenocarcinomas

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Introduction: The genetic characterization of lung cancer (LC) has been of paramount importance to improve its diagnosis and treatment. Identification of oncogenes that are involved in LC development has allowed for the development of novel and effective therapeutic strategies, such as tyrosine kinase inhibitors. However, to this date, no therapeutic strategies are available based on the presence of inactivating mutations at tumor suppressor genes (TSGs). An earlier report from our group found epigenetic regulator ATF7IP to show a strong bias towards inactivating mutations in lung adenocarcinoma (LuAD) cohorts, making it a strong TSG candidate. ATF7IP's best known function is to promote the nuclear activity of epigenetic silencer SETDB1, which catalyzes the deposition of H3K9me3, an epigenetic mark that leads to gene silencing. Because ATF7IP's role in LuAD development remains unexplored, we aim to understand its loss' contribution to oncogenesis.

Methods: We selected a panel of ATF7IP-deficient LuAD cell lines and restored wild-type ATF7IP in them in a doxycycline-inducible manner. We measured global changes in ATF7IP, SETDB1 and H3K9me3 levels upon doxycycline induction using Western Blot, and immunofluorescence was used to evaluate ATF7IP's impact on SETDB1's subcellular localization. In order to study ATF7IP's impact in tumor growth, tumor spheroids were established using low-adherence 96-well plates. To understand ATF7IP's impact on transcription, we performed bulk mRNA-seq from induced and control cells. We also performed ChIP-seq of both SETDB1 and H3K9me3 to evaluate how ATF7IP affects SETDB1's binding to chromatin, as well as to assess its function.

Results: We show that restoring wild-type ATF7IP expression leads to an accumulation at the protein level- but not at the mRNA level- of SETDB1, concomitant with a global increase in global H3K9me3. We observe that ATF7IP-deficient LC cells show a mostly cytosolic location of SETDB1, which becomes intranuclear upon ATF7IP recovery, consistent with previous reports. Upon overexpression of wild-type ATF7IP, tumor spheroid growth was impaired in ATF7IP-deficient cells, unlike control cells. Re-expression of ATF7IP in deficient cells results in global transcriptional repression. Genes related to meiosis, extracellular matrix remodeling and neuronal development experience a strong downregulation. Notably, transcripts derived from endogenous retroviruses (ERVs), such as DHRS2, are also particularly repressed. ChIP-seq revealed that ATF7IP promotes SETDB1's binding to chromatin and the deposition of H3K9me3 in regions surrounding SETDB1 peaks. Downregulated genes are significantly close to SETDB1 peaks. Of note, SETDB1 binds to the 3' end of zinc finger proteins (ZFPs) found in clusters scattered throughout the genome, as well as to other clustered families of genes.

Conclusions: Our work offers evidence of ATF7IP's role as a TSG, and explores the consequences at the molecular and cellular levels of the loss of ATF7IP in LuAD cells. We provide an insight into the pathways that become deregulated in ATF7IP-deficient tumors and the epigenetic mechanisms that mediate these changes. This knowledge informs us of upstream and downstream pathways that ATF7IP-deficient cells may grow dependent on, and that we may potentially target pharmacologically, allowing us to selectively attack tumor cells.

Keywords: Cancer Genetics, Cancer Epigenetics, Molecular Biology

OA14 CANCER EVOLUTION AND DRUG RESISTANCE
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 13:00

OA14.05 Panorama of Chromosomal Instability in 1209 Lung Cancer Genomes

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Introduction: Lung cancer is the leading cause of cancer death worldwide in both men and women. It is a highly heterogeneous disease primarily driven by tobacco smoking. About 20% of lung cancers occur among never smokers. There are major differences between lung cancers in patients who have never smoked (LCINS) and who have smoked in patient ancestry, sex, tumor histology, and clinical features. For example, LCINS occur more frequently in Asians and females and are predominantly adenocarcinomas. EGFR mutations are enriched in LCINS, whereas KRAS and TP53 mutations are more common in tumors from smokers. Our understanding of the etiology of lung cancer in patients who have never smoked is still limited.

Methods: Here, we perform a comprehensive study in 1,209 whole-genome sequenced (WGS) lung cancers collected from 30 different locations across four continents through Sherlock-Lung Project from the National Cancer Institute (NCI) as well as published studies. Among these tumors, 1024 of them are adenocarcinomas and 864 are from patients who have never smoked. Two-thirds (811) of the patients are of European ancestry whereas one-third (359) are of East Asian ancestry. A small fraction of patients (39) had South American and African ancestries. This cohort represents the largest genomics cohort in lung cancer to date. In addition to WGS, other omics data are generated on Sherlock-Lung samples, including RNA-Seq and methylation arrays. Our study focuses on chromosomal instability which is of clinical importance in lung cancer because gene fusions caused by somatic structural variations (SVs), large-scale chromosomal rearrangements, are major oncogenic drivers of lung cancer. Somatic SVs are detected in tumor samples by comparing tumor genomes against germline genomes from blood or adjacent normal tissues from the same patients. We perform comprehensive analysis of somatic SVs in this diverse cohort to better understand the genomic landscape of lung cancer.

Results: In total, we detect 182,429 somatic SVs in 1209 tumor samples with an average of 151 SVs per sample. Complex SVs, such as chromothripsis and chromoplexy, are studied separately from simple SVs which are composed of deletions, tandem duplications, inversions and translocations. This is because complex SVs arise through one-time catastrophic events and are distinct from simple SVs which occur one by one and accumulate in the genome over time. In these catastrophic events, chromosomes are shattered into pieces, rejoin and form new chromosomes with many SVs formed. About two-thirds of the SVs in our cohort are part of complex events. We further derive SV-based mutational signatures, reflecting molecular mechanisms that can be mathematically decomposed. We deconvolute complex SV signatures based on SV breakpoint and copy number patterns and decompose simple SV signatures based on SV type and size using a non-negative matrix factorization approach. A total of 8 complex SV signatures and 8 simple SV signatures are discovered in our cohort which likely represent divergent molecular mechanisms. Among these, chromatin bridge signature, driven by dicentric chromosomes, is the most abundant complex SVs and median size deletion is the most common simple SVs. SVs are more abundant in tumors from patients who have smoked; however, they are more complex and play more important roles in tumorigenesis in tumors from patients who have never smoked. The SV breakpoints have distinct distributions across the genome depending on the signatures due to combined effects of mutagenesis and positive selection. Many established cancer-driving genes are recurrently rearranged by multiple SV signatures suggesting functional convergence of these genome instability mechanisms. We find that, in addition to smoking, EGFR mutations and KRAS mutations profoundly and independently shape the SV landscape. EGFR-mutant tumors have higher SV burden and more cancer-driving SVs. In contrast, KRAS mutations are associated with lower SV burden and less driver SVs. In a separate analysis using the same Sherlock-Lung samples and recently published in Nature (https://www.nature.com/articles/s41586-025-09219-0), we report that mutational signatures in tumors from patients who have never smoked are primarily driven by aging and other endogenous processes, and are positively associated with air pollution but not associated with secondhand smoking. Our study, in conjunction with multiple companion studies on this patient cohort, has deepened our understanding of genomic landscape and etiology of lung cancer.

Keywords: Never smokers, Genome instability, Structural variations

OA15 GLOBAL LUNG CANCER SCREENING STRATEGIES
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA15.01 Results of the Croatian National Lung Cancer Screening Program

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Introduction: Lung cancer is the leading cause of death from malignant diseases, both worldwide and in Croatia. With more than 3300 new diagnoses of lung cancer and more than 2800 lung cancer deaths in 2019, lung cancer remains one of the main public health problems in Croatia. Taking into consideration the aforementioned data, along with a high smoking prevalence among adults, high incidence to mortality ratio and large proportion of lung cancer in advance stages in Croatia, Ministry of health formed a multidisciplinary working group with the task of implementing a nation wide lung cancer screening program.

Methods: The Croatian National Lung Cancer Screening Program was implemented in Oct 2020 in accordance with published scientific data and recommendations from European Position Statement on Lung Cancer Screening, adopting modified I-ELCAP guidelines, using Low Dose CT scans (LDCT), artificial intelligence, volumetric analysis of lung nodules and is completely digitalized. This is the first national lung cancer screening program in the European Union and completely integrated into the existing healthcare system. The main difference when compared to other lung cancer screening programs is the placement of General Practitioners in the central role of enrolling the high-risk population. The results shown focus on cancer findings.

Results: From October 2020 - October 2024, 34 648 participants were screened, age range 50-75, persons who smoke or had quit smoking during the last 15 years, with at least 30 pack years smoking history. There were 45 341 LDCT scans performed, 34 648 baseline scans and 10 693 follow up scans; 54% male vs 46% female with an median age of 62. Among these 34 648 participants there were 2 027 (5.8%) who required referral to one of six Lung Nodule Clinics that were established as a part of the screening program, for further investigation. There were 669 cancers found; 615 lung cancer (92%) and 54 other sites (8%). Out of 615 lung cancers, 46.5% were diagnosed in early stage and had a surgical resection; 35.8% stage 1 and 10.7% stage 2; the remaining cases included 21.5% stage 3 and 29.5% stage 4 (staging for 2.5% in this moment is unknown). Additionally, within the cohort, there were 14 hamartomas found and 22 nonmalignant resections (TBC, granuloma ect.)

Conclusions: These initial results on a national level show an evident stage shift in lung cancer diagnosis, with an increase in early stage (stage 1 and 2). It is expected that the proportion of early stages will be higher as the program continues to run, which leads to improved survival rate and treatment outcomes. The final goal of the program is to decrease the mortality of lung cancer by 20% after 10 years of its implementation and to improved cure rate of lung cancer.

Keywords: Lung Cancer Screening, Early Detection, Stage Shift

OA15 GLOBAL LUNG CANCER SCREENING STRATEGIES
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA15.02 Preliminary Results of the Singapore Lung Cancer Screening Through Integrating CT With Other Biomarkers (SOLSTICE) Study

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Introduction: Lung cancer (LC) is one of the leading causes of cancer-related mortality in Singapore with approximately 60% of patients diagnosed with advanced, incurable disease. LC screening may potentially increase early detection and reduce mortality. While smoking is traditionally the key risk factor for LC development, family history is increasingly recognized as an association particularly amongst never smokers. With recommendations for screening by low-dose CT thorax (LDCT) limited to smokers in many countries including Singapore, we sought to conduct the ongoing SOLSTICE study (NCT05724264) to evaluate the feasibility of a LC screening programme in both smokers and at-risk non-smokers.

Methods: This single arm prospective screening trial is the first LC screening study in Singapore. Both smokers (S) and non-smokers (NS) with known family history of LC up to 2nd degree are eligible, and age range for inclusion is 50-80 years. All participants undergo a baseline LDCT reported based on Lung-RADS v1.1 (LR), which guides downstream management including interval of surveillance or intervention. A negative result (LR 1/2) is followed by 2 annual LDCT for S and 1 biennial LDCT for NS. All incidental findings are managed with multidisciplinary input via standardized pathways.

Results: 420 participants (62 S, 358 NS) underwent a baseline LDCT between 17 Feb 2023 and 12 Feb 2025. Their median age was 61 years (range, 50-78 years). 305 (85.2%) of NS had a 1st degree relative with lung cancer. At baseline, 5 were LR0 (1.2%), 165 (39.3%) were LR1, 236 (56.2%) were LR2, 7 (1.7%) were LR3, and 7 (1.7%) were LR4. 1 LR4 lesion was histologically proven as organizing pneumonia on biopsy. There were 8 diagnosed cancers for a LC detection rate of 1.9%, all of which were stage 1A lung adenocarcinomas (LUAD) in NS that underwent surgical resection. 7/8 (87.5%) had a 1st degree family history and 4/8 (50%) were female. 5/8 LC (62.5%) were LR2 on baseline LDCT, while the other 3/8 consisted of 1 LR3 (12.5%) and 2 LR4 (25%). Of the 6 LUAD with genomic profiling, 5 (83.3%) had EGFR mutation and 1 (16.7%) had ERBB2 mutation.

330 incidental findings were picked up in 232/420 (55.2%) participants, with 15/330 (4.5%) deemed potentially significant. Cardiac incidentals were most common (130, 39.4%), followed by liver (69, 20.9%) then thyroid (33, 10%). All 130 participants with incidental cardiac abnormalities had coronary calcifications, of which 1 required cardiac revascularization for ischemic heart disease. There was also 1 participant with an incidental diagnosis of Type AB thymoma, Modified Masaoka Stage IIB, who underwent surgical resection.

Conclusions: Preliminary results from SOLSTICE have demonstrated a LC detection rate of 1.9%, comparable to the Taiwanese TALENT study in NS, and NLST/ NELSON in S. Geographical diversity of LC molecular subtypes, as well as a preponderance for ground glass opacity-associated LC, will warrant a relook at the eligibility criteria for LC screening and the adoption of LR for management of screen-detected nodules in Asia. Standardized reporting of incidentals is also crucial for stratification and rationalization of downstream subspecialty referrals.

Keywords: Lung Cancer, Screening, Low-dose CT

OA15 GLOBAL LUNG CANCER SCREENING STRATEGIES
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA15.03 Female Asian Nonsmoker Screening Study (FANSS): A U.S. Based Lung Cancer Screening Program in a Non-Smoking Population

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This abstract is under embargo until September 9 at 10:15 CET.

OA16 BUILDING BRIDGES BETWEEN RESECTABLE AND UNRESECTABLE STAGE III NSCLC
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA16.02 RAPID-RT: Using Rapid-Learning to Assess the Survival Impact of Limiting Dose to a New Cardiac Avoidance Area During Lung Cancer Radiotherapy

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Introduction: Evaluating radiotherapy changes in conventional trials is challenging due to a lack of equipoise, selection bias, and resource limitations. High-quality prospective real-world data and rapid-learning approaches offer a more inclusive, practical solution. Emerging evidence suggests that limiting radiation dose to a new Cardiac Avoidance Area (CAA)—comprising the right atrium, proximal coronary arteries, and aortic valve—may improve survival in lung cancer patients receiving curative-intent radiotherapy (doi:10.1016/j.jtocrr.2024.100742). The RAPID-RT study (ISRCTN17129364) is the first prospective study using rapid-learning and opt-out consent to evaluate the impact of CAA dose limitation on survival.

Methods: In April 2023 our institution became the first to implement CAA-based planning for all patients receiving non-SABR, curative radiotherapy for stage I-III lung cancer. Dmax to 1cc of the CAA is limited to 19.5Gy for 20 fractions (or equivalent) unless conflicting with target coverage. Patients treated with the CAA dose limit (cohort 2) are prospectively enrolled via an informed opt-out consent process and compared to those treated prior to its introduction (cohort 1). Routine clinical data is collected from the electronic patient record, including demographic, tumour, treatment, and survival data. Missing data will be addressed via Multiple Imputation. The primary endpoints are overall survival and survival at one year. Survival was modelled using a Bayesian parametric Weibull distribution adjusting for prognostic factors and using uninformative priors.

Results: Between 1/2021 - 2/2025, 922 and 786 patients were included in cohorts 1 and 2 (average missingness 6.7%). Cohorts were well balanced (figure1), except for volumetric arc therapy use increasing from 93.2% in cohort 2 vs 31.6% of cohort 1. The proportion of patients not achieving the CAA constraint reduced from 56.8% to 29.7%, with little impact on other organs-at-risk dose-volume histograms. Early results show that the rapid-learning method is highly inclusive as all patients received the new technique, with only 1 out of 786 patients choosing to opt out in cohort 2. Initial findings suggest a survival benefit in cohort 2 with a population average 12-month survival probability of 0.738 (0.673, 0.802) in cohort 2 compared to 0.682 (0.642, 0.744) in cohort 1. Updated data will be presented at WCLC 2025.

Conclusions: We demonstrate, for the first time, that rapid-learning using real-world data can quickly evaluate a change in radiotherapy practice. Initial results suggest improved survival with CAA dose limitation in a representative lung cancer population. Ongoing analyses will assess the impact on longer-term survival, toxicities, and explore alternative modelling approaches.

		Cohort 1 N=922 n (%)		Cohort 2 N=732 n (%)	
Sex	Female	483	(52.3)	382	(52.2)
	Male	439	(47.7)	350	(47.8)
Age at first treatment median (IQR) (years)		72.7 (65.5, 78.5)		72.9 (67.3, 79.6)	
IMD*	1 (Least deprived)	100	(10.9)	74	(10.1)
	2	111	(12.0)	107	(14.6)
	3	108	(11.7)	101	(13.8)
	4	208	(22.6)	149	(20.4)
	5 (Most deprived)	393	(42.6)	299	(40.9)
	Not recorded	2	(0.2)	2	(0.3)
Diagnosis	SCLC	112	(12.2)	94	(12.8)
	NSCLC	784	(85.0)	682	(86.8)
	Not recorded	26	(2.8)	10	(1.3)
Clinical stage (overall)					
	1	216	(23.4)	205	(26.1)
	2	169	(18.3)	140	(17.8)
	3	429	(46.5)	367	(46.7)
	Not recorded	108	(11.7)	74	(9.4)
Fractions	15	86	(9.3)	65	(8.8)
	20	678	(73.5)	549	(75.0)
	25	6	(0.7)	1	(0.1)
	30	116	(12.6)	113	(15.4)
	33	35	(3.8)	4	(0.6)
Chemotherapy treatment					
	Sequential	151	(16.4)	108	(14.8)
	Concurrent	156	(16.9)	114	(15.6)
	Radio. alone*	615	(66.7)	510	(69.7)
Performance status	ECOG 0	92	(10.0)	76	(10.4)
	ECOG 1	375	(40.7)	315	(43.0)
	ECOG 2	270	(29.3)	257	(35.1)
	ECOG 3	71	(7.7)	63	(8.6)
	ECOG 4	1	(0.1)	0	(0.0)
	Not recorded	113	(12.3)	21	(2.9)
Overall ACE comorbidity score	0	94	(10.2)	69	(9.4)
	1	247	(26.8)	239	(32.7)
	2	230	(25.0)	216	(29.5)
	3	188	(20.4)	160	(21.9)
	Not recorded	163	(17.7)	48	(6.6)

Figure 1 – Summary of key cohort demographic, tumour and treatment factors.

Keywords: Rapid-learning, cardiac toxicity, real-word data

OA16 BUILDING BRIDGES BETWEEN RESECTABLE AND UNRESECTABLE STAGE III NSCLC
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA16.03 Sequencing of Radiotherapy and Immunotherapy Stratifies Pneumonitis Risk: A Propensity-Matched Multicenter Study

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Introduction: The combination of immune checkpoint inhibitors (ICIs) with radiotherapy (RT) improves survival in advanced lung cancer. Evidence for the impact of sequencing radiotherapy and immunotherapy on treatment-related penumonitis (TRP) risk stratification is limited.

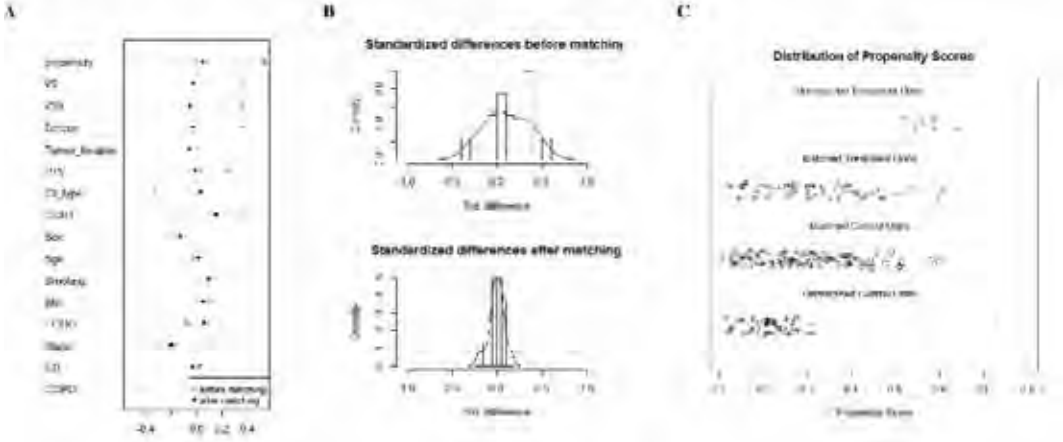
Methods: In a multicenter retrospective cohort of 1376 lung cancer patients from 2021 to 2023, 262 receiving thoracic radiotherapy combined with ICIs selected after rigorous screening. Patients were categorized into two groups based on treatment sequence(immunotherapy followed by sequential radiotherapy/ICIs+RT vs radiotherapy followed by sequential immunotherapy/RT+ICIs). A balanced cohort was constructed using 1:2 propensity score matching (PSM) with covariates including V5, V20, Dmean, and ICI type. Univariate and multivariate logistic regression models analyzed interaction between treatment sequence and treatment-related parameters, and helped select variables to establish a nomogram for TRP.

Results: Prior to matching, the ICIs+RT group (n=187) exhibited a significantly higher incidence of TRP than the RT+ICIs group (61.0% vs. 49.3%, n=75). Baseline imbalances were observed in dosimetric parameters (PTV, V5, V20, Dmean), ICIs type/cycles, and CCRT utilization (all P<0.05). Following 1:2 PSM, covariates between the ICIs+RT (n=126) and RT+ICIs cohorts (n=67) were balanced (P>0.05). Multivariate analysis identified treatment sequence as an independent predictor of TRP risk, with adjusted odds ratios (ORs) of 0.434 (95% CI: 0.217-0.868; P=0.018) for grade ≥1 TRP and 0.433 (95% CI: 0.213-0.880; P=0.021) for grade ≥2 TRP, suggesting improved safety with RT-ICIs sequencing. Additionally, ICIs cycles and Dmean were integrated with treatment order to develop a nomogram for grade ≥2 TRP prediction. The model demonstrated robust performance, supported by an AUC of 0.726 (95% CI: 0.654-0.789), well-fitted calibration curves, and favorable clinical utility on decision curve analysis.

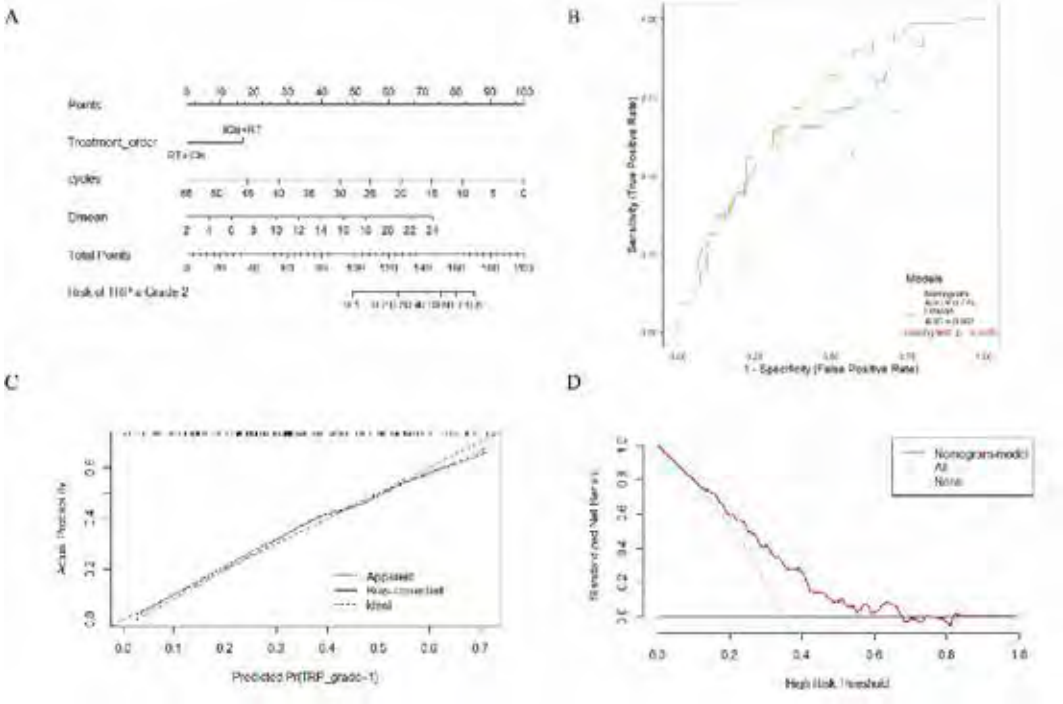
Conclusions: This study applies propensity score matching-adjusted analysis to reveal graded impacts of treatment sequence on TRP severity, providing pivotal evidence to optimize combined therapy safety and personalize treatment strategies in lung cancer.

Treatment characteristics before and after PSM

	Primary cohort			PSM cohort		
	RT+ICIs (n=15)	ICIs +RT (n=187)	p value	RT+ICIs (n=67)	ICIs +RT (n=126)	p value
Median radiation EQD2, Gy	60.0 (60.4/3.3)	60.0 (59.3/3.8)	0.730	60.0(60.7/3.2)	60.00 (59.2/4.0)	0.654
Median dose fraction, Gy (IQR)	2.0 (2.0-2.2)	2.0 (2.0-2.1)	0.869	2.0 (2.0-2.2)	2.0(2.0-2.1)	0.105
GTV, median ,mm³ (IQR)	137.4 (80.9-221.8)	125.8 (79.7-228.5)	0.161	126.5 (72.1-200.1)	127.4 (83.4-240.1)	0.710
PTV, median ,mm³ (IQR)	260.1 (175.3-325.1)	221.6 (137.0-363.4)	0.016	251.2 (157.4-336.8)	230.0 (148.3-371.4)	0.944
V5, median ,%(IQR)	47.2 (33.4-58.3)	40.0 (27.5-57.7)	0.016	44.8 (30.8-56.4)	42.9 (29.2-54.0)	0.644
V20, median ,%(IQR)	19.0 (14.70-24.9)	16.5 (12.5-22.4)	0.009	18.0 (13.9-23.0)	16.3 (13.6-22.9)	0.408
Dmean, median,Gy(IQR)	11.3 (8.75-13.9)	9.8 (7.8-13.2)	0.014	10.8 (8.5-13.5)	10.1 (8.2-13.8)	0.625
Tumor location (n,%)			0.607			0.619
upper lobe	33 (57.3%)	90 (48.1%)		40 (59.7%)	66 (52.4%)	
lower lobe	21 (32.0%)	68 (36.4%)		21 (31.3%)	46 (36.5%)	
Central	8 (10.7%)	29 (15.5%)		6 (9.0%)	14 (11.1%)	
Radiotherapy technology (n,%)			0.747			0.771
IMRT	58 (77.3%)	154 (89.7%)		51 (76.1%)	97 (77.0%)	
VMAT	16 (21.3%)	31 (16.6%)		15 (22.4%)	25 (19.8%)	
TOMO	1 (1.3%)	5 (2.7%)		1 (1.5%)	4 (3.2%)	
ICI type (n,%)			0.668			0.534
PD-1 inhibitor	51 (68.0%)	155 (82.9%)		50 (74.6%)	99 (78.6%)	
PD-L1 inhibitor	24 (32.0%)	32 (17.1%)		17 (25.4%)	27 (21.4%)	
Cycles of ICIs before TRP (n,%)			0.031			0.193
1-3	29 (38.7%)	41 (21.9%)		25 (37.3%)	32 (25.4%)	
4-6	18 (24.0%)	53 (28.4%)		17 (25.4%)	33 (26.2%)	
>6	28 (37.3%)	93 (49.7%)		25 (37.3%)	61 (48.4%)	
CCRT			0.015			0.204
Yes	47 (62.7%)	86 (46.0%)		42 (62.7%)	67 (53.2%)	
No	28 (37.3%)	101 (54.0%)		25 (37.3%)	59 (46.8%)	



PSM Efficiency and Score Distribution



Keywords: Treatment sequence, Propensity score matching, Treatment-related pneumonitis

OA16 BUILDING BRIDGES BETWEEN RESECTABLE AND UNRESECTABLE STAGE III NSCLC
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

OA16.04 Prognostic Value of Residual Viable Tumor in Lymph Nodes of Non-Small Cell Lung Cancer After Neoadjuvant Chemoimmunotherapy

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Introduction: Current major pathologic response (MPR) criteria for neoadjuvant chemoimmunotherapy in non-small cell lung cancer (NSCLC) primarily focus on primary tumor (PT) response, with lymph node response inconsistently incorporated. The prognostic significance of pathologic regression in metastatic lymph nodes (mLNs) remains unclear. This study aimed to assess its impact on recurrence-free survival (RFS) and establish an effective prognostic stratification system.

Methods: We identified 87 patients with resectable NSCLC and pathologically confirmed mLNs who underwent neoadjuvant chemoimmunotherapy and surgery between 2021 and 2024. The percentage of residual viable tumor (%RVT) in mLNs was quantified (range 0-100%) based on pan-tumor immune-related pathologic response criteria. The mean %RVT in mLNs and positive lymph node ratio (LNR) of each patient were calculated, and their optimal cutoffs for RFS were determined using maximally selected rank statistics. Kaplan-Meier analysis and Cox regression was performed to evaluate prognostic significance.

Results: The median follow-up time was 12.8 months (95%CI: 10.1-16.8), during which 25 recurrences were observed. The median %RVT in mLNs was 24% (IQR 0-60%). A %RVT cutoff of 20% in mLNs was significantly associated with RFS (HR = 0.27, 95%CI: 0.11-0.68, p = 0.003). Multivariable Cox regression confirmed %RVT > 20% as an independent risk factor for RFS (HR = 3.18, 95%CI: 1.20-8.38, p = 0.020). Using optimal cutoffs for LNR and %RVT (both at 20%), we developed a lymph node tumor burden (LNTB) score: score 1 for %RVT≤20%, score 2 for %RVT>20% and LNR ≤20%, and score 3 for %RVT>20% and LNR>20%. A novel prognostic stratification model integrating LNTB score and PT-MPR status effectively distinguished patients into three risk groups: low (PT-MPR+LNTB 1), intermediate (PT-non-MPR+ LNTB 1& PT-MPR/non-MPR+LNTB 2), and high (PT-MPR/non-MPR+LNTB 3). RFS differed significantly across them (log-rank p < 0.001), with 2-year RFS rates of 91.6%, 59.0%, and 38.7%, respectively. The low-risk group demonstrated significantly improved RFS than intermediate-risk group (HR = 0.20, 95%CI: 0.05-0.91, p = 0.037), and the intermediate-risk group had better outcomes than high-risk group (HR = 0.40, 95%CI: 0.18-0.92, p = 0.030). The combined model demonstrated superior predictive accuracy, with an AUC of 0.78 (95%CI: 0.65-0.90), outperforming other models including ypTNM staging.

Conclusions: The pathologic response in lymph nodes independently predicts recurrence risk in NSCLC patients following neoadjuvant chemoimmunotherapy. Compared to conventional ypTNM staging, the novel stratification system-integrating lymph node tumor burden and primary tumor response-provides more accurate prognostic information and may offer valuable guidance for postoperative management.

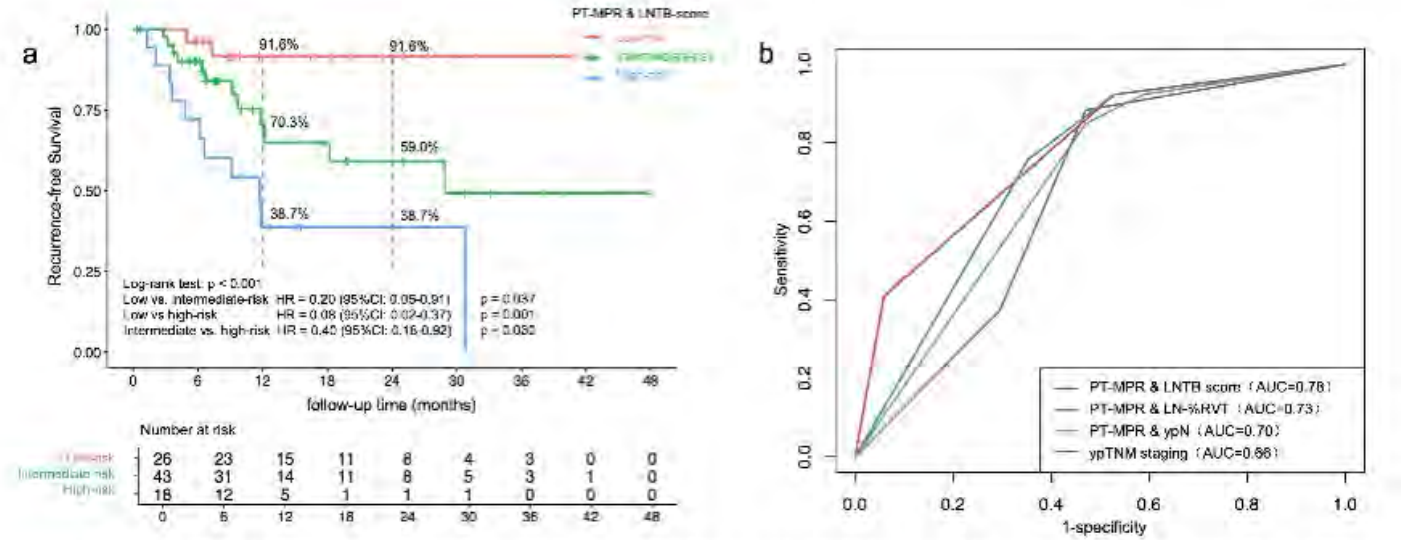

Figure 1. (a) Kaplan-Meier curves comparing recurrence-free survival for three risk groups based on the model and (b) ROC curve for 2-year RFS

Keywords: metastatic lymph nodes, neoadjuvant chemoimmunotherapy, residual viable tumor

OA17 BALANCING COST, CARE AND PATIENT CHOICE IN REAL WORLD JOURNEY AND RESEARCH
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA17.01 Stigma and Psychological Distress in Patients with Lung Cancer: A Possible Role of EMDR (Eye Movement Desensitization and Reprocessing) Therapy

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Introduction: Psychological distress is common in patients with lung cancer, and has a severe negative impact on quality of life. Anxiety and depression are the most frequently reported symptoms . In some cases cancer may cause stigma , often linked to the belief that the patient's behavior (e. g . smoking) caused the disease , and may represent a traumatic event leading to Post Traumatic Stress Disorder (PTSD). Eye Movement Desensitization and Reprocessing (EMDR) therapy is an evidence-based treatment for PTSD, and has shown promising results in reducing anxiety and depression.

Methods: The primary aim of this study was to assess distress levels and the presence of health-related stigma in patients with lung cancer. A secondary aim was to evaluate emotional distress before and after EMDR therapy.

Participants completed questionnaires collecting data on age, sex, education, PTSD symptoms by IES-R (Impact Event Symptoms -Revised), HADS (Hospital Anxiety and Depression Scale) and health-related stigma by CLCSS (Cataldo Lung Cancer Stigma Scale).

Results: From March 2024 to March 2025, 19 participants with lung cancer were enrolled. Mean age was 63 years (SD = 8.3, range = 36-74), 53% were female, and 54% were current or former smokers.

The mean IES-R score was 47.8 (SD ± 23.2). While 74% scored below the PTSD threshold (<21), 26% met criteria for mild PTSD (>21). 63% (N=12) were above the HADS global distress cut-off (≥16). 68.4% (N=13) exceeded the HADS-Anxiety cut-off (≥8), and 52.6% (N=10) exceeded the HADS-Depression cut-off.

Higher stigma levels were significantly associated with more depression ($r = .49$; $p < .05$), PTSD intrusion symptoms ($r = .48$; $p < .05$), and hyperarousal ($r = .47$; $p < .05$). No significant differences were found between persons who currently smoke or who don't smoke .

Pre- and post-EMDR assessments showed significant reductions in PTSD symptoms (IES-R, all scales $p < .05$), anxiety, and depression (HADS, $p < .05$).

Conclusions: Stigma can worsen psychological well-being in patients with lung cancer . Routine assessment of stigma may help identify those at higher risk of distress. Trauma-focused treatments like EMDR may represent a valuable addition in the oncological care setting.

Keywords: stigma, lung cancer, EMDR

OA17 BALANCING COST, CARE AND PATIENT CHOICE IN REAL WORLD JOURNEY AND RESEARCH
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA17.02 Knowledge and Shared Decision Making - a European Experience

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This abstract is under embargo until September 9 at 10:15 CET.

OA17 BALANCING COST, CARE AND PATIENT CHOICE IN REAL WORLD JOURNEY AND RESEARCH
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA17.03 The Patient Voice on Required Research Biopsies: Results of a Survey Study Exploring the Perspective of Patients With Lung Cancer

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Introduction: In the last 20 years, biopsies in patients with lung cancer have led to major discoveries and advances. However, mandatory, research-only biopsies in clinical trials are a controversial and timely topic given the recent FDA's draft guidance. Access to new and innovative therapies through clinical trials can be contingent upon a patient's willingness to undergo CT-guided or bronchoscopic biopsies, which carry risk of pneumothorax and hospitalization. For this reason, understanding the patient perspective is more important than ever. These are the first results from a patient-centered survey exploring the perspectives of patients with lung cancer on the role and impact of research biopsies.

Methods: This survey study was conducted from October 2024 to January 2025 following approval by the University of Chicago Institutional Review Board. The study was designed in collaboration with patient advocates with lung cancer and the University of Chicago Booth School of Business. Patients were recruited by LUNGevity and the Lung Cancer Research Foundation. A 40-item, self-administered online survey assessed demographics, stage, number of prior treatments, and academic versus non-academic treatment. Also assessed were prior biopsies, clinical trial participation, and six items evaluating willingness to consent to biopsies in clinical trials solely for research purposes. These six items were summed to provide a general acceptance of research-only biopsies. Results of a two-step hierarchical regression predicted the influence of treatment (Step 1) and demographic factors (Step 2) on acceptance of research-only biopsies. Statistical analysis was conducted using SPSS v29. All the analyses were blinded to the investigators and performed by an independent team.

Results: Of the 118 responses, participants were predominantly under 60 (51%), female (60%), non-Hispanic (83%), stage IV diagnosis (41%), and had received 1-2 prior treatments (62%). Over 75% of participants indicated a willingness to undergo research-only biopsies, and indicated it was definitely or probably OK to obtain those biopsies (Range1(definitely no)-5(definitely yes); M = 3.883, SD = 0.937). Participants were also open to asking patients to have a lung biopsy for research, even knowing that there is a chance of lung puncture (Range 1 (never ok)-5 (always ok); M = 4.551; SD = 0.843). Receiving treatment at an academic facility predicted a lower level of acceptance (β = -0.234, $p < .01$) and having received a higher number of prior treatments for lung cancer predicted higher acceptance of biopsies (β = 0.238, $p < .01$; adjusted $R2 = .089$, $p = .003$). Gender, age, education, and race predicted nearly 27% of the variance in acceptance (adjusted $R2 = .269$, $p < .001$) with higher acceptance reported by male (β = -0.241, $p < .001$) and younger (β = -0.293, $p < .001$) participants.

Conclusions: This is the first survey that explored patient's perspective in an independent way. Overall, patients with lung cancer express a willingness to undergo research-only biopsies, recognizing their potential to drive scientific progress. Their perspectives are critical and must be central to ongoing discussions surrounding FDA guidance on tissue biopsies in clinical trials.

Keywords: Patient advocacy, Research biopsies

OA17 BALANCING COST, CARE AND PATIENT CHOICE IN REAL WORLD JOURNEY AND RESEARCH
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA17.04 Financial Toxicity in Patients Who Received Targeted Therapy for Lung Cancers

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Introduction: Financial toxicity (FT) is an increasingly recognized effect of cancer therapy and is associated with worsened quality of life, compliance, and possibly, mortality. Oral targeted therapy (OTT) has improved survival in lung cancer but little is known about the FT experienced by lung cancer survivors (LCS) receiving OTT. We evaluated clinical and sociodemographic factors in LCS receiving OTT, and whether receiving OTT was associated with greater FT.

Methods: LCS (defined as alive ≥1 year from diagnosis) treated at Johns Hopkins between 2020-2024 completed the COmprehensive Score for Financial Toxicity (COST), which is a validated, patient-reported outcome measure to assess subjective FT. Answers are rated on a 5-point Likert scale with lower scores representing higher financial needs. Demographic and clinical information was collected by chart review and survey response. The Wilcoxon rank sum test or Kruskal-Wallis test were used to assess univariate associations between patient demographic, clinical characteristics, and COST score.

Results: Of 326 patients enrolled, 307 had complete survey data (>80% items complete) and were included for analysis (Table 1). Respondents who ever received OTT (n=111) were younger (51% <65), less likely to have ever smoked (61% never smoker), more likely to be privately insured (79%), endorse household income >$75,000 (67%), and educational attainment of college degree or greater (47%) compared to respondents who never received OTT. The majority of OTT patients had adenocarcinoma (96%) and were Stage IV (69%) at time of diagnosis. Financial needs were reported by all patients regardless of OTT treatment (45% vs 33%, ever vs never OTT). Patients who received OTT had comparable FT scores with patients who never received OTT (ever vs never OTT, COST = 26, 28, respectively). Similarly, when limited to patients who were receiving palliative intent therapy, OTT treatment was not associated with a significant difference in COST score (95% CI -1.03, 3.39, p=0.295). Among patients who ever received OTT, age (<65 vs > 65, COST = 25, 28, respectively; p=0.009) and patient-identified race (Caucasian, African-American, Asian, Other, COST= 26.5, 27.5, 23, 37.4, respectively, p=0.034) were significantly associated with lower FT scores.

Conclusions: OTT treatment was not associated with differences in FT in a large group of LCS, even after excluding patients on curative intent therapy. Among patients receiving OTTs, younger age and race were associated with significant differences in FT. Targeted inventions to address these unmet needs and financial toxicity in LCS, regardless of therapy type, are crucial.

Table 1. Demographics of enrolled patients

Characteristic	Complete survey, n=307 (%)	Ever targeted-oral therapy, n=111 (%)	Never targeted-oral therapy, n=196 (%)
Sex			
Female	184 (59.9)	76 (68.5)	108 (55.1)
Male	123 (40.1)	35 (31.5)	88 (44.9)
Median age (IQR)	68 (60, 75)	64 (55, 72)	70 (62, 76)
Age			
<65 years	119 (38.8)	57 (51.4)	62 (31.6)
≥65 years	188 (61.2)	54 (48.6)	134 (68.4)
Race			
Caucasian	227 (73.9)	72 (64.9)	155 (79.1)
African American	46 (15.0)	18 (16.2)	28 (14.3)
Asian	26 (8.5)	19 (17.1)	7 (3.6)
Other	8 (2.6)	2 (1.8)	6 (3.1)
Smoking status			
Never	114 (37.1)	68 (61.3)	46 (23.5)
Current	19 (6.2)	2 (1.8)	17 (8.7)
Former	174 (56.7)	41 (36.9)	133 (67.9)
Stage at diagnosis			
Stage I-II	118 (38.4)	20 (18.0)	98 (50.0)
Stage III	57 (18.6)	15 (13.5)	42 (21.4)
Stage IV	132 (43.0)	76 (68.5)	56 (28.6)
Tumor histology			
Adenocarcinoma	249 (81.1)	106 (95.5)	143 (73.0)
Squamous	36 (11.7)	0 (0.0)	36 (18.4)
Other	22 (7.2)	5 (4.5)	17 (8.7)
ECOG at survey			
0	137 (44.6)	44 (39.6)	93 (47.4)
1	144 (46.9)	59 (53.2)	85 (43.3)
2+	26 (8.5)	8 (7.2)	18 (9.2)
Time since diagnosis			
1-2 years	106 (34.5)	42 (37.8)	64 (32.7)
2-5 years	119 (38.8)	45 (40.5)	74 (37.8)
5+ years	82 (26.7)	24 (21.6)	58 (29.6)
Lines of systemic therapy			
1	131 (42.7)	40 (36.0)	91 (46.4)
2+	127 (41.4)	71 (64.)	56 (28.6)
Other	49 (16.0)	0 (0.0)	49 (25.0)
Active therapy			
No	138 (45.0)	8 (7.2)	130 (66.3)
Yes	169 (55.0)	103 (92.8)	66 (33.7)
Intent of last/active therapy			
Curative	120 (39.1)	9 (8.1)	111 (56.6)
Palliative	187 (60.9)	102 (91.9)	85 (43.4)
Current insurance			
Private w/ or w/o Medicare		87 (78.4)	142 (72.4)
Medicare only		19 (17.1)	39 (19.9)
Medicare and Medicaid		3 (2.7)	7 (3.6)
Current employment			
Employed		10 (9.0)	15 (7.7)
Retired		42 (37.8)	51 (26.0)
Unemployed		57 (51.4)	118 (60.2)
Household income			
<$30,000		5 (4.5)	31 (15.8)
$30,000-75,000		27 (24.3)	46 (23.5)
>$75,000		74 (66.7)	109 (55.6)
Education			
HS or less		10 (9.0)	46 (23.5)
Some college/college graduate		49 (44.1)	92 (46.9)
More than college graduate		52 (46.8)	57 (29.1)

Keywords: Financial toxicity, Oral targeted therapy, Lung cancer survivors

OA18 THE BEST ROAD: REDUCING DISPARITIES AND IMPROVING EARLY DETECTION RATES
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA18.01 Improving Lung Cancer Outcomes Through Policy a Global Perspective on Risk Reduction, Early Detection, Care and Survivorship

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Introduction: Over 2 million people are diagnosed with lung cancer globally each year; that number is expected to almost double by 2050. The majority (80%) of cases are thought to be due to exposure to modifiable risk factors. Currently, 70% of people are diagnosed in advanced stages, limiting potentially curative treatment options. Policymakers are uniquely positioned to address these challenges. Therefore, this research aims to identify challenges in lung cancer risk reduction, early detection, treatment and survivorship, and highlights opportunities to enact policy change.

Methods: A comprehensive situational analysis of global lung cancer policy challenges was conducted across four themes: risk reduction, early detection, treatment and survivorship. Best-practice strategies and initiatives were also identified. The analysis was completed through a structured review of peer-reviewed and grey literature from 2018-2025, expert interviews and an online survey. Nine in-depth interviews were conducted with healthcare professionals and patient advocates in Australia, Canada, Colombia, Croatia, Hong Kong, Malaysia, the United Kingdom and the United States; 12 more interviews were planned at time of writing. Additionally, an online survey was completed by 25 International Association for the Study of Lung Cancer (IASLC) Committee members.

Results: Opportunities for policy action were identified across the four themes, and corresponding policy recommendations will be developed. While tobacco use remains a key risk factor for lung cancer, implementation of the World Health Organization's (WHO's) Framework Convention for Tobacco Control (FCTC) varies considerably. However, countries that have adhered to the FCTC, particularly those with increased tobacco taxation, have seen greater cessation rates. Other risk factors, including outdoor and household air pollution, occupational exposures (coal dust, silica dust, asbestos, diesel exhaust fumes) and radon exposure, are of growing concern.Lung cancer is being detected in advanced stages in many countries, precluding potentially curative therapeutic options. National screening programs are important for earlier detection, but equitable access remains a challenge and implementation is limited. Other early detection strategies (including awareness campaigns and rapid referral pathways) present further opportunities to expedite earlier detection, particularly in countries where screening is not feasible, and where rates of lung cancer in non-smoking populations are high. Access to care (including palliative care) is impeded by sociocultural and geographical barriers, and limited reimbursement of treatments. People can become lost in a complex system, with specialists spread across different health settings. Telehealth and patient navigators may ameliorate some of these challenges and facilitate more equitable care. Many countries do not have survivorship models incorporated into care pathways, and access to supportive care varies. Increased access to survivorship services (including rehabilitation and social support) would promote person-centered care.

Conclusions: The report - the first from the IASLC Global Policy and Partnerships Committee - identifies opportunities for policymakers to enact changes to promote equitable, person-centered lung cancer care that enhances survival and quality of life. These changes would lead to more efficient healthcare delivery, allowing for more proactive and preventive care, aligned with the United Nations' Sustainable Development Goals 3a and 3.4.

Keywords: Global Policy, Policy Challenges, Best Practices

OA18 THE BEST ROAD: REDUCING DISPARITIES AND IMPROVING EARLY DETECTION RATES
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA18.02 Emerging Disparities in Lung Cancer Burden in the Americas: A GLOBOCAN-Based Projection to 2050

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Introduction: Lung cancer is the leading cause of cancer-related mortality in the Americas, driven by an aging population, increasing exposures (pollution), social inequalities, and poor access to healthcare services. Despite advancements in risk reduction and early detection, significant disparities persist across countries, particularly those with limited resources. This study assessed lung cancer incidence and mortality rates for 2022 and projected trends up to 2050. It employs stratification by sex, age, and the Human Development Index (HDI) to emphasize the increasing regional and socioeconomic disparities regarding lung cancer.

Methods: Lung cancer incidence and mortality estimates for 2022, along with projections for 2050, were retrieved from GLOBOCAN 2022 database, the latest available. Age-standardized incidence and mortality rates (ASIR and ASMR, respectively) per 100,000 person-years were used for regional comparisons. Population data were obtained from the World Bank. Countries were categorized by HDI level (low, medium, high, very high), and analyses were stratified by sex and age group. Mann-Whitney U and Kruskal-Wallis tests were used for between-group comparisons, with Dunn's post hoc test for pairwise analysis. Median values were reported, with significance set at $p < 0.05$.

Results: Data from 34 countries in the Americas representing over 1 billion people (50.4% female) were analyzed. In 2022, the median ASIR and ASMR were 25.87 and 21.87 per 100,000, respectively. Lung cancer rates were significantly higher in males (ASIR: 14.23; ASMR: 11.99) than in females (ASIR: 6.32; ASMR: 5.08; $p < 0.001$). Uruguay reported the highest male lung cancer burden (ASIR: 46.56; ASMR: 41.76), whereas Guatemala had the lowest (ASIR: 4.50; ASMR: 4.23). Among female individuals, the United States had the highest ASIR (30.40), and Canada the highest ASMR (19.13). Guyana had the lowest female rates (ASIR and ASMR: 2.39). By 2050, lung cancer incidence and mortality are projected to increase at higher rates in female vs male individuals, by 87.9% and 89.4% vs 97.1% and 98.8%, respectively. Countries with low/medium HDI are expected to experience the most significant increases in incidence (118.9%) and mortality (120.0%) compared to high/very high HDI countries (87.5% and 89.2%, respectively). From the countries analyzed, nineteen (high/very high HDI: 14; low/medium HDI: 2; no HDI data available: 2) will see the greatest increase in female burden, when compared to male, highlighting an emerging gender and equity gap in lung cancer.

Conclusions: The lung cancer burden in the Americas is projected to rise substantially by 2050, with higher increases among women for the first time in history. Higher incidence increase was also seen in low/medium HDI countries. These findings highlight the urgent need for regionally tailored risk reduction strategies, enhanced access to screening and early diagnosis, and both regional and global collaboration to address the growing burden of lung cancer across the Americas.

Keywords: Epidemiology, Disparities, Global Oncology

OA18 THE BEST ROAD: REDUCING DISPARITIES AND IMPROVING EARLY DETECTION RATES
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA18.03 Cost Effectiveness of Australian Lung Cancer Screening Eligibility Criteria: A Comparison Study

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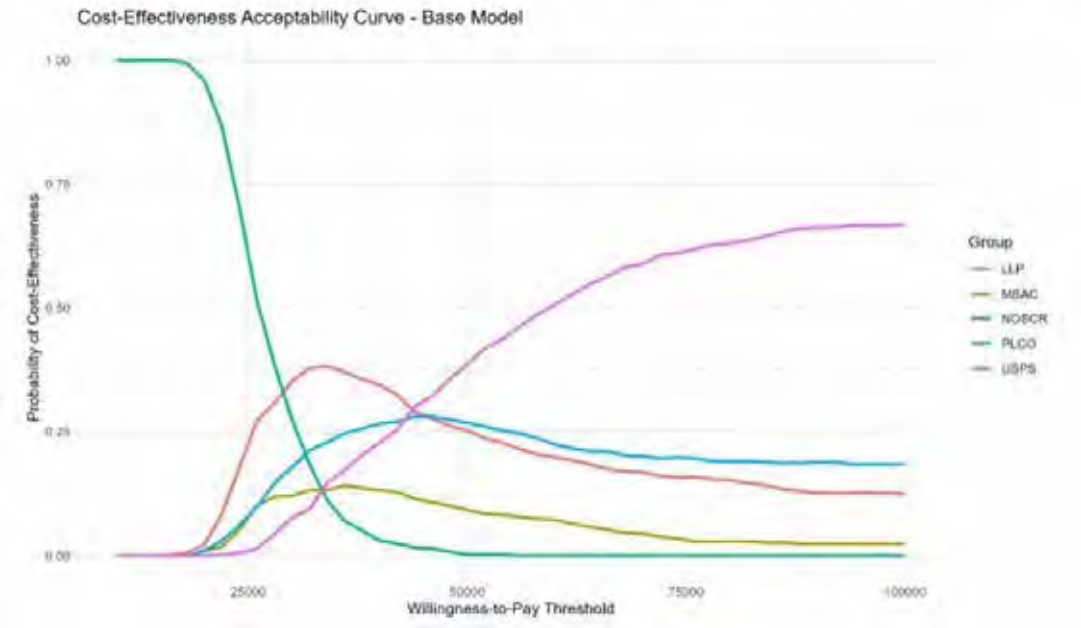
Introduction: The Australian National Lung Cancer Screening Program (NLCSP) will commence in 2025. Screen eligibility for NLCSP uses smoking and tobacco exposure recommendations from the Medical Services Advisory Committee (MSAC). The MSAC criteria is stricter than similar criteria (USPSTF2021) used in the USA. Canadian provinces assess eligibility using the PLCOm2012 risk model, UK uses a combination of the PLCOm2012 and LLPv2 risk models. This study aimed to compare the cost effectiveness of the MSAC criteria against other eligibility criteria, using a microsimulation model estimating the benefit (life-years gained) of each criterion in a simulated Australian population.

Methods: The model simulated individual level outcomes based on initial parameters of age, sex and smoking status using Monte Carlo methods. The model was designed with 5 primary states, which included a baseline "healthy" state, and 4 disease states, each corresponding to the stages of LC diagnosis (Stage I - IV). There two additional terminal states: "lung-cancer mortality" and "other-cause mortality". Transition between these states were determined based on age, sex and stage specific LC incidence rates and mortality rates derived from data published by the Australian Institute of Health and Welfare (AIHW). Risk of lung cancer incidence and mortality due to tobacco smoking was adjusted using the Australian 45 and Up Study data.The final outcomes for each individual were: no disease, LC death, or death due to other causes. If death occurred due to LC, then the model also provided the number of years the individual spent in disease state, as well as the LC stage at which the individual was diagnosed.

Results: The model reported the potential life-years gained by screening under each eligibility criteria for a simulated population of 10,000 individuals, across 400 iterations of lifetime screening. Cost Effectiveness Acceptability Curves comparing each eligibility criteria (as an intervention versus a no-screening scenario) demonstrated that MSAC criteria was least likely to be cost effective at any given willingness-to-pay threshold for the health system (including screening and treatment costs: figure 1). One-way sensitivity analysis varying the CT costs, stage 4 treatment costs, incidence and other cause mortality rates, consistently highlighted MSAC as the least likely to be cost effective amongst all evaluated LC eligibility criteria.

Conclusions: Compared to other selection criteria, the Australian MSAC criteria is least likely to be cost-effective from a health system perspective. Refinement of selection criteria for the Australian NLCSP will likely be required after commencement in 2025.

Figure 1. Cost Effectiveness Acceptability (CEAC) curve comparing the assessed lung cancer eligibility criteria against no lung cancer screening



Keywords: Lung Cancer Screening, Participant Eligibility Criteria, Comparative Cost-effectiveness

OA18 THE BEST ROAD: REDUCING DISPARITIES AND IMPROVING EARLY DETECTION RATES
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

OA18.04 Sociodemographic and Healthcare Factors Associated With Enrollment in a Clinical Trial Integrating Tobacco Cessation and Lung Cancer Screening

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Introduction: The factors influencing enrollment in a tobacco-cessation clinical trial (Screen ASSIST) among patients undergoing lung cancer screening (LCS) remain poorly understood. This study aims to assess the association of sociodemographic and healthcare factors with enrollment in the Screen ASSIST trial among individuals undergoing LCS.

Methods: This retrospective study used Screen ASSIST data, a Phase 4 randomized clinical trial that integrated tobacco cessation services and social support services among patients who currently smoke and were and scheduled for LCS across 11 sites within a large academic health system from April 2019-July 2023. Eligible participants included current smoking patients scheduled for LCS. Recruitment occurred at three points: (1) After LCS was ordered, (2) when performing LCS (RP2), and (3) after LCS results were available (RP3). Enrolled participants were randomly assigned in equal portions to one of eight study arms, following a 3-factor, fully crossed factorial design.Sociodemographics (age, gender, race, ethnicity, language, insurance, zip-code, and education) and healthcare-related factors (primary care physician visits over the past year, and Charlson comorbidity index) were extracted from electronic medical record. Neighborhood-level socioeconomic disadvantage was assessed using the Area deprivation index (ADI), based on participants' residential zip-code. Data were summarized using means with SD (continuous variables) and frequencies (categorical variables). Logistic regression assessed factors associated with enrollment, including variables of a priori importance (e.g. Charlson index, ADI) and significant factors identified in the univariate analysis ($p<0.05$). The primary outcome was enrollment in the clinical trial among individuals who met Screen ASSIST eligibility criteria.

Results: Among 4,090 eligible individuals, 642 (15.7%) were enrolled and randomized. Eligible individuals had a mean age of 63.0 (SD 6.5) and were predominantly White (80.1%), Non-Hispanic (83.7%), had English as preferred language (96.9%), and had high school degree or greater (77.1%). Groups did not differ by ADI or Charlson comorbidity scores. Univariate analyses showed higher enrollment among females ($p=0.019$), non-Hispanic Blacks ($p=0.002$), college graduates ($p<0.001$) and those without PCP visits in the previous year ($p=0.005$). Unenrolled individuals had a higher number of prior PCP visits (5.2, SD 6.9 visits) compared to enrolled individuals (4.7, SD 5.8 visits; $p=0.022$). Logistic regression analyses showed that factors associated with enrollment included: age 70 years or older (adjusted odds ratio [aOR]:1.29, 95% CI: 1.00 - 1.66); female gender (aOR: 1.26 95% CI: 1.06-1.50); self-reported non-Hispanic Black race (aOR: 1.87 95% CI: 1.37-2.54); college graduates education level (aOR: 1.47 95% CI: 1.03-2.12); and those with 0 PCP visits over the past year (aOR: 1.43 95% CI: 1.16-1.76).

Conclusions: Several sociodemographic and healthcare-related factors previously associated with lower clinical trial participation were, in this study, associated with a higher likelihood of enrollment in our tobacco cessation clinical trial integrated into LCS. These findings underscore a valuable opportunity to improve diversity in clinical trial participation and bridge existing disparities in lung cancer outcomes, cardiovascular disease and other smoking related diseases.

Keywords: sociodemographic, tobacco, clinical trial

03 | MINI ORAL ABSTRACT SESSIONS

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.01 Surgical Outcomes and Oncological Quality of Surgery According to IASLC Criteria in NADIM II Trial

J.R. Jarabo[1], E. Fernández[1], I. Macía[2], L. Romero[3], C.A. Fraile[1], F. Rivas[2], C. Deniz[2], A.I. Blanco[4], L. Sánchez[3], C. Rodrigu[5], G. Foschini[5], F. Ascanio[3], S. Monge[4], M. Rubio[5], E.M. Garcia-Fontán[6], J.L. Villalobos[4], M. Blanco[6], R. Carrasco[6], C. Gálvez[7], S. Bolufer[7], J.L. Campo-Cañaveral[8], S. Crowley[9], S. Figueroa[10], R. Wins[10], G. Galán[10], C. Marrón[8], A. Romero[9], R. Ramos[11], M. Boada[11], A. Ureña[11], D. Sánchez[12], E. Corpa[13], R. Vicente[13], C. Partida[13], M. Delgado[14], M. de la Torre[14], R. Mongil[15], Á. Guirao[16], R. Arrabal[17], J.J. Fibla[16], U. Jiménez[18], M. Lorenzo[18], E. Pastor[19], R. Guijarro[19], Á. Cilleruelo[20], C. Martínez-Barenys[21], A. Álvarez[22], M. Provencio[9], F. Hernando[1]
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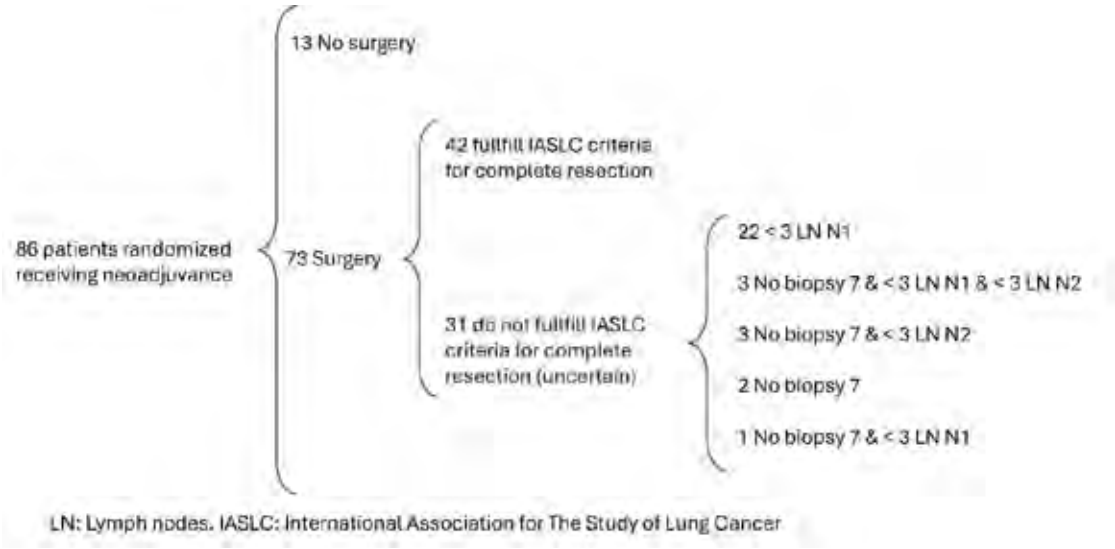
Introduction: Phase 2 NADIM II trial demonstrated that patients with resectable stage IIIA/IIIB NSCLC who received nivolumab in combination with platinum-based chemotherapy, achieved higher rates of pathological complete response and survival than those receiving chemotherapy alone. We analyze here perioperative outcomes and oncological quality of surgical procedures.

Methods: Variables related to surgical procedure were prospectively collected according to the study design. Additional data for the current analysis (surgical approach, operative time, hospital stay, 30 and 90-days mortality and surgical complications), were subsequently obtained from the surgeons participating in the trial. Complications were scored according to Clavien-Dindo Classification. Comprehensive Complication Index (CCI) was also used. Fulfillment of IASLC complete resection criteria was also evaluated.

Results: From the 86 randomized patients, 53 from the experimental group (93%) and 20 from the control arm (69%) finally underwent surgery as planned. No differences were found between both groups regarding comorbidities and basal lung function tests. Evolution of FEV1 and DLCO did not differ regardless type of neoadjuvance. Most tumors were in the upper lobes (64.4%) and in the right lung (72.8%). Mean time between the end of the induction treatment and surgery was 27.6 days. Lobectomy was performed in 79.4% of cases, whereas there were seven pneumonectomies (9.6%). Surgery was performed through a minimally invasive approach in 27% of cases. There were no differences in the type of resection and duration of surgical procedure. Postoperative complications appeared in 42.5% of patients, without differences between both groups. Persistent air leak (>5 days) was the most common (11 cases). Cardiac arrhythmia and pneumonia were recorded in 3 and 4 patients, respectively. CCI at discharge was 10.2 for control group and 7.8 for experimental arm (p=0.57). Median chest tube removal time (3 days) and hospital staying (4 days) non-significantly tended to be shorter in the experimental group. No re-operations were necessary. Four patients were readmitted after discharge (5.5%) and one patient undergoing right pneumonectomy died 13 days after surgery (30 and 90-days mortality 1.4%). Despite all the patients underwent R0 resection, 31 procedures (42.8%) did not fulfill IASLC criteria for complete resection. Figure shows reasons for non-compliance with them.

Conclusions: Induction treatment with the combination of platinum-based chemotherapy and nivolumab was safe and did not increase postoperative complications among patients included in NADIM II trial. Rates of R0 and uncertain resection were 100% and 42.8%, respectively. (NADIM II ClinicalTrials.gov number, NCT03838159; EudraCT number, 2018-004515-45.)



Keywords: Early, Surgery, Neoadjuvance

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.03 Metabolomic Analysis Identifies Histamine as a Key Predictive Factor for Perioperative Chemoimmunotherapy in NADIM II Trial

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide. In locally advanced stages, the advent of perioperative chemoimmunotherapy has significantly improved survival outcomes. However, treatment responses remain highly variable, underscoring the need for reliable biomarkers to predict therapeutic efficacy. Metabolomics (the comprehensive analysis of small-molecule metabolites) has emerged as a powerful tool to identify metabolic alterations associated with cancer and immune modulation. Increasing evidence suggests that metabolic reprogramming plays a critical role in cancer development and may influence the response to immunotherapy. The NADIM II is an open-label, randomized, two-arm, phase II, multi-center trial designed to evaluate the efficacy of perioperative chemoimmunotherapy in patients with resectable stage IIIA-IIIB non-small cell lung cancer (NSCLC). Here, we present preliminary findings from a metabolomic analysis of plasma samples from study participants

Methods: In the NADIM II trial, patients with resectable stage IIIA/B NSCLC were randomized to receive neoadjuvant nivolumab plus platinum-based chemotherapy (experimental arm) or chemotherapy alone (control arm), followed by surgical resection. Patients in the experimental arm who achieved an R0 resection received adjuvant nivolumab for six months. Of the 86 patients randomized (57 in the experimental arm and 29 in the control arm), 81 plasma samples were available for metabolomic analysis (54 from the experimental arm and 27 from the control arm). Metabolomic profiling was conducted using liquid chromatography coupled with triple quadrupole mass spectrometry (LC-QqQ-MS/MS) in hydrophilic interaction liquid chromatography (HILIC) mode, targeting 190 polar metabolites. Compounds ionizing in positive mode were normalized using isotopically labeled internal standards. Statistical analysis was performed using RStudio to identify metabolites associated with survival outcomes.

Results: Among the 190 polar metabolites analyzed, histamine and 4-acetamidobutyric acid were significantly associated with improved survival in patients treated with neoadjuvant nivolumab plus chemotherapy ($P < 0.05$). This association was not observed in the control arm, where these metabolites did not correlate with survival outcomes. Conversely, orotic acid, 1-methylnicotinamide, and trigonelline emerged as independent negative predictive factors for response to perioperative chemoimmunotherapy, with significantly higher levels observed in patients with poorer survival outcomes ($P < 0.05$). Again, this pattern was not seen in the control arm. Notably, patients with histamine levels above the median were significantly more likely to achieve a pathological complete response ($P < 0.001$, Bonferroni-adjusted), and all of these patients were alive at the data cutoff (PlogRank = 0.002). In the same way, elevated histamine plasma levels were associated with significantly improved disease-free survival compared to patients with levels below the median (HR: 0.28; 95% CI: 0.092-0.83). No significant association between histamine levels and survival outcomes was observed in the control arm.

Conclusions: Plasma histamine levels are associated with pathological complete response and improved survival outcomes in patients with resectable NSCLC treated with perioperative chemoimmunotherapy.

Keywords: Nadim II trial, histamine key predictive factor, metabolomic analysis

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.04 Neoadjuvant PD-(L)1 Blockade in Combination With Chemotherapy for Borderline Resectable and Unresectable Stage III Non-Small Cell Lung Cancerl

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Introduction: Patients with borderline resectable or unresectable stage III non-small cell lung cancer (NSCLC) characterized by T4 and/or N2-N3 involvement face significant therapeutic challenges and generally poor outcomes. While concurrent chemoradiation has long been the standard of care, emerging evidence supports the potential of neoadjuvant chemo-immunotherapy to improve both surgical resectability and pathological response rates. However, data specific to this high-risk population remain limited as most of these patients have been excluded from clinical trials.

Methods: We conducted a multicenter cohort study of 112 patients with stage III NSCLC and T4 and/or N2-N3. All patients received neoadjuvant PD-1 blockade in combination with platinum-based chemotherapy. Pathological outcomes, including pathological complete response (pCR) and major pathological response (MPR), surgical resectability rates, and event-free survival (EFS) were assessed. Correlations between molecular features and treatment response were also explored.

Results: Of the 112 patients with borderline resectable and unresectable stage III NSCLC included, 75% proceeded to surgical resection following neoadjuvant treatment. Among resected patients, the pCR rate was 29.0%, and the MPR rate was 42.2% (Figure 1A). Patients with single versus multi-station N2 or N3 disease demonstrated comparable pathological response rates (P=0.6). The median EFS for resected patients was 52.6 months (95% CI: 27.8-not reached), and patients achieving pCR experienced significantly improved EFS (not reached vs. 27.8 months; P< 0.01). Patients who underwent surgery after neoadjuvant chemo-immunotherapy had significantly improved EFS and OS compared to those who were converted to definitive chemoradiotherapy (EFS HR: 0.31; P<0.01; OS HR: 0.33, P=0.01).

The pCR rate was highest (44.4%) among patients with both high PD-L1 expression (≥50%) and high TMB (≥50th percentile), compared to 33.3% in high PD-L1/low TMB, 14.3% in low PD-L1/high TMB, and 0% in low PD-L1/low TMB groups (P=0.03) (Figure 1B). Co-mutations in KRAS/STK11 or KRAS/KEAP1 were negatively associated with achieving pCR (pCR rate 0%, P<0.01 and P=0.05, respectively; Figure 1C). Clinical and genomic correlates of pCR and MPR are summarized in Figure 1D.

Conclusions: Neoadjuvant PD-1 blockade combined with platinum-based chemotherapy is associated with high pathological response rates and favorable surgical outcomes in patients with T4 and/or N2-N3 stage III NSCLC initially considered borderline resectable or unresectable. Biomarkers such as PD-L1 TPS, TMB, and co-mutation status may help identify patients most likely to benefit. These findings support the incorporation of neoadjuvant chemo-immunotherapy into treatment paradigms for locally advanced NSCLC and warrant further prospective validation.

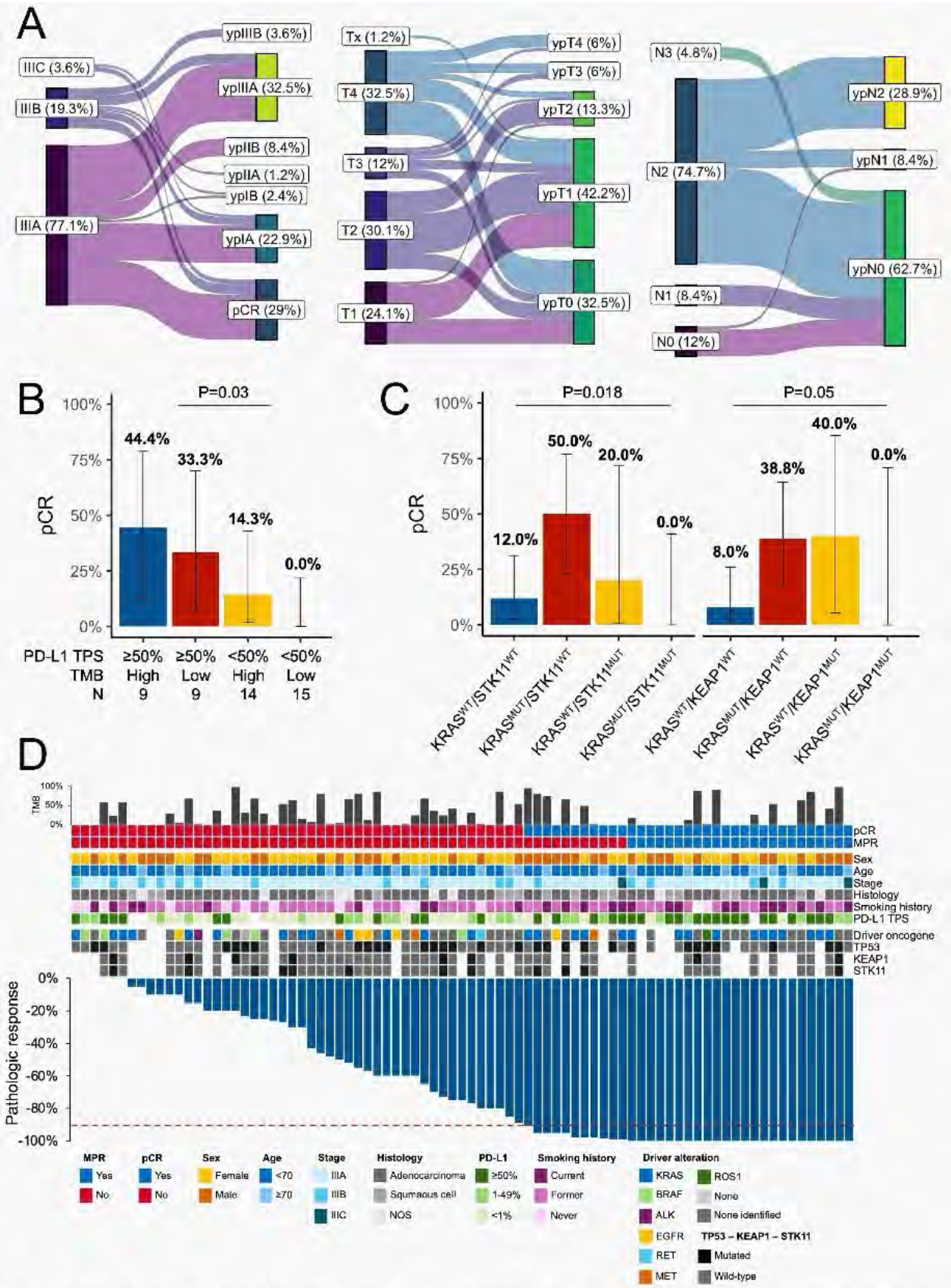

Figure 1. (A) Sankey diagrams showing changes in stage primary tumor (T), and lymph node involvement (N) before and after neoadjuvant chemo-immunotherapy followed by surgery. Association of combined PD-L1 and TMB (**B**), concurrent KRAS/STK11 and KRAS/KEAP1 (**C**) and pathologic complete repose rate (pCR). (**D**) Oncoprint plot summarizing the clinico-pathologic and genomic factors associated with pCR and MPR.

Keywords: Neoadjuvant PD-(L)1 blockade, Stage III unresectable lung cancer, Biomarkers

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.05 Tislelizumab Plus Chemotherapy Followed by Surgery or Radiotherapy and Adjuvant Tislelizumab in Unresectable Stage III NSCLC

J. Liu, L. Tu, Y. Li, Y. Li, Z. Li, T. Wang, T. Wang, Q. Wu, L. Wang, X. Zhai, J. Dong, M. Fan, P. Tian, D. Pu, Y. Zhang, F. Luo, Y. Liu, J. Wang, F. Xu, Y. Lai, K. Wang, X. Zheng, G. Che
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Introduction: With neoadjuvant chemoimmunotherapy followed by surgery providing significant high pCR/MPR rates and survival benefit for resectable NSCLC, the current "Pacific Mode" of consolidation immunotherapy (IO) after chemoradiation for initially unresectable stage III NSCLC is being challenged. IO-based induction therapy may provide more survival benefit, partly by enabling surgery. However, the specific treatment modalities and beneficiary populations remain unclear. In this trial, we assessed induction tislelizumab (TIS) + chemo, followed by surgery or radiotherapy (RT), and TIS ± chemo as adjuvant therapy in unresectable stage III NSCLC to answer these questions. Here are the preliminary results.

Methods: This phase 2 study enrolled patients with histologically confirmed stage III NSCLC (per AJCC 8th edition) deemed initially unresectable based on at least one of the following criteria: (1) T4 tumors invade vital organs precluding R0 resection, (2) multi-station N2 metastases or N2 metastases fused into masses, and (3) N3 metastases. N2/N3 status was confirmed by PET/CT or pathology. Patients received 2-4 cycles of induction TIS plus nab-paclitaxel and platinum. Post-induction, MDT assessment will guide treatment with surgery or RT, followed by adjuvant TIS ± chemo for up to 1 year. The primary endpoint was 1-year EFS rate. Secondary endpoints included surgery rate, pCR, MPR and safety. The planned sample size was 55.

Results: As of March 14, 2025, 28 patients were enrolled, with 28.6% classified as stage IIIA, 46.4% stage IIIB, and 25.0% stage IIIC. 13 patients have completed induction therapy and post-induction MDT assessment, with an ORR of 100%. 3 patients (23.1%) underwent RT and 10 (76.9%) underwent surgery. All surgery patients achieved R0 resection; pCR and MPR rates were 60.0% (6/10) and 90.0% (9/10), respectively. Clinical and pathological downstaging occurred in 76.9% (10/13) and 90% (9/10) of patients. Specifically, patients who received 4 cycles of induction therapy exhibited numerically higher pCR and MPR rates (100% [4/4] for both) compared to those who received 3 cycles (33.3% [2/6] and 83.3% [5/6]), while the ORR was the same in both subgroups (100%). Among 28 patients enrolled, grade ≥3 TRAEs occurred in 7 (25.0%) patients, with frequency of ≥10% being hematotoxicities. No new safety signals were identified.

Conclusions: Induction tislelizumab plus chemo demonstrated preliminary promising antitumor activity with a tolerable safety profile in stage III NSCLC. A notable proportion of patients were enabled to receive radical surgery and attained good pathological response. Recruitment is ongoing, and efficacy and safety will be continuously monitored.

Table

cTNM at baseline	cTNM post-induction	Cycles of induction treatment	Surgery/RT	Pathological response
T4N3M0	T2aN0M0	4	Surgery	pCR
T4N3M0	T1bN0M0	4	Surgery	pCR
T4N3M0	T1bN2M0	4	Surgery	pCR
T1cN3M0	T1cN0M0	4	Surgery	pCR
T1bN3M0	T1aN0M0	3	Surgery	pCR
T4N2M0	T4N0M0	3	Surgery	non-MPR
T4N2M0	T1bN2M0	3	Surgery	MPR
T4N1M0	T1cN0M0	3	Surgery	pCR
T4N1M0	T4N1M0	3	Surgery	MPR
T4N0M0	T1bN0M0	3	Surgery	MPR
T4N3M0	T1N3M0	4	RT	-
T2aN3M0	T1N3M0	4	RT	-
T4N1M0	T4N1M0	3	RT	-

Keywords: non-small cell lung cancer, initially-unresectable, induction chemoimmunotherapy

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.06 Phase I/II Trial of Canakinumab With Chemoradiation and Durvalumab in Stage III Non-Small Cell Lung Cancer (CHORU

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Introduction: More than half of patients with unresected stage III non-small cell lung cancer (NSCLC) progress within 2 years after treatment with concurrent chemoradiation (cCRT) and durvalumab consolidation. Interleukin (IL)-1β signaling has been implicated in treatment resistance and tumor progression in NSCLC. We prospectively evaluated the addition of canakinumab, a human monoclonal IL-1β antibody, to cCRT and durvalumab consolidation in patients with unresected stage III NSCLC.

Methods: CHORUS was a single-arm, open label phase I/II trial that enrolled unselected patients with unresected stage III NSCLC (NCT04905316). Canakinumab was administered as a subcutaneous injection (200mg every 3 weeks) starting within 5 days of cCRT for up to 3 cycles, and then was administered intravenously (200mg every 4 weeks) with durvalumab consolidation for up to 12 additional cycles. Concurrent chemoradiation included conventionally fractionated radiation (60 Gy in 30 fractions) with platinum-doublet chemotherapy. Durvalumab consolidation was administered as standard of care. The primary objective was to improve the 2-year progression-free survival (PFS) compared to the historical rate of 46%, using a one-sided test based on the Kaplan-Meier method. Patients were evaluable for the primary endpoint if they received ≥1 cycle of consolidation with canakinumab plus durvalumab. Response was per RECIST 1.1 criteria and was initially evaluated 4 weeks post-cCRT, then every 3 months.

Results: Between 11/2021 and 4/2022, 41 patients were enrolled, 37 started protocol therapy, and 32 patients were evaluable for the primary endpoint. The median follow-up was 24.6 months (95% CI 21.2, 27.3). The median age was 70 years, 56% (n=18) of patients were female, 66% (n=21) were ECOG 0, 88% (n=28) had a smoking history and 59% (n=19) had adenocarcinoma histology. Most patients had stage IIIB (n=14, 44%) or IIIA (n=10, 31%) disease. PD-L1 expression was known for 29 patients (91%) of which 48% (n=14) were PD-L1 <1% and 28% (n=8) were PD-L1 ≥ 50%. Most patients, 91% (n=29), received at least 2 doses of canakinumab concurrent with cCRT. Patients received a median of 7 (range: 1-12) cycles of canakinumab consolidation. An objective response to canakinumab + cCRT was observed in 74% (n=23) of patients on initial imaging post-cCRT and prior to consolidation. In total, an objective response was seen in 81% (n=26) of patients. The 12- and 24-month PFS rates were 75% (95% CI 61% - 93%) and 67% (95% CI 52% - 88%), respectively. The 12- and 24-month overall survival rates were 93% (95% CI 84% - 100%) and 73% (57% - 92%), respectively. There were no canakinumab treatment-related deaths. Grade 3/4 (n=7) canakinumab related toxicities occurred most commonly during cCRT and included grade 3 febrile neutropenia (n=1), neutropenia (n=4), lymphopenia (n=1) and grade 4 neutropenia (n=1). Grade 3 (n=3) canakinumab related toxicities occurring during durvalumab consolidation included lung infection (n=1), fatigue (n=1) and hypertension (n=1).

Conclusions: In this phase I/II trial, canakinumab with concurrent chemoradiation and durvalumab consolidation in unresected stage III NSCLC met the primary endpoint of improving 2-year PFS to > 46%, with acceptable safety, suggesting a possible new therapeutic approach for this patient population.

Keywords: Multimodality, Locally Advanced NSCLC, Canakinumab

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.07 Preliminary Results of the Phase I LuCa-MERIT-1 Trial: An Advanced NSCLC pt Cohort Treated With BNT116 + Cemiplimab Post CRT

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Introduction: Patients with locally advanced unresectable stage III non-small cell lung cancer (NSCLC) receive concurrent chemoradiotherapy (cCRT) as standard of care (SOC) followed by consolidation treatment with PD-L1 inhibition. BNT116, an intravenously administered, unmodified RNA-based lipoplex cancer immunotherapy, is composed of six mRNAs, each encoding a tumor-associated antigen frequently expressed in NSCLC: CLDN6, KK-LC-1, MAGE-A3, MAGE-A4, MAGE-C1, or PRAME. Preliminary results suggest a well-tolerated safety profile for BNT116 alone and in combination with cemiplimab. We present preliminary data for BNT116 plus cemiplimab in patients with advanced NSCLC after cCRT.

Methods: The open label, multi-cohort Phase I LuCa-MERIT-1 trial (NCT05142189) aims to determine the safety (treatment-emergent adverse events [TEAEs]) and clinical activity of BNT116, alone or in combination with immunotherapy or chemotherapy. This cohort will evaluate BNT116 plus cemiplimab for up to 12 months in patients with advanced NSCLC with previous SOC cCRT. BNT116 is administered weekly for the first 6 weeks, followed by once every 3 weeks. Cemiplimab is administered concomitantly every 3 weeks. Biomarker analysis includes immunogenicity (ELISpot), cytokines (MSD/ELISA), ctDNA (Avenio ctDNA Surveillance), and PD-L1 (immunohistochemistry).

Results: As of 01MAR2025, 20 patients (median age 67.5 years; range 42-82, 30.0% ECOG PS 0, 70.0% ECOG PS 1, 13 patients [65.0%] with PD-L1 tumor proportion score <50.0%) received BNT116 plus cemiplimab (median follow-up time 6.3 months; range 2-13). Eleven patients (55.0%) discontinued treatment, five (25.0%) due to adverse events (Table). All patients experienced treatment-related adverse events (TRAEs) to BNT116, and 15 patients (75.0%) experienced TRAEs to cemiplimab. Four patients (20.0%) experienced serious TRAEs to BNT116 (cytokine release syndrome in two patients and pneumonitis in two patients, three patients resolved without sequelae and one patient was recovering at the timepoint of reporting). No fatal TEAE was observed. BNT116 plus cemiplimab treatment led to tumor control or continued reduction in tumor size in most patients with a 6-month event-free survival (EFS) rate of 72.1% (95% CI 45.0-87.4) and an overall survival (OS) rate of 95.0% (95% CI 69.5-99.3). Cytokine analysis showed that patients mounted a strong type 1 interferon response, as expected based on the mode-of-action of BNT116.

Conclusions: BNT116 plus cemiplimab demonstrated a manageable safety profile dominated by short lasting, mostly mild-to-moderate cytokine-induced symptoms, comparable to patients who had not received prior cCRT, and showed no increase or recall of radiotherapy-related adverse events. Promising EFS and OS rates were observed. Updated safety, clinical activity, and biomarker data will be presented.

Table: Safety

Patients with reported TEAE, n (%)	N=20
Treatment discontinuation	**11 (55.0%)**
▪ completed per protocol	3 (15.0%)
▪ progressive disease	2 (10.0%)
▪ investigator's decision	1 (5.0%)
▪ due to adverse event(s)	5 (25.0%)
At least 1 TEAE	**20 (100%)**
▪ related to BNT116*	20 (100%)
▪ related to cemiplimab	15 (75.0%)
TEAE ≥ Grade 3	**11 (55.0%)**
▪ related to BNT116	6 (30.0%)
○ cytokine release syndrome	2 (10.0%)
○ infusion related reaction	1 (5.0%)
○ hypoxia	1 (5.0%)
○ pneumonitis	2 (10.0%)
○ hypertension	1 (5.0%)
▪ related to cemiplimab	4 (20.0%)
TEAE with fatal outcome	0
Serious TEAE related to BNT116	**4 (20.0%)**
▪ cytokine release syndrome**	2 (10.0%)
▪ pneumonitis***	2 (10.0%)
Dermatitis related to treatment	
▪ Grade 1	1 (5.0%)
▪ Grade ≥ 2	0

* 70% Grade 1 and 2
** recovered within 24 hours at the latest
*** serious for 7-8 days, recovered/recovering (downgrading of severity to Grade 1) 26-28 days

Keywords: consolidation therapy, vaccine, RNA

MA01 NEW DRUGS AND STRATEGIES IN LOCALLY ADVANCED NSCLC
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA01.08 Sequential Chemo-SAbR Following by Immunotherapy in Unresectable LA-NSCLC Unfit for Concurrent ChT-RT According to the START-NEW-ERA Trial

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Introduction: The PACIFIC trial introduced a new treatment paradigm by introducing immunotherapy (IO) after concurrent chemo-radiotherapy (ChT-RT). The PACIFIC 6 shown safety profile in a frailer population. However there is a lack of data of IO consolidation after stereotactic ablative radiotherapy (SAbR). This is a single arm phase 2 trial (Clinical trials.gov NCT05291780) to assess efficacy and safety of SAbR in unresectable LA-NSCLC patients unfit for concurrent ChT-RT (1). Here we report clinical outcomes of SAbR in LA-NSCLC patients treated with radical-intent based on PACIFIC trial.

Methods: Between December 31, 2015 and 17 March 31, 2025 115 LA-NSCLC patients were enrolled. After 2017 PD-L1 ≥1% fit for ChT patients were treated according to this scheme: ChT + SAbR + IO. Up today 32 LA-NSCLC patients were enrolled. The tumor volume included primary tumor (T) and any regionally positive node/s (N). The co-primary study endpoints were LC and safety.

Results: The median age was 73 years (range, 52-78). Histology was adenocarcinoma (ADC) and squamous cell carcinoma (SCC) and in 9 (60%) and 6 (40%), respectively. The stage was IIIA, IIIB and IIIC in 7 (44%), 6 (37%) and 3 (19%) patients, respectively. Median prescribed dose was 45 Gy (range, 40-50) and 40 Gy (35-50) in 5 daily fractions to T and N, respectively. After a median follow-up of 20 months (range, 9-67), 5 (16%) patients had experienced local recurrence (LR) at a median time of 13 months (range, 7-34). The median LR-free survival (FS) was 34 months (95% CI, 14 to 34). The 1-, 2- and 4- year LR-FS rates were 92±8%, 72±14% and 48±22%, respectively. At last follow-up, 23 (74%) patients were alive. Median overall survival (OS) was 50 months (95% CI, 31-55). The 1, 2, and 4-year OS rates were 92±5%, 70±8% and 51±9%, respectively. 4 (27%) patients developed distant progression (dP). The median dP-FS was not reached (95% CI, 14 to not reached). The 1, 2, and 4-year dP-FS rates were 100%, 50±19% and 50±19%, respectively. 7 patients had disease recurrence, 4 and 3 during and after completion of Durvalumab. The pattern of disease recurrence was distant and local in 4 and 3 patients, oligo-metastatic disease recurrence in 9 patients. 3 (10%) discontinued IO due to esophageal and lung G3 toxicity.

Conclusions: To our knowledge this is the first trial to report efficacy and safety of ChT-SAbR-IO. LA-NSCLC patients treated had optimal LC and promising OS with low rate of G3 toxicity. Our early outcomes would suggest the feasibility of SAbR as sequential schedule approach in LA-NSCLC patients unfit for concurrent ChT-RT.

1. Int J Radiat Oncol Biol Phys 2023;115(4):886-896. doi: 10.1016/j.ijrobp.2022.10.025.

Keywords: stereotactica ablative radiotherapy (SAbR), locally advanced non-small cell lung cancer, immunotherapy

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.01 Contemporary Landscape of Acquired Resistance to Next-Generation ALK Inhibitors: Paired Pre-/Post-Treatment Biopsy Analysis

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Introduction: Next-generation ALK tyrosine kinase inhibitors (TKIs) have supplanted the first-generation (1G) TKI crizotinib as first-line (1L) treatment for patients with ALK-rearranged advanced lung cancer. Data are lacking on the landscape of mechanisms of acquired resistance (AR) that emerge after 1L next-generation TKIs, without prior crizotinib. Here, we report the largest analysis, to our knowledge, of paired pre- and post-ALK TKI biopsies evaluating AR.

Methods: This retrospective study included patients treated with second-generation (2G; alectinib, brigatinib, ceritinib) and/or third-generation (3G; lorlatinib) ALK TKIs with paired (pre- and post-TKI) biopsies assessed with next-generation sequencing (NGS). Pre-treatment biopsies were obtained immediately before TKI of interest. Alteration frequencies were compared between biopsies post- versus pre-TKI (McNemar's exact test) and with versus without prior crizotinib (Chi-Square or Fisher's exact test).

Results: We identified 101 patients with 152 paired biopsies. Sixty-eight patients had 84 paired pre/post-2G TKI biopsies. Acquired ALK resistance mutations were identified in 8 (61.5%) post-2G TKI biopsies with prior crizotinib versus 24 (33.8%) without prior crizotinib (p=0.07). Recurrent acquired gene alterations in ≥5% of post-2G TKI biopsies included TP53 (11.5%), SETD2 (11.1%), SMARCA4 (8.8%), MET (7.1%; amplification: 4.8%; VUS: 2.4%), SMAD4 (6.5%), EGFR (6.0%; amplification: 1.2%; VUS: 4.8%), KEAP1 (5.9%), NOTCH2 (5.6%), and CDKN2A/B (5.4%), with similar frequencies with versus without prior crizotinib (Table). Among patients without prior crizotinib, MET amplification was numerically more frequent on post- versus pre-2G TKI biopsies (5.6% vs 1.4%, p=0.25). Acquired alterations were not identified in ALK or other genes in 20 (23.8%) post-2G TKI biopsies. Sixty patients had 68 paired pre/post-lorlatinib biopsies. Acquired ALK mutations were identified in 12 (37.5%) post-lorlatinib biopsies with prior crizotinib versus 5 (13.9%) without prior crizotinib (p=0.048). Recurrent acquired gene alterations in ≥5% of post-lorlatinib biopsies included CDKN2A/B (15.2%), TP53 (13.4%), MDM2 (13.0%), MET (11.8%; all amplifications), EGFR (7.4%; amplification: 4.4%; VUS: 2.9%), and NF1 (6.5%). Among patients without prior crizotinib, MET amplification was more frequent on post- versus pre-lorlatinib biopsies (22.2% vs 2.8%, p=0.016). Acquired gene alterations were not identified in 23 (33.8%) post-lorlatinib biopsies.

Conclusions: First-line versus post-crizotinib use of next-generation ALK TKIs was associated with lower frequency of acquired ALK mutations, implicating greater role for off-target AR. MET amplification represents a recurrent off-target AR mechanism and highlights the critical role for post-TKI biopsies to enable consideration of ALK/MET co-inhibition. NGS does not identify putative AR mechanisms for significant proportion of patients, emphasizing a need to investigate non-genomic AR mechanisms.

Table: Landscape of Acquired On-Target and Off-Target Genomic Alterations after Next-Generation ALK TKIs Per Paired Pre- and Post-TKI Analyses

Acquired Alterations after 2G ALK TKIs				Acquired Alterations after 3G ALK TKI (Lorlatinib)			
	Prior Criz (N=13)	No Prior Criz (N=71)	*P* Value		Prior Criz (N=32)	No Prior Criz (N=36)	*P* Value
***ALK* Mutations (On-Target)**				***ALK* Mutations (On-Target)**			
≥1 mut	8/13 (61.5%)	24/71 (33.8%)	0.07	≥1 mut	12/32 (37.5%)	5/36 (13.9%)	0.048
≥2 co-occurring mut	6/13 (46.2%)	6/71 (8.5%)	0.002	≥2 co-occurring mut	11/32 (34.4%)	5/36 (13.9%)	0.047
Off-Target				**Off-Target**			
TP53 mut	2/12 (16.7%)	7/66 (10.6%)	-	*CDKN2A/B* loss	7/31 (22.6%)	3/35 (8.6%)	-
SETD2 mut	0/0 (0%)	2/18 (11.1%)	-	*TP53*	6/32 (18.8%)	3/35 (8.6%)	-
SMARCA4 mut	0/3 (0%)	3/31 (9.7%)	-	*TP53* mut	5/32 (15.6%)	3/35 (8.6%)	-
MET	1/13 (7.7%)	5/71 (7.0%)	-	*TP53* deletion	1/32 (3.1%)	0/35 (0%)	-
MET amp*	1/13 (7.7%)	3/71 (4.2%)	-	*MDM2* amp	1/10 (10.0%)	2/13 (15.4%)	-
MET mut §	0/13 (0%)	2/71 (2.8%)	-	*MET*	1/32 (3.1%)	7/36 (19.4%)	-
SMAD4 mut	1/12 (8.3%)	4/65 (6.2%)	-	*MET* amp*	1/32 (3.1%)	7/36 (19.4%)	-
EGFR	1/13 (7.7%)	4/70 (5.7%)	-	*EGFR*	3/32 (9.4%)	2/36 (5.6%)	-
EGFR amp	1/13 (7.7%)	0/70 (0%)	-	*EGFR* mut †	1/32 (3.1%)	1/36 (2.8%)	-
EGFR mut †	0/13 (0%)	4/70 (5.7%)	-	*EGFR* amp	2/32 (6.3%)	1/36 (2.8%)	-
KEAP1 mut	0/3 (0%)	2/31 (6.5%)	-	*NF1* mut	2/28 (7.1%)	2/34 (5.9%)	-
NOTCH2 mut	0/4 (0%)	2/32 (6.3%)	-				
CDKN2A/B loss	0/12 (0%)	4/62 (6.5%)	-				
No acquired gene alteration identified ‡	4/13 (30.8%)	16/71 (22.5%)	0.50	**No acquired gene alteration identified ‡**	8/32 (25.0%)	15/36 (41.7%)	0.15

Genes identified as having acquired alterations in ≥5% of post-2G TKI or post-3G TKI biopsies compared to the immediate pre-treatment biopsies per paired biopsy analyses are shown. Denominators represent the number of biopsies evaluated by next-generation sequencing assays that covered each respective gene.
*Acquired *ALK* mutations and *MET* amplification were mutually exclusive except in one post-2G TKI biopsy (with prior crizotinib).
§ All identified acquired *MET* mutations have unknown functional significance.
† All identified acquired *EGFR* mutations have unknown functional significance, except for one post-2G TKI biopsy (without prior crizotinib) with a potentially activating *EGFR* mutation (*EGFR* P596L) with concurrent *MET* amplification.
‡ Of the 43 patients with no identified acquired gene alterations (including in *ALK* or other genes), *ALK* fusion was not detected in three post-3G TKI biopsies (prior crizotinib: n=2, no prior crizotinib: n=1) and was not evaluated in one post-2G TKI (without prior crizotinib) and two post-3G TKI biopsies (without prior crizotinib).
Abbreviations: 2G, second-generation; 3G, third-generation; amp, amplification; criz, crizotinib; mut, mutation; TKI, tyrosine kinase inhibitor.

Keywords: Next-generation ALK TKIs, Acquired resistance, MET amplification

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.02 Updated Efficacy and Safety of Taletrectinib in Patients With ROS1+ Non-Small Cell Lung Cancer: The Global TRUST-II Study

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Introduction: Taletrectinib, an oral, potent, central nervous system-active, selective next-generation ROS1 inhibitor, demonstrated high and durable responses, robust intracranial activity, prolonged progression-free survival (PFS), favorable tolerability, and low rates of neurologic adverse events in a pooled analysis from the regional TRUST-I (NCT04395677) and global TRUST-II (NCT04919811) trials (Pérol M, et al. J Clin Oncol. 2025:epub April 3, 2025). With 5 months of additional follow-up since our last publication (Liu G, et al. J Thorac Oncol. 2024;19:S72), we report updated efficacy and safety in tyrosine kinase inhibitor (TKI)-naive and TKI-pretreated patients from the registrational arms of the TRUST-II trial evaluating the efficacy and safety of taletrectinib in patients with advanced ROS1+ non-small cell lung cancer (NSCLC).

Methods: TRUST-II is a global, multicenter, single-arm pivotal phase 2 study of taletrectinib 600 mg once-daily in patients with ROS1+ tumors and included 2 registrational NSCLC cohorts: 1) TKI naive, ≤1 line of chemotherapy, and 2) TKI pretreated, 1 prior ROS1 TKI, and ≤1 line of chemotherapy. The primary endpoint was objective response rate (ORR) by independent review committee per RECIST v1.1. Key secondary endpoints included duration of response (DOR), PFS, and safety.

Results: As of October 28, 2024, 105 patients were enrolled in TRUST-II registrational cohorts (median age: 57 years; 55% female; 55% never smoked); 47% were from North America/Europe. Among TKI-naive and TKI-pretreated patients, 16% and 32% had measurable baseline brain metastases, respectively. In 54 efficacy-evaluable TKI-naive patients, ORR was 85% (95% CI: 73, 93) and median DOR was not reached (NR). In 47 efficacy-evaluable TKI-pretreated patients, ORR was 62% (95% CI: 46, 75) and median DOR was 19.4 months (95% CI: 10.7, NR). Median PFS was NR in TKI-naive patients and 11.8 months (95% CI: 7.7, 20.6) in TKI-pretreated patients (Table). The most common treatment-emergent adverse events (TEAEs) among patients receiving taletrectinib 600 mg were increased ALT (67%), increased AST (65%), and diarrhea (58%). Rates of neurologic TEAEs were low (dysgeusia: 19%; dizziness: 18%) and mostly grade 1. TEAEs led to discontinuation in 9% of patients; most (11 of 15) were considered unrelated to taletrectinib.

Conclusions: With longer follow-up in a geographically diverse population, taletrectinib continues demonstrating high and durable objective responses and a favorable safety profile. Enrollment in TRUST-II is ongoing. Efficacy and safety of taletrectinib will be directly compared with crizotinib in an ongoing randomized head-to-head phase 3 trial in TKI-naive patients with locally advanced or metastatic ROS1+ NSCLC (NCT06564324).

Table: Responses in Evaluable Patients With *ROS1*+ NSCLC[a]

	TKI naive (n=54)	TKI pretreated (n=47)
ORR, % (95% CI)	85 (73, 93)	62 (46, 75)
Complete response, n (%)	4 (7)	5 (11)
Partial response, n (%)	42 (78)	24 (51)
Median DOR[b], months (95% CI)	NR (20.6, NR)	19.4 (10.7, NR)
Median PFS, months (95% CI)	NR (NR, NR)	11.8 (7.7, 20.6)

[a]Response-evaluable patients had received ≥1 dose of taletrectinib 600 mg and had ≥1 measurable lesion at baseline.
[b]DOR was calculated for patients with confirmed responses.
DOR, duration of response; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Keywords: ROS1+, Non-small cell lung cancer (NSCLC), Taletrectinib

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.03 Repotrectinib in Patients With ROS1 Fusion-Positive (ROS1+) NSCLC: Long-Term Follow-Up From the Phase 1/2 TRIDENT-1 Trial

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Introduction: Repotrectinib is a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI) approved for treatment of adult patients with locally advanced/metastatic ROS1+ NSCLC and adult or pediatric patients (≤12 y) with locally advanced/metastatic NTRK+ solid tumors based on the pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). Herein, long-term follow-up data are reported for 2 ROS1+ NSCLC cohorts and safety in all patients treated at the recommended phase 2 dose (RP2D).

Methods: Patients with ROS1+ NSCLC were assigned to 1 of 4 cohorts based on treatment history. In phase 2, patients received repotrectinib 160 mg QD for 14 days, then 160 mg BID. Primary endpoint of phase 2 was confirmed objective response rate (cORR) by blinded independent central review per RECIST v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), intracranial ORR (icORR), and safety. Safety assessments included patients treated at the RP2D across all study cohorts.

Results: At data cutoff of September 3, 2024, median follow-up was 44.6 months (range, 34.7-87.1) in the TKI-naïve cohort (n=71) and 42.0 months (range, 34.7-79.1) in the 1 prior TKI and no chemo cohort (n=56). In the TKI-naïve cohort, cORR was 79% (95% CI, 68-88); median DOR was 36.8 months (95% CI, 27.4-not estimable [NE]), and median PFS was 31.1 months (95% CI, 21.9-NE). Among TKI-naïve patients with measurable brain metastases at baseline (n=9), icORR was 89% (95% CI, 52-100). In the 1 prior TKI and no chemo cohort, cORR was 41% (95% CI, 28-55); median DOR was 17.8 months (95% CI, 7.5-31.4), and median PFS was 8.6 months (95% CI, 5.5-14.5). Among patients in this cohort with measurable brain metastases at baseline (n=13), icORR was 38% (95% CI, 14-68). Of all patients treated at the RP2D (n=502), the most common treatment-emergent adverse event (TEAE) was dizziness (64%). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 164 (33%) patients. TRAEs leading to dose reduction or treatment discontinuation occurred in 39% and 4% of patients, respectively. Additional data will be presented, including OS, subsequent therapies, and efficacy outcomes in an expanded population.

Conclusions: Repotrectinib continued to demonstrate durable efficacy and intracranial activity in patients with ROS1+ NSCLC in the TKI-naïve and the 1 prior TKI and no chemo cohorts of TRIDENT-1, with median follow-up of ≥42 months. Safety outcomes were consistent with previous reports.

Table: Efficacy of Repotrectinib in Patients With *ROS1+* NSCLC

ROS1+ NSCLC cohorts	TKI-naive (n=71)	1 TKI and no chemo (n=56)
cORR (CR + PR) per BICR,[a] n (%) [95% CI]	**56 (79) [68–88]**	**23 (41) [28–55]**
CR, n (%)	10 (14)	4 (7)
PR, n (%)	46 (65)	19 (34)
SD, n (%)	11 (15)	21 (38)
PD, n (%)	2 (3)	9 (16)
Not evaluable, (%)	0	2 (4)
Duration of response		
Events, n (%)	25 (45)	15 (65)
Median, months (95% CI)	36.8 (27.4–NE)	17.8 (7.5–31.4)
Progression-free survival		
Events, n (%)	34 (48)	38 (68)
Median, months (95% CI)	31.1 (21.9–NE)	8.6 (5.5–14.5)
Efficacy in patients with measurable brain metastases at baseline[b]	**(n=9)**	**(n=13)**
Intracranial ORR per BICR, % (95% CI)	**89 (52–100)**	**38 (14–68)**
CR, n (%)	4 (44)	0
PR, n (%)	4 (44)	5 (38)
Efficacy in patients with *ROS1+* G2032R NSCLC[c]	-	**(n=17)**
cORR, % (95% CI)	-	59 (33–82)
Median duration of response, months (95% CI)	-	7.6 (3.7–NE)

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; NE, not estimable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; *ROS1+*, *ROS1* fusion–positive; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a]In the TKI-naive cohort, 2 patients (3%) had missing data; in the 1 TKI and no chemo cohort, 1 patient (2%) had missing data.
[b]Intracranial cORR was assessed by modified RECIST v1.1 in evaluable patients in the phase 2 portion of study.
[c]Among all TKI-pretreated patients across EXP 2-4.

Keywords: ROS1, NSCLC, TKI

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.04 Updated Efficacy, Safety, and Genomic Data in Patients With Trk Fusion Lung Cancer Treated With Larotrectinib

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Introduction: NTRK gene fusions are oncogenic drivers in a variety of cancers including lung cancer. Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in TRK fusion cancer. Here, we report an additional year of follow-up after the previously published larotrectinib efficacy and safety data, as well as a biomarker analysis, in patients with TRK fusion lung cancer.

Methods: Patients with TRK fusion lung cancer treated with larotrectinib in 2 clinical trials (NCT02122913 and NCT02576431) were included. Larotrectinib was administered at 100 mg twice daily. Response was assessed by an independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors version 1.1. Tumor DNA or circulating tumor DNA (ctDNA) next-generation sequencing (NGS) was performed before (baseline) and after larotrectinib initiation. On-target NTRK (solvent front, gatekeeper, and xDFG) mutations and COSMIC-classified tier 1/2 off-target alterations were identified. Secondary (acquired) resistance was defined as the development of resistance after meaningful clinical benefit (complete response [CR]/partial response [PR]/stable disease [SD] ≥4 months). The data cutoff was July 20, 2024.

Results: At data cutoff, 32 patients with a median age of 56 years (range 25-81) with TRK fusion lung cancer were enrolled, including 12 with known CNS metastases at baseline. Patients had received a median of 2 prior lines of systemic therapies; 1 patient was systemic treatment-naïve in the metastatic/unresectable setting. The overall response rate was 69% (95% confidence interval [CI] 50-84): 4 CR, 18 PR, 6 SD, 2 progressive disease [PD], and 2 not evaluable. The median time to response was 1.8 months (range 1.5-7.3). Median duration of response was 34 months (95% CI 13-not estimable [NE]) with a median follow-up of 37 months. Median progression-free survival was 22 months (95% CI 10-39) with a median follow-up of 38 months. Median overall survival was 41 months (95% CI 17-NE) with a median follow-up of 46 months. Median duration of treatment was 20 months (range 2-75). At data cutoff, 8 (25%) patients remained on treatment: 7 had responded and 1 was not evaluable for response. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 10 (31%) patients. One patient discontinued treatment due to TRAEs (increased alanine aminotransferase, aspartate aminotransferase, and gammaglutamyl transferase). Secondary larotrectinib resistance was observed in 5 patients with valid post-baseline ctDNA; acquired alterations were identified in 2 of these patients. An acquired on-target alteration was identified in 1 patient (NTRK1 F589L). An acquired off-target alteration was identified in 1 patient (TP53 C238F). Acquired on- and/or off-target alterations were identified in 3 other patients that did not have PD by IRC assessment (TP53 G245V in 1 patient, NTRK1 F589L in 1 patient; and both NTRK1 F589L and KRAS G12D in 1 patient).

Conclusions: Larotrectinib continues to demonstrate rapid and durable responses, extended survival benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer. These results support the wider adoption of NGS panels that incorporate NTRK gene fusion detection.

Keywords: larotrectinib, lung cancer, TRK fusion

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.05 Liquid Biopsy in BRAF V600E NSCLC Treated With Dabrafenib Plus Trametinib: Final Analysis of LiBRA Study (GOIRC-03-2020)

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Introduction: Dabrafenib plus trametinib (D+T) is the standard first-line (1L) treatment of advanced BRAF V600E mutated non-small cell lung cancer (NSCLC). To date, the role of liquid biopsy monitoring activity for predicting outcomes of 1L D+T in advanced BRAF V600E mutated NSCLC has not been assessed.

Methods: We conducted a prospective multicentric study in 25 Italian Centers aimed at exploring the role of liquid biopsy in advanced BRAF V600E mutated NSCLC patients treated with 1L D+T. Plasma samples were collected before treatment start (t0), after 4 weeks (t1), every 4 weeks during the first 16 weeks of treatment and every 8 weeks until progression (PD). Digital droplet PCR (ddPCR) was performed to monitor BRAF V600E in plasma samples. Next-Generation Sequencing (NGS) analysis was conducted on plasma samples at t0 and PD.

Results: We enrolled 40 BRAF V600E mutated NSCLC patients treated with 1L D+T. Overall, 24 (60%) patients were male, median age was 71 years (Interquartile Range [IQR], 65-77), and 28 (70%) patients were smokers. D+T resulted in an Overall Response Rate of 43% (95% Confidence Interval [CI], 27-58) and a Disease Control Rate of 70% (95% CI, 56-84). After a median follow-up of 17.8 months (95% CI, 14.0-21.8), 24 (60%) patients progressed and 18 (45%) patients died. Median progression-free survival (mPFS) was 8.3 months (95% CI, 4.4- Not Reached [NR]) and median Overall Survival (mOS) was 21.1 months (95% CI, 8.6-NR).

ddPCR analysis at t0 revealed that ctDNA was positive for BRAF V600E in 24/39 (62%) evaluable patients (shedders), with a median variant allele frequency (AF) of 1.1% (IQR, 0.6-5.2). At NGS, baseline shedding was observed in 26/39 (67%) evaluable patients. Co-mutations were detected in NGS analysis at t0 in 19/26 (73%) shedders, with TP53 being the most frequent (14/26, 54%). Among baseline shedders evaluable for clearance at t1 (n=21), 17 (81%) cleared BRAF V600E. At PD, 11/20 (55%) evaluable patients had detectable BRAF V600E on ctDNA, eight of whom experienced an increase in AF. Among patients who experienced a biological PD (n=10), all of them had a radiologic/clinical PD with a median interval of 4.9 weeks (IQR 1.4-9.8). All the patients harbored a co-mutation at PD, and putative resistance mechanisms included mutations in NRAS, KRAS, TP53 and CNV in MET, EGFR, and ERBB2.

Among baseline shedders, higher BRAF V600E AF was associated with shorter PFS and OS: Cox Regression for continuous variable PFS HR 1.09 (95% CI, 1.02-1.17, p=0.013), OS HR 1.10 (95% CI, 1.02-1.18, p=0.010). Baseline EGFR and MET amp were associated with poor PFS (3.4 vs 10.3, p<0.001; 3.4 vs 10.3, p=0.018) and OS (3.4 vs NR, p<0.001; 3.7 vs NR, p=0.009). Clearance of BRAF V600E by t1 was associated with improved PFS (8.3 vs. 1.4 months, p<0.001) and OS (10.5 vs. 2.2 months, p<0.001).

Conclusions: Liquid biopsy might be a promising tool to predict the outcomes of 1L D+T in advanced BRAF V600E mutated NSCLC. The dynamics of ctDNA shedding provide potential early biomarkers of treatment response.

Keywords: liquid biopsy, BRAF V600E, NSCLC

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.06 Efficacy and Safety of 1L Olomorasib Plus Pembrolizumab in KRAS G12C-Mutant NSCLC: Results From LOXO-RAS-20001 and SUNRAY-01

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Introduction: Olomorasib, a potent and selective second-generation KRAS G12C inhibitor, has demonstrated promising antitumor activity and a manageable safety profile in KRAS G12C-mutant NSCLC in combination with pembrolizumab, a current first-line (1L) standard of care (SOC) for patients (pts) with NSCLC and PD-L1 expression ≥50%. Here we report results of an integrated analysis in 1L pts who received olomorasib plus pembrolizumab from the dose optimization cohorts in LOXO-RAS-20001 (Phase 1) and SUNRAY-01 (Phase 3).

Methods: Pts with advanced KRAS G12C-mutant NSCLC (ECOG PS 0-1) were randomized to olomorasib (50 or 100 mg, orally BID) with pembrolizumab (200 mg Q3W) and stratified based on PD-L1 expression (0-49% versus ≥50%). One prior cycle of pembrolizumab was allowed when timely initiation for treatment was medically indicated. Safety was assessed across all treated pts. ORR was assessed in the efficacy evaluable population, including pts with ≥1 post-baseline response assessment or who discontinued treatment before the first response assessment.

Results: As of 15 January 2025, 85 pts received olomorasib plus pembrolizumab including 14 pts (17%) who received 1 cycle of pembrolizumab prior to enrollment; 63% were PD-L1 ≥50%, 21% were PD-L1 1-49%, and 16% were PD-L1 <1% (1 pt unknown). With a median follow-up of 7.6 months (IQR: 5.5-9.5), any grade treatment-related adverse events (TRAEs) in ≥20% of pts were diarrhea (29%) and ALT/AST increased (26%/25%). The most common grade ≥3 TRAEs were ALT/AST increased (18%/14%), and diarrhea (7%). Hepatic events were overall manageable with dose adjustments and/or corticosteroids. TRAEs led to olomorasib dose reduction in 29% of pts and discontinuation of combination treatment in 9% of pts. The ORR was 71% in all pts (n=82) regardless of PD-L1 expression and 85% in pts with PD-L1 ≥50% who received olomorasib 100 mg BID (n=26). Responses were durable across all pts, as the median DOR was not yet reached and 6-month PFS rate was 77% (Table 1). Updated data will be presented.

Conclusions: In this merged dataset with double the number of 1L pts relative to previous presentations, olomorasib plus pembrolizumab continues to demonstrate a manageable safety profile and promising efficacy. These updated findings, including longer follow-up on LOXO-RAS-20001 pts, provide additional support for the ongoing Phase 3 SUNRAY-01 trial, comparing olomorasib (100 mg BID) plus pembrolizumab versus placebo plus pembrolizumab as 1L treatment in pts with KRAS G12C-mutant NSCLC and PD-L1 ≥50%.

Table. Response and Time-To-Event Endpoints in the Efficacy Evaluable Population

	Olomorasib (50 mg or 100 mg BID) + Pembrolizumab	
Endpoint	All Pts (PD-L1 0-100%) N = 82	Pts with PD-L1 ≥50%* N = 52
ORR†, % (n/N)	71 (58/82)	79 (41/52)
BOR, n (%)		
CR†	2 (2)	0 (0)
PR†	56 (68)	41 (79)
SD	17 (21)	7 (14)
PD	4 (5)	2 (4)
NE	3 (4)	2 (4)
DCR, % (n/N)	92 (75/82)	92 (48/52)
mDOR, months (95% CI)	NE (10.5-NE)	NE (10.5-NE)
mPFS, months (95% CI)	NE (12.0-NE)	NE (12.0-NE)
6-month PFS rate, % (95% CI)	77 (65-86)	83 (69-91)

†Includes responses confirmed and pending. *Target population in Phase 3 study.

Keywords: KRAS G12C, olomorasib, immunotherapy

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.07 Efficacy and Safety of GFH375 in Advanced Non-small Cell Lung Cancer Patients with KRAS G12D Mutation

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Introduction: Kirsten rat sarcoma (KRAS) G12D mutation ranks among the most prevalent oncogenic drivers in human cancers, occurring in approximately 4% of NSCLC cases and associated with poorer prognosis. To date, no targeted therapies for KRAS G12D have been approved, leaving a significant unmet medical need. GFH375 is a potent, highly selective, and orally bioavailable KRAS G12D inhibitor that showed encouraging preliminary clinical efficacy (presented in ASCO 2025). Herein, we report the cumulative safety data of GFH375 and preliminary efficacy in NSCLC from the phase I/II study (NCT06500676).

Methods: Eligible patients (pts) who had advanced KRAS G12D mutant solid tumors and failed prior standard therapies were enrolled and received GFH375 once daily (QD) at dose levels 100, 200, 400, 600, 750, 900 mg, or twice daily (BID) 300 mg. Key study endpoints included safety and anti-tumor activities according to RECIST v1.1.

Results: 142 pts were enrolled, including 28 NSCLC, 85 pancreatic ductal adenocarcinoma (PDAC) and 29 other solid tumors. The median exposure time of GFH375 was 2.2 (range: 0.2-11.3) months as of 17-Jun-2025. The most common treatment-related adverse events (TRAEs) (reported in ≥20% pts) were diarrhea, vomiting, nausea, anemia, decreased appetite, neutrophil count decreased, white blood cell count decreased, aspartate aminotransferase increased, asthenia, hypoalbuminemia and alanine aminotransferase increased, primarily grade 1 or 2. Treatment-related grade 3/4 AEs and SAEs occurred in 27.5% (39/142) and 7.7% (11/142) of pts. 11 pts (7.7%) had dose reduction, and 6 (4.2%) discontinued due to TRAEs. No treatment-related death. 28 pts with NSCLC (100% adenocarcinoma, 53.6% male, and median age 61) were treated. 17 (60.7%) pts were never-smoker. 22 pts had baseline PD-L1 TPS reported: 13 (59.1%), 8 (36.4%) and 0 pts had TPS <1%, 1%-49% and ≥50%, respectively. All pts had metastatic disease at baseline. 64.3% (18/28) of pts received at least 2 prior lines of systemic therapies and 96.4% (27/28) received anti-PD1/PD-L1. As of 15-Jul-2025, the median follow-up time was 4.5 (range: 1.8-12.2) months. Tumor response was observed at all dose levels. Among the 26 evaluable pts, objective response rate (ORR) was 57.7% (15/26, 90%CI: [39.8%, 74.2%]) and disease control rate (DCR) 88.5% (23/26, 90%CI: [72.8%, 96.8%]). At 600 mg QD, ORR was 68.8% (11/16, 90%CI: [41.3%, 89.0%]) and DCR was 93.8% (15/16, 90%CI: [69.8%, 99.8%]). Among the 18 pts with baseline ctDNA test, 9 had detectable KRAS G12D mutation. Co-mutation genes included KEAP1 (33.3%, 6/18), STK11 (33.3%, 6/18), TP53 (27.8%, 5/18) and PIK3CA (11.1%, 2/18). Conclusion: GFH375 is well tolerated. As monotherapy, it demonstrates promising anti-tumor activity in NSCLC pts with KRAS G12D mutations, warranting further clinical development.

Keywords: NSCLC, Target therapy, KRAS G12D inhibitor

MA02 NEW TREATMENT STRATEGIES IN OTHER THAN EGFR-POSITIVE TUMORS
SUNDAY, SEPTEMBER 7, 2025 - 12:00 - 13:15

MA02.08 Upfront Management of Brain Metastases (BM) in Oncogene-Addicted NSCLC Treated With Targeted Therapies: An EORTC Survey

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Introduction: BM are frequent in patients with oncogene-addicted non-small cell lung cancer (NSCLC). Although patients with untreated asymptomatic BM are increasingly allowed in registrational trials, data regarding intracranial efficacy of targeted therapies (TT) in this setting is limited resulting in a lack of evidence for decision-making.

Methods: A web-based survey was distributed among EORTC and ESTRO members to understand the preferred management of untreated asymptomatic BM (asBM) and symptomatic BM (sBM) in patients with oncogene-addicted NSCLC.

Results: Responses from 166 participants were received (57.2% medical oncologists, 41.0% radiation oncologists): 81.9% of the participants routinely screen for BM, and 98.9% have access to local brain therapies such as stereotactic radiotherapy. Access to TT differed across oncogenes: EGFR and ALK had the highest (~ 97%) and NTRK and HER2 the lowest (~ 60%). Overall, the preferred treatment for asBM were TT (68.8%) while it was local therapy (42.9%) for sBM (Table 1), but there were differences according to the intracranial objective response rate (icORR) of TT, oncogene and participants' specialty. TT were grouped according to icORR: 39.6%, 26.4% and 32.0% of participants had access to TT with 'high', 'medium' and 'low/unknown' icORR (defined as icORR ≥75%, 50-75%, <50%/unknown respectively). In asBM, TT were the preferred treatment across icORR groups, with a higher % in the 'high' versus (vs) 'low/unknown' (75.3% vs 63.6%). For sBM, local therapy was more often preferred, with a higher % for low/unknown' vs 'high' icORR (48.3% vs 37.1%). Importantly, in sBM, TT were preferred in 27.1% vs 11.9% of participants in the 'high' vs 'low/unknown' icORR groups. When oncogenes were grouped in 'Classic' (ALK/EGFR/ROS1) vs 'Emergent'; the preferred treatment for asBM were TT (80.9% vs 61.5%). For sBM, the preferred treatment was local therapy + TT (34.7%) in 'Classic' vs local therapy alone (49.2%) in 'Emergent' oncogenes. The factors that influenced decision-making were icORR for TT (85.5%), disease burden (81.3%), but also participants' specialty. Medical oncologists more often preferred TT for asBM compared to radiation oncologists (81.8% vs 50.9%). Almost half (47.8%) of participants do not give TT concurrently with cranial radiotherapy, 7.9% are unsure, but no significant differences were found across oncogenes/ specialty.

Conclusions: Management of BM is different for asBM vs sBM, but also for the different oncogenes (probably related to available evidence and icORR of TT) and across specialities. Research efforts should be directed to improve evidence-based decision-making via dedicated clinical trials and/or prospective data collection.

Table 1. Preferred management of symptomatic and asymptomatic brain metastases in the overall analysis (all) and subgroup analysis by medical specialty, targeted therapy (TT) intracranial response rate (icORR) and oncogene type.

	All	Medical Specialty		Targeted therapy icORR			Oncogene	
Preferred upfront treatment		**Medical Oncology**	**Radiation Oncology**	**High**	**Medium**	**Low/ Unknown**	**Classic**	**Emergent**
Symptomatic								
TT	18.9%	25.9%	10.4%	27.1%	15.6%	11.9%	31.5%	11.4%
Local Therapy	42.9%	36.2%	52.7%	37.1%	45.2%	48.3%	32.6%	49.2%
TT + Local Therapy	35.4%	36.7%	33.7%	34.7%	35.1%	36.7%	34.7%	35.9%
Don't know	2.6%	1.23%	3.2%	1.2%	4.1%	3.2%	1.2%	3.5%
Asymptomatic								
TT	68.8%	81.8%	50.9%	75.3%	65.5%	63.6%	80.9%	61.5%
Local Therapy	10.0%	6.3%	15.6%	7.3%	12.3%	11.4%	2.7%	14.4%
TT + Local Therapy	18.3%	10.4%	30.1%	16.1%	18.1%	21.4%	15.4%	20.1%
Don't know	2.9%	1.5%	3.4%	1.4%	4.1%	3.6%	1.0%	4.0%

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.01 Ultrasensitive MRD Improves Detection in Resectable Stage I NSCLC

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Introduction: Circulating tumor (ct)DNA is a powerful prognostic marker in early-stage NSCLC, however detecting ctDNA in the blood of stage I non-small cell lung cancer (NSCLC) patients has been limited, especially for adenocarcinomas. The ctDNA Lung DETECT study evaluated perioperative ctDNA and recurrence-free survival (RFS) in patients with clinical stage I NSCLC (NCT05254782), and previously reported suboptimal sensitivity using a first-generation whole exome sequencing (WES) based tumor-informed assay (Khan et al, ASCO 2024). Foresight CLARITY (Foresight Diagnostics, Aurora CO) tracks tumor-specific variants identified from whole genome sequencing (WGS), with 95% LOD of 0.3 x 10-6 (Cabel et al, ESMO 2024). Here we applied this ultrasensitive approach to patients from ctDNA Lung DETECT to test if it can improve MRD detection in stage I NSCLC, focusing on peri-operative detection, association with RFS, lead time, and ctDNA clearance with adjuvant therapy.

Methods: Patients with stage I NSCLC planned for resection at University Health Network consented to banking of surgical tissue and blood pre-operatively, 3-6 weeks post-resection (MRD landmark), and one-year post-operatively. Bespoke panels targeting up to 5000 somatic variants identified via WGS of FFPE tumor tissue were generated. Blood plasma samples were analysed for MRD, with the laboratory blinded to outcomes. Outcomes included ctDNA detection, sensitivity and association with RFS.

Results: We profiled 140 blood and tissue specimens from 30 patients with clinical stage I NSCLC (pathologic stage: I-16, II-8, III/IV-6). Most had adenocarcinoma (83%), 57% received adjuvant therapy and 37% had cancer recurrence. Bespoke assays were successfully generated for 100% of patients and applied to plasma samples before and after resection. ctDNA was detected in 67.9% of preoperative and 37.9% of postoperative samples, substantially higher than the previously reported rate in the full ctDNA Lung DETECT study with a first-generation assay (22.7% and 2.0%, respectively). Preoperative ctDNA detection rates in pathologic stage IA and IB were 33% and 71%, respectively; 75% of these had adenocarcinoma. Landmark MRD was detectable in 55% of relapse cases, higher than the 10% detection rate reported previously with a first-generation assay (Khan et al, ASCO 2024). This included patients with stage I disease and MRD levels as low as 1.0x10-6. Both preoperative ctDNA and postoperative MRD were associated with a trend to shortened RFS, even though a significant fraction of MRD positive patients later received adjuvant chemotherapy or osimertinib (ongoing). MRD detection at one year was strongly associated with RFS (P=0.0001, HR 10.7, 95% CI 2.4-48). In patients with recurrence and MRD at the landmark, the median lead-time to recurrence was 10 months (range: 4-24, n=6). Moreover, 92.9% (13/14) of samples collected within 12 months of relapse had detectable MRD. Finally, MRD clearance was observed in a subset of patients receiving adjuvant therapy.

Conclusions: Ultrasensitive MRD detection using a WGS tumor-informed assay demonstrated higher rates of MRD detection in clinical stage I patients than prior reports using a first-generation assay. MRD detection was associated with RFS and provided clinically relevant lead times. These results support exploring ultrasensitive ctDNA MRD-guided treatment strategies in stage I NSCLC.

Keywords: ctDNA, Minimal Residual Disease (MRD), Stage I NSCLC

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.02 Clinical Performance of a Tumor Informed Whole Genome Based ctDNA Assay for Predicting Recurrence in Early-Stage Resectable NSCLC

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Introduction: Circulating tumor DNA (ctDNA) is a clinically validated biomarker for detecting molecular residual disease (MRD) and guiding treatment decisions in non-small cell lung cancer (NSCLC). Early-stage, resectable NSCLC exhibits an aggressive biology despite limited radiographic burden. This creates a critical need for sensitive tools to inform prognosis and guide therapeutic strategies. Therefore, we assessed the clinical performance of the SignateraTM Genome assay to determine its prognostic value for risk stratification in this patient population.

Methods: We performed a retrospective analysis of residual plasma samples from a real-world dataset. Patients who underwent curative-intent surgery for stage I-III resectable NSCLC between September 25, 2017, to September 3, 2024, were included. Signatera Genome assays were designed from the respective patients' matched tumor and normal whole genome sequencing (WGS) data. ctDNA was subsequently tracked in the patients' longitudinal blood samples, which were collected postoperatively until recurrence/end of follow-up. The MRD window was defined as 2 months from surgery and prior to adjuvant therapy. The correlation between landmark-adjusted ctDNA status within the MRD window and recurrence-free survival (RFS) was assessed using Cox regression analysis. Additionally, any time postsurgical ctDNA positivity across serial time points and RFS was assessed using the Kaplan-Meier method.

Results: In total, 277 patients with Stage I-III resectable NSCLC and available clinical data were identified with a median age of 69 years at the time of surgery. A preliminary analysis was performed on 73 patients with a median follow-up of 3.3 years (range 1.6-7 years) and a median of 7 tests were performed per patient. Detection of ctDNA during the MRD window was associated with significantly worse RFS (HR: 20, 95% CI: 1.8-230, p=0.00061) compared to patients with non-detectable ctDNA. Additionally, among ctDNA-positive patients during the MRD window, those who received adjuvant therapy benefitted, reaching non-detectable ctDNA levels and remaining recurrence-free, compared to patients who did not receive adjuvant therapy. Conversely, ctDNA-negative patients showed no benefit of adjuvant therapy with no significant RFS change observed. Overall, 100% of ctDNA-positive patients at any time post-definitive therapy developed clinically confirmed recurrences. Notably, with serial testing, the assay demonstrated 100% specificity and positive predictive value (PPV), with a negative predictive value (NPV) of 100% for extra-cranial recurrences. Of the two patients with brain-only recurrences, one had detectable ctDNA prior to recurrence. The lead time analysis revealed ctDNA detection to precede any radiological recurrence by a median of 6.5 months (range: 1.3-12.3 months).

Conclusions: These findings demonstrate the value of the WGS-based ctDNA assay for identifying MRD and predicting relapse and adjuvant chemotherapy benefit in patients with early-stage resectable NSCLC. The high specificity and PPV highlight its potential utility in post-surgical risk stratification and individualized patient care. Full cohort analysis will be presented at the time of presentation.

Keywords: ctDNA, Whole genome sequencing, Biomarker

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.03 SAVANNAH: Biomarker Concordance and Acquired Resistance in Patients with EGFRm MET-OverExp and / or Amp NSCLC

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Introduction: Savolitinib is a potent, highly selective and CNS-penetrant oral MET-tyrosine kinase inhibitor. In the Phase II SAVANNAH study (NCT03778229), osimertinib + savolitinib had a high rate of durable responses in patients with EGFR-mutated (EGFRm) advanced NSCLC and high tumour MET overexpression (OverExp) and/or amplification (Amp) after disease progression on osimertinib. We report exploratory analyses of concordance between next-generation sequencing (NGS) of tissue and of circulating tumour DNA (ctDNA) versus fluorescent in-situ hybridisation (FISH) ± immunohistochemistry (IHC) in detecting MET Amp ± OverExp. Plasma analyses for acquired resistance mechanisms to savolitinib ± osimertinib were reported.

Methods: Patients with EGFRm advanced NSCLC and MET OverExp and/or Amp after disease progression on osimertinib received osimertinib 80mg QD + savolitinib 300mg QD, 300mg BID or 600mg QD or savolitinib 300mg BID + placebo. MET OverExp /Amp was centrally confirmed (IHC [Roche], 3+ intensity in ≥50% of tumour cells [MET IHC3+/≥50%]; FISH [Abbott Molecular], ≥5 MET gene copies or MET:CEP7 ratio ≥2 [FISH5+]) or at higher thresholds (MET IHC3+/≥90% [IHC90+] or FISH10+) using tissue obtained following progression on prior osimertinib. Concordance between MET Amp by baseline tissue NGS (FoundationOne® CDx) or baseline ctDNA NGS (GuardantOMNI®) versus FISH ± IHC was assessed. Baseline ctDNA content was estimated using EGFRm (Ex19del/L858R) ctDNA. Paired plasma samples collected at baseline and treatment discontinuation (TD) were analysed using ctDNA NGS to identify acquired resistance mutations. The association of baseline EGFRm ctDNA with PFS was analyzed. DCO: 23 Aug 2024.

Results: Of 343 patients with valid NGS ctDNA data at baseline, 229 had high MET (IHC90+ and/or FISH10+) and 114 did not. Overall, 296/343 (86%) patients had detected EGFRm ctDNA at baseline; of these, 208/296 (70%) and 88/296 (30%) did and did not have high MET, respectively. Among patients with high MET treated with osimertinib + savolitinib, median PFS (mPFS) was numerically longer in patients with baseline undetected EGFRm ctDNA than detected EGFRm ctDNA (mPFS, months [95% CI]: 10.4 [5.3, 16.5] versus 5.7 [4.5, 7.4]). Comparison of MET ctDNA NGS to MET FISH showed modest positive-percent agreement (PPA, sensitivity; 47%) but high negative-percent agreement (NPA, specificity; 86%). Comparison of MET tissue NGS (n=70) to MET FISH showed high PPA (95%) and NPA (86%). When MET IHC90+ and/or FISH10+ were considered, PPA for both ctDNA and tissue NGS decreased to 36% and 62%, respectively, while maintaining high specificity (89% and 96%, respectively). In 105 patients with PFS ≥2 months and paired baseline and TD NGS ctDNA, the most commonly acquired events at TD associated with resistance mechanisms were in EGFR (13%), BRAF (11%), MET (10%), RAS (8%) and ERRB2/ERBB3 (5%).

Conclusions: Baseline detected EGFRm ctDNA was associated with high MET status (MET IHC90+ and/or FISH10+) and numerically shorter PFS on osimertinib + savolitinib vs undetected EGFRm, suggestive of a negative prognostic subgroup. MET ctDNA NGS had high specificity but modest sensitivity for MET FISH10+ detection, with further reduced sensitivity when IHC90+ was also considered. Acquired resistance mutation profiles to savolitinib ± osimertinib included known on-target and suspected bypass signalling resistance mechanisms.

Keywords: SAVANNAH clinical study, MET ctDNA, Acquired resistance

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.04 Comparative Analysis of Circulating Tumor DNA Monitoring Strategies in Advanced NSCLC With MET Exon 14 Skipping Treated With Ensartinib

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Introduction: Circulating tumor DNA (ctDNA) has emerged as a promising tool for therapeutic monitoring. We have previously reported the main findings of the EMBRACE trial, based on which we further conducted a translational biomarker study.

Methods: Plasma samples were collected at baseline (V0), week 4 of treatment (V1), and at end of treatment (EOT). ctDNA was analyzed using a hybrid-capture NGS panel and categorized by three strategies: METex14 mutation only, Class I/II driver mutations, and all detectable mutations. ctDNA dynamics were correlated with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: Among 30 evaluable patients, baseline ctDNA positivity varied by definition: 48.3% for METex14, 48.3% for Class I/II mutations, and 75.9% for all mutations. Early ctDNA clearance at V1 predicted superior outcomes across strategies. METex14 clearance at V1 was associated with ORR of 80% vs 20% ($p = 0.03$) and mPFS of 9.33 vs 2.23 months ($p < 0.001$). Similar trends were observed for Class I/II and pan-mutation monitoring, although specificity declined with broader mutation inclusion. Persistent or re-emergent ctDNA positivity correlated with shorter survival. Longitudinal ctDNA positivity (>=2 positive timepoints) was a strong predictor of early progression. Notably, ctDNA dynamics preceded radiologic progression by a median of 1.61 months using METex14 or Class I/II monitoring, and up to 5.04 months with pan-mutation analysis, highlighting the trade-off between specificity and early molecular relapse detection. Multivariate analysis confirmed V1 ctDNA status as an independent prognostic factor for PFS.

Conclusions: This is the first study to prospectively compare mutation-specific ctDNA monitoring strategies in METex14 NSCLC. METex14 ctDNA clearance offers the highest specificity for treatment response, while broader mutation panels improve sensitivity for molecular progression. Our findings support the integration of early and longitudinal ctDNA dynamics into personalized monitoring and therapeutic decision-making for MET-targeted therapy.

Keywords: ctDNA, METex14, NSCLC

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.05 Circulating Tumor DNA Tumor Fraction as a Precision Biomarker for Radiotherapy in Oligometastatic NSCLC

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Introduction: Local treatments are routinely used in addition to systemic therapy for treatment of oligometastatic lung cancers. However, there are significant challenges in identifying patients with oligometastatic NSCLC that are likely to benefit from local consolidative radiotherapy. Negative results from NRG-LU002 further highlight limitations in accurate patient identification. Our prior work demonstrated that higher pre-radiotherapy (RT) circulating tumor DNA (ctDNA) maximum variant allele fraction (VAF) was associated with worse OS (HR 5.7, p=0.004) and PFS (HR 4.7, p=0.02) in multivariate Cox regression analysis. Here we hypothesize that applying a multimodal algorithm-based cell-free DNA analytic approach (ctDNA-derived tumor fraction estimation or CTFE) to determine pre-RT ctDNA tumor fraction (ctDNA TF) can more robustly stratify patients who stand to benefit from consolidative RT for oligometastatic NSCLC.

Methods: Patients with oligometastatic NSCLC (metastasis in 1-5 organ systems) who underwent liquid biopsy ctDNA analysis using the 105-gene, hybrid-capture, NGS-based Tempus xF assay at any time prior to receiving RT were included in this study. ctDNA TF was estimated (CTFE) using an ensemble algorithm that incorporates pathogenic variant allele frequencies, copy number information, and germline information from plasma cell-free DNA. Limit of blank (LOB) was determined using 20 healthy subjects using the classical non-parametric rank-based approach. Overall survival (OS) and progression-free survival (PFS) were calculated from time of RT to minimize guarantee-time bias.

Results: Out of a real-world cohort of 1,487 patients with oligometastatic NSCLC, 309 patients who underwent RT were included in the final analysis. Median and mean ctDNA TF were 0.007 and 0.053, (range 0-0.522), respectively. Using LOB TF (0.0009) to determine ctDNA TF detectable versus undetectable, 221 patients were ctDNA TF detectable and 88 patients were ctDNA TF undetectable prior to RT. Median OS from time of RT was 25 months for ctDNA TF undetectable compared to 16.8 for ctDNA TF detectable patients (p=0.007). Median PFS was 8.7 months for ctDNA TF undetectable versus 5.2 months for ctDNA TF detectable patients (p=0.01). In multivariate Cox proportional hazards regression analysis, we observed that age, histology, and gender were not associated with OS or PFS. However, ctDNA TF was independently associated with worse OS (HR 23.0, 95% CI 4.038-109.0, p=0.0002) and worse PFS (HR 45.2, 95% CI 7.776-218.4, p<0.0001).

Conclusions: In oligometastatic NSCLC, pre-RT liquid biopsy-based ctDNA TF is a stronger predictor of survival (HR 23.0) than ctDNA maximum VAF (HR 5.7) and can be successfully utilized to risk-stratify patients who are likely to benefit from consolidative RT. Lack of ctDNA detection prior to RT based on CTFE analysis, likely reflective of minimal micrometastatic disease burden, was associated with significantly improved PFS and OS in patients who underwent RT.

Keywords: ctDNA, oligometastatic lung cancer, radiotherapy

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.06 Intrathecal Pemetrexed for Lung Adenocarcinoma Leptomeningeal Metastasis: A Study on Efficacy and Liquid Proteomics

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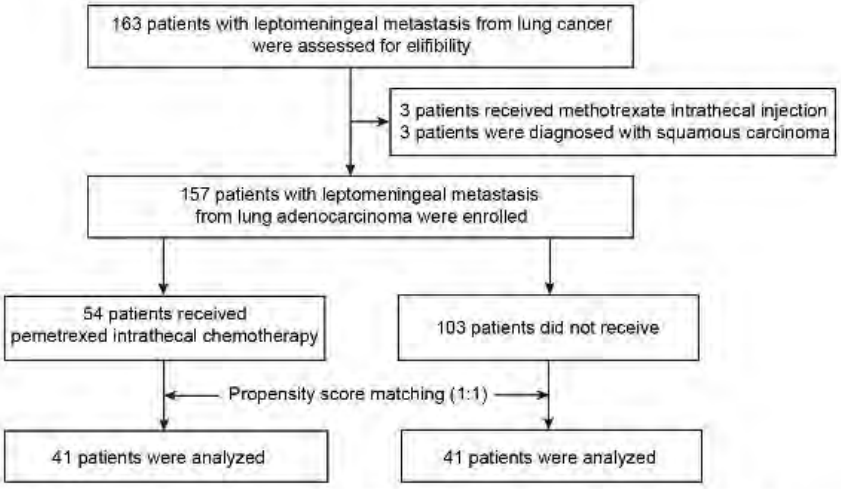
Introduction: Leptomeningeal metastasis (LM), a devastating neurological complication of advanced lung adenocarcinoma (LUAD). The therapeutic potential of intrathecal pemetrexed (IP) and associated biomarkers remains unexplored. Therefore, we investigated the efficacy of IP and identified biomarkers through proteomic profiling of cerebrospinal fluid (CSF) and plasma samples.

Methods: This study enrolled LUAD patients with LM. Following 1:1 propensity score matching (PSM) patients were stratified into IP and non-IP cohorts. IP patients were divided into responders (R) who achieved partial response (PR) and nonresponders (NR) who with stable disease (SD) and progressive disease (PD). Paired baseline plasma and CSF proteomic profiling was performed using Olink Immuno-Oncology panels. Differential expression protein (DEP) analysis was conducted between two cohorts.

Results: The analysis included 163 LM patients, 82 balanced pairs were established in each matched cohort. Multivariable Cox regression revealed that IP reduced mortality risk (HR = 0.427, p = 0.022) and Eastern Cooperative Oncology Group (ECOG) 3-4 conferred higher mortality (HR = 2.737, p = 0.005). The survival benefit of IP was particularly demonstrated in ECOG 3-4 subgroup with median overall survival 11.2 vs 2.5 months (IP vs non-IP, log-rank p = 0.0029). In the Olink proteomic analysis of 18 patients (8 responders (PR) vs 10 nonresponders (SD=8, PD=2) showed that lower plasma MCP-2 and higher CSF ARG1 levels significantly distinguished the responders from the nonresponders (AUC=0.873 and 0.875, respectively).

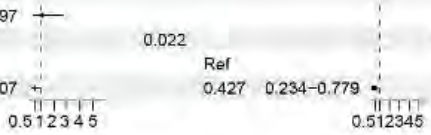
Conclusions: IP treatment is an independent factor for improving survival in LUAD patients with LM, particularly as salvage therapy for ECOG 3-4 patients. IP treatment response may be predicted through CSF and plasma biomarkers identified via proteomic profiling.

A



B

Characteristic	Univariable HR	95%CI	P-value	Multivariable HR	95%CI	P-value
Sex						
Female	Ref					
Male	0.995	0.565–1.755				
Age			0.701			
≤60	Ref					
>60	0.876	0.444–1.727				
Primary leptomeningeal metastasis			0.901			
No	Ref					
Yes	1.081	0.418–2.696				
Brain metastasis			0.525			
No	Ref					
Yes	1.230	0.649–2.330				
ECOG			<0.001			0.005
1–2	Ref			Ref		
3–4	2.866	1.541–5.329		2.737	1.361–5.504	
Brain radiotherapy before LM			0.374			
No	Ref					
Yes	0.691	0.306–1.561				
Cytotoxic chemotherapy before LM			0.022			0.180
No	Ref			Ref		
Yes	2.049	1.110–3.780		1.588	0.808–3.122	
EGFR–TKI therapy before LM			0.899			
No	Ref					
Yes	1.062	0.418–2.697				
Intrathecal pemetrexed			0.022			0.022
No	Ref			Ref		
Yes	0.505	0.281–0.907		0.427	0.234–0.779	



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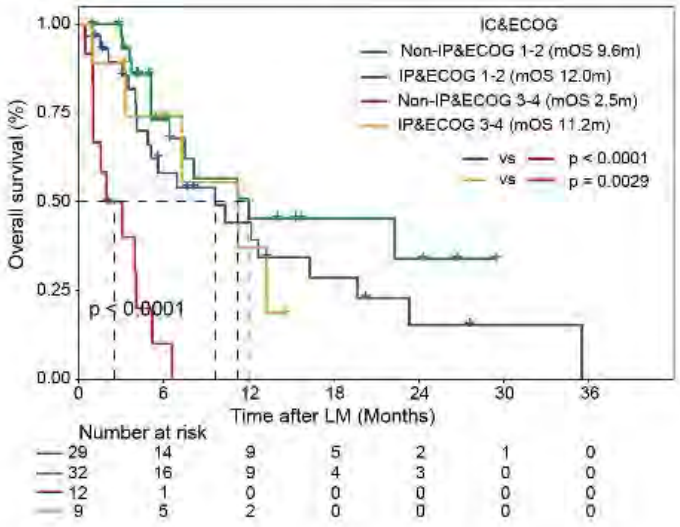

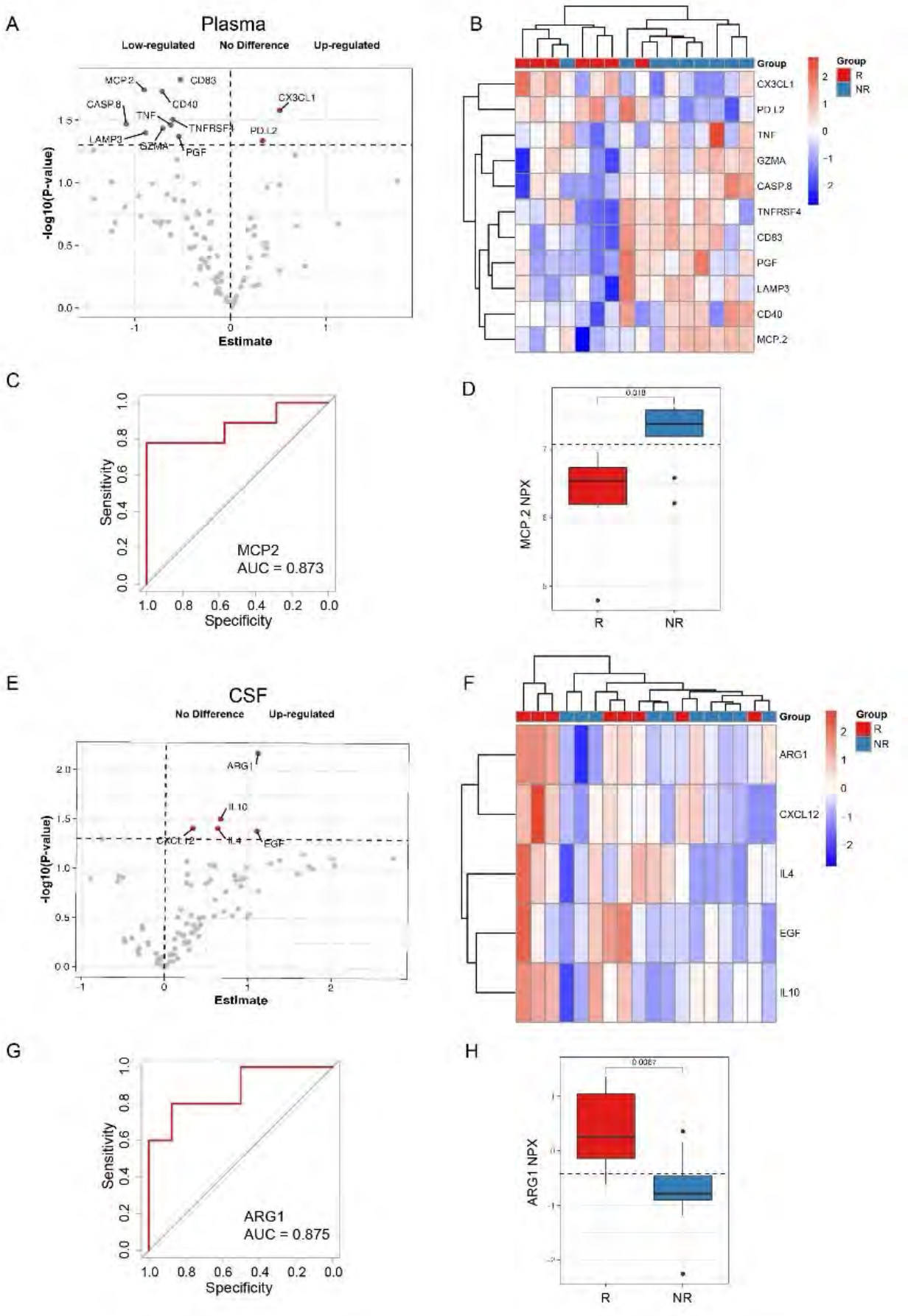

Keywords: leptomeningeal metastasis, intrathecal pemetrexed, proteomics

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.07 Multi-Omic Analyses of CSF Reveal Genomic Instability and Suppressed Microenvironment After TKI Resistance in Patients With Brain Metastases

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Introduction: Patients with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) and brain metastases show notable response to tyrosine kinase inhibitors (TKI) treatment, and almost all patients eventually develop resistance. However, treatment options are limited after TKI resistance, and underlying resistance mechanism of approximately 50% patients remained unknown, especially for patients with brain metastases. Cerebrospinal fluid (CSF) can be used as a type of liquid biopsy to detect brain tumors. Here, we explore the dynamic changes of genetics and microenvironment before and after TKI resistance based on CSF in patients with brain metastases.

Methods: We performed circulating tumor DNA (ctDNA) 425-genes targeted sequencing and single-cell RNA sequencing from a total 164 CSF samples of patients with EGFR mutated NSCLC and brain metastases (51 samples on baseline and 113 samples on TKI resistance).

Results: The CSF ctDNA genomic profiling revealed higher levels of tumor mutation burden (TMB), intratumor heterogeneity (ITH), and copy number variants (CNVs) after TKI resistance, indicating a strong signal of genomic instability. Higher levels of TMB and ITH in resistance CSF were also associated with poor prognosis in patients with brain metastases. The patients with EGFR 21L858R or 3rd-generation TKIs resistance showed an increased incidence of undefined resistance mechanisms. CSF scRNA-seq showed that increased macrophages proportion and decreased T cells proportion after TKI resistance. The macrophages in resistance CSF displayed enhanced immunosuppressive and lipid metabolism phenotype. We defined a population of lipid-associated macrophages, named FABP5_M, was significantly increased after TKI resistance, which may regulated by endothelin-1 (EDN1) from malignant epithelial cells. A receptor-ligand interaction analysis revealed that FABP5_M may contribute to immunosuppressive microenvironment through interaction with exhausted T cell via LGALS9-HAVCR2 axis. Particularly, we found a population of cancer stem-like cells in CSF, which highly expressed CD44, HLDH1A1 and BMI1, may develop leptomeningeal metastases after TKI resistance.

Conclusions: We revealed a comprehensive understanding of genetic profiling and tumor microenvironment remodeling after TKI resistance based on CSF sequencing, and provided potential target strategy for patients with EGFR mutated NSCLC and brain metastases after TKI resistance.

Keywords: Immune Microenvironment, Genomic Instability, Cerebrospinal fluid

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.08 Identification of Circulating microRNA Signature for Diagnosis and Prognosis of Checkpoint Inhibitor-Related Pneumonitis

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The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University,, Guangzhou/CN

Introduction: Checkpoint inhibitor-related pneumonitis (CIP) represents a highly lethal immune-related adverse event. The early diagnosis of CIP is crucial for timely intervention and improved prognosis; however, the absence of precise and effective diagnostic techniques often leads to its underdiagnosis and misdiagnosis. This study aims to identify microRNA (miRNA) features from serum and serum-derived extracellular vesicles (EVs) for the early detection and prognostic evaluation of CIP.

Methods: Small RNA sequencing was conducted to identify candidate miRNAs as potential diagnostic biomarkers in 27 serum-derived EV samples from patients with CIP (CIP group) and non-CIP patients, including those with lung cancer who received immunotherapy without developing CIP (ICI group) and patients with infectious pneumonia (PNE group). These miRNA candidates were screened in the discovery cohort (n=48) and further validated in serum and EV samples within a training cohort (n=106) and a validation cohort (n=72) using a quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and a logistic regression model to establish and validate the diagnostic signature. Using a Cox regression model, we built a prognostic risk stratification for CIP patients based on three miRNAs.

Results: The sequencing analysis initially screened and identified a panel of 13 overexpressed miRNAs in patients with CIP. Subsequently, qRT-PCR demonstrated that three specific miRNAs (EVs miR-193a-5p, serum miR-193a-5p, and serum miR-378a-3p), effectively distinguished CIP patients from non-CIP individuals [training cohort: AUC=0.870, 95% confidence interval (CI), 0.778-0.962; validation cohort: AUC=0.837, 95%CI, 0.712-0.962). Notably, this miRNA signature was equally robust in differentiating CIP from the ICI group (training cohort: AUC=0.823, 95%CI: 0.695-0.950; validation cohort: AUC=0.845, 95%CI: 0.710-0.979) and the PNE group (training cohort: AUC=0.892, 95%CI: 0.794-0.989; validation cohort: AUC=0.907, 95%CI: 0.810-1.000). Furthermore, when combined with lymphocyte levels, the miRNA signature significantly enhanced the overall diagnostic accuracy in distinguishing CIP from non-CIP patients (training cohort: AUC=0.900, 95%CI: 0.808-0.993; validation cohort: AUC=0.932, 95%CI: 0.865-1.000), and maintained its robustness in distinguishing CIP from the ICI group (training cohort: AUC=0.898, 95%CI: 0.798-0.998; validation cohort: AUC=0.946, 95%CI: 0.880-1.000) and the PNE group (training cohort: AUC=0.938, 95%CI: 0.858-1.000; validation cohort: AUC=0.959, 95%CI: 0.899-1.000). Additionally, the three-miRNA panel was independently and significantly associated with overall survival in CIP patients (hazard ratio: 2.827; 95% CI, 1.051-7·603; p=0.040).

Conclusions: Our circulating miRNA-based signature represents a noninvasive and robust diagnostic tool for CIP patients, and could accurately predict their prognosis. This signature may facilitate early detection and personalized management of these patients.

Keywords: Checkpoint inhibitor-related pneumonitis, extracellular vesicles, microRNA signature

MA03 NEW ADVANCES IN CIRCULATING BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 15:15 - 16:30

MA03.09 Minimal Residual Disease Dynamic Monitoring in First-Line Serplulimab Plus Chemotherapy in Treatment of Extensive-Stage Small Cell Lung Cancer

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Introduction: Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive type of lung cancer exhibiting rapid growth with a poor prognosis, and although etoposide plus platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors (e.g., Serplulimab) has significantly prolonged survival, there is still significant heterogeneity in the depth and duration of patients' remission. Minimal residual disease (MRD), detected by circulating tumor DNA (ctDNA), dynamically reflects residual tumor load after treatment and has gradually become a biomarker for predicting recurrence and survival in solid tumors. However, its value in ES-SCLC, especially its dynamic evolution pattern in chemo-immunotherapy modality and its association with long-term prognosis is unclear. Our prospective study(NCT05873790) aims to longitudinally monitor MRD dynamics to evaluate treatment efficacy in ES-SCLC.

Methods: This study prospectively enrolled previously untreated ES-SCLC patients. All patients received 6 cycles of standard chemotherapy combined with serplulimab, followed by serplulimab monotherapy maintenance. Plasma ctDNA samples were collected at multiple time points, including the baseline, after 2 and 6 cycles of chemo-immunotherapy, at 6 months post-chemotherapy cessation, and upon tumor progression. The MRD status was identified by a next-generation sequencing panel covering 2365 lung cancer-relevant genes with an average sequencing depth of approximately 30000×. Kaplan-Meier curves and log-rank tests were performed in survival analyses.

Results: A total of 13 eligible patients were consecutively enrolled between November 2023 and December 2024. At the data cutoff, the median progression-free survival (PFS) was 6.67 months. MRD positivity was observed in all baseline samples, and the positivity rate decreased dramatically to 54% after 2 cycles of chemo-immunotherapy (p=0.003).Patients with MRD negativity after 2 treatment cycles had significantly prolonged PFS compared to MRD-positive patients (7.23 vs. 5.97 months, P=0.031). Among patients with MRD conversion to negativity during treatment, PFS was not reached, while those with persistent MRD positivity had a median PFS of 6.45 months (P=0.043). Most patients exhibited MRD conversion to positivity or increased ctDNA levels at tumor progression. Three patients showed re-elevation of ctDNA levels post-treatment, with radiographic progression confirmed 2.27, 1.7, and 1.6 months later, respectively. These findings indicate that patients with residual MRD positivity post-treatment harbor a higher risk of progression, and MRD status may precede radiographic detection of tumor progression.

Conclusions: This is the first prospective study to evaluate ctDNA-MRD systematically in ES-SCLC patients receiving chemo-immunotherapy. ctDNA-derived MRD can identify ES-SCLC with a high disease progression risk through longitudinal monitoring.

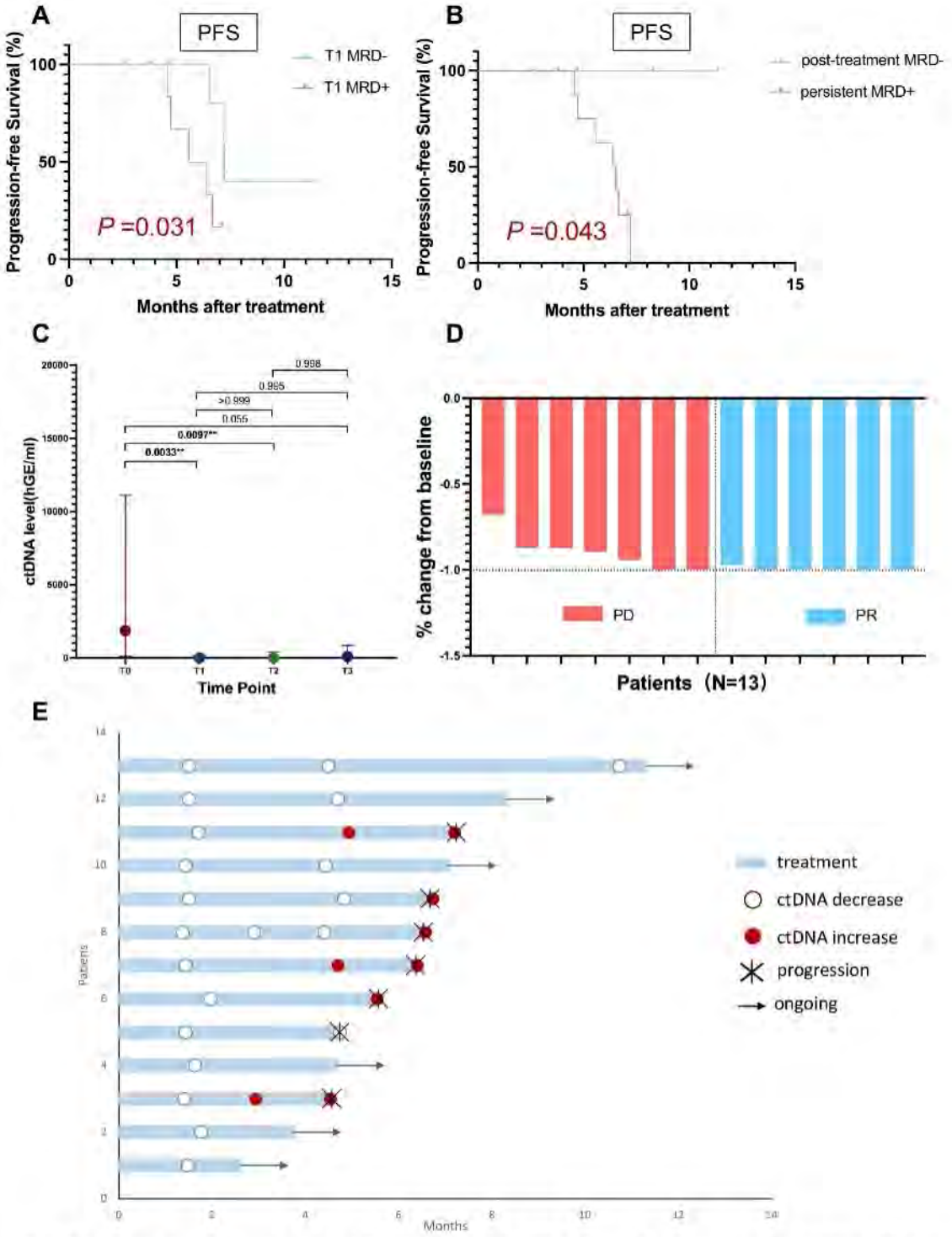

Fig.1 Longitudinal assessment of MRD dynamics and clinical outcomes. **A,** Kaplan–Meier curves comparing progression-free survival (PFS) between MRD-positive and MRD-negative patients after 2 cycles of treatment. **B**, Kaplan–Meier analysis of PFS in patients with persistent MRD positivity versus those achieving MRD clearance during treatment. **C**, Longitudinal changes in ctDNA levels across predefined timepoints: baseline (T0), post-cycle 2 (T1) and 6 (T2), 6 months post-chemotherapy cessation (T3), and tumor progression. **D**, Percentage reduction in ctDNA levels from baseline after treatment. **E**, Swimmer plot illustrating MRD trajectory and treatment response for all enrolled patients.

Keywords: Extensive-stage small cell lung cancer, Chemo-immunotherapy, Minimal residual disease

MA04.01 No Versus Systematic Mediastinal LN Dissection for GGO-Dominant Lung Adenocarcinoma: A Multicenter, Phase III, Non-Inferiority RCT

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Introduction: Systematic mediastinal lymph node dissection (LND) or sampling is currently recommended for patients with early-stage non-small cell lung cancer (NSCLC). However, the potential harm resulting from removing non-metastatic LN remains under-recognized.

Methods: We conducted a multicenter, open-label, phase III, non-inferiority randomized controlled trial comparing systematic mediastinal LND versus no mediastinal LND in patients with ground glass opacity (GGO)-dominant invasive lung adenocarcinoma, who were predicted to have no LN metastasis based on criteria established in our prior trial. The primary endpoint was 3-year disease-free survival. An interim analysis was planned upon enrollment of 300 patients, with predefined termination criteria if no mediastinal LN metastasis is detected and life-threatening complications occur in the systematic LND arm. This trial is registered on ClinicalTrials.gov (ECTOP-1009, NCT04527419).

Results: Interim analysis of 302 patients revealed no LN metastasis in either study arm. The no LND group had significantly reduced surgery duration (mean: 73 min vs. 109 min, P<0.001), blood loss (mean: 45 ml vs. 89 ml, P<0.001), and postoperative hospital stay (mean: 3.7 days vs. 4.4 days, P=0.002). Complications observed in the systematic LND group included arrhythmia in three patients (2.0%), chylothorax in one patient (0.7%), and one case (0.7%) of intraoperative massive bleeding due to superior vena cava injury. No lymphadenectomy-related complications occurred in the no LND group.

Conclusions: Based on interim findings and the principle of non-maleficence, the trial should be terminated. Systematic mediastinal LND should no longer be recommended for patients with GGO-dominant lung adenocarcinoma.$$graphic_{89D1A54C-228E-4D34-ABFC-75D5EA23C5EC}$$$$graphic_{2AD4A8BD-CFF9-4BC8-8D4C-20C1D636616A}$$

Keywords: lung cancer, ground glass opacity, lymph node dissection

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.02 Nautika1: Clinical Outcomes and Pathologic Regression With Neoadjuvant Alectinib in Resectable Stage IB-IIIB ALK + NSCLC

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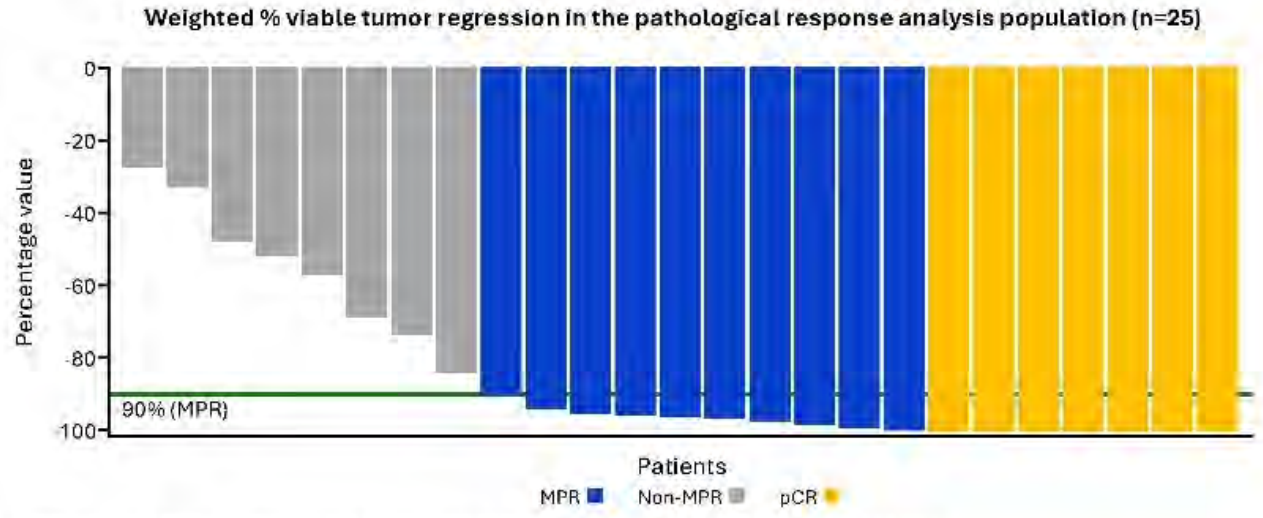
[1]University of California, Los Angeles/CA/USA ,[2]MD Anderson Cancer Center, Houston/TX/USA ,[3]David Geffen School of Medicine at the University of California, Los Angeles/CA/USA ,[4]NYU Langone Perlmutter Cancer Center, New York/NY/USA ,[5]University of Colorado Cancer Center, Aurora/CO/USA ,[6]University of Michigan Medical School, Ann Arbor/MI/USA ,[7]Columbia University Medical Center, New York/NY/USA ,[8]Moffitt Cancer Center, Tampa/FL/USA ,[9]Dana-Farber Cancer Institute – Harvard Medical School, Boston/MA/USA ,[10]University of California, San Francisco/CA/USA ,[11]Brigham and Women's Hospital, Boston/MA/USA ,[12]Genentech, Inc., South San Francisco/CA/USA ,[13]MSKCC and Weill Cornell Medical College, New York/NY/USA

Introduction: Alectinib is globally approved in the adjuvant setting for patients with resected, anaplastic lymphoma kinase-positive (ALK+), stage IB–IIIB (AJCC 8th edition) non-small cell lung cancer (NSCLC). There is a need for exploring targeted therapies in the neoadjuvant setting in this population. NAUTIKA1 (NCT04302025) is a phase II umbrella study investigating targeted treatments in the neoadjuvant/adjuvant setting in early-stage NSCLC with study-eligible alterations (e.g., ALK, ROS1, NTRK and KRAS G12C). Preliminary data from 12 patients in the ALK+ cohort were previously presented. We present new clinical and surgical outcomes from 33 patients in this cohort.

Methods: Eligible patients were ≥18 years old with stage IB, II, IIIA or selected IIIB (T3N2 only) ALK+ NSCLC, and ECOG PS 0/1. Patients received neoadjuvant alectinib (600mg, twice-daily [BID]) for eight weeks followed by surgery, platinum-based chemotherapy (≤4 cycles) unless refused, not indicated or contraindicated, then adjuvant alectinib (600mg BID) for two years. Primary endpoint was locally assessed major pathological response (MPR; ≤10% residual viable tumor cells). Secondary endpoints included pathological complete response (pCR), radiographic response, nodal downstaging and safety.

Results: At data cutoff (02 September 2024), 33 patients were enrolled; see Table for baseline characteristics. Primary endpoint of MPR was achieved in 17/28 (60.7%) patients, and pCR in 7/28 (25.0%) (Figure). Radiographic objective response was observed in 19/30 patients (63.3%), and nodal downstaging in 8/30 (26.7%). No intraoperative complications occurred. In patients who underwent surgery, 25/27 (92.6%) had R0 resections; see Table for surgical outcomes. Adverse events led to dose reduction/interruption or discontinuation in 12/33 (36.4%) and 3/33 (9.1%) patients, respectively. Neoadjuvant alectinib was well tolerated with no new safety signals.

Conclusions: Neoadjuvant alectinib achieved clinically meaningful MPR/pCR rates with no new safety signals, and can be added to ALINA as a promising perioperative approach for patients with resectable, stage IB-IIIB ALK+ NSCLC.



MPR, major pathological response (primary endpoint); pCR, pathological complete response.

Weighted % viable tumor regression values were set to 'missing' for patients who did not undergo primary tumor R0 resection.

Baseline characteristics (N=33)	
Tobacco use, n (%)	
Current	0
Former	6 (18)
Never	27 (82)
ECOG PS, n (%)	
0	23 (70)
1	10 (30)
Non-metastatic lung cancer histology, n (%)	
Non-squamous carcinoma	31 (94)
Squamous cell carcinoma	2 (6)
Clinical staging (AJCC 8th edition), n (%)	
IB	3 (9)
IIA	2 (6)
IIB	3 (9)
IIIA	23 (70)
IIIB	2 (6)
Lymph node stage at diagnosis, n (%)	
N0	5 (15)
N1	7 (21)
N2	21 (64)
Primary tumor, n (%)	
T1b	9 (27)
T1c	4 (12)
T2a	9 (27)
T2b	5 (15)
T3	4 (12)
T4	2 (6)
Neoadjuvant treatment exposure[1] (N=30)[2]	
Treatment duration (weeks), median (range) (n=28)	3.14 (2.9–9.7)
Pathological response (N=28)[3]	
MPR, n (%) [95% CI]	17 (60.7) [40.6–78.5]
pCR,[4] n (%) [95% CI]	7 (25.0) [10.7–44.9]
Radiographic best overall response (unconfirmed) by investigator during neoadjuvant phase (N=30)[2]	
Objective response rate, n (%) [95% CI]	19 (63.3) [43.9–80.1]
Partial response	19 (63.3) [43.9–80.1]
Stable disease	9 (30.0) [14.7–48.4]
Progressive disease	1 (3.3) [0.1–17.2]
Not evaluable	1 (3.3)
Surgical outcomes (N=27)[5]	
Days from first neoadjuvant treatment to surgery, median (range)	62.0 (39–104)
Days from last neoadjuvant treatment to surgery, median (range) (n=26)	1.5 (1–49)
Reported surgical delays[6], n (%)	
Adverse events	1 (4)
Scheduling	3 (11)
Duration of surgery (minutes), median (range)	222.0 (104–364)
Days in hospital, median (range) (n=26)	3.0 (0–13)
R0 resection, n (%)	25 (93)
No resection, n (%)	2 (7)[8]
Resection approach, n (%) (N=25)	
Robotically assisted VATS	14 (56)
Thoracotomy	4 (16)
VATS	4 (16)
VATS or robotically assisted VATS converted to thoracotomy	3 (12)
Extent of resection, n (%) (N=25)	
Left lower lobectomy	8 (32)
Left upper lobectomy	1 (4)
Right lower lobectomy	7 (28)
Right middle lobectomy	7 (28)
Right upper segmentectomy	1 (4)
Other	1 (4)[9]
Intraoperative events (N=27)	
Intraoperative complications, n (%)	0
Estimated blood loss (mL), median (range) (n=19)	100.0 (10.0–650.0)
Peri-hilar/lobar adhesions, n (%)	
Yes	4 (15)
No	23 (85)
Severity of peri-hilar/lobar adhesions, n (%) (N=4)	
Grade 1	1 (25)
Grade 2	3 (75)
AEs during neoadjuvant phase (N=33)	
Any grade AE, n (%)	30 (91)
Grade 3–4 AE, n (%)	2 (6)
Any grade treatment related AE, n (%)	28 (85)
Most common AEs (in ≥20% of patients)	
Constipation	16 (48)
Fatigue	12 (36)
Missed dose	11 (33)
CPK increase	9 (27)
Peripheral edema	7 (21)
Myalgia	7 (21)
AE leading to dose reduction or interruption, n (%)	12 (36)
AE leading to treatment discontinuation, n (%)	3 (9)[7]

AE, adverse event; AJCC, American Joint Committee on Cancer; CI, confidence interval; CPK, creatine phosphokinase; ECOG PS, Eastern Cooperative Oncology Group performance status; MPR, major pathological response; pCR, pathological complete response; VATS, video-assisted thoracoscopic surgery.

Data cutoff date 02 September 2024, for patients enrolled on or before 28 May 2024. [1]Per protocol, patients were to be treated until the day before surgery. [2]Assessed in eligible and treated patients. [3]Pathological response was assessed locally; pathological response analysis population defined as all eligible and treated patients who either underwent post-neoadjuvant surgery (with or without resection; n=27) or discontinued due to AE or disease progression (n=1 due to PD) with pathological response for patients without R0 resection set to non-MPR. [4]Defined as the lack of any viable tumor cells on review of hematoxylin and eosin stained slides, determined by local pathologist after complete evaluation of a resected lung cancer specimen including all sampled regional lymph nodes. [5]Eligible and treated patients who underwent post-neoadjuvant surgery (with or without resection). [6]Surgery was considered to be delayed if performed after Day 57 on study. [7]One patient had pneumonitis after completion of neoadjuvant treatment which led to the physician decision for patient to not receive adjuvant treatment. [8]One patient did not proceed with resection due to surgeon decision as the patient required a pneumonectomy; second patient did not proceed with resection due to pleural disease (indicating metastatic disease) found at the time of surgery. [9]Left upper lobectomy, mediastinoscopy.

Keywords: Alectinib, Neoadjuvant, NAUTIKA1

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.03 Efficacy and Safety of Aumolertinib as Adjuvant Therapy in Resectable Stage I A EGFR Mutated NSCLC With High Risk (APPOINT)

W. Zhang[1], W-T. Fang[2], C. Chen[3], B. Zhang[1], F. Yao[1], J-X. Shi[1], D-S. Yue[4], Y. Qi[5], Z-Y. Zhu[6], J-B. Xie[7], B-H. Han[1]
[1]Shanghai Chest Hospital Affiliated to Shanghai Jiao Tong University, Shanghai/CN ,[2]Shanghai east hospital, Shanghai/CN ,[3]Shanghai Pulmonary Hospital, Shanghai/CN ,[4]Tianjin Medical University Cancer Institute Hospital, Tianjin/CN ,[5]The First Affiliated Hospital of Zhengzhou University, Zhengzhou/CN ,[6]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou/CN ,[7]Affiliated Hospital of Putian College, Putian/CN

Introduction: Pathological subtypes are prognostic indicators independent of TNM stage. Patients (pts) with high risk (solid, micropapillary, or complex gland) had poorer prognosis. APPOINT (NCT04922138) is the first two-arm study to explore the efficacy and safety of the third-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) aumolertinib as adjuvant therapy in stage I A EGFR mutated NSCLC pts with high risk factors. Previously, we reported 1-year disease free survival (DFS) rate (ELCC 2025 145P), here, we update the primary endpoint data.

Methods: This prospective, multi-center, two-arm study aims to enroll 102 stage I A EGFR-mutated NSCLC pts with solid, micropapillary, and/or complex gland components ≥10%. After radical lung cancer surgery, they will receive oral aumolertinib 110 mg qd as adjuvant therapy (arm A) or observation (arm B) for 3 years. The primary endpoint is 2-year DFS rate, and secondary endpoints include 3-, 4-, and 5-year DFS rate, 5-year overall survival rate and safety.

Results: At data cut off, a total of 97 stage I A EGFRmutated (19Del, L858R and uncommon mutations) NSCLC pts were enrolled with at least one high-risk factors, including solid, micropapillary, and/or complex gland components. 46 in arm A and 51 in arm B. The median age was 57 and 66 years, 62.2 % and 62.7% were female, respectively. At data cut-off, the median follow up time was 20 months, all pts in arm A had no symptoms of tumor recurrence and 4 pts in arm B had recurrence, the special disease of 2-year DFS was 100% vs 75% (p=0.033). There were no grade ≥3 AE occurred during aumolertinib treatment group, and no new safety signals were observed.

Conclusions: The data demonstrated that compared with the observation group, aumolertinib treatment group exhibited superior efficacy and safety in stage IA EGFR mutated NSCLC pts with high-risk pathological features, highlighting its clinical utility potential for EGFR mutated stage IA NSCLC management.

Keywords: Aumolertinib, Adjuvant targeted therapy, High risk

MA04.04 Perioperative Pembrolizumab in Non-Small Cell Cancer (NSCLC): 4-Year Outcomes by Nodal Status in the KEYNOTE-671 Study

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Introduction: In the phase 3 KEYNOTE-671 study (NCT03425643), neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved event-free survival (EFS), overall survival (OS), major pathological response (MPR), and pathological complete response (pCR) versus neoadjuvant chemotherapy and surgery alone. In this exploratory analysis, we report outcomes by baseline clinical nodal status in participants from KEYNOTE-671.

Methods: Participants aged ≥18 years with previously untreated resectable stage II, IIIA, or IIIB (N2) NSCLC were randomized to pembrolizumab 200 mg or placebo plus chemotherapy Q3W for 4 cycles, then surgery and adjuvant pembrolizumab or placebo for ≤13 cycles (~9 months). Exploratory analyses of EFS, OS, MPR, and pCR were performed in subgroups of participants with clinically node-negative (cN0) and node-positive (cN1/cN2) disease at baseline.

Results: Of 797 participants enrolled in KEYNOTE-671, 290 participants had cN0 disease (n = 148 randomized to pembrolizumab and n = 142 to placebo) and 506 participants had cN1/cN2 disease (n = 248 randomized to pembrolizumab and n = 258 to placebo) at baseline. Median follow-up time as of the data cutoff (August 19, 2024) was 41.1 (range, 0.4-75.3) months. Among participants who underwent surgery, 108/117 (92.3%) in the pembrolizumab arm and 98/115 (85.2%) in the placebo arm of the cN0 subgroup and 190/207 (91.8%) and 169/202 (83.7%), respectively, in the cN1/cN2 subgroup had R0 resections. EFS, OS, MPR, and pCR favored pembrolizumab versus placebo irrespective of nodal status (Table). Outcomes by disease stage within each nodal subgroup will also be presented. Grade 3 to 5 treatment-related AEs occurred in 68/147 participants (46.3%) in the pembrolizumab arm and 55/142 participants (38.7%) in the placebo arm in the cN0 subgroup and in 111/248 participants (44.8%) and 96/257 participants (37.4%), respectively, in the cN1/cN2 subgroup.

Conclusions: In this exploratory analysis, perioperative pembrolizumab improved efficacy outcomes versus neoadjuvant chemotherapy alone regardless of nodal status after ~4 years of follow-up in participants with stage II to IIIB (N2) NSCLC.

	Node-Negative (cN0)		Node-Positive (cN1/cN2)	
	Pembrolizumab n = 148	Placebo n = 142	Pembrolizumab n = 248	Placebo n = 258
EFS, median (95% CI), mo	69.1 (37.5–NR)	19.6 (14.3–25.8)	47.6 (27.7–68.9)	17.9 (14.0–22.2)
HR (95% CI)	0.56 (0.40–0.77)		0.57 (0.45–0.72)	
OS, median (95% CI), mo	NR (NR–NR)	NR (47.8–NR)	NR (63.7–NR)	NR (45.7–NR)
HR (95% CI)	0.70 (0.47–1.04)		0.77 (0.58–1.01)	
MPR (95% CI), %	33.1 (25.6–41.3)	10.6 (6.0–16.8)	28.2 (22.7–34.3)	11.2 (7.7–15.7)
Difference (95% CI)	22.5 (13.3–13.7)		17.0 (10.2–23.9)	
pCR (95% CI), %	20.3 (14.1–27.7)	4.9 (2.0–9.9)	16.5 (12.1–21.8)	3.5 (1.6–6.5)
Difference (95% CI)	15.3 (8.1–23.1)		13.0 (8.1–18.5)	

NR, not reached

Keywords: Perioperative pembrolizumab, Early-stage NSCLC, Anti-PD-1

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.05 Patient-Reported Outcomes With Perioperative Nivolumab by Nodal Status in Patients With Resectable NSCLC From Checkmate 77T

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MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.06 Neoadjuvant Pembrolizumab: Multi-Omics Characterization of the Tumoral Immune Response Reveals Distinct Mechanisms of Action

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Introduction: Immune checkpoint inhibitors (ICI) can lead to a major pathological response (MPR) in a subset of patients, but the immunological drivers of response remain elusive. This study is a secondary analysis of the prospective, phase II NEOMUN trial, leveraging multi-omics data to characterize the tumor microenvironment (TME) after mono-immunotherapy with Pembrolizumab from a controlled clinical setting. We hypothesized that distinct immunological functions would contribute to efficacy of Pembrolizumab, and that therefore changes in the TME would be detectable in tumors with MPR as compared to non-responders or untreated controls.

Methods: In the NEOMUN trial, 29 patients were treated with neoadjuvant mono-immunotherapy with Pembrolizumab. 7 patients showed MPR with less than 10% vital tumor cells in resected specimen, all others were classified as non-MPR. Treatment-naïve controls were matched to the study cohort. Transcriptomics analysis and cytokine/chemokine measurements were performed to investigate functionality of the TME.

Results: Subpopulations of tumor-infiltrating leukocytes (TILs) were investigated based on a deconvolution approach using the tools CIBERSORT and xCell, revealing significant differences of TME composition in the MPR group compared to non-MPR and untreated controls. In particular, the infiltration of specific TIL subpopulations related to adaptive immunity was associated with MPR including B cells ($p<0.01$), CD8+ T cells ($p<0.001$), follicular helper T cells ($p<0.05$) and gamma-delta T cells ($p<0.001$). Interestingly, the TME composition of tumors in the non-MPR group resembled that of untreated controls, both regarding infiltration levels of specific TIL subpopulations associated with MPR and overall immune scores and stromal scores. Functional and network analysis of differentially expressed genes demonstrated a significant upregulation of T cell receptor signaling, B cell differentiation, B cell proliferation, B cell activation, B cell receptor signaling pathway and complement activation in the MPR group based on gene ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. To validate how transcriptional changes correspond to actual functional immune signaling, we proceeded to conduct a proteomic analysis measuring a panel of 50 cytokines and chemokines. We observed a significant elevation of cytokines in the MPR group including CCL3, CCL4, CCL5, IL9, IL16, TNF-β and G-CSF, suggesting a complex immune activation signature involving both innate and adaptive immune activation with T Cell recruitment and activation, as well as NK cell and monocyte involvement.

Conclusions: In this deep exploratory analysis, several distinct mechanisms associated with major pathologic response were demonstrated. While confirming activation of CD8+ T cells as a key mechanism of action, B cell immunity might also play a substantial role for Pembrolizumab efficacy. Further studies are needed to determine if characterization of the TME and functionality of the involved pathways could be performed on preoperative tissue biopsy to predict therapy response.

Keywords: neoadjuvant, checkpoint inhibitors, tumor microenvironment

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.07 A Phase 2 Multicenter Umbrella Trial Assessing Tislelizumab ± Anti-TIGIT or Anti-LAG-3 mAb ± Chemotherapy in Resectable NSCLC

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Introduction: Neoadjuvant chemotherapy plus immunotherapy with adjuvant immunotherapy is the current standard of care for resectable NSCLC. There is an unmet need for additional neoadjuvant regimens containing novel agents that retain efficacy but minimize safety risks. We report results from a phase 2, randomized, open-label, multicenter umbrella trial of neoadjuvant tislelizumab (TIS) monotherapy and TIS-based immunotherapy combinations ± chemotherapy in Chinese patients with resectable NSCLC (NCT05577702).

Methods: Eligible patients had Stage II-IIIA NSCLC without EGFR sensitizing mutations or ALK rearrangement. Patients with PD-L1 TC ≥50% were assigned to Substudy 1 and randomized to TIS (anti-PD-1; Arm 1A), TIS plus ociperlimab (anti-TIGIT; Arm 1B), or TIS plus LBL-007 (anti-LAG-3; Arm 1C); patients with PD-L1 TC <50% were assigned to Substudy 2 and randomized to TIS and chemotherapy (Arm 2A) or TIS plus LBL-007 and chemotherapy (Arm 2C). Patients received 2-4 cycles of treatment and then surgery. The primary objective was evaluation of major pathological response (MPR) per blinded independent pathology review (BIPR); select secondary objectives were evaluation of the pathological complete response (pCR) per BIPR and feasibility of surgery.

Results: As of February 5, 2025, 121 patients were enrolled. The median number of treatment cycles of TIS or TIS-based immunotherapy combinations was 3, 2, and 2 for 1A, 1B and 1C, and 3 and 2.5 for 2A and 2C, respectively. The overall MPR rates were 64.3% (27/42) for Substudy 1, and 52.1% (25/48) for Substudy 2. Detailed MPR and pCR rates are summarized in the Table. Notably, in the experimental arms, the MPR rate in patients with non-squamous NSCLC in 1B was 100% (6/6) and in patients with squamous NSCLC with PD-L1 TC <1% in 2C was 75% (9/12). TEAEs were reported in most patients. The three most common treatment-related TEAEs were AST increased, anemia and ALT increased in Substudy 1, and neutrophil count decreased, anemia and WBC count decreased in Substudy 2. An increase in treatment-related Grade ≥3 and serious TEAEs, and immune-mediated AEs were reported for 1B and 1C versus 1A, and 2C versus 2A. Few treatment-related TEAEs leading to surgery withdrawal were reported.

Conclusions: Neoadjuvant TIS as monotherapy or TIS-based immunotherapy combinations in PD-L1 TC ≥50% NSCLC had promising MPR/pCR; the addition of other immunotherapy to neoadjuvant TIS and chemotherapy in PD-L1 TC <50% did not provide additional efficacy benefit. Treatment guided by histology and PD-L1 expression is suggested for future exploration.

Efficacy in Patients Receiving Surgery (Efficacy Evaluable Analysis Set)

	Substudy 1 (PD-L1 ≥50%)			Substudy 2 (PD-L1 <50%)	
	Arm 1A (N=20)	Arm 1B (N=20)	Arm 1C (N=20)	Arm 2A (N=20)	Arm 2C (N=41)
Overall	n=16	n=14	n=12	n=17	n=31
MPR, n (%)	9 (56.3)	10 (71.4)	8 (66.7)	11 (64.7)	14 (45.2)
pCR, n (%)	6 (37.5)	6 (42.9)	8 (66.7)	7 (41.2)	7 (22.6)
				n=13	n=23
Squamous	n=15	n=8	n=11	PD-L1 <1%=4 PD-L1 1-49%=9	PD-L1 <1%=12 PD-L1 1-49%=11
MPR, n (%)	9 (60.0)	4 (50.0)	8 (72.7)	8 (61.5)	14 (60.9)
PD-L1 <1%				2 (50.0)	9 (75.0)
PD-L1 1-49%				6 (66.7)	5 (45.5)
pCR, n (%)	6 (40.0)	1 (12.5)	8 (72.7)	5 (38.5)	7 (30.4)
PD-L1 <1%				2 (50.0)	6 (50.0)
PD-L1 1-49%				3 (33.3)	1 (9.1)
				n=4	n=8
Non-squamous	n=1	n=6	n=1	PD-L1 <1%=3 PD-L1 1-49%=1	PD-L1 <1%=4 PD-L1 1-49%=4
MPR, n (%)	0	6 (100.0)	0	3 (75.0)	0
PD-L1 <1%				2 (66.7)	0
PD-L1 1-49%				1 (100.0)	0
pCR, n (%)	0	5 (83.3)	0	2 (50.0)	0
PD-L1 <1%				1 (33.3)	0
PD-L1 1-49%				1 (100.0)	0

Median (range) study follow-up was 10.5 months (1.0-22.3) for Substudy 1 and 9.2 months (0.2-15.0) for Substudy 2.

Keywords: Neoadjuvant, Tislelizumab, Non-Small Cell Lung Cancer

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.08 Perioperative Tislelizumab for Resectable Non-small Cell Lung Cancer: Final Analysis of RATIONALE-315

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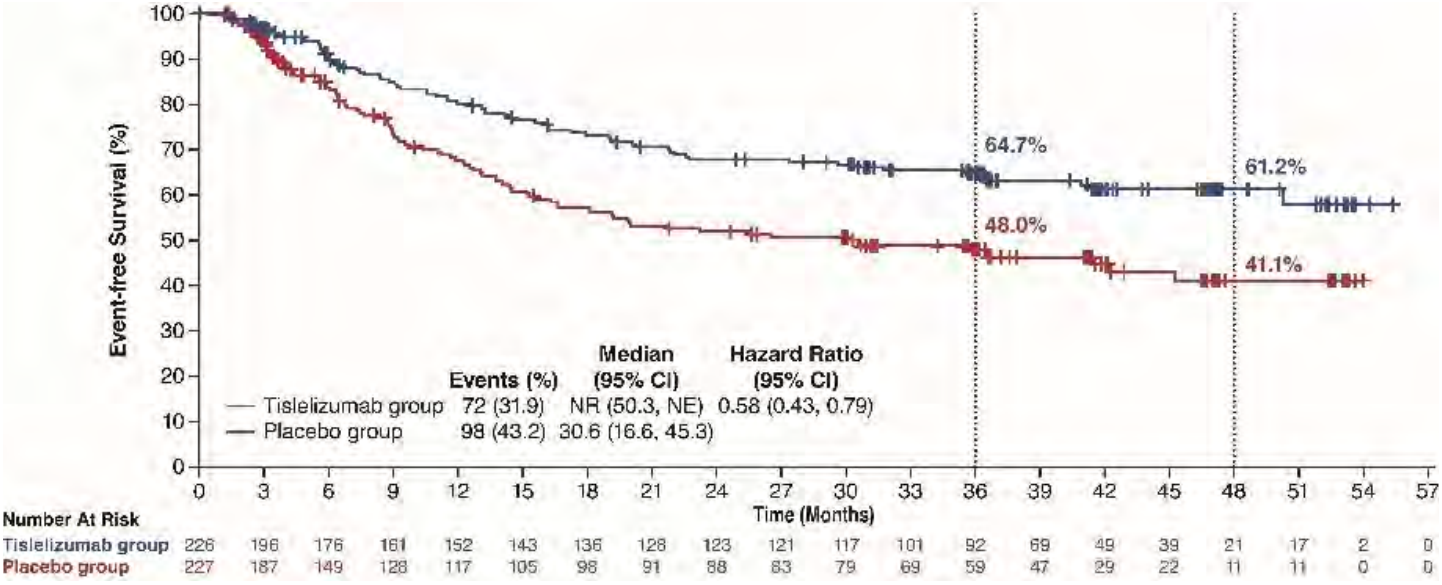
Introduction: Interim analyses (IAs) from RATIONALE-315 demonstrated that perioperative tislelizumab plus neoadjuvant chemotherapy had clinically meaningful and statistically significant improvement in major pathological response (MPR), event-free survival (EFS), and pathological complete response (pCR), with a manageable safety/tolerability profile, compared with neoadjuvant chemotherapy in patients with resectable non-small cell lung cancer (NSCLC). We report results of the prespecified EFS/OS final analysis (FA).

Methods: Adults with untreated, resectable, stage II-IIIA NSCLC were randomised 1:1 to neoadjuvant tislelizumab 200 mg or placebo every 3 weeks plus platinum-based doublet chemotherapy for 3-4 cycles, followed by surgery and adjuvant tislelizumab 400 mg or placebo every 6 weeks for ≤8 cycles. As MPR, EFS, and pCR were statistically significant at IAs, only OS was statistically tested at FA.

Results: Overall, 453 patients were randomised (tislelizumab, n=226; placebo, n=227). Over 90% of patients completed neoadjuvant treatment (tislelizumab, n=211; placebo, n=210), 363 (80.1%) had surgery (tislelizumab, n=190; placebo, n=173), and 224 (49.4%) completed adjuvant treatment (tislelizumab, n=115; placebo, n=109). With a median study follow-up of 38.5 months (data cutoff: Mar 7, 2025), a statistically significant and clinically meaningful OS benefit was observed in the tislelizumab arm vs placebo arm (HR=0.65 [95% CI: 0.45, 0.93]; one-sided P=.0093). The significant EFS benefit reported with tislelizumab over placebo in the IAs was sustained (Figure 1; HR=0.58 [95% CI: 0.43, 0.79]), and improvement in EFS was consistent whether assessed by independent review committee (IRC) or the investigator. EFSIRC and OS benefits observed with tislelizumab were also observed across major subgroups, regardless of PD-L1 expression, disease stage, and histology type. Disease-free survival, assessed by IRC, was also improved with tislelizumab vs placebo in patients with complete resection. With the longer follow-up, safety/tolerability profiles were consistent with IAs, and no new or worsening signals emerged. Rates of grade ≥3 and serious TRAEs were 73.0% vs 67.3% and 15.5% vs 8.8% in the tislelizumab and placebo arms, respectively. The most frequently reported TRAEs of any grade were neutropenia (tislelizumab, 78.8%; placebo, 78.3%) and leukopenia (tislelizumab, 63.3%; placebo, 67.3%); these were also the most common grade ≥3 TRAEs in both arms (neutropenia: tislelizumab, 61.5%; placebo, 59.3%; leukopenia: tislelizumab, 16.8%; placebo, 14.2%). **Conclusions:** Neoadjuvant tislelizumab plus chemotherapy and adjuvant tislelizumab demonstrated statistically significant, clinically meaningful OS benefit and sustained significant EFS improvement compared with neoadjuvant chemotherapy in patients with resectable NSCLC, potentially offering a new treatment paradigm that is generally well tolerated and safe for this population.
CI, confidence interval; NE, not estimable; NR, not reached.



Keywords: Non-Small Cell Lung Cancer, neoadjuvant, tislelizumab

MA04 MULTI-MODAL TREATMENT OF RESECTABLE LUNG CANCER - OUTCOMES OF TARGETED TREATMENTS AND IMMUNOTHERAPIES IN EARLY-STAGE LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 12:00 - 13:15

MA04.09 Patterns of Progression and Recurrence with Perioperative Durvalumab in Patients with Resectable NSCLC from AEGEAN

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Introduction: In the phase 3 AEGEAN trial of patients with resectable NSCLC (R-NSCLC), perioperative durvalumab plus neoadjuvant chemotherapy significantly improved the primary endpoints of EFS and pathological complete response versus neoadjuvant chemotherapy alone. Here, we report patterns of progression and recurrence in AEGEAN.

Methods: AEGEAN is a double-blind, placebo-controlled study (NCT03800134) of patients with treatment-naïve R-NSCLC (stage II-IIIB[N2]) and ECOG PS 0/1. Patients were randomised (1:1) to neoadjuvant chemotherapy plus durvalumab or placebo IV (Q3W for 4 cycles) before surgery, followed by adjuvant durvalumab or placebo IV (Q4W, up to 12 cycles). Randomisation was stratified by stage and PD-L1 status. Efficacy was analysed in the modified intent-to-treat (mITT) population, which excluded patients with EGFR/ALK aberrations. EFS was defined as time from randomisation to PD precluding or preventing completion of surgery, recurrence, or death. PD precluding/preventing completion of surgery was based on clinical assessment by the investigator (among patients unable to undergo/complete surgery for reasons other than PD, it was assessed by BICR [RECIST v1.1]). Recurrence was assessed by BICR (RECIST v1.1) for patients after resection of the primary disease and included new NSCLC lesions, categorised as distant (including the pleura) or locoregional, but excluded new primary malignancies. The proportions of patients with progressions or recurrences were descriptively summarized.

Results: 802 patients were randomised (mITT, n=740); 799 received treatment (durvalumab arm, n=400; placebo arm, n=399). As of May 10, 2024, proportionally fewer patients in the durvalumab versus placebo arm had PD that precluded (7.7% vs 9.6%) or prevented completion of (1.4% vs 3.5%) surgery (Table); 0.8% and 2.7%, respectively, had PD after surgery was not undertaken/completed for reasons other than PD. Among patients who completed surgery, proportionally fewer in the durvalumab versus placebo arm had recurrences (14.5% vs 22.2%) (Table); median time to recurrence was longer in the durvalumab arm, irrespective of location, and proportionally fewer in the durvalumab arm had locoregional or distant only recurrences. Among patients who did not undergo/complete surgery, 39.0% in the durvalumab arm and 44.8% in the placebo arm received post-discontinuation therapy (Table); among patients who completed surgery, approximately twice as many in the placebo arm had subsequent therapy (13.7% vs 25.1%). **Conclusions:** The addition of perioperative durvalumab to neoadjuvant chemotherapy reduced PD precluding/preventing completion of surgery and both locoregional and distant post-surgery recurrences. In addition, time to recurrence was longer with perioperative durvalumab, providing further support for its use as a new treatment option.

Table

	Durvalumab arm (n=366)	Placebo arm (n=374)
Total EFS events, n (%)	124 (33.9)	165 (44.1)
PD precluding surgery	28 (7.7)	36 (9.6)
PD after surgery not undertaken for reasons other than PD	3 (0.8)	5 (1.3)
PD preventing completion of surgery	5 (1.4)	13 (3.5)
PD after surgery not completed for reasons other than PD	0	5 (1.3)
RECIST v1.1 recurrence	53 (14.5)	83 (22.2)
Death without PD or recurrence	38 (10.4)	33 (8.8)
Median time to recurrence (range),* months		
Any location	8.2 (1–39)	5.6 (1–41)
Locoregional only	8.4 (1–22)	6.0 (1–28)
Distant only	7.2 (1–39)	5.6 (1–41)
Site of first recurrence, n (%)		
Locoregional only	20 (5.5)	39 (10.4)
Distant only	32 (8.7)	40 (10.7)
Locoregional and distant	1 (0.3)	4 (1.1)
Post-discontinuation anticancer therapy,† n (%)		
Patients who did not undergo/complete surgery	n=82	n=87
Any anticancer therapy	32 (39.0)	39 (44.8)
First systemic therapy‡	32 (39.0)	39 (44.8)
Cytotoxic chemotherapy	16 (19.5)	21 (24.1)
Immunotherapy	14 (17.1)	16 (18.4)
Targeted therapy	1 (1.2)	0
Radiotherapy	23 (28.0)	24 (27.6)
Patients who completed surgery	n=284	n=287
Any anticancer therapy	39 (13.7)	72 (25.1)
First systemic therapy‡	39 (13.7)	72 (25.1)
Cytotoxic chemotherapy	22 (7.7)	20 (7.0)
Immunotherapy	12 (4.2)	44 (15.3)
Targeted therapy	5 (1.8)	5 (1.7)
Radiotherapy	21 (7.4)	42 (14.6)

*Time to recurrence was measured from the date of surgery. †Patients with therapies in more than one category are counted once in each of those categories. ‡Other first systemic therapies were administered in 3 patients who did not undergo/complete surgery (durvalumab arm, n=1; placebo arm, n=2) and 4 patients who completed surgery (durvalumab arm, n=1; placebo arm, n=3). BICR, blinded independent central review; EFS, event-free survival; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Keywords: Durvalumab, Perioperative, Recurrence

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.01 A Systematic Approach to Appropriate Guideline-Based Management of Incidentally Detected Pulmonary Nodules the Mayo Clinic Experience

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Introduction: Pulmonary nodules are detectable in approximately 50% of the general population. With increased utilization of modern cross-sectional chest imaging, incidentally detected pulmonary nodules (IPN) continue to increase. While the Fleischner Society guidelines provide the framework for appropriate follow-up, operationalizing guideline-based follow up remains challenging and burdensome to the healthcare system. According to previous studies, only 10-50% of patients with IPN are managed according to current guidelines. This lack of guideline based follow up can lead to increased morbidity and mortality due to delayed cancer diagnoses, increased patient anxiety, and health care cost.

Methods: A quality-improvement project was conducted at the Mayo Clinic in Rochester MN (USA) to evaluate the use of a third-party commercial vendor's product to improve guideline-based management of IPN. This software uses natural language processing to analyze all cross-sectional imaging reports capturing the lungs performed for any indication in any care location including inpatient, outpatient, and the emergency department. NLP identified the notation of lung nodules by the interpreting radiologist and then flagged these reports for further review. Scan reports were excluded if the patient was actively treated for cancer, or the scan was requested by a provider in oncology or in the pulmonary practice. Utilizing adapted Mayo Clinic IPN management guidelines (based on Fleischner guidelines) a team of Mayo-accredited registered nurses (provided by the third-party vendor) communicated appropriate management recommendations to the patient and their primary care providers. A lung nodule expert was available to the nurses for management questions for nodules that did not fit standard categories. If that primary care provider (PCP) was within Mayo Clinic, management recommendation-based orders were pre-scripted for their review and signature. If the PCP was outside of Mayo Clinic, the recommendation was communicated for follow up.

Results: Between December 2023 and March 2025, 25,944 patients with IPN were identified in the Mayo Clinic Rochester practice. 4,875 patients are currently under surveillance. This includes 4038 (84%) IPNs with appropriate initial IPN evaluation /follow up initiated by their Mayo Clinic PCP. For the remaining 837 (16%) patients nurse navigators facilitated guideline based follow up. This resulted in the identification of 8 new cancers, including primary lung and metastatic disease. The diagnostic workup of these patients included 167 CT scans, 21 PET-CT scans, 2 bronchoscopic and 1 CT guided biopsy, 63 referrals to the pulmonary lung nodule clinic. One patient underwent surgical resection, 5 were referred to radiation and 7 to medical oncology.

Conclusions: PCP-based initial management of IPN at Mayo Clinic was better than expected. Yet, despite that, the implementation of this program already helped to identify 8 new cancers by re-engaging 837 additional patients. Program implementation was simple, reduced workload burden on the care team, and was received positively by the care team all leading to improved IPN management and incidental cancer diagnosis.

Keywords: Lung cancer screening, Incidental pulmonary Nodule, Fleischner Guidelines

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.02 The Preliminary Results of Taiwan National LDCT Lung Cancer Screening for Smokers and Nonsmokers With a Family History of Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide. While smoking remains the primary risk factor, lung cancer among nonsmokers is increasing, accounting for over 30% of global lung cancer deaths. In Taiwan, more than 60% of lung cancer patients have no history of smoking, and a family history of lung cancer (LCFH) may elevate the risk. This study reports the implementation and initial two-year findings of a low-dose computed tomography (LDCT) lung cancer screening program targeting heavy smokers and nonsmokers with a LCFH, assessing stage-shifting and the anticipated long-term impact on reducing advanced disease and mortality.

Methods: The Taiwan National Lung Cancer Early Detection Program (TNLCEDP), a large-scale, biennial LDCT screening initiative, was launched on July 1, 2022, to offer screening to heavy smokers (≥30 pack-years) and nonsmokers (including light smokers) with a LCFH. In addition to evaluating basic screening outcomes, we assessed changes in lung cancer staging before and after the introduction of TNLCEDP. To simulate a randomized controlled trial, a pseudo-control study was conducted using a five-state stage-based disease natural history model, incorporating Markov machine learning algorithms trained on first-round screening data and lung cancer incidence statistics from the national cancer registry prior to TNLCEDP. This model was employed to estimate the long-term effectiveness of biennial LDCT screening over a six-year period, followed by a five-year follow-up. Here, we report the initial screening results from the first two years and evaluate the reduction in stage II+ cases and lung cancer mortality in both target groups, accounting for potential over-detection due to screening.

Results: A total of 108,720 individuals underwent their first LDCT screening, including 63,175 males (58.1%) and 45,545 females (41.9%). Of these, 45,601 (41.9%) were heavy smokers, 59,038 (54.3%) were nonsmokers with a LCFH, and 4,081 (3.8%) had both risk factors. Lung cancer was confirmed in 1,389 individuals, with 83.2% detected at stage 0-1 (stage 0: 8.8%, stage I: 74.4%). The overall detection rate was 1.3%, with higher rates in individuals with a LCFH (1.7% overall; 1.8% in nonsmokers and 1.1% in light smokers) compared to heavy smokers (0.8%) and those with both risk factors (1.1%). A substantial shift toward earlier-stage lung cancer detection was observed following screening. The projected long-term benefits of biennial screening include a 72% (67.7%-75.8%) reduction in advanced-stage lung cancer for nonsmokers with a LCFH and a 43.3% (35.0%-50.6%) reduction for heavy smokers. Corresponding mortality reductions were estimated at 66.7% (66.1%-67.2%) for nonsmokers with a LCFH and 35.6% (34.7%-36.4%) for heavy smokers, accounting for over-detection rates of 28.9% in heavy smokers and 14.4% in nonsmokers with a LCFH. The predicted mortality reduction in heavy smokers aligns with findings from the NELSON randomized controlled trial.

Conclusions: The TNLCEDP demonstrated significant early-stage detection and projected long-term benefits in reducing lung cancer mortality for heavy smokers and nonsmokers or light smokers with a LCFH, even after considering over-detection. The inclusion of nonsmoking individuals with a LCFH is crucial and may provide valuable insights for other countries considering the implementation of similar LDCT screening.

Keywords: Lung cancer, Low dose computed tomography (LDCT), Nonsmoking lung cancer

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.03 Validation of Sybil in a Minority Population: Results from the Sybil Implementation Consortium: UIC, MGH, Baptist, Wellstar

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This abstract is under embargo until September 6 at 17:45 CET.

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.04 SENTINL0 Systemwide Early Notification Tool for Imminent Nascent Lung Cancer

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Introduction: Early detection for lung cancer through low-dose computed tomography (LDCT) screening significantly improves survival rates. However, racial and ethnic disparities persist due to differences in access, adherence, and eligibility criteria that are largely based on non-Hispanic White cohorts. AI-driven models, such as Sybil, a validated Resnet18 3D neural network trained on the National Lung Screening Trial LDCT images, have demonstrated the ability to predict lung cancer risk from LDCT scans, yet their performance in diverse populations remains uncertain. This study evaluates whether Sybil, applied to prior available thoracic imaging, can predict lung cancer development relative to standard LDCT screening. By assessing the model's efficacy in a racially diverse cohort, we aim to determine if AI-driven risk stratification can enhance screening effectiveness, reduce disparities, and improve personalized screening strategies.

Methods: This ambidirectional, prospective-retrospective study analyzed patients who underwent lung cancer screening (LCS) at University of Illinois Health system (UIH). Multimodal AI inference (Zakkar et al. MedRxiv, 2024) was used to predict lung cancer risk from clinical and radiographic features. Outcomes of lung cancer diagnosis was determined by review of Electronic Health Record.

Results: At the time of this analysis, a total of 1,584 individuals who underwent LDCT procedures were included, with a median follow-up period of approximately six months. The predictive model demonstrated strong discriminative ability, achieving a Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) of 0.82.Precision-recall analysis resulted in an Area Under the Curve (PR AUC) of 0.41. At a sensitivity threshold of 0.79, the model achieved a specificity of 0.96. Additionally, the positive predictive value (PPV) was 0.26 while the negative predictive value (NPV) was 0.97

Conclusions: In this interim analysis of diverse lung cancer screening patients, preliminary findings show multimodal AI has promising predictive ability of diagnosed lung cancer. These results highlight the model's effectiveness in distinguishing cases with a high degree of specificity and negative predictive value, making it a potentially valuable tool in clinical decision-making for LDCT-based assessments. Long-term follow up to ensure accuracy of complete diagnostic workups are required to definitively assess performance.

Keywords: early detection, multimodal AI, LDCT

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.05 Analysis of Longitudinal Low-Dose CT Sybil Scores in Two Canadian Cohorts

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Introduction: Sybil is a deep learning model developed to predict lung cancer risk using a single low-dose computed tomography (LDCT) scan, without requiring clinical data. While prior studies have validated its predictive accuracy, time-patterns in Sybil scores from single-patient longitudinal LDCT scans, and variability of scores across risk groups remain under-explored. Understanding these is critical to assess the potential of Sybil for clinical use. We thus conducted an analysis of longitudinal Sybil risk scores using data from two Canadian lung cancer screening cohorts.

Methods: We analyzed LDCT imaging and clinical data from 2537 participants in the Pan-Canadian Early Detection of Lung Cancer Screening Study and 2110 participants in the British Columbia Lung Screening Study. Screening eligibility criteria were: age 50-75 with PLCOm2008 risk score 2%, and 50-80 years with a PLCOm2012 risk score of >1.51% over 6 years and/or USPSTF 2013 criteria, respectively. On average, cancer cases had 3.3 scans and non-cases had 2.96 scans per patient. A total of 270 (179,91 respectively) lung cancer cases were detected. Sybil scores were computed for each LDCT scan and trajectories were examined for individuals who developed lung cancer (cases) and those who did not (non-cases). We investigated how Sybil scores evolved relative to the time of diagnosis, age at baseline, and smoking status.

Results: Sybil scores were consistently higher for individuals who developed lung cancer compared to those who remained cancer-free (Figure 1A, $p < 0.001$). Among cases, mean/median Sybil scores increased as time to diagnosis decreased (Figure 1B). However, there was high heterogeneity in trajectories, with some cases having decreasing scores, and some non-cases having increasing scores (Figure 1A). Notably, we observed an age effect among cases: Sybil scores rose with increasing age at scan, a pattern not observed among controls, whose scores remained relatively flat across age (Figure 1C). When stratified by smoking status, both current and former smokers who developed lung cancer exhibited similar Sybil score trajectories.

Conclusions: Our analysis suggests that Sybil scores differentiate in aggregate individuals at risk of lung cancer with average scores increasing as diagnosis approaches. The model appears robust to smoking status and reflects subtle age-related risk dynamics in cancer cases, suggesting it detects radiographic features of malignancy independent of risk factors. These findings support a potential role of Sybil in risk stratification. However, the large heterogeneity in individual trajectories indicates that further refinements might be needed before clinical use.

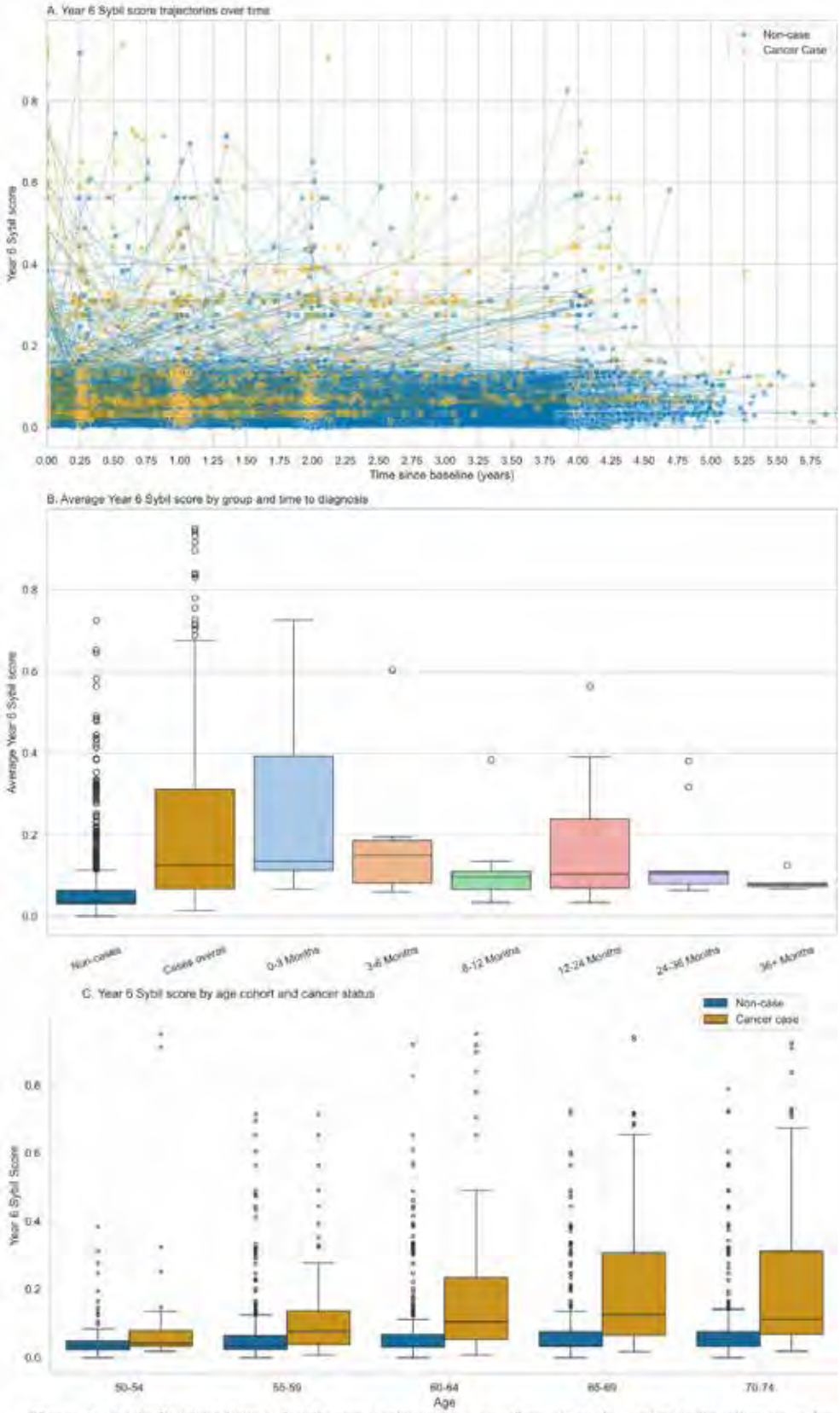

Figure 1: (A) Individual Year 6 Sybil score trajectories over time since the patient's baseline scan for cancer cases and non-cases. Each line represents a single participant. (B) Distribution of Year 6 Sybil scores by group. Cancer cases are further stratified by time from scan to diagnosis. (C) Distribution of Year 6 Sybil score stratified by age at scan and cancer status. Cancer Case refers to individuals diagnosed with lung cancer during follow-up; Non-case refers to those not diagnosed.

Keywords: Lung cancer screening, Deep learning, Longitudinal analysis

MA05 PRECISION IN LUNG CANCER SCREENING
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MA05.06 Integrating Circulating Protein Biomarkers in Nodule Malignancy Prediction Model Based on Five International Lung Cancer Screening Cohorts

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Introduction: Low-Dose Computed Tomography (LDCT) screening can significantly improve early lung cancer detection and reduce its mortality. However, it remains a challenge to optimize the clinical management of pulmonary nodules detected within screening programs. Our previous work identified a set of informative circulating protein markers for predicting pulmonary nodule malignancy. In this study, we evaluated whether incorporating these circulating protein biomarkers along with clinical, epidemiological and image data could enhance the predictive accuracy of risk models for pulmonary nodules.

Methods: This study is part of the Integrative Analysis of Lung Cancer Risk and Etiology (INTEGRAL) research program and is based on data from 5 LDCT screening programs in US, Canada and Europe with a total of 2,039 participants (683 cancer patients, 687 frequency matched controls with benign nodules and 669 healthy controls without nodules, nested in the same cohort). From a proteomic screening of over 1,100 circulating protein markers, 21 top-performing markers were selected in collaboration with the Lung Cancer Cohort Consortium, including six population-based cohorts. These 21 selected proteins were then quantified using absolute values. Model development was conducted using data from four LDCT screening studies: Pan-Canadian Early Detection of Lung Cancer Study (PanCan), International Early Lung Cancer Action Program (IELCAP)-Toronto, UK Lung Cancer Screening Trial (UKLS), and Pamplona-IELCAP. The model was externally evaluated in an independent cohort, the Pittsburgh Lung Screening Study-PLuSS (258 cancer patients, 257 frequency-matched controls with benign nodules).We identified the top-performing sets of protein markers using a support vector machine-recursive feature elimination (SVM-RFE) approach. For each set, we trained models to predict the risk of a benign nodule becoming malignant within five years post screen using machine learning (ML) approaches. ML models included logistic regression, random forest, and support vector machine (SVM), with logistic regression achieving the highest area under the receiver operating characteristic curve (AUC) when combined with epidemiological and imaging features through an ensemble approach. The final model was recalibrated using a logistic recalibration method.

Results: In the independent validation set, the INTEGRAL-Proteins for Nodules (INTEGRAL-PEN) model demonstrated strong predictive performance, with an overall AUC of 0.87 (95%CI=0.83-0.90) and 0.80 (95%CI=0.77-0.83) for predicting malignancy within the first- and 5-years post screen, respectively. Our model significantly outperformed both the Brock/PanCan model (AUC=0.74) and Lung Imaging Reporting and Data System (LungRADS) (AUC=0.65) in predicting malignancy up to 5 years post screen. Compared to the other risk assessment approaches, the INTEGRAL-PEN model performed better at identifying cancers among small nodules (<10mm), among those with longer follow-up (>1 year), and at identifying early-stage lung cancers. Those without nodules have similar protein profiles to those with benign nodules. This finding suggests that the protein profiles we identified are specific to the presence of malignant nodules, not just to the presence of any type of nodules.

Conclusions: The INTEGRAL-PEN model, validated in an external cohort, demonstrated strong performance in distinguishing malignant from benign pulmonary nodules. These findings highlight the added value of circulating protein biomarkers in improving nodule stratification in lung cancer screening.

Keywords: Lung Cancer, Nodule malignancy, Protein biomarkers

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.07 Breathomics for Early Non-Invasive Detection of Lung Cancer: A Propectively Multicenter Study Using TD-GC-MS and Portable Micro-GC

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Introduction: This study evaluates the diagnostic accuracy of breathomics, using TD-GC-MS for model development and a portable micro gas chromatography- micro photoionisation detector (µGC-µPID) system for validation, to establish a non-invasive, accessible lung cancer screening method aimed at reducing mortality rates and healthcare costs of late-stage lung cancer.

Methods: A prospective, multicenter study enrolled 5,292 participants across four hospitals, including 1,676 lung cancer patients and 4,616 controls (472 healthy individuals, 2,993 with chronic respiratory diseases). Thermal desorption-gas chromatography-mass spectrometry (TD-GC-MS) analysis of exhaled breath samples, with feature selection via orthogonal partial least squares discriminant analysis, was used to train (n=2,132) and internally validate (n=719) a logistic regression model. External validation (2,441 samples) used data from the portable µGC-µPID system, which integrates three microfabricated chips for volatile organic compound capture, separation, and detection.

Results: Fourteen breathomic biomarkers were identified for distinguishing lung cancer patients from controls. In internal validation, the model achieved an AUC of 0.91 (95% CI: 0.88-0.94), accuracy of 78%, sensitivity of 95%, specificity of 60%, and a Negative Predictive Value (NPV) of 91%. External validation using the µGC-µPID system confirmed these results, with an AUC of 0.87, accuracy of 51%, sensitivity of 91%, specificity of 45%, and NPV of 96%. The model demonstrated high sensitivity in detecting lung cancers of various sizes, particularly excelling in identifying lesions smaller than 10 mm (AUC 0.92, sensitivity 98.2% internally; AUC 0.90, sensitivity 92.8% externally) and AJCC stage IA1 lung cancer (sensitivity 95.5% internally and 94.8% externally). In a real-world screening subset of the external validation group (n=2,055), the model correctly identified 80% of lung cancer cases and excluded 45.7% of non-cancer individuals.

Conclusions: This largest-scale study to date demonstrates the potential of machine learning-enhanced breathomics as a highly sensitive and non-invasive approach for early lung cancer detection. Utilizing portable µGCs, this cost-effective screening method offers feasible deployment across diverse clinical settings, particularly benefiting high-risk populations by minimizing radiation exposure and improving access to care. By facilitating earlier diagnosis, breathomics has the potential to significantly reduce lung cancer mortality and enhance quality of life, supporting its integration into public health strategies.

Keywords: Breathomics, Lung cancer, Cancer screening

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.08 Cell-Free DNA Methylation Markers in Serum and Bronchial Washing for Lung Cancer Detection: A Prospective Observational Study

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Introduction: In the era of lung cancer screening, the use of peripheral bronchoscopy has increased due to the rising detection of small peripheral lung nodules. However, the development of biomarkers for the early and accurate diagnosis of lung cancer using bronchial washing (BW) specimens remains a clinical challenge. This study aimed to evaluate the clinical utility of DNA methylation markers in serum and BW samples for distinguishing malignant from benign pulmonary nodules detected through chest CT screening.

Methods: We prospectively enrolled 200 individuals with pulmonary nodules between May 2024 and February 2025 at Asan Medical Center, South Korea. Clinical demographics, nodule characteristics, and methylation profiles of 4 genes (PCDHGA12, OLIG3, NKX2-5, FOXC2) in serum, and 2 genes (PCDHGA12, PRRX1) in BW samples were analyzed. Diagnostic performance was evaluated using ROC curve analysis, and the association between methylation status and clinicopathologic features was also assessed.

Results: Among 200 initially enrolled participants, 9 were excluded due to the diagnosis of other malignancies or withdrawal of informed consent. The final analysis included 191 patients (123 with malignancy, 68 with benign nodules). Patients with malignancy were older (median age 70 vs. 64 years, $p < 0.001$) and had a lower BMI (mean 23.1 vs. 24.8 kg/m^2, $p = 0.046$). Malignant nodules were larger (mean size 29.3 mm vs. 18.0 mm, $p < 0.001$) and had significantly higher Lung-RADS categories ($p < 0.001$). Adenocarcinoma was the most common malignant histology (77 of 123, 62.6%), while inflammatory nodules (26 of 68, 38.2%) were the most frequent etiology in the benign group. The serum based 4 gene methylation panel demonstrated an AUC of 0.600 (95% CI, 0.526 - 0.671), with 80.0% sensitivity and 40.0% specificity. The BW based 2 gene panel showed superior diagnostic performance, with an AUC of 0.785 (95% CI, 0.687 - 0.864), 74.7% sensitivity, and 82.4% specificity. Methylation positivity in serum samples was observed in 80.0% of lung cancer patients and was not significantly associated with age, sex, tumor location, histology, or stage. Similar trends were observed in BW samples.

Conclusions: Cell-free DNA methylation panels using serum and bronchial washing specimens demonstrated promising diagnostic performance for lung cancer detection. Notably, the 2 gene panel in bronchial washing samples showed higher diagnostic accuracy than the serum panel, supporting its potential as a useful diagnostic tool for early lung cancer detection in clinical practice.*English language editing was assisted by the AI tool ChatGPT-4.

Keywords: Cell-free DNA methylation, Bronchial washing, Lung cancer screening

MA05 PRECISION IN LUNG CANCER SCREENING
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA05.09 Precise Diagnosis of Small Malignant Pulmonary Nodules Driven by Peripheral Single-Cell Immune Signatures: A Prospective Multi-Center Study

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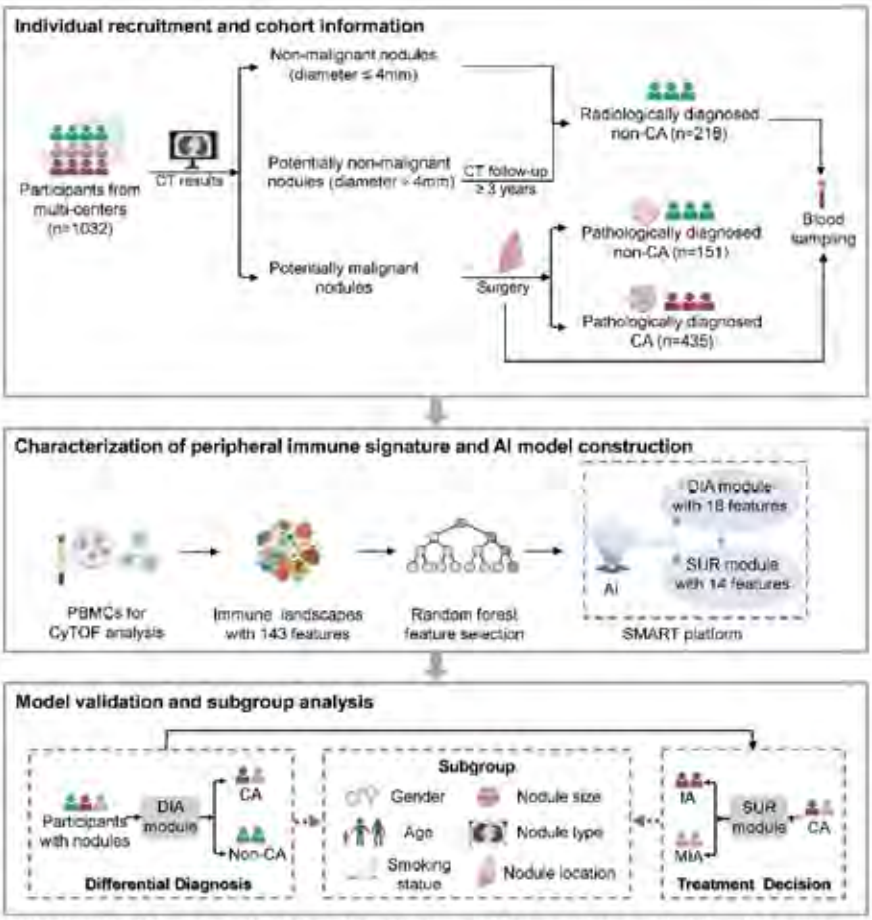
Introduction: Early detection of pulmonary nodules is critical for improving outcomes in lung cancer patients. However, accurately diagnosing malignant nodules, especially those ≤10 mm, and predicting tumor invasiveness to guide surgical decisions remain significant challenges. Immune dysfunction is known to contribute to cancer development, and we hypothesize that alterations in peripheral blood immune profiles could provide a novel approach for the diagnosis and management of pulmonary nodules.

Methods: We conducted a prospective study involving three cohorts: healthy controls, individuals with pulmonary nodules, and patients with advanced lung cancer. Peripheral blood samples were collected and analyzed using mass cytometry to characterize immune signatures. Machine learning algorithms were applied to identify immune profiles associated with lung cancer, leading to the development of the SMART platform, driven by AI-mined single-cell immune signatures. This platform consists of two consecutive modules: the Diagnostic Decision (DIA) module for distinguishing malignant from benign nodules, and the Surgical Decision (SUR) module for predicting tumor invasiveness.

Results: A total of 1032 participants were recruited from three medical centers, with 930 blood samples qualified for analysis. The early-stage lung carcinoma (CA) and non-carcinoma (non-CA) nodule samples were divided into a training cohort (396 participants) and a testing cohort (408 participants). The DIA module achieved high accuracy in distinguishing malignant from benign nodules, with an AUC of 0.952 in the testing cohort, significantly outperforming existing models such as the Mayo (AUC = 0.751), Veterans Association (AUC = 0.733), and Brock (AUC = 0.840) models. The DIA module also performed well in an independent set, including healthy controls without pulmonary nodules and patients with advanced lung cancer (AUC = 0.945). For lung cancer samples (N = 435), the SUR module accurately differentiated minimal invasive adenocarcinoma (MIA) from invasive adenocarcinoma (IA), with AUCs of 0.984 in the training cohort (N = 218) and 0.949 in the testing cohort (N = 217), outperforming the average accuracy of experienced clinicians making assessments based on CT images and clinical data.

Conclusions: By leveraging peripheral blood immune profiles, we have developed the SMART platform, which effectively and accurately facilitates differential diagnosis of small pulmonary nodules and the assessment of lung tumor invasiveness. The SMART platform offers substantial clinical benefits and hold promise as a crucial tool in the comprehensive management of pulmonary nodules.



AI=artificial intelligence, CA=carcinoma, CyTOF=time-of-flight mass cytometry, CT=computerized tomography, MIA=minimal invasive adenocarcinoma, IA=invasive adenocarcinoma, DIA=diagnostic decision, SUR=surgical decision, PBMCs=peripheral-blood mononuclear cells

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.01 Real-World Outcomes of First-Line Immunotherapy Intensification of Patients With Advanced Non-Small Cell Lung Cancer (aNSCLC)

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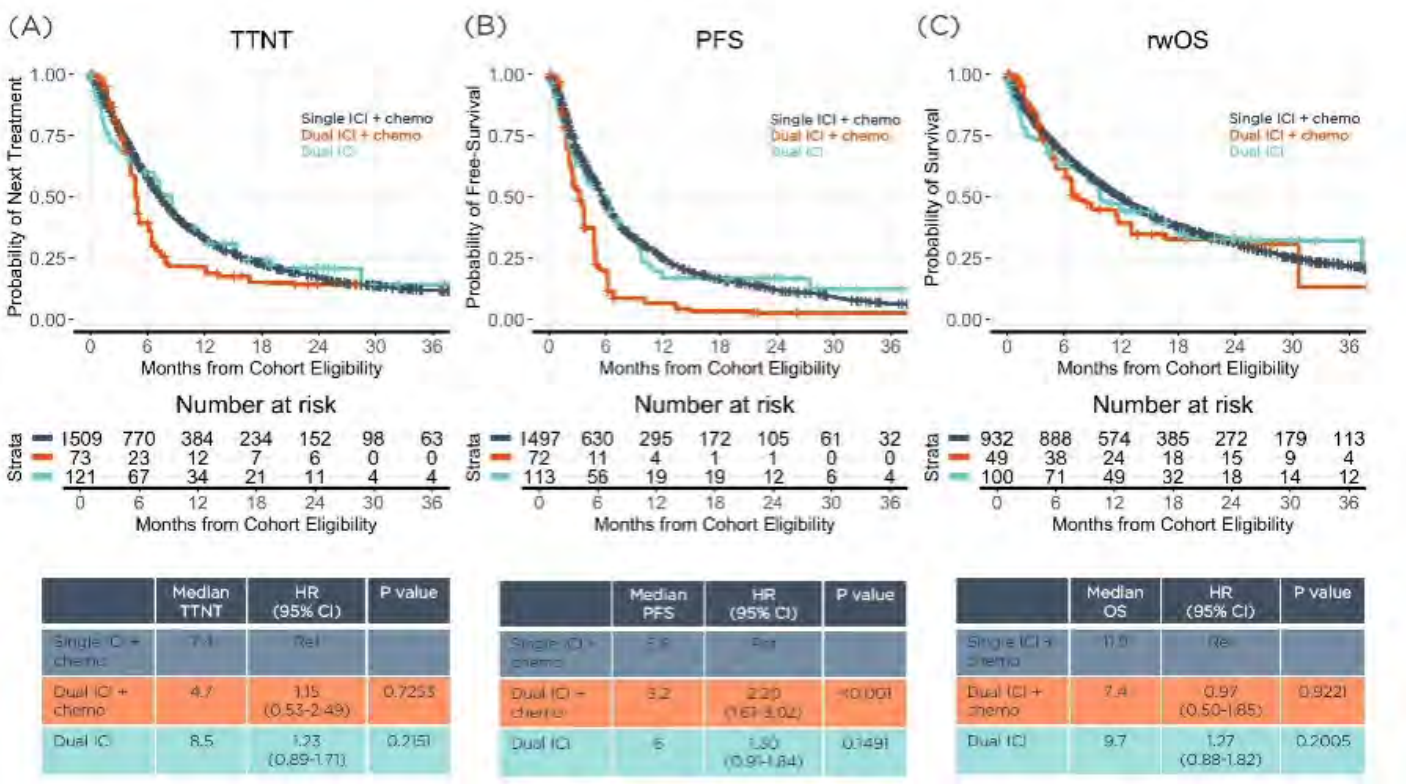
Introduction: There are multiple first-line (1L) immune checkpoint inhibitor (ICI)-based treatment options for patients with aNSCLC. Intensification of ICI treatment from single ICI with chemotherapy (single ICI-chemo) to dual ICI regimens with (dual ICI-chemo) or without (dual ICI) chemotherapy has been suggested for patients with risk factors for ICI resistance, such as cancers with alterations in STK11/KEAP1. However, these intensified regimens have not been compared prospectively in either broad or selected at-risk populations.

Methods: We conducted a retrospective observational study of real-world 1L clinical outcomes data for United States (US) patients with aNSCLC who underwent tissue Foundation Medicine comprehensive genomic profiling, using the US-based deidentified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database. We categorized patients diagnosed 2020-2024 by 1L regimen (single ICI-chemo, dual ICI-chemo, dual ICI) and propensity weighted by age, ECOG performance status, PD-L1, liver/brain metastasis, practice setting (academic/community), smoking status, and year of diagnosis. We then calculated time-to-next treatment (TTNT), real-world progression-free survival (rwPFS), and overall survival (OS) by multivariable Cox proportional hazards regression, adjusting for histology and alterations in TP53, KRAS, and STK11/KEAP1, as well as the interaction between STK11/KEAP1 alteration and treatment.

Results: Our samples included 1,703 patients (median age 69.0 years, 44.9% female; 88.6% single ICI-chemo, 4.3% dual ICI-chemo, 7.1% dual ICI). Overall, dual ICI-chemo was associated with worse rwPFS compared to single ICI-chemo (HR 2.20, p < .001), though this difference was not seen in TTNT (p = .72). No differences were seen in OS (median OS 11.9 months single ICI-chemo, 7.4 months dual ICI-chemo, 9.7 months dual ICI; all p > .05). STK11/KEAP1 alteration status (HR 1.32, p < .001) and squamous histology (HR 1.36, p < .001) were associated with worse OS in multivariable analysis, though the interaction of STK11/KEAP1 alteration and treatment was not significant (p > .1).

Conclusions: In this large, real-world cohort of US patients with aNSCLC, similar clinical outcomes were seen between all three 1L treatment regimens, suggesting that patients exposed to potentially more toxic and costly regimens did not derive additional clinical benefit. STK11/KEAP1 alteration status had an independent association with worse OS but was not associated with a differential benefit in ICI intensification. Further prospective studies are needed to identify appropriate patients for ICI intensification.



	Median TTNT	HR (95% CI)	P value
Single ICI + chemo	7.1	Ref	
Dual ICI + chemo	4.7	1.15 (0.53-2.49)	0.7253
Dual ICI	8.5	1.23 (0.89-1.71)	0.2151

	Median PFS	HR (95% CI)	P value
Single ICI + chemo	5.6	Ref	
Dual ICI + chemo	3.2	2.20 (1.61-3.02)	<0.001
Dual ICI	6	1.30 (0.91-1.84)	0.1491

	Median OS	HR (95% CI)	P value
Single ICI + chemo	11.9	Ref	
Dual ICI + chemo	7.4	0.97 (0.50-1.85)	0.9221
Dual ICI	9.7	1.27 (0.88-1.82)	0.2005

Keywords: immunotherapy, first-line treatment, real-world data

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.02 Paradigm Shift in Lung Cancer Mortality in the United States: A Multifaceted Success Story

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Introduction: Lung cancer remains the second most diagnosed cancer in the United States and the leading cause of cancer-related deaths. While mortality rates have declined over the past two decades, the extent of this decline varies by gender and socio-economic factors. Research suggests that disparities in lung cancer outcomes are influenced by economic development, healthcare accessibility, policy regulations, and environmental exposures. This study explores the role of socio-economic indicators, policy-level factors, and environmental influences, such as air pollution, in shaping lung cancer mortality trends. By analyzing publicly available data on lung cancer deaths, healthcare expenditures, smoking trends, and air quality, we aim to understand the key drivers behind the reduction in lung cancer mortality in the United States.

Methods: We conducted an ecological study analyzing lung cancer mortality trends in the United States over the past two decades. Data on lung cancer mortality were obtained from the Cancer Over Time database. At the same time, socio-economic indicators such as the Human Development Index (HDI), Gini coefficient, and healthcare expenditure inflation were sourced from publicly available repositories, including the United Nations Development Programme and World Bank. Environmental data, including PM2.5 levels, were collected from the State of Global Air database. Using statistical modeling and trend analysis, we examined the associations between lung cancer mortality and these factors. Since all data were publicly available, ethical approval was not required.

Results: Joinpoint regression analysis revealed substantial declines in lung cancer Age-Standardized Mortality Rates (ASMR) from 1994-2020, with male mortality decreasing by 58.9% and female mortality by 40.3%. The most accelerated declines occurred after 2014, coinciding with the FDA approval of 30 new lung cancer drugs during the study period. Male mortality decline accelerated from -2.31% (1994-1998) to -5.62% (2014-2018), while female mortality remained stable until 2004 before declining, reaching -4.43% (2014-2018). The male-to-female mortality gap narrowed from 1.98:1 in 1994 to 1.36:1 in 2020. Histological analysis showed gender-specific trends, with adenocarcinoma increasing 7.4% in females while declining 28.5% in males. Smoking prevalence decreased substantially (males: 47.8%, females: 51.3%), with regression analysis revealing stronger associations between smoking and mortality in males (coefficient=2.14, $p<0.001$) than in females (coefficient=0.97, $p<0.001$). Ridge logistic regression identified smoking as increasing mortality risk by 3 times in males and 5.7 times in females. PM2.5 concentration declined from 13.8 $\mu g/m^3$ to 7.81 $\mu g/m^3$, with environmental exposure more strongly associated with male mortality ($\beta=4.11$, $p<0.001$) compared to females ($\beta=1.48$, $p<0.001$). HDI showed a negative correlation with mortality rates ($r=-0.61$), while healthcare inflation demonstrated a weaker positive correlation ($r=0.34$). Despite doubling healthcare expenditure and reducing uninsured rates from 15.2% to 8.6%, the Gini index remained relatively stable (39.7 to 41.5), suggesting persistent socioeconomic disparities alongside improved healthcare access.

Conclusions: The significant reduction in U.S. lung cancer mortality over three decades results from a comprehensive multisectoral approach combining environmental controls, anti-tobacco campaigns, healthcare reforms, and precision medicine advances. Despite this progress, further improvements require addressing four key areas: expanding equitable access, implementing value-based care, strengthening prevention, and ensuring fair distribution of personalized treatments.

Keywords: Lung cancer, Multisectoral approach, risk reduction model

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.03 Pharmacoeconomic Analysis of NADIM 2 Trial: Cost-Effectiveness of Perioperative Chemo-Immunotherapy in Resectable Stage III NSCLC

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Introduction: Neoadjuvant and perioperative chemoimmunotherapy is increasingly used in resectable NSCLC. Several trials achieved improvement in EFS and OS, and most used a perioperative strategy. There is poor compliance of post-op IT and its duration and value is not well established. Until now there are no cost-value analysis of these approaches. Here, we report a pharmacoeconomic analysis of NADIM 2 trial.

Methods: 86 patients with resectable Stage IIIA/B NSCLC were randomly assigned in a 2:1 ratio to receive 3 cycles of preoperative nivolumab plus chemotherapy (experimental group, Exp) versus chemotherapy alone (control group) and after R0 surgery, patients assigned to Exp arm received nivolumab monthly for 6 months (m). Improvement in OS (secondary end-point) was observed after a median follow-up of 22.6 m improving 14 m OS from 63.6 % to 85% (NEJM 2023;389:504-513). Nivolumab was administered at flat dose of 360 mg preop and 480 mg postop. An intention to treat analysis was performed using patient crude survival time and cost of delivered immunotherapy according to nivolumab price in Spain.

Results: Only 2 out of 57 p do not received 3 preoperative treatment cycles. 36/57 p (63%) completed planned postop Nivolumab. 11 p (19%) do not received any postoperative dose. Overall, the delivered doses of Nivolumab achieved 72% of planned treatment. The mean survival in the Exp group was 41.7m vs 21.3m in Control with an increase of 20.3m. Total cost of nivolumab treatment per protocol accounted for 50,371€, while the cost of delivered treatment was 31,016€. After adjusting for OS, the benefit per patient resulted in 18,299€ per gained year of life.

Conclusions: Perioperative chemo-immunotherapy is the current standard of care in resectable Stage III NSCLC and improved OS in NADIM 2 trial. Compliance of post-operative immunotherapy was 72% of planned dose. Cost per life years gained of 3 cycles pre and 6 cycles postop Nivolumab accounts for 18.299 € below the threshold of cost-effectiveness accepted in most European countries.

Keywords: Cost-effectiveness, Neoadjuvant chemo-immunotherapy, Pharmacoeconomics

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.04 Improving Preoperative ctDNA Detection in NSCLC Through Mechanistic Profiling and Multiregion-Informed Customization

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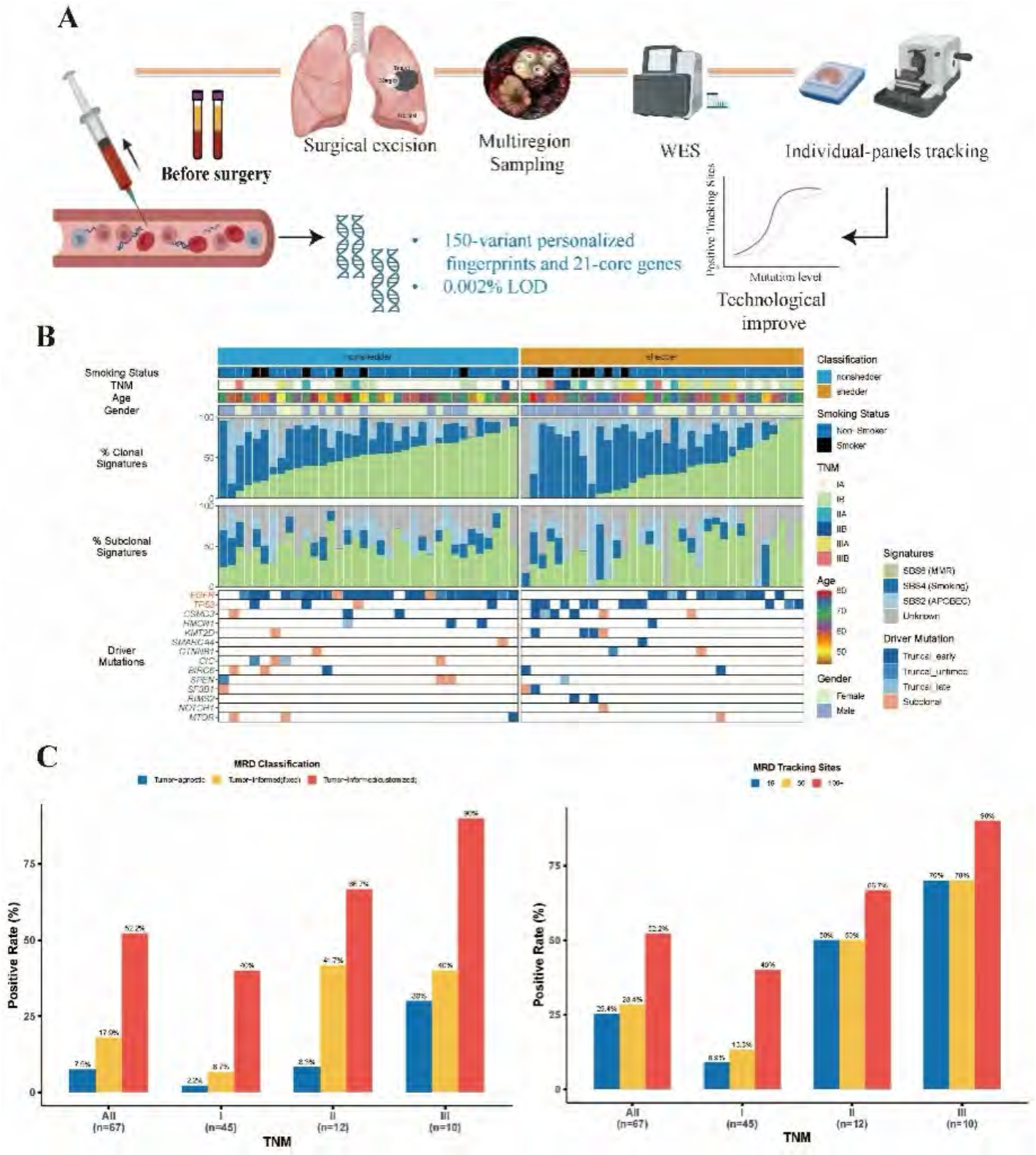
Introduction: Circulating tumor DNA (ctDNA) is a highly promising biomarker for the precise management of NSCLC, yet its clinical utility remains limited by technical challenges. Preoperative ctDNA shedding has been associated with poorer prognosis, and numerous ongoing RCTs employing ctDNA to guide postoperative treatment underscore the need for enhanced detection sensitivity. In this study, we further investigated the mechanisms underlying nonshedding in certain patient populations.

Methods: We prospectively enrolled 73 patients with primary NSCLC. Preoperative blood samples were collected using cfDNA-free tubes, and intraoperative multi-region tumor sampling was performed for WES. Our platform, Variant-Integrated Genomic Insight for Longitudinal tracking (VIGIL™), integrates 150 personalized somatic variants and 21 core genes, including SNVs, indels, and fusions, achieving a LOD of 0.002%.

Results: Patients in the Shedder group—defined by detectable preoperative ctDNA—were more likely to be male and to present with solid lesions rather than ground-glass opacities. Consistent with previous studies, non-adenocarcinoma histology was more commonly observed in this group. The Shedders also exhibited a more activated immune microenvironment, characterized by enrichment of CD4+ T cells, γδ T cells, CD8+ memory T cells, and M1 macrophages. Preoperative ctDNA shedding was significantly associated with an increased risk of recurrence. EGFR mutations were more frequent in the Nonshedder group, whereas TP53 mutations predominated among Shedders; notably, these two driver mutations were mutually exclusive in the Shedder group. Retrospective probe analysis revealed higher levels of clonal neoantigens in Shedders and more subclonal neoantigens in Nonshedders, suggesting a stronger role for clonal neoantigens in facilitating ctDNA release across various evolutionary contexts. To enhance objectivity, we further analyzed a subset of 67 patients with over 100 mutation-tracking loci. Compared to fixed tumor-informed or tumor-agnostic approaches, the customized tumor-informed strategy significantly increased detection rates, particularly in stage I cases (40% detection). Moreover, increasing the number of tracking loci to over 100 nearly doubled detection sensitivity relative to 16 (TRACERx, 2017) or 50 (MEDAL, 2023) loci. This improvement is likely due to multi-region sampling and an increased number of tracking loci, which correct for clonal illusion and enable more comprehensive capture of both clonal and subclonal mutations.

Conclusions: This study refines the tumor-informed ctDNA detection strategy, effectively reducing false negatives in nonshedders and enhancing the robustness of ctDNA as a clinical biomarker. Although our findings are based on preoperative blood samples, the high sensitivity of this approach suggests strong potential for postoperative longitudinal monitoring as well.



Keywords: ctDNA, tumor-informed panal, NSCLC

MA06.05 Impact of Bronchoalveolar Lavage Combined With mNGS in Patients With Checkpoint Inhibitor Pneumonia: A Prospective Cohort Study

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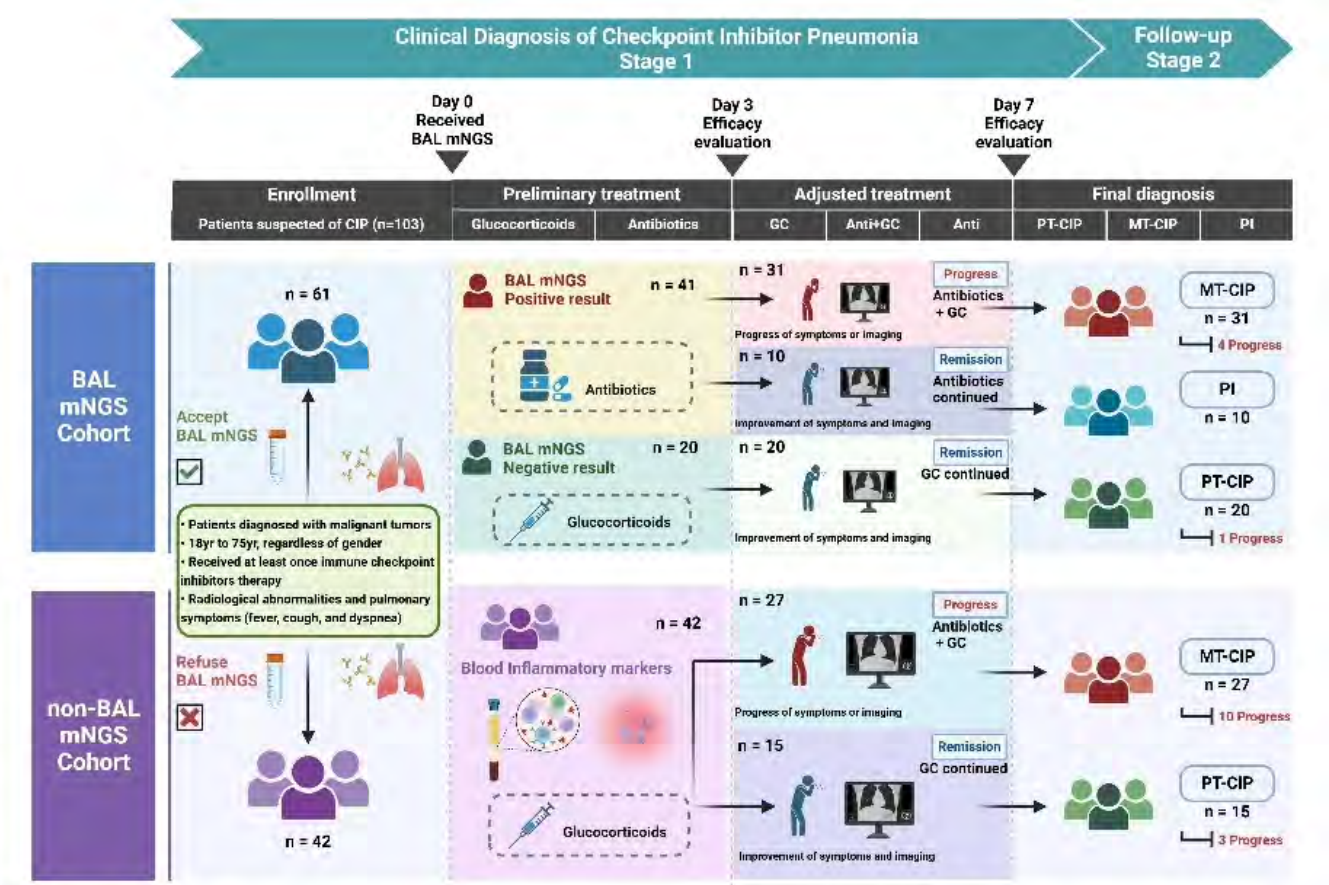
Southern Medical University Nanfang Hospital, GuangZhou/CN

Introduction: Checkpoint inhibitor pneumonia (CIP) is a serious immune-related adverse event with high morbidity and mortality, currently lacking specific diagnostic methods and posing significant challenges in diagnosis and management. This study aims to investigate the value of bronchoalveolar lavage (BAL) combined with metagenomic next-generation sequencing (mNGS) in the diagnosis and precision treatment of CIP for providing evidence-based medicine.

Methods: This prospective clinical trial (NCT06192303) enrolled a total of 103 patients suspected checkpoint inhibitor pneumonia (CIP). Clinicians integrated patient clinical data and treatment outcomes to make final diagnosis, which included 35 cases of pure-type CIP (PT-CIP), 58 cases of mixed-type CIP (MT-CIP), and 10 cases of pulmonary infections (PI). We evaluated the diagnostic efficacy of BAL mNGS in CIP and explored the clinical characteristic differences among different subtypes of CIP patients. Additionally, receiver operating characteristic (ROC) analysis and logistic regression analysis was utilized to investigate the potential efficacy of immune-inflammatory markers in distinguishing MT-CIP from PI. Furthermore, the value of BAL mNGS in guiding treatment for CIP patients was assessed by the total time to relief to grade I or below, the short-term treatment effectiveness within 7 days, the proportion of relief within 3 months, and the intensity of antibiotic use during hospitalization.

Results: BAL combined with mNGS indicated high sensitivity and specificity in diagnosing CIP. 100%(20/20) of patients with negative mNGS results were finally diagnosed as pure-type CIP(PT-CIP), and 75.6%(31/41) of patients with positive mNGS results were finally diagnosed as mixed-type CIP(MT-CIP). Notably, 24.4%(10/41) of patients with positive mNGS results achieved recovery from targeted antibiotic therapy alone, avoiding unnecessary corticosteroid treatment. Immune-inflammatory markers, including ALC, NLR, MLR, PLR, and SII, showed significant diagnostic efficacy in distinguishing mixed-type CIP from pulmonary infections. Treatment guided by BAL mNGS significantly reduced the total recovery time of CIP patients, and improved both 7-days (90.2% vs 69.0%, P<0.05) and 3-months (58.1% vs 32.3%, P<0.05) outcomes. Furthermore, BAL mNGS-guided treatment increased antibiotic use intensity in severe CIP patients with Grade 3-4, highlighting its clinical utility in timely pathogen detection and targeted therapy.

Conclusions: This study demonstrated the critical role of BAL mNGS in enhancing CIP diagnosis, guiding treatment, and improving patient prognosis. A stratified treatment strategy based on BAL mNGS results and immune-inflammatory markers was proposed for advancing the management of CIP patients.



Keywords: Checkpoint inhibitor pneumonia, Metagenomic next-generation sequencing, Bronchoalveolar lavage

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.06 Overall Survival Among Patients With Oncogene Driven Lung Cancers Treated on Clinical Trials Compared to Standard Care

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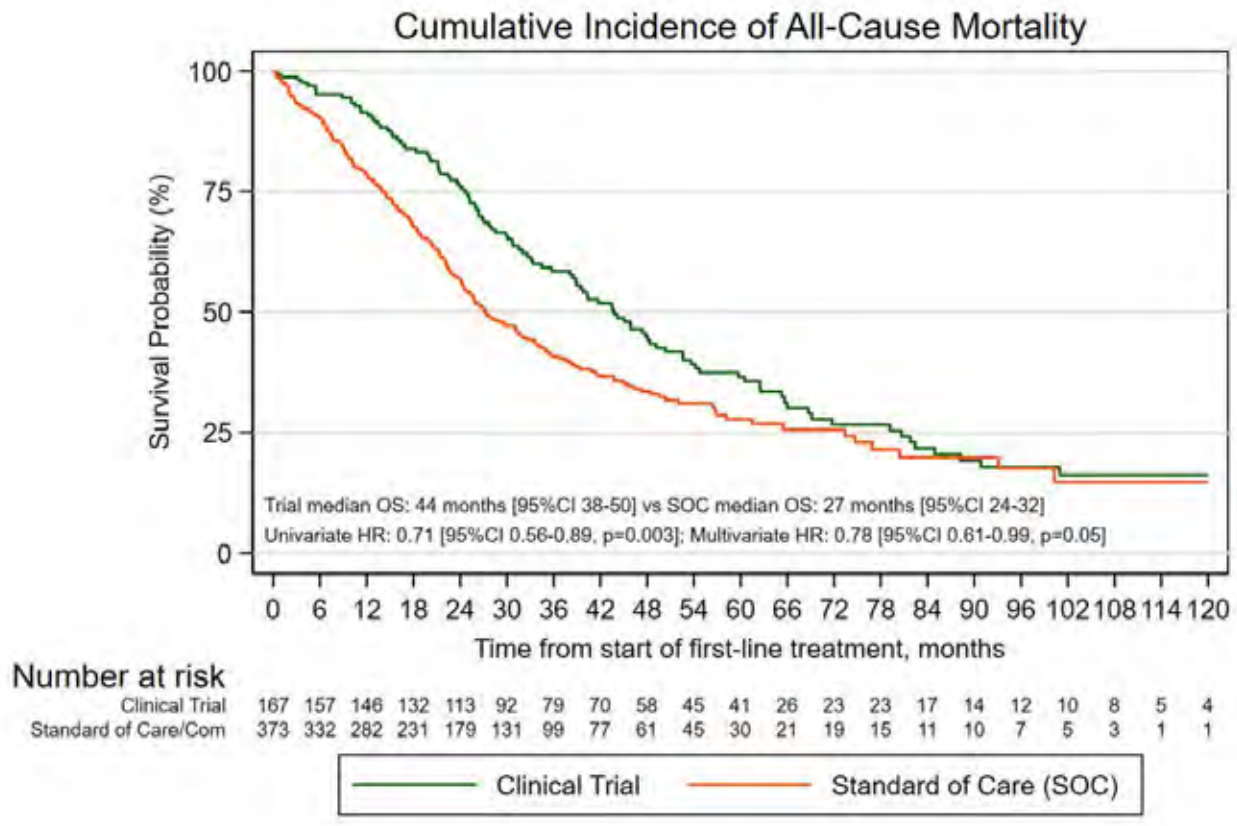
[1]Peter MacCallum Cancer Centre, Melbourne/AU ,[2]Peter MacCallum Cancer Centre, Melbourne Australia, and Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville/AU

Introduction: Targeted treatments for oncogene-driven lung cancers have transformed care and survival. While trials offer novel therapies and structured monitoring, real-world treatment varies. This study compared survival outcomes for patients on clinical trials versus standard-of-care (SOC) therapies.

Methods: This analysis includes patients with advanced/metastatic oncogene-driven NSCLC from the AUstralasian thoRacic cancers lOngitudinal cohoRt study and biobAnk (AURORA) at Peter MacCallum Cancer Centre (ACTRN12625000038493). Eligible patients (≥18 years) had ALK, BRAF, EGFR, ERBB2, KRAS G12C, MET14, RET, or ROS1 NSCLC diagnosed 2013-2023 and received ≥1 line of systemic therapy for advanced disease (early-stage treatments permitted). The primary endpoint, overall survival (OS), was defined from first-line treatment initiation to death or last follow-up. Kaplan-Meier estimates, log-rank tests, and multivariate Cox regression assessed survival differences and covariate effects (age, sex, mutation, stage, performance status). Exploratory analyses within larger EGFR, ALK, and KRAS G12C subgroups.

Results: Among 540 patients, 167 received clinical trial treatment and 373 SOC therapy. Trial patients were younger (mean 57±12.1 vs. 63±12.3 years, p<0.001) and fewer had ECOG≥2 (3% vs. 9%, p=0.01). Other demographics were similar: advanced-stage disease (IIIB, IIIC, IV) at diagnosis: 90% vs. 85%, female: 55% vs. 60%, never-smokers: 55% vs. 53%, White/Caucasian: 61% vs. 60%, Asian: 37% vs. 38%. Mutation distribution (N,%) in trial vs. SOC cohorts was: ALK (26,16% vs. 55,15%), BRAF (9, 5% vs. 19, 5%), EGFR (79, 47% vs. 223, 60%), ERBB2 (4, 2% vs. 3, 1%), KRAS G12C (25, 15% vs. 62, 17%), MET14 (0, 0% vs. 1, <1%), RET (4, 2% vs. 4, 1%), and ROS1 (20, 12% vs. 6, 2%). Median OS was longer in the trial cohort (44 months, 95%CI: 38-50) vs. SOC (27 months, 95%CI: 24-32) (univariate HR 0.71, 95% CI: 0.56-0.89, p=0.003; multivariate HR 0.78, 95%CI: 0.61-0.99, p=0.05). In adjusted analyses by mutation, EGFR OS was 40 months (95%CI: 33-49) in trials vs. 27 months (95%CI: 24-33) in SOC (HR 0.70, 95%CI: 0.51-0.97, p=0.035), for ALK was not reached (95% CI: 44-NR) in trials vs. 77 months (95%CI: 39-NR) in SOC (HR 0.63, 95%CI: 0.26-1.50, p=0.296), and for KRAS G12C was 21 months (95%CI: 11-38) in trials vs. 16 months (95% CI: 9-22) in SOC (HR 1.1, 95%CI: 0.61-1.88, p=0.804).

Conclusions: Patients with oncogene-driven NSCLC enrolled in clinical trials have longer overall survival than those treated with SOC, even after adjusting for trial eligibility confounders.



Keywords: Oncogene, Clinical trial, Overall survival

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.07 Benchmarking CT Foundation Models for Survival Prediction in NSCLC Patients

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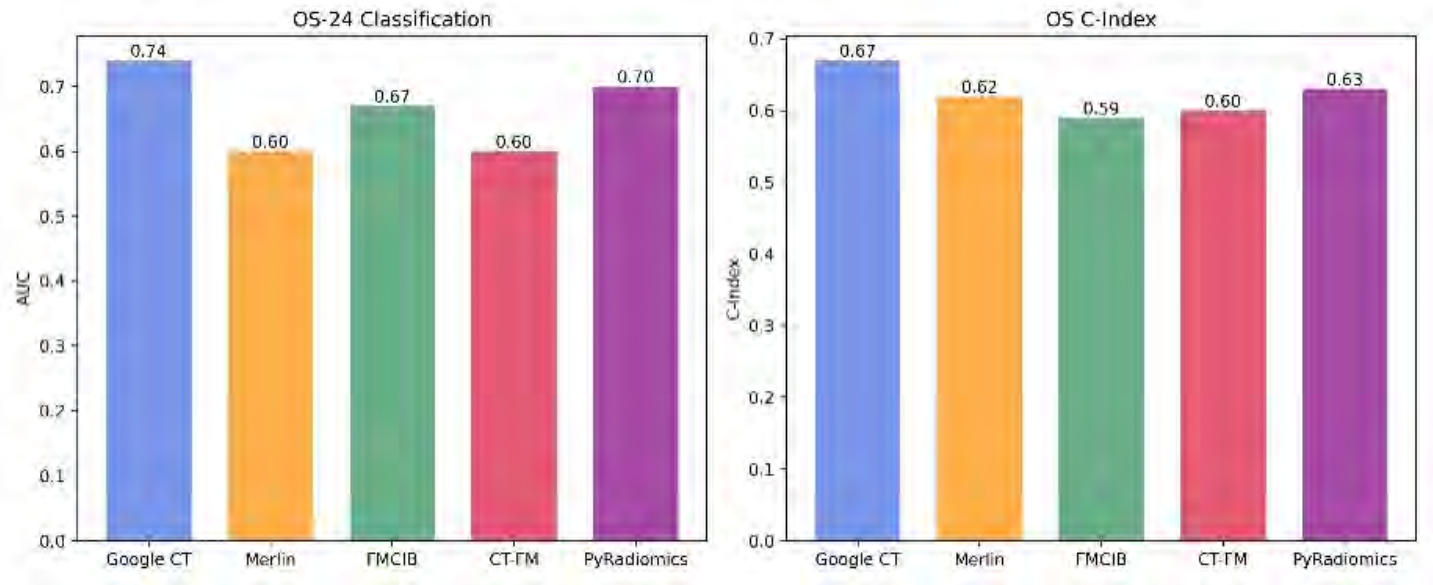
Introduction: Radiomic features extracted from Computed Tomography (CT) images have shown promise in capturing tumour prognostic characteristics. Despite PyRadiomics being a state-of-the-art method for this task, foundation models (FMs) showed promising results for feature extraction. This study investigates the use of FMs, comparing their performance with PyRadiomics for extracting CT features to develop robust prognostic signatures for NSCLC patients.

Methods: We analysed 553 CT scans with corresponding lesion segmentations from publicly available TCIA datasets (NSCLC Radiomics and NSCLC Radiogenomics). For each patient, we predicted 24-month survival status (classification, OS-24) and conducted a survival analysis. Features were extracted using 5 methods within two approaches: FMs (Merlin, Google CT, FMCIB, CT-FM; respectively pre-trained on about: 15.000, 600.000, 30.000, and 140.000 CTs), and PyRadiomics. All the FMs, except FMCIB, used the full 3D scan as input, while FMCIB used a portion of the CT containing the main lesion. PyRadiomics features were extracted from the main lesion segmented by an expert radiologist. We relied on standard pre-processing Machine Learning pipelines for data preparation. We trained our method over 443 CTs, and tested it over an independent set of 110 CTs (20% of the total, never seen by the model). Performance was evaluated using Area Under the Curve (AUC) scores for classification and Concordance Index (C-Index) for survival analysis.

Results: In our analysis, Google CT FM achieved the best results in predicting OS-24 (AUC 0.74, 95% CI [0.64, 0.83]), and OS (C-index 0.67, 95% CI [0.60, 0.74]). Google CT demonstrated strong generalizability and minimal overfitting, consistently outperforming PyRadiomics.

Conclusions: Google FM demonstrated strong prognostic capabilities in NSCLC, showing robust and consistent performance across both survival prediction and classification tasks. Notably, this approach achieves superior results without requiring tumour segmentations, offering a significant practical advantage over traditional radiomics methods like PyRadiomics, which rely on precise lesion delineation. These procedures can save radiologists time while maintaining diagnostic performance. Our findings suggest that FMs, when pre-trained on large-scale medical imaging datasets, can effectively capture clinically relevant patterns across the entire CT volume, potentially enhancing the development and application of imaging biomarkers in clinical practice, and allowing the use of small datasets thanks to the reduced risk of overfitting.



Keywords: Radiomics, Foundation Models, Survival

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.08 Is Weight-Based Pembrolizumab Dosing as Effective as Standard Fixed Dose in Advanced Nsclc?

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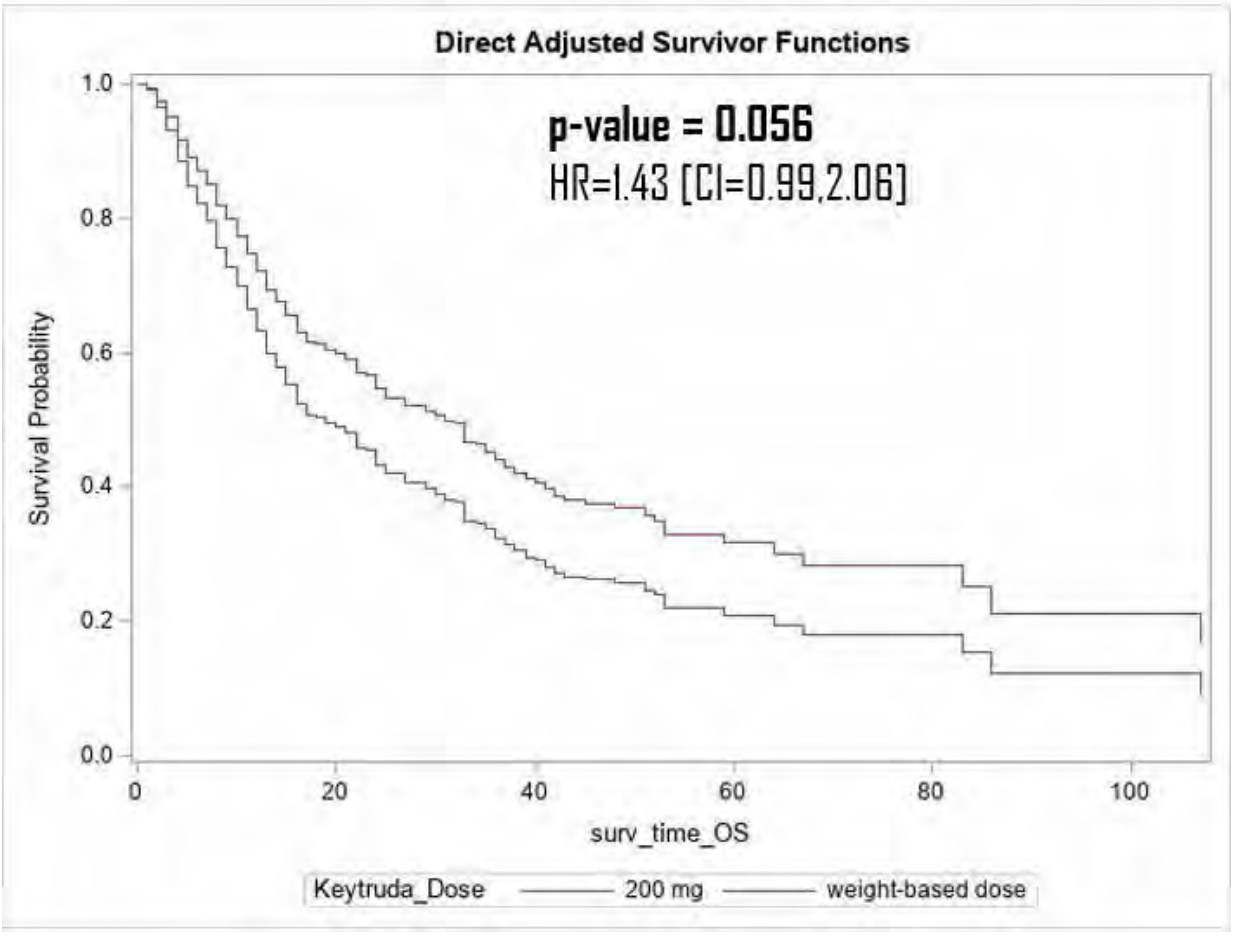
Introduction: Immunotherapy has significantly advanced the treatment of patients diagnosed with non-small cell lung cancer (NSCLC). Pembrolizumab was initially studied at doses of 2 mg/kg and was ultimately adopted at a fixed dose of 200 mg every 3 weeks. This strategy was based on pharmacokinetic modeling and clinical trial data demonstrating efficacy and safety across cancer types. The fixed dose was intended to simplify administration and ensure consistent drug exposure. However, it was derived from higher-than-average body weights in U.S. trials, without accounting for lower weights in other regions, among women and individuals with advanced disease, who often experience weight loss. In 2022, Clalit Health Services—the largest health fund in Israel, covering ~50% of the population—adopted weight-based reimbursement for pembrolizumab. The policy was approved and supported by emerging evidence from studies suggesting that lower doses remain effective. Additionally, PD-1 receptor saturation occurs even at relatively low concentrations. This policy unintentionally created a quasi-random division in the population, enabling a real-world comparison of dosing strategies. This study evaluates the efficacy and safety of fixed versus weight-based pembrolizumab.

Methods: We conducted a retrospective cohort study of individuals with advanced NSCLC receiving first-line pembrolizumab, either as monotherapy or in combination with platinum-based chemotherapy. Participants were categorized based on dosing strategy: weight-based (2 mg/kg every 3 weeks) or fixed (200 mg every 3 weeks). Collected variables included age, sex, smoking history, histological subtype, PD-L1 tumor proportion score (TPS), ECOG performance status, body mass index (BMI), and immune-related adverse events (irAEs). Overall survival (OS) was assessed using Kaplan-Meier estimates, with multivariable Cox regression to adjust for relevant clinical factors.

Results: Among 414 individuals, 337 (81.6%) received fixed-dose and 76 (18.4%) weight-based pembrolizumab. Treatment regimens were comparable. A non-significant trend toward improved OS was observed in the weight-based group (p = 0.056). The incidence of irAEs did not differ significantly between groups (p = 0.83), nor did OS among those who experienced irAEs (p = 0.53).

Conclusions: Weight-based dosing of pembrolizumab showed similar efficacy and safety to fixed dosing in this real-world cohort. These findings align with accumulating evidence in recent years suggesting that lower doses may be sufficient for therapeutic effect. Given the potential for substantial cost savings, weight-based dosing may be a viable and sustainable strategy. Prospective studies are needed to confirm these results and inform policy and clinical practice.



Keywords: Weight-based immunotherapy, Real-world NSCLC treatment, Financial toxicity

MA06 IMPROVING CARE JUDICIOUSLY
MONDAY, SEPTEMBER 8, 2025 - 15:30 - 16:45

MA06.09 Assessing the Impact of Project ASCENT, a Multi-Level Lung Cancer Screening Intervention Targeting Hispanic/Latin Individuals

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Introduction: Despite proven efficacy of lung cancer screening (LCS) using low-density computed tomography (LDCT) in reducing lung cancer mortality, LCS uptake in screening-eligible individuals remains low nationally and in Florida. Hispanic/Latin (H/L) individuals have lower access to LCS due to a combination of structural and socioeconomic barriers, and cultural norms around screening. To bridge these gaps, Miami Cancer Institute (MCI), in partnership with LUNGevity Foundation, launched Project ASCENT, a multi-level LCS program rooted in culturally sensitive patient navigation, education, and community engagement in 2023 in Miami, Florida. MCI serves a diverse community of H/L individuals. This report evaluates the project's impact on systemwide LCS uptake, engagement, and tobacco cessation.

Methods: Project ASCENT is guided by a Lung Cancer Task Force, consisting of members of H/L community organizations and clinicians. We developed community-specific, pertinent education materials, and two Spanish-English bilingual patient navigators (Care Coaches) conducted extensive community engagement. Multi-year internal data on LDCT screening volume, community engagement metrics (number of events attended, event location ZIP code, estimated event reach), and tobacco cessation referral outcomes between 2022 and 2024 were analyzed. LDCT volume metrics were adjusted for demographics and screening center ZIP code and compared against county-specific and overall catchment area demographics using 2020 U.S. Census data.

Results: We analyzed data from multiple sources to evaluate Project ASCENT's impact (Table 1). • Notable increases in total LDCTs were observed system-wide (4,186 vs. 2,867) and among Hispanics (1,804 vs. 1,184) in 2024 vs. 2022. When further stratified by LDCTs performed at sites within Miami-Dade County, the cohort's H/L makeup increased from 58.7% to 61.5% between 2022 and 2024, with notable volume increases in sites within predominantly H/L ZIP codes. • MCI facilitated targeted LCS outreach at one event in 2022, reaching 550 participants, which grew to 20 events, reaching 39,675 South Floridians in 2024. • Tobacco cessation events increased dramatically between 2022-2024 (32 vs. 189), with 64 patients accepting services in 2024 (vs. 10 in 2022).

Conclusions: Our evaluation suggests that a community engagement strategy with culturally sensitive tobacco cessation information can increase LCS and tobacco cessation utilization in H/L community members. Marked improvements in LDCT volume overall and within the H/L population, community engagement, and tobacco cessation referral outcomes were noted since the implementation of Project ASCENT. Future work rooted in targeted patient and primary care provider education and engagement is necessary to further enhance screening uptake and reduce barriers to care.

Table 1: Lung Cancer Screening and Tobacco Metrics, 2022-2024

Metric	2022	2023	2024	Total
Total LDCT Volume (n, %)				
Entire Catchment Area	2,867 (26.8)	3,650 (34.1)	4,186 (39.1)	10,703
Miami Dade County	1,377 (26.9)	1,752 (34.3)	1,985 (38.8)	5,114
Hispanic/Latinx Individuals Who Underwent LDCT (n, % of yearly total)				
Entire Catchment Area	1,184 (41.3)	1,562 (42.8)	1,804 (43.1)	4,550
Miami Dade County	808 (58.7)	1,060 (60.5)	1,221 (61.5)	3,089
Lung Cancer Screening Outreach Events (n)				
Number of Events	1	4	20	25
Estimated Total Reach	550	638	39,675	40863
Completed Tobacco Cessation Events (n)	32	14	189	235
Tobacco Cessation Event Outcomes (n, %)				
Accepted Services	10 (31.3)	1 (7.1)	64 (33.9)	75
Declined	8 (25.0)	2 (14.3)	43 (22.8)	53
No Contact	12 (37.5)	9 (64.3)	64 (33.9)	85
Unavailable	2 (6.2)	2 (14.3)	17 (8.9)	21
Ineligible	0 (0.0)	0 (0.0)	1 (0.5)	1

Keywords: Lung cancer screening, Tobacco cessation, Hispanic/Latin

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.01 A Grading System for Invasive Squamous Cell Carcinoma of the Lung: A Multi-Institutional Study by the IASLC Pathology Committee

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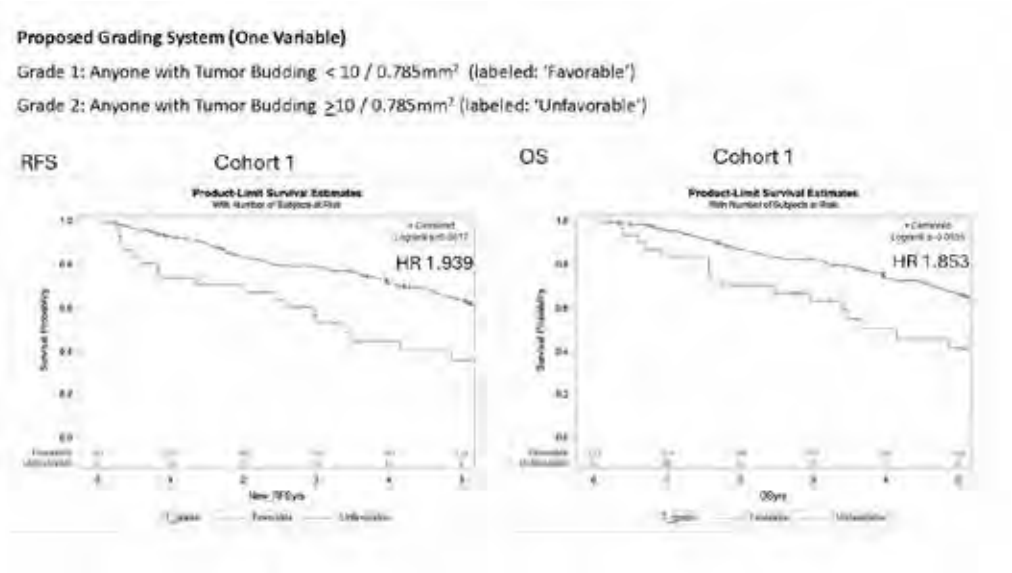
Introduction: Tumor grading has been a traditional component of pathologic evaluation and offers guidance to therapy and patient management in many organs. However, there is no consensus on a grading system for invasive squamous cell carcinoma of the lung (SCC), while a few groups have proposed distinct grading systems using their own cohorts. Thus, we sought to establish a globally acceptable grading system for SCC by using international cohorts.

Methods: Adverse histologic features were evaluated in SCC resected at 3 institutions. The histologic features included the extent of keratinization, basaloid features, tumor budding (TB; 2-tiered or 3-tiered classification), size of the smallest tumor nest at the invasive front (SSTN-FRT), nuclear size, mitosis, necrosis, and tumor spreading through airspaces (STAS) along with lymphovascular and pleural invasion. Kaplan Meier analysis and Proportional Hazards Models were used to identify histologic features associated with recurrence-free survival [RFS] and overall survival [OS] in cohort 1 (from institution 1) and cohort 2 (from institutions 2 and 3 combined) independently. Univariable models included age, sex, smoking history, entire tumor size, pathological tumor stage (AJCC 8th), the resection margin status, and surgery type, along with the histologic features. Multivariable models used step-wise regression ($p<0.1$ for inclusion, $p<0.05$ for retention) to identify significant prognostic factors. Histologic features, which were prognostically significant in both cohorts, were used to construct a grading system.

Results: The study cohort consisted of 689 patients with resected SCC. Cohort 1(n=262) was: age 35-89 years [mean=70.2]; female/male: 44%/56%; stage I/II/III: 62%/25%/13%. Cohort 2 (n=427) was: age 42-91 years [mean=69.7], female/male: 11%/89%; stage I/II/III/IV: 41%/32%/26%/1%. Of the histologic features, TB (2-tiered with a cut-off of 10 tumor buds / 0.785mm2, p=0.001 and p=0.006) and STAS ($p<0.001$ and p=0.006) were statistically significant for RFS and OS, respectively, in cohort 1. In cohort 2, TB (p=0.046) and mitosis (p=0.045) were statistically significant for RFS, and SSRT_FRT (p=0.003), TB (p=0.01), and mitosis (p=0.012) were statistically significant for OS. Given that TB was the only histologic feature statistically significant for both RFS and OS across the cohorts, a 2-tiered grading system based on TB was constructed and clearly stratifies the patient outcomes (Figure).

Conclusions: A 2-tiered grading system based on a single parameter, TB, is practical and predictive of patient outcomes. Validation of the grading system in several independent cohorts is underway, and the reproducibility of the grading system will also be assessed to establish the grading system for SCC.



Keywords: Squamous cell carcinoma of the lung, Grading, Tumor budding

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.02 Development and Prospective Validation of a Chromatin-Based Classification for Small-Cell Lung Cancer

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Introduction: Small-cell lung cancer (SCLC), the most aggressive form of lung cancer, is characterized by rapid progression, extensive heterogeneity, and a lack of clinically actionable biomarkers. Existing gene expression-based classifications are confounded by stromal and immune cell signals, limiting precision and reproducibility. These classifications were derived from bulk tumor data, which obscures tumor-intrinsic changes by averaging signals from tumor, stromal, and immune components. Currently, no classification system independently predicts prognosis or treatment response beyond standard clinical factors, such as the presence of liver metastases.

Methods: We hypothesized that chromatin accessibility, as measured by ATAC-seq, could more effectively define SCLC subtypes than gene expression-based classifications by capturing epigenetic differences and differentiation states. We established a biobank of relapsed SCLC patient-derived xenografts (PDXs) and performed ATAC-seq and RNA-seq on 39 metastatic SCLC PDXs. Non-negative matrix factorization was applied to classify tumors based on chromatin accessibility and identify key transcription factors driving each subtype. RNA-seq-derived signatures were validated across bulk and single-cell RNA-seq data from cell lines and patient samples to assess their prognostic and predictive value

Results: Through ATAC-seq on the newly established biobank of relapsed SCLC PDXs, we defined the tumor-intrinsic chromatin landscape of SCLC and identified three distinct subtypes: (i) SCLC-NE, ASCL1/NEUROD1-driven neuroendocrine subtype, (ii) SCLC-IM, Interferon regulatory factor-associated immunogenic subtype, and (iii) SCLC-SL, a novel stem cell-like subtype marked by TEAD/OCT activation. This classification was validated using bulk and single-cell RNA-seq data across over 800 tumors, including 313 newly profiled samples, consistently reproducing the three-subtype structure in both early and advanced disease. Notably, SCLC-SL, representing one-third of all SCLC cases, was the second most prevalent subtype. In metastatic SCLC patients treated with chemotherapy or chemoimmunotherapy, SCLC-SL was associated with significantly worse overall survival (OS) (HR 1.82, 95% CI 1.34-2.47), independent of clinical factors. Among chemoimmunotherapy-treated patients (n=132), SCLC-SL was an independent predictor of poor prognosis (HR 2.22, 95% CI 1.27-3.89), alongside known adverse factors such as brain metastases, liver metastases, and elevated serum lactate dehydrogenase levels.

Conclusions: This study establishes a clinically actionable chromatin-based classification for SCLC, identifying a novel stem-like subtype associated with poor prognosis and chemoimmunotherapy resistance. Our classification outperforms prior systems (Gay et al., 2021; Nabet et al., 2024) in multivariate analyses, representing the first reproducible prognostic and predictive biomarker in SCLC.

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.03 Morphological Implication of Invasive Lung Adenocarcinoma -Analysis Employing AI Method Based on Noguchi's Classification-

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Introduction: The size of invasion in lung adenocarcinoma (LUAD) correlates with patients' prognosis and is necessary to decide pT factor. Based on the WHO classification, invasive areas include non-lepidic tumor cells and fibrosis with active fibroblasts (AFs). The histological heterogeneity of invasion might relate to different prognosis. As invasive areas often show intricate mixture of non-lepidic tumor cells and fibrosis with AFs, and non-invasive areas such as alveolar collapse are frequently entrapped in non-lepidic areas, interobserver variability for the pathological diagnosis of invasion occurs in routine pathological diagnosis. This study aims to establish diagnostic tool utilizing artificial intelligence (AI) and support to decrease interobserver variability in pathological diagnosis of LUAD invasion.

Methods: We collected two sets of LUAD resected at Tsukuba University Hospital (Japan). First cohort included 35 cases (2cm or less in diameter) resected from 2007 to 2013. Second cohort included 191 cases (3cm or less in diameter) resected from 2014 to 2024. First, two pathologists (HK and NM) diagnosed all cases according to Noguchi's classification (Cancer, 1995) and WHO histological classification (5th Edition, 2021). Histologically, non-lepidic areas in first cohort were divided into 'non-lepidic tumor cells' (type D-F of Noguchi's classification, solid, acinar and papillary type, and micropapillary type of WHO classification) and 'fibrosis and alveolar collapse' (type C of Noguchi's classification). Since we could easily detect the fibrosis and alveolar collapse by elastic fiber staining, we scanned elastic fiber-stained histological slides by Nano Zoomer (Hamamatsu Photonics, Japan) and whole slide images (WSIs) were annotated by ASAP (Automated Slide Analysis Platform, https://computationalpathologygroup.github.io/ASAP/). We extracted small-sized patches from annotation and divided them into training, validation and test datasets for supervised learning using ResNet50 models. Then we let the trained AI to judge whole non-lepidic areas of second cohort to verify how this AI analyzed histologically heterogeneous areas. Finally, we checked the relationship between prognostic information and AI analysis.

Results: The AI trained based on pathologists' annotation of first cohort achieved 86.2% test accuracy for 'non-lepidic tumor cells' and 92.2% test accuracy for 'fibrosis and alveolar collapse'. After this trained AI analyzed whole non-lepidic region of second cohort (n=191), two pathologists (HK and MN) reviewed the original histology of analyzed cases and compared to the AI's analysis. This AI tended to judge the histologically heterogeneous areas mixed with non-lepidic tumor cells and fibrosis with AFs as 'fibrosis and alveolar collapse' based on the existence of collagenous fiber proliferation. In pT1 cases (n=136), high ratio of 'non-lepidic tumor cells' (>50%) groups showed poor prognosis in 5-years disease-free survival (DFS) rate (76.3% vs 93.3%, p=0.005) and in high ratio of 'non-lepidic tumor cells' groups, central distribution of 'fibrosis and alveolar collapse' was poor prognostic factor in 5-years DFS rate (n=76, 50.0% vs 83.3%, p=0.009).

Conclusions: Utilizing elastic fiber-stained histological slides, we developed an AI engine to distinguish 'non-lepidic tumor cells' and 'fibrosis and alveolar collapse'. We found several prognostic factors based on AI analysis for whole non-lepidic areas, suggesting the possibility of AI-based prognostic criteria of invasive LUAD with low interobserver variability.

Keywords: lung adenocarcinoma invasion, elastic fiber staining, AI

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.04 Integration of a Molecular Prognostic Classifier Enhances Conventional Staging of Lung Adenocarcinoma

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Introduction: The International Association for the Study of Lung Cancer (IASLC) recently released the 9th edition of the lung cancer staging system. Although this edition introduced a few updates compared to the previous edition, it underscored the necessity of integrating novel non-anatomic prognostic factors in future revisions. This study aims to evaluate the incorporation of a molecular prognostic classifier into the conventional staging system, assessing its potential to improve the prediction of overall survival in patients with lung adenocarcinoma (LUAD).

Methods: We included 502 stage I to III LUAD patients who underwent lung cancer resection at IUCPQ-Université Laval, Canada between 2006 and 2021. Survival time was defined as the time from surgical resection to death or censoring at 5 years. The least absolute shrinkage and selection operator (LASSO) was performed to identify the most prognostically relevant genes among 62,700 gene transcripts analysed using bulk RNA sequencing. A molecular risk score was calculated for each patient as a weighted sum of the selected gene expression levels. Patients were subsequently stratified into low-, intermediate-, and high-risk groups based on risk scores. These classifications were integrated into the 9th edition TNM staging (from stage IA1 to IIIC) to create a novel staging system, the TNMEx (where Ex represents gene expression). High-risk patients were up-staged by one level, low-risk patients were down-staged by one level, and intermediate-risk patients remained in their original stage. To evaluate survival prediction and model performance, we calculated the hazard ratio (HR), concordance index (C-index), the area under the curve (AUC), chi-square value, and Akaike information criterion (AIC) for the 8th, 9th edition, and TNMEx staging systems.

Results: We identified 30 predictive genes, which were then integrated into the 9th edition TNM staging to create the novel TNMEx staging. Overall, 67% of patients were reclassified, with most being up-staged to more advanced disease stages due to gene expression data. The final distribution with TNMEx staging was 310, 125, and 67 patients in stages I, II, and III, respectively. The TNMEx staging demonstrated improved predictive ability, with a higher HR (4.3, 95% CI: 3.8-4.9, p = 3.17e-12), and chi-square value (280) compared to the 9th edition (HR = 3.2, 95% CI: 2.6-3.9, p = 4.37e-09; chi-square 80). The TNMEx staging exhibited superior prognostic performance with a C-index of 0.75 (p=7.1e-06), an AUC of 0.77 (p = 1.07e-05), and an AIC of 1097 (ΔAIC=33), compared to the 9th edition with a C-index of 0.64, AUC of 0.68, and AIC of 1130. While the 8th and 9th editions showed no significant improvement in prognostic performance, with a C-index of 0.62 (p = 0.45), AUC of 0.67 (p = 0.29), and AIC score of 1130 (ΔAIC=0) in the 8th edition, the TNMEx system demonstrated a significant enhancement in survival prediction.

Conclusions: The TNMEx staging system was associated with improved prediction of overall survival compared to conventional TNM staging. The integration of a molecular prognostic classifier into the conventional staging system may lead to the enhanced identification of high-risk patients, survival predictions, and treatment decisions.

Keywords: Lung adenocarcinoma, TNM staging, Gene expression

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.05 Lung Cancer With Spread of Tumor Through Air Spaces: Transcriptomic Biosignature of Primary Tumors and Expression Analysis Airway Tumor Clusters

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Introduction: Objective: Up to 40% of resected lung cancer is found to have spread of tumor through air spaces (STAS), a pathological finding associated with poor survival and increased recurrence. However, little is known about genomic and transcriptomic differences in primary tumors with STAS (SP) and without STAS (SN) or expression profiles of the cancer cells within the airway themselves (tumors nests [TN]).

Methods: Methods: To address this knowledge gap, we compared (a) genomic differences between SP and SN tumors, (b) transcriptomic differences between SP and SN tumors, and (c) transcriptomic differences between matched SP tumors and TNs. Extraction of DNA and RNA from fresh frozen tumors was performed for DNA and RNA sequencing. Whole exome sequencing (WES) was performed using 100X depth in SN versus SP tumors matched to normal lung (50X). RNA sequencing was performed using the SigmaPlex kit. RNA from SP and SN tumors was evaluated after normalization using the DESeq2 package in R. Expression differences between SP and the corresponding TNs from the same primary tumor were compared by creating two unique tissue microarrays (TMA) containing 20 cores of SP tumors and 20 cores of TNs from the SP tumors. Slides were created, stained with histologic & eosin stain (H&E), and run on the Visium 10X genomics transcriptomic analysis platform. Genes were considered differentially expressed if they had a false-discovery ratio p-value <0.05 and fold change > 1. Pathway analysis was performed using the GSEA platform and MDSigB Hallmark pathway analysis.

Results: Results: Comparison between 11 SP versus 21 SN tumor was performed for SP vs SN DNA and RNA analysis. (A) WES revealed two genes were significantly differentially altered between groups MOV10L1 (36.4% SP versus 4.72% SN, p=0.04) and CACNA1A (36.4% SP versus 4.72% SN, p=0.04). There was no significant difference in major oncologic drivers including KRAS, EGFR, ALK, TP53, or RET mutation frequency between groups. (B) RNA expression analysis revealed SP tumors had 154 of 19,040 protein-coding genes differentially expressed. Pathway analysis revealed these genes had increased expression of UV response-related genes. (C) Spatial transcriptomic analysis of SP versus matched TNs consisted of 14 adenocarcinomas and 2 squamous cell lung cancers. SP tumors revealed 472 of 15,045 (3.13%) differentially expressed genes in TN versus SP including MMP19, COL3A1, COL1A2, and CDKN2A (Figure 1). Of these 472 genes, there were six differentially expressed pathways in TNs including genes involved in E2F targets, G2-M Checkpoint, Epithelial to Mesenchymal Transition (EMT), and mitotic spindle formation (Table 1).

Conclusions: Conclusions: This preliminary analysis demonstrates unique transcriptomic differences in SP and SN tumors. TNs themselves may represent a more aggressive subset of the primary tumors with increased expression of EMT and DNA repair pathway genes, which may allow them to survive in the airway more readily. If validated, an RNA biosignature could help predict SP tumors prior to resection and potential targeted therapies for STAS could be evaluated in this subpopulation of patients with aggressive lung cancer.

Keywords: Spread of Tumor through Air Spaces, Molecular Pathology, Biosignature

MA07.06 Characterization of Protein Arginine Methyltransferase 5 (PRMT5) Expression in Methylthioadenosine Phosphorylase (MTAP) Deleted NSCLC

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Introduction: PRMT5 is a lethal target for cancers with deletion of MTAP gene. As there are PRMT5 inhibitors in development for MTAP deleted (MTAP-del) solid tumors, we wanted to evaluate PRMT5 high expressors and MTAP-del non-small cell lung cancer (NSCLC).

Methods: NSCLC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ). PRMT5 high (H) vs PRMT5 not high (NH) was defined as top quartile vs lowest to 3rd quartile of RNA expression, respectively. Real-world overall survival (OS) was calculated from tissue collection or treatment to last contact using Kaplan-Meier estimates. Statistical significance was assessed using chi-square and Mann-Whitney U with multiple comparison adjustments (q<0.05).

Results: Of 39,124 tumors, 6837 (17.4%) were MTAP-del. There was a greater proportion of MTAP-del tumors in PRMT5-H (34.2% vs 25.7%) versus PRMT5-NH. There were more MTAP-del tumors in PRMT5-H adenocarcinoma (33.5% vs 24.6%) and in squamous cell carcinoma (SCC) (35% vs 29%). MTAP-del tumors had worse median OS (16.4 vs 20.5 m, p<0.0001) versus MTAP-not deleted (-ND); this was seen in adenocarcinoma (18.9 vs 25.2 m, p <0.0001) but not in SCC (p=0.8). The combination of PRMT5-H/MTAP-del tumors had worse mOS (12.7 vs 22.1 m) versus PRMT5-NH/MTAP-ND (p<0.0001). MTAP-del had lower mutations in RB1 and CDKN2A versus MTAP-ND in both PRMT5-H and PRMT5-NH while TP53 and RASA1 were only lower in PRMT5-H/MTAP-del and KRAS in PRMT5-NH/MTAP-del. EGFR, APC, STK11, KEAP1 and SMARCA4 mutations were higher in both PRMT5-H/MTAP-del and PRMT5-NH/MTAP-del (Table). PRMT5-H/MTAP-del and PRMT5-NH/MTAP-del had lower prevalence of PD-L1+ (q<0.05). MTAP-del had lower infiltration of M1, M2 macrophages, CD8+ T cell, and Tregs in PRMT5-H and -NH tumors (all q<0.05), (Table). PRMT5-H/MTAP-del and PRMT5-NH/MTAP-del had lower IFNγ score (q<0.05). PRMT5-H/MTAP-del tumors treated with immune checkpoint inhibitors (ICI) had worse mOS (13.8 vs 19 m, p<0.0001) versus PRMT5-NH/MTAP-ND. KRAS-mutated PRMT5-H/MTAP-del tumors treated with ICI ahad worse mOS (11.8 vs 21.4 m, p<0.0001). In EGFR-mutated treated with osimertinib and KRAS G12C mutated treated with sotorasib and adagrasib, there was no mOS difference by MTAP-del status though PRMT5-H tumors trended towards worse mOS.

Conclusions: PRMT5-H/MTAP-del tumors had worse mOS, were enriched in EGFR and APC mt and had lower PD-L1+ prevalence. PRMT5-H/MTAP-del tumors had a less robust and inflamed immune microenvironment, and this was reflected in worse mOS to ICI. Combination strategies of PRMT5 inhibition with ICI or targeted therapy may be merited to improve OS in PRMT5-H expressors that are MTAP-deleted.

Table: Prevalence of mutations, PD-L1+, and IFN-gamma score by *PRMT5* expression and MTAP deletion status

	PRMT5 high (H)			*PRMT5* not high (NH)		
	MTAP not deleted	*MTAP* deleted	q-value	*MTAP* not deleted	*MTAP* deleted	q-value
TP53 %	77.75	73.62	0.001	64.13	64.27	0.88
RB1 %	13.22	5.95	<0.0001	9.21	3.94	<0.0001
EGFR %	9.07	11.06	0.03	11.21	14.32	<0.0001
CDKN2A %	12.96	9.35	0.0002	11.42	7.91	<0.0001
APC %	3.2	4.52	0.02	2.37	3.22	0.002
STK11 %	12.91	15.28	0.02	11.8	15.48	<0.0001
KEAP1 %	18	19.81	0.13	12.45	15.53	<0.0001
KRAS %	25.6	25.81	0.89	29.5	25.32	<0.0001
SMARCA4 %	7.37	10.44	0.0002	5.31	8.12	<0.0001
RASA1 %	42.33	25.49	0.007	40.83	40.23	0.88
PD-L1 %	59.54	47.18	<0.0001	60.02	48.33	<0.0001
B cell (median %)	4.11	3.82	<0.0001	4.49	3.89	<0.0001
M1 Macrophages (median %)	4.51	3.33	<0.0001	5.21	4.2	<0.0001
M2 Macrophages (median %)	5.28	4.76	<0.0001	5.52	4.97	<0.0001
Neutrophil (median %)	5.57	5.8	0.02	5.47	5.69	<0.0001
T cell CD8+ (median %)	0.53	0.31	<0.0001	0.78	0.4	<0.0001
Tregs (median %)	2.3	1.91	<0.0001	2.93	2.24	<0.0001
IFNγ score	-0.28	-0.39	<0.0001	-0.19	-0.31	<0.0001

Keywords: MTAP, PRMT5, MTAP deletion

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.07 Validation Analysis of MET IHC as a Biomarker for Amivantamab-Lazertinib Response in Post-Osimertinib EGFR-Mutated NSCLC

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Introduction: Amivantamab, an EGFR-MET bispecific antibody, is approved with the tyrosine kinase inhibitor (TKI) lazertinib for first-line EGFR-mutated advanced/metastatic NSCLC, and with chemotherapy after progression on EGFR-TKIs such as osimertinib. Resistance mechanisms to osimertinib are diverse, polyclonal, and include MET alterations (Besse et al. ESMO. 2024), which underscores the importance of administering the most effective treatment first. MET positivity (MET+ [MET 3+ staining on ≥25% of tumor cells]) was identified as a potential biomarker for response to amivantamab-lazertinib after disease progression on osimertinib in the CHRYSALIS-2 study (Besse et al. ASCO. 2023). CHRYSALIS-2 (NCT04077463) Cohorts E and F aimed to prospectively validate this potential biomarker among amivantamab-lazertinib and amivantamab monotherapy recipients, respectively.

Methods: Cohorts E and F enrolled participants with EGFR Ex19del or L858R-mutated advanced NSCLC with tumor tissue collected for immunohistochemistry (IHC) staining post-progression on osimertinib. Prior chemotherapy was exclusionary. Participants were randomized 1:1 to receive standard-dose intravenous amivantamab with oral lazertinib (Cohort E) or amivantamab monotherapy (Cohort F). The Bayesian posterior probability of investigator-assessed ORR for both the MET+ group (ORR >35%) and the MET- group (ORR <20%) should be >85% for acceptance. Interim analysis was prespecified when ~55 response-evaluable participants with IHC data were in each cohort.

Results: As of 11-Jul-2024, 68 and 64 participants from Cohorts E and F, respectively, were response-evaluable and had IHC data (median follow-up of 4.5 months). Of these, 27 (40%) in Cohort E and 20 (31%) in Cohort F were MET+. Most participants in Cohort E were White (60%), while most in Cohort F were Asian (59%).

ORR (confirmed responses) in Cohort E was 30% (95% CI, 14-50) for MET+ and 15% (95% CI, 6-29) for MET- (Table). ORRs in Cohort F were 30% (95% CI, 12-54) and 11% (95% CI, 4-25), respectively. While ORRs were numerically higher in the MET+ groups, prespecified validation criteria were not met. Median progression-free survival (PFS) was 6.9 months (95% CI, 4.4-NE) for MET+ and 4.3 months (95% CI, 2.8-8.1) for MET- in Cohort E. In Cohort F, median PFS was 5.6 months (95% CI, 2.8-NE) and 4.4 months (95% CI, 1.6-NE), respectively.

Conclusions: In this analysis, IHC MET+ was not validated as a biomarker for response to amivantamab-lazertinib or amivantamab monotherapy among participants with EGFR-mutated NSCLC after osimertinib treatment. Nevertheless, amivantamab alone or with other agents is efficacious for advanced/metastatic NSCLC. Additional results will be reported at the meeting.

Table. Efficacy Endpoints

Endpoint	Amivantamab-lazertinib (Cohort E)		Amivantamab monotherapy (Cohort F)	
	MET+ n=27	MET⁻ n=41	MET+ n=20	MET⁻ n=44
ORR, % (95% CI)[a]	30 (14-50)	15 (6-29)	30 (12-54)	11 (4-25)
Median PFS, months (95% CI)[b]	6.9 (4.4-NE)	4.3 (2.8-8.1)	5.6 (2.8-NE)	4.4 (1.6-NE)

CI, confidence interval; NE, not estimable; ORR, objective response rate.
[a]In confirmed responders.
[b]Note that median follow-up for this analysis was short, at 4.5 months.

Keywords: Biomarker, MET positivity, amivantamab

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.08 MFAP4+ Pericytes Promote Tc17-Mediated Pneumonitis Induced by the Combination of Radiotherapy & Immunotherapy

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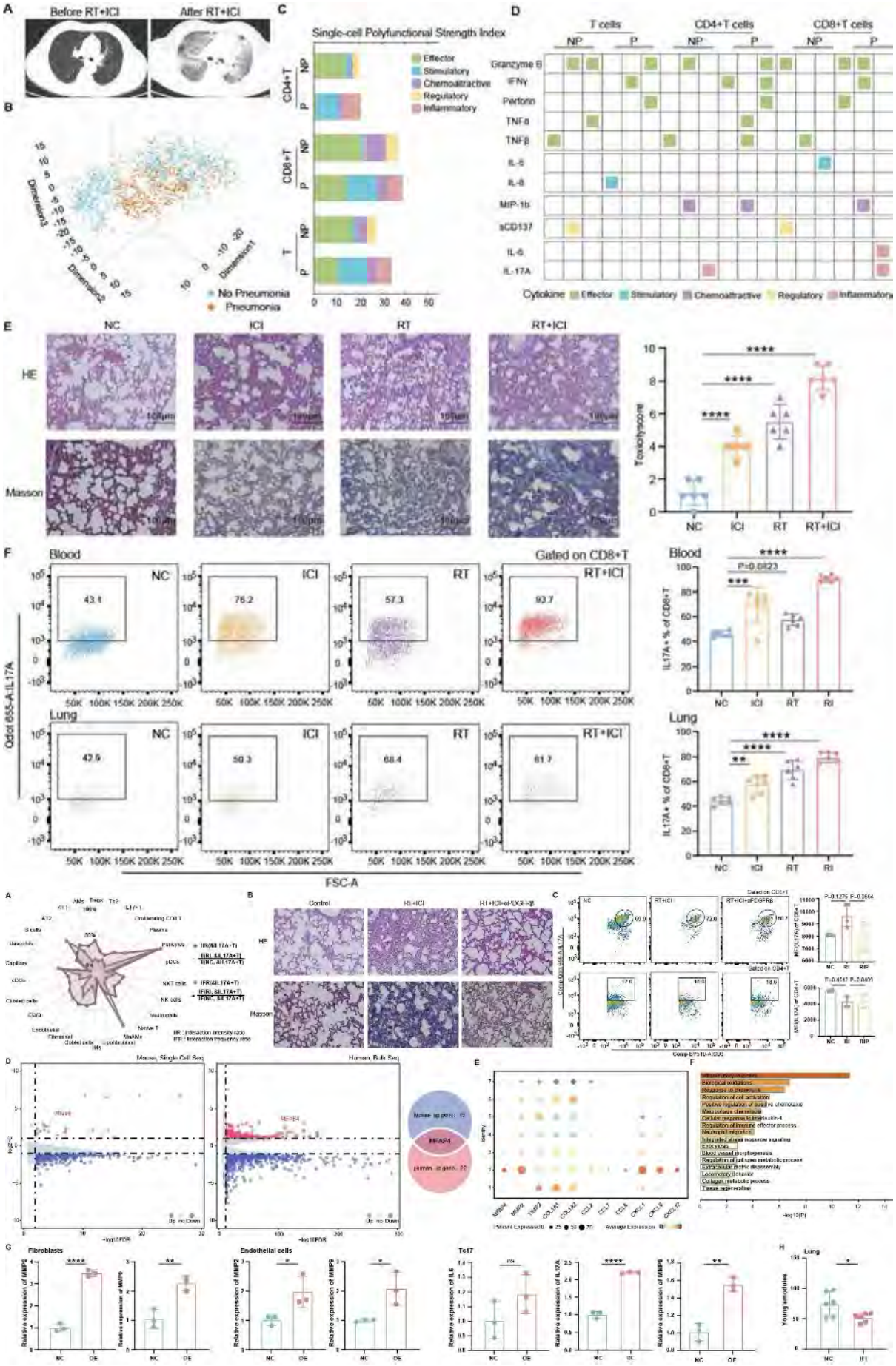
[1]Southern Medical University, Guang Zhou/CN

Introduction: Radiotherapy's immunogenic effects make it an attractive partner for immunotherapy. However, combined radio-immunotherapy is associated with significant adverse events, including pneumonitis, a frequent ≥Grade 3 toxicity. Early identification of susceptible patients and mitigation strategies are urgently needed.

Methods: Peripheral blood was prospectively collected from patients undergoing radio-immunotherapy. Pneumonitis was assessed clinically and by CT. Single-cell secretome profiling was performed to identify key T cell populations, validated using a murine radio-immunotherapy-induced pneumonitis model. Cell-cell interaction maps were generated from murine lungs post-radio-immunotherapy, and candidate target inhibitors were used to identify factors driving Tc17 recruitment. Single-cell multi-omics and in vitro/in vivo experiments were combined to investigate underlying mechanisms.

Results: Single-cell secretome profiling and the murine model confirmed Tc17 cells as key effector cells in radio-immunotherapy-associated pneumonitis, with radiotherapy-mediated lung recruitment being critical. Cell communication maps identified pericytes as the most significant cell type interacting with Tc17 cells in the irradiated lung. PDGFRβ inhibition to deplete pericytes reduced Tc17 infiltration and attenuated pneumonitis. Integrated RNA sequencing and single-cell transcriptomics identified MFAP4 as a specific and evolutionarily conserved pericyte marker. Enrichment analysis revealed involvement of MFAP4+ pericytes in pro-inflammatory responses and matrix degradation. In vitro co-culture further demonstrated that MFAP4+ pericytes can upregulate MMP2/MMP9 in the microenvironment, leading to matrix softening, promotion of an inflammatory microenvironment, Tc17 activation, and exacerbated inflammation. Notably, stiffness measurements confirmed lung softening in irradiated mice.

Conclusions: Tc17 cells are key effectors in radio-immunotherapy-related pneumonitis. MFAP4+ pericytes, by mediating their recruitment and activation, contribute to pneumonitis development. Targeting MFAP4+ pericytes may be a novel strategy to mitigate radio-immunotherapy-induced pneumonitis.


A
Before RT+ICI
After RT+ICI
B
No Pneumonia
Pneumonia
C
Single-cell Polyfunctional Strength Index
Effector
Stimulatory
Chemoattractive
Regulatory
Inflammatory
D
T cells
CD4+T cells
CD8+T cells
Granzyme B
IFNγ
Perforin
TNFα
TNFβ
IL-5
IL-8
MIP-1b
sCD137
IL-6
IL-17A
Cytokine
E
NC
ICI
RT
RT+ICI
HE
Masson
Toxichyzone
F
Blood
Lung
Gated on CD8+T
IL17A+ % of CD8+T
FSC-A

MA07 NEW PERSPECTIVES IN PATHOLOGY BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA07.09 Three-Year Survival Update and Biomarker Analysis of Neoadjuvant Chemoimmunotherapy in Potentially Resectable Stage IIIA/IIIB NSCLC

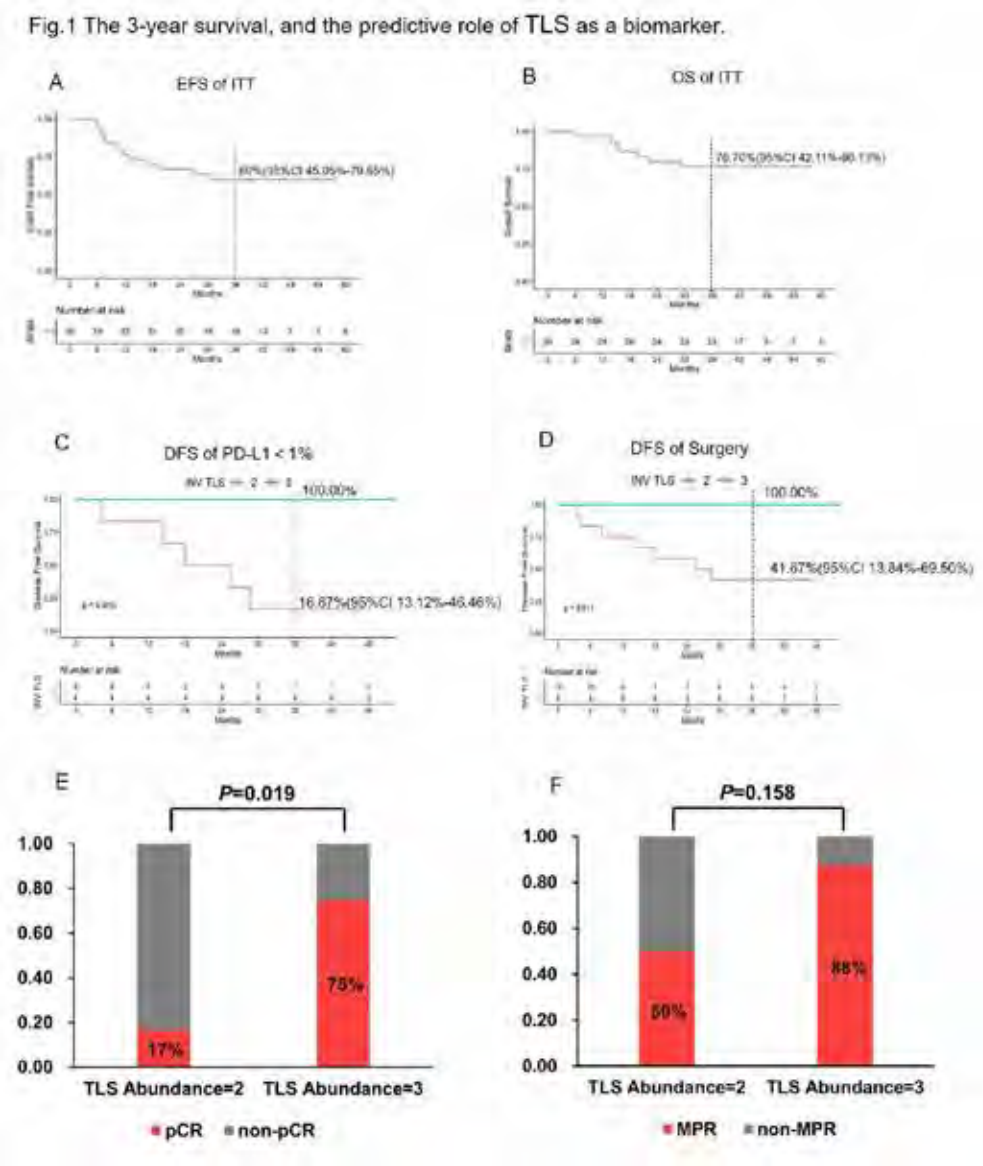
K. Ma, C. Sun, X. Wang, Y. Xu, S. Qiu
First Hospital of Jilin University, Changchun/CN

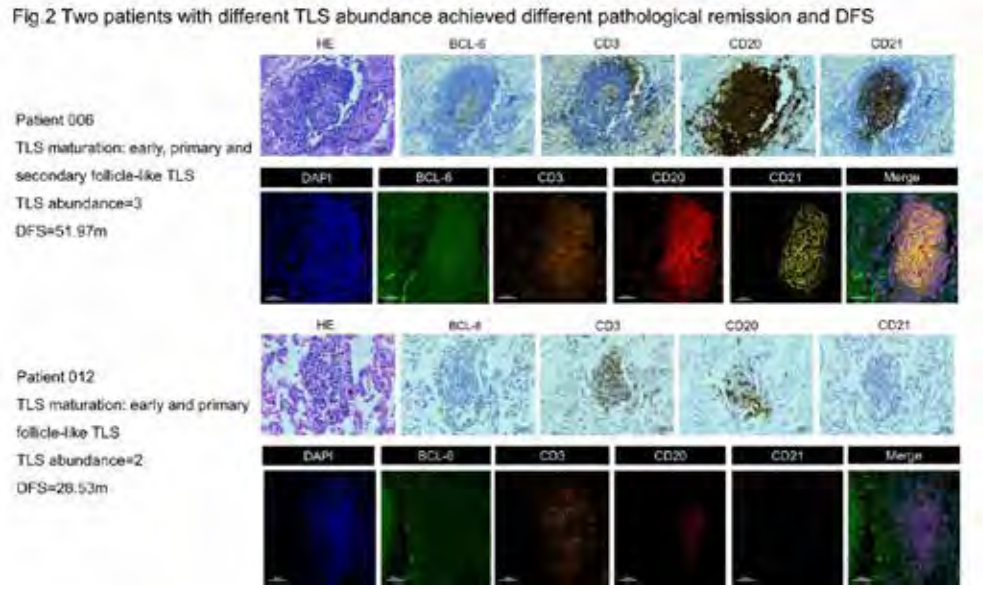
Introduction: Accurate biomarker identification for stratifying patients undergoing surgery following neoadjuvant chemoimmunotherapy remains a pivotal challenge, requiring further exploration.

Methods: This study utilized a prospective, single-arm, phase II clinical trial (NCT04326153) to evaluate treatment-naïve patients with "potentially resectable" stage IIIA/IIIB NSCLC. Patients received neoadjuvant therapy comprising Sintilimab, nab-paclitaxel, and carboplatin for 2-3 cycles, followed by surgical resection and systematic nodal dissection. Adjuvant therapy included nab-paclitaxel, carboplatin, with optional Sintilimab as maintenance treatment. The primary endpoint—2-year disease-free survival (DFS) rate—has been previously reported. This analysis updates 3-year survival outcomes while examining tertiary lymphoid structures (TLS) as a biomarker for long-term prognosis. TLS maturation and abundance were assessed using immunohistochemical and multiplex immunofluorescence (CD3, CD20, CD21, BCL-6). TLS maturation was categorized into three stages: early, primary follicle-like, and secondary follicle-like TLS. TLS abundance scores ranged from 0 to 3.

Results: After a median follow-up of 51.7 months (data cutoff: August 2024), 36-month event-free survival (EFS) and overall survival (OS) rates for the intent-to-treat (ITT) population were 60% and 76.7%, respectively(Fig1AB). Notably, patients with TLS abundance scores of 3 achieved significantly superior 3-year DFS rates compared to those with scores of 2 (100% vs. 41.67%, $p<0.05$)(Fig1D) and also demonstrated higher pathological complete response (pCR) rates (75% vs. 17%, $p=0.019$)(Fig1EF). In patients with PD-L1 expression <1%, those with TLS abundance scores of 3 experienced no recurrence, whereas 83.33% of patients with scores of 2 experienced disease recurrence(Fig1C). Regardless of maintenance immunotherapy, patients with TLS abundance scores of 3 showed no disease progression. TLS abundance emerged as a strong independent predictor of DFS with an impact weight of 0.75.

Conclusions: Neoadjuvant chemoimmunotherapy has significantly improved long-term survival for patients with potentially resectable stage IIIA/IIIB NSCLC. TLS abundance enables precise prognosis stratification and personalized treatment strategies, thereby optimizing outcomes.





Keywords: tertiary lymphoid structures, neoadjuvant chemoimmunotherapy, long-term survival

MA08 COMMON AND UNCOMMON EGFR MUTATIONS, NEW TREATMENTS IN THE HORIZON
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA08.01 A Multinational Phase 2 Randomized Pivotal Study of Sunvozertinib in Pretreated NSCLC With EGFR Exon 20 Insertion Mutations

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Introduction: Sunvozertinib (DZD9008) is a rationally designed, potent, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations (exon20ins). Here we report the updated results of the multinational phase 2 randomized pivotal study (WU-KONG1 Part B, NCT03974022) of sunvozertinib in platinum pretreated NSCLC with EGFR exon20ins. The results of the study support its NDA application currently under US FDA review.

Methods: NSCLC patients with EGFR exon20ins with at least one line of prior systemic therapy were enrolled into WU-KONG1B study. Based on earlier studies, patients were initially randomized into 200 mg or 300 mg once daily (QD). A planned interim analysis was performed to determine the optimal dosage to complete the study. The primary and key secondary endpoints were objective response rate (ORR) and duration of response (DoR), as assessed by Blinded Independent Central Review (BICR) per RECIST 1.1. Safety was assessed by investigators and graded per CTCAE 5.0.

Results: As of December 2, 2024, a total of 184 eligible patients were randomized into 200 mg (N=91) and 300 mg (N=93) dose cohorts, respectively. Among them, 85 and 89 patients were included in the efficacy analysis from each cohort, 45.4% of patients were ≥65 years old, and 60.9% of patients were female. More than 47 different EGFR exon20ins subtypes were enrolled, and 24.1% of patients had brain metastasis at baseline. All efficacy evaluable patients were treated with platinum-based chemotherapy, and 13.8% had prior amivantamab treatment. The confirmed ORRs, as evaluated by BICR, were 45.9% (97.5% CI: 33.6%, 58.5%) and 47.2% (97.5% CI: 35.1%, 59.5%), respectively, for 200 mg and 300 mg cohorts. The study met its primary endpoint with statistical significance (p <0.0001). At 200 mg and 300 mg, the median DoR were 11.1 months (95% CI: 8.2, NE) and 13.8 months (95% CI: 8.3, NE), respectively. Patients with baseline brain metastasis and prior amivantamab treatment benefited more from 300 mg dose cohort, with higher confirmed ORRs at 300 mg (52.4% and 41.7%) compared to those of 200 mg (28.6% and 25%). The safety profile of sunvozertinib was similar to what has been previously reported. At both dose levels, the most common grade 3 or above drug-related treatment-emergent adverse events (TEAEs) included diarrhea, blood creatine phosphokinase increased and anemia. TEAEs were clinically manageable. Drug-related TEAEs leading to treatment discontinuation were 4.4% (200 mg) and 7.5% (300 mg), respectively. No drug-related TEAEs with fatal outcome were reported at both dose levels.

Conclusions: Consistent with earlier report, significant antitumor efficacy was confirmed in the study with longer follow-up time. No new safety findings have been reported. Overall, 300 mg once daily showed more favorable clinical outcomes, especially for patients with prior amivantamab treatment or baseline brain metastasis. Detailed data will be presented at the conference.

Keywords: Sunvozertinib, EGFR exon20ins, Randomization

MA08.02 Zipalertinib in NSCLC Patients (Pts) With EGFR Exon 20 Insertion (Ex20Ins) Mutations Who Received Prior Amivantamab

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Introduction: While amivantamab (ami) is approved for the first and second-line treatment of EGFR ex20ins+ NSCLC, a significant unmet need remains for pts intolerant to or progressing on or after ami. Zipalertinib (CLN-081, TAS6417) is a novel EGFR TKI with promising clinical activity and manageable safety as reported previously (Piotrowska et al, JCO 2023). We present updated data from the phase 2b REZILIENT1 study with a focus on patients with EGFR ex20ins mutant NSCLC previously treated with amivantamab.

Methods: Pts with prior treatment including ami were enrolled. Zipalertinib was orally administered at 100 mg BID. Tumor response was assessed by independent central review per RECIST v1.1.

Results: As of the 10 Dec 2024 data cut-off (DCO), 83 pts with prior ami were enrolled. Pts had a median age of 62 years (31-85) and had received a median of 2 (1-7) prior treatment lines, including chemotherapy in 79 (95.2%) pts, anti-PD(L)1 in 38 (45.8%), ex20ins-specific TKIs in 33 (39.8%), and common EGFR TKIs in 23 (27.7%). Treatment-related AEs (TRAEs) occurring in > 10% of pts were paronychia (36.1%), rash (30.1%), dermatitis acneiform (20.5%), anemia (20.5%) nausea (16.9%), dry skin (15.7%), pruritus (14.5%), stomatitis (13.3%), and diarrhea (13.3%). Grade > 3 TRAEs reported in > 2 pts included anemia in 6 (7.2%) and pneumonitis, rash and platelet count decrease each in 3 pts (3.6%). TRAEs led to dose reduction or discontinuation in 7 pts (8.4%) each. At the current DCO, 30 pts with prior ami but no other ex20ins targeted therapy (ami alone) and 21 pts with prior ami and other ex20ins targeted therapy (ami plus) were evaluable for response with at least ~8 months follow-up (total 51 pts). As shown in the table, the ORR in ami only pts was 30% (95% CI: 14.7, 49.4) and disease control rate (CR + PR + SD) was 96.7%. Median DOR and PFS were 14.7 (95% CI: 4.2, NE) and 7.6 (95% CI: 5.4, 9.8) months, respectively. 12-month overall survival rate was 66.1%. Mature efficacy data, including at least 9 months follow up for all 83 pts will be presented.

	ORR (%, 95% CI)	DOR (%, 95% CI)	PFS (m,95% CI)	OS rate @12 month
Ami alone	30.0 (14.7, 49.4)	14.7 (4.2, NE)	7.6 (5.4, 9.8)	66.1%
Ami plus	14.3 (3.0, 36.3)	4.2 (3.9, NE)	5.2 (3.2, 11.5)	51.1%
Overall	23.5 (12.8, 37.5)	8.5 (4.2, 14.8)	7.3 (5.3, 9.7)	59.8%

Conclusions: Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in pts with exon20ins NSCLC who have received prior chemotherapy and prior amivantamab, reflecting a clinically-relevant patient population for which there are currently no approved therapies.

MA08.03 First-Line Subcutaneous Amivantamab Plus Chemotherapy in EGFR Exon 20 Insertion-Mutated Advanced NSCLC: Results From PALOMA-2

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Introduction: Intravenous amivantamab plus chemotherapy (carboplatin-pemetrexed)is approved for first-line treatment of patients with EGFR exon 20 insertion(Ex20ins)-mutated advanced non-small cell lung cancer (NSCLC), based on the resultsof the PAPILLON study. In PAPILLON (median follow-up, 14.9 months), amivantamab-chemotherapydemonstrated a median progression-free survival (PFS) of 11.4 months (95% CI,9.8-13.7) and an investigator-assessed objective response rate (ORR) of 66%. Inthe PALOMA-3 study, subcutaneous amivantamab administered every 2 weeks demonstratednoninferior pharmacokinetics and efficacy versus intravenous amivantamab, with fewerinfusion-related reactions, shorter administration time

(<5 minutes), and higher patient convenience. PALOMA-2 (NCT05498428) is a bridging study evaluating the efficacy, pharmacokinetics, and safetyof subcutaneous amivantamab in various EGFR-mutated advanced NSCLCsettings.

Methods: Cohort2 enrolled participants with treatment-naïve EGFR Ex20ins-mutatedadvanced NSCLC. Subcutaneousamivantamab (co-formulated with hyaluronidase; rHuPH20) was administeredas an abdominal injection with an every 3 weeks (Q3W) dosing regimen of 1600 mg(≥80 kg: 2240 mg) on Cycle 1 Day 1, then 2400 mg

(≥80 kg: 3360 mg) on Days 8 and 15 of Cycle 1, and Q3W thereafter. Carboplatin wasadministered Q3W for up to 4 cycles, and pemetrexed was administered Q3W untildisease progression. The primary endpoint was investigator-assessed ORR perRECIST v1.1.

Results: As of the data cut off (24 October 2024), 66 participantshave received subcutaneous amivantamab Q3W, with the cohort fully enrolled.Median age was

63 years, 52% of participants were male, and 56% were Asian. At a medianfollow-up of 10.4 months, the median treatment duration was 9.3 months. At datacutoff, 37 (56%) participants remained on treatment.Investigator-assessed ORR was 76% (confirmedresponders, 71%) and independent central review-assessed ORR was 77% (confirmedresponders, 67%). Responses were rapid, with a median time to response of 6.4 weeks(range, 3.5-21.7). Median duration of response was 10.6 months (95% CI, 8.3-notestimable [NE]). Among confirmed responders, 66% (31/47) had an ongoingresponse. Median PFS was 12.2 months (95% CI, 8.4-NE) while median overallsurvival was NE. Mean (SD) amivantamab concentration on Cycle 2 Day 1 was 439(117) µg/mL (n=41), consistent with historical intravenous amivantamab Q3Wdata.No new safety signals were observed. Most treatment-emergentadverse events (AEs) were EGFR/MET-related or reversible hematologic AEs, with paronychia,hypoalbuminemia, and neutropenia being the most common. Administration-relatedreactions (ARRs) were reported in 4 (6%) participants (none grade ≥3). Discontinuationof amivantamab due to treatment-related AEs was 12%.

Conclusions: Among participants with EGFR Ex20ins-mutatedadvanced NSCLC, first-line treatment with subcutaneous amivantamab Q3W plus chemotherapydemonstrated a response rate and safety profile consistent with historical intravenousamivantamab Q3W data, with a reduced incidence of ARRs.

Keywords: Subcutaneous amivantamab, Ex20ins, NSCLC

MA08 COMMON AND UNCOMMON EGFR MUTATIONS, NEW TREATMENTS IN THE HORIZON
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA08.04 Phase 2 Interim Results of Zipalertinib in Patients With NSCLC Harboring Uncommon Non-Exon 20 Insertion EGFR Mutations

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Introduction: Patients with non-small cell lung cancer (NSCLC) harboring uncommon non-exon 20 insertion (non-ex20ins) epidermal growth factor receptor (EGFR) mutations (EGFRmt), including G719X, S768I, and L861Q among the most prevalent, have a worse prognosis than those with common single/compound EGFRmt. Responses to currently approved EGFR tyrosine kinase inhibitors (TKIs) are variable in these patients, highlighting the need for novel treatment options. Zipalertinib is an oral, highly selective, irreversible EGFR TKI that has demonstrated preliminary clinical activity against ex20ins and preclinical activity against uncommon, non-ex20ins EGFR-mutated NSCLC. Here, we present preliminary efficacy and safety results for zipalertinib in patients with NSCLC with uncommon, non-ex20ins EGFRmt from the ongoing, multicohort, phase 2b REZILIENT2 trial (NCT05967689).

Methods: Eligible patients had locally advanced/metastatic NSCLC, documented single or compound uncommon, non-ex20ins EGFRmt, and any line of prior therapies. Patients received zipalertinib 100 mg orally twice daily until progressive disease or meeting other withdrawal criteria. The primary endpoint was confirmed objective response rate (ORR) per investigator-assessed Response Evaluation Criteria in Solid Tumours (RECIST) v1.1; secondary endpoints included duration of response (DoR), disease control rate (DCR), and safety.

Results: At data cutoff (February 17, 2025), 40 patients were enrolled, with a median age of 66 (range, 47-85) years, 55% were female, and a median of 2 (range, 1-12) prior lines of therapy. The most frequent EGFRmt were G719X (n=20) and L861Q (n=11); three patients had compound mutations. Overall, confirmed ORR was 30% (95% confidence interval [CI]: 16.6, 46.5), with a median DoR of 7.75 months (95% CI: 3.48, not estimable) and a DCR of 70% (95% CI: 53.5, 83.4). For treatment-naïve patients (n=8), ORR was substantially higher (ORR: 62.5%; 95% CI: 24.5, 91.5) compared with patients with ≥1 prior treatment (n=32; ORR: 21.9%; 95% CI: 9.3, 40.0). Safety findings for zipalertinib 100 mg twice daily were similar to previous studies. Treatment-related adverse events (TRAEs) of any grade occurring in ≥30% of patients were paronychia (47.5%), dermatitis acneiform (37.5%), stomatitis (32.5%), and anemia (30.0%). Grade ≥3 TRAEs reported in ≥2 patients were paronychia and anemia (n=2 each). Dose reductions, interruptions, or treatment discontinuations due to AEs occurred in 10 (25.0%), 19 (47.5%), and six (15.0%) patients, respectively.

Conclusions: Zipalertinib demonstrated preliminary clinical efficacy in patients with NSCLC harboring uncommon, non-ex20ins EGFRmt. The safety profile of zipalertinib was manageable, with no new safety signals. Enrollment in this study is ongoing, focusing on previously untreated patients to confirm the observed preliminary clinical efficacy.

Keywords: zipalertinib, EGFR, uncommon mutations

MA08 COMMON AND UNCOMMON EGFR MUTATIONS, NEW TREATMENTS IN THE HORIZON
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA08.05 PALOMA-2: Subcutaneous Amivantamab Administered Every 4 Weeks Plus Lazertinib in First-Line EGFR-Mutated Advanced NSCLC

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This abstract is under embargo until September 9 at 11:30 CET.

MA08 COMMON AND UNCOMMON EGFR MUTATIONS, NEW TREATMENTS IN THE HORIZON
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA08.06 Comparison of Asandeutertinib and Osimertinib in EGFR-Mutated NSCLC With Brain Metastases: Interim Analysis of the ESAONA Pivotal Study

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Introduction: Non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations and brain metastases (BM) is associated with very limited outcomes using current EGFR-tyrosine kinase inhibitors (TKIs) or treatments. Asandeutertinib (TY-9591), a novel EGFR-TKI candidate, has shown outstanding efficacy and manageable safety in the interim analysis derived from the ESAONA-pivotal study.

Methods: ESAONA-pivotal is an open-label, multi-center, randomized phase II study evaluating first-line treatment between asandeutertinib and osimertinib in untreated NSCLC patients with EGFR-sensitive mutations and stable BM. Patients were enrolled and randomized at 1:1 to receive either asandeutertinib (160mg orally, QD) or osimertinib (80mg orally, QD). Randomization was stratified by intracranial lesions (> 3 or ≤3) and mutation type (L858R or 19Del). The primary endpoints were blinded independent central review (BICR)-assessed intracranial objective response (iORR), with the sample size estimated as 220 (conditional approval by China National Medical Products Administration (NMPA) based on the interim analysis) based on effect size of 15%, and intracranial progression free survival (iPFS) per RECIST v1.1, with the sample size of 420 (full approval by China NMPA) assuming a hazards ratio of 0.737 (both at one-side alpha of 0.025 and beta of 0.2). The secondary endpoints included investigator (INV)-assessed iORR and iPFS, ORR, PFS, overall survival (OS), safety.

Results: As the data cut-off date on Feburary 28, 2025, 257 eligible patients were enrolled from 51 centers. In the interim analysis, baseline characteristics were generally balanced across asandeutertinib (n=111) and osimertinib groups (n=113): median ages 61.0/58.0 (range 38-75/39-76) years, male 32.4%/41.6%, non-smoker 74.8%/68.1%, ECOG PS 1 of 90.1%/79.6%, intracranial lesions > 3 of 58.6%/57.5%, EGFR mutation types with L858R/19Del of 45.9%/54.1% in the asandeutertinib group, 47.8%/52.2% in the osimertinib group. All were adenocarcinoma. The confirmed BICR-iORR was significantly improved for asandeutertinib compared to osimertinib (91.9%, 95% CI 85.2-96.2% vs. 76.1%, 95% CI 67.2-83.6%; P=0.001). The confirmed INV-iORR was also significantly higher for asandeutertinib compared to osimertinib (91.0%, 95% CI 84.1-95.6% vs. 75.2%, 95% CI 66.2-82.9%; P=0.002). The confirmed BICR-ORR showed a trend in favor of asandeutertinib compared to osimertinib (84.7%, 95% CI 76.6-90.8% vs. 75.2%, 95% CI 66.2-82.9%; P=0.095). Median iPFS and PFS had not been reached. OS remained immature. Grade ≥ 3 treatment-related adverse events (TRAEs) were reported in 31.5%/15.0% for asandeutertinib vs. osimertinib. In the asandeutertinib group, Grade ≥ 3 TRAEs occurring ≥ 3 times included increased creatine phosphokinase (n=6, 5.4%), prolonged QTcf (n=5, 4.5%), lymphocytopenia (n=3, 2.7%), neutropenia (n=3, 2.7%), leukopenia (n=3, 2.7%), weight loss (n=3, 2.7%), stomatitis (n=3, 2.7%), and rash (n=3, 2.7%). Serious TRAEs occurred in 9.0%/6.2% (asandeutertinib vs. osimertinib). Adverse events of special interest included 7 patients with interstitial lung disease (ILD) and 5 patients with prolonged QTcf in the asandeutertinib group (11/111, 9.9%, one patient experiencing both events), and 2 patients with ILD in the osimertinib group (2/113, 1.8%).

Conclusions: The interim results of ESAONA-pivotal study demonstrated that asandeutertinib pronouncedly improved intracranial efficacy compared to osimertinib with a manageable safety profile. Asandeutertinib is a promising new first-line option for EGFR-mutated NSCLC patients with BM.

Keywords: asandeutertinib, osimertinib, NSCLC with brain metastases

MA08 COMMON AND UNCOMMON EGFR MUTATIONS, NEW TREATMENTS IN THE HORIZON
TUESDAY, SEPTEMBER 9, 2025 - 11:30 - 12:45

MA08.07 OCELOT: A Pan-Canadian Study of Osimertinib for Patients with Treatment Naive Advanced NSCLC with Uncommon EGFR Mutations

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Introduction: Osimertinib is a popular and well tolerated first-line (1L) option for patients with the two 'common' types of epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small-cell lung cancer (aNSCLC), based on the FLAURA study. Uncommon EGFR mutations (non-exon 19 del and L858R) occur in up to 25% of patients; however, the efficacy of osimertinib in this population is not well understood. To date, small prospective studies and retrospective case series have signalled that osimertinib has a role in the treatment of patients with uncommon EGFR mutations.

Methods: This is a multicentered Canadian phase II investigator-initiated study of 1L osimertinib (cohort B) in patients with uncommon activating EGFR mutations (exon 20 insertions are not permitted). Patients with stable and/or treated brain metastasis, and ECOG performance status 0-3 were permitted on study. Patients with compound mutations that included exon 19 del and L858R were not permitted following an early protocol amendment. Patients were not required to have measurable disease by RECIST and imaging reassessments were every 12 weeks. Key endpoints included objective response rate (ORR), progression free survival (PFS), time to treatment failure (TTF) and overall survival (OS). NCT04335292

Results: Ninety-two patients have been accrued to date with a median follow-up of 8.4 months (IQR: 4.1, 16.6), of whom 62 had evaluable disease (16 had inadequate follow-up time, 14 did not have evaluable disease). Deomgraphics: 67% female; 59% Causasian and 25% East Asian; 33% had brain metastasis at enrollment; median age 69 years. Four patients had compound mutations containing a common EGFR variant, and were excluded from subgroup analyses. The most frequent 'uncommon' EGFR mutation was G719X (n=35), followed by L861X (n=24) and S768I (n=18). The confirmed ORR was 45% (95% CI: 33.4-57.5%) and disease control rate (DCR) was 77% (65.6-86.0%). Median PFS was 14.3, and TTF was 14.9 months. Patients with PACC mutations and common-uncommon mutations (containing G719X, L861X, and/or S768I) had a median PFS of 14 and 14.3 months, respectively, and a median TTF of 14.8 and 16.7 months, respectively. Median overall survival was not reached. Two patients discontinued osimertinib because of adverse events without progressive disease, the overall safety and toxicity profile is consistent with published data. **Conclusions:** Osimertinib appears to be highly active and well tolerated in patients EGFR+ aNSCLC harboring uncommon mutations. The OCELOT study supports the use of osimertinib in this population as a standard of care option.

Keywords: EGFR, Uncommon mutations, PACC mutations

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.01 Association of Air Pollution Exposure With Lung Screening Outcomes and Lung Cancer Risk in the Taiwan TALENT Study

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Introduction: Air pollution is associated with increased lung cancer risk, with recent evidence suggesting a role in tumor promotion among people who have never smoked. However, the temporal relationship between exposure and outcome remains unclear. Moreover, as lung cancer screening is being considered for people with other risk factor exposures than smoking, it is critical to assess the impact that air pollution might have on screening outcomes in non-smoking populations.

Methods: We used data from the Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT) study to assess the association between air pollution PM2.5 exposures and lung cancer screening outcomes and lung cancer risk among people who have never smoked. Participants' residential address at enrollment was geocoded and then used to estimate past 3-year average PM2.5 concentration at the baseline residence. Outcomes studied included 1) having a nodule present at the baseline screen, 2) having a positive screen (TALENT criteria), 3) LungRADS 3 or 4 screening result, 4) LungRADS 4 screening result, 5) lung cancer diagnosis within a year, and 6) advanced lung cancer diagnosis within a year. Logistic regression was used to assess the association between PM2.5 exposure and each outcome, adjusting for relevant covariates (age, sex, COPD, TB, indoor cooking, and family history of lung cancer). Both age and average 3-year PM2.5 exposure were modeled continuously using restricted cubic splines.

Results: Average annual past 3-year PM2.5 exposure ranged from 12.75 to 32.53 µg/m3, with a median of 22.11 among cancer patients and 21.22 among non-cases. PM2.5 exposure was statistically significantly associated with all study outcomes, including lung cancer, with non-linear inverted U-shaped dose responses. For all outcomes, risk increased with PM2.5 at exposure levels from 12 to 20 µg/m3, peaking between 20 and 25 µg/m3 and then decreasing. For lung cancer, increasing age, female sex, and the number of first-degree family members with a history of lung cancer were positively associated with higher risk.

Conclusions: Recent PM2.5 exposure was associated with lung cancer risk and with the risk of having nodules, having a positive screen, and having advanced lung cancer screening results at a baseline screening exam among people who never smoked in Taiwan. These results are consistent with research suggesting a role of air pollution in tumor promotion. Future studies should evaluate the effects of air pollution exposures at different time periods (recent vs distant) on tumor dynamics and lung cancer risk.

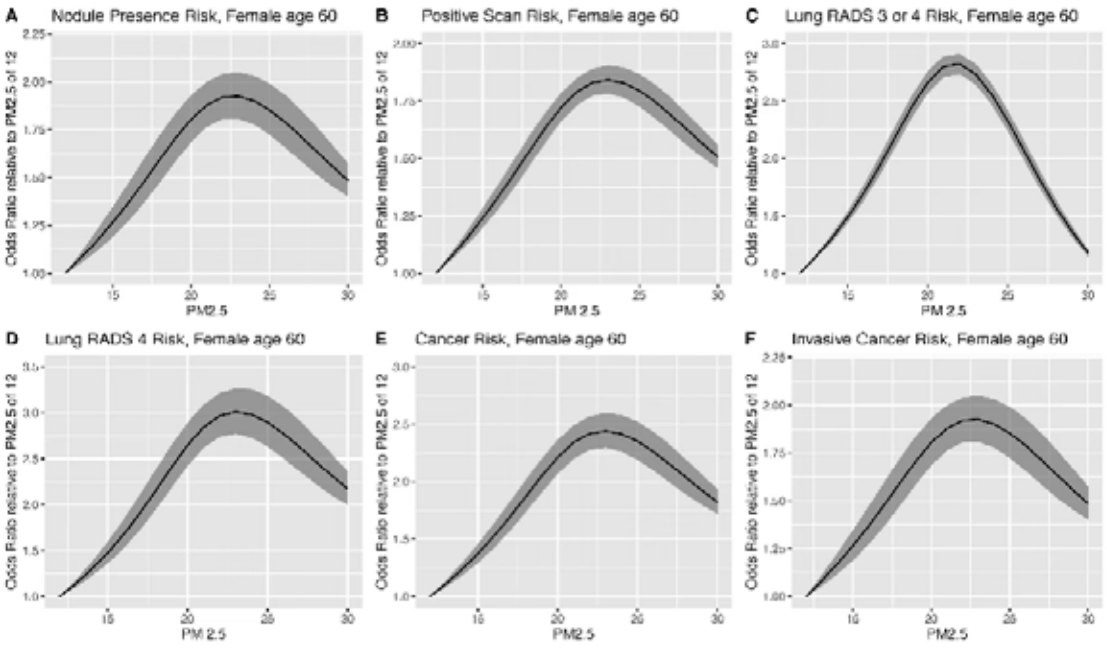

Figure 1. Association between PM2.5 exposure and different lung screening and lung cancer outcomes among never smokers in the TALENT study. A. Presence or not of nodules in the baseline scan. B. Having a positive scan according to the TALENT criteria. C. Having a LungRADS 3 or 4 baseline screening result. D. Having a LungRADS 4 baseline screening result. E. Having a lung cancer diagnosed within a year of the baseline screen. F. Having an advanced lung cancer diagnosed within a year of the baseline screen. PM2.5 exposure was measured based on the average past 3-year annual levels at the baseline residential address. Figures show relative odds for a female aged 60, with no COPD, TB nor first degree relatives with lung cancer.

Keywords: air pollution, lung cancer risk, lung screening outcomes

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.02 Impact of Air Pollution and EGFR Mutation on Epigenetic Age and Lung Cancer: A Pilot Study

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Introduction: The Global Burden of Disease Study shows that exposure to air pollution is the second leading cause of non-small cell lung cancer (NSCLC). Specifically, fine particulate matter known as PM 2.5 is a major cause of lung cancer in individual with no history of tobacco use. PM 2.5 can induce oxidative stress, affect genetic alterations, and activate oncogenes such as the epidermal growth factor receptor (EGFR), all of which may contribute to the advancement of lung cancer. This study aims to investigate the relationship between PM 2.5 exposure and EGFR mutation status on epigenetic age and the development of lung cancer by investigating the epigenome and epigenetic markers of aging (i.e., epigenetic clocks).

Methods: Lung tissue samples were processed for DNA methylation profiling using the Infinium Methylation EPICv2.0 chip after DNA extraction and bisulfite conversion. Six epigenetic clocks (DNAmAge, DNAmAgeHannum, DNAmAgeSkinBlood, DNAmPhenoAge, DNAmGrimAge1, DNAmGrimAge2, and DNAmTL) were generated from the DNA methylation profiles using the clock foundation web tool (https://dnamage.clockfoundation.org/). We tested the effect of PM 2.5 (20 years exposure) and EGFR mutation on epigenetic age; significant results were defined at $p<0.05$. As measures of global methylation (i.e.; proxy for aging), Alu and Line1 (transposable elements) methylation sites were imputed using the repetitive element methylation prediction machine learning tool. An epigenome-wide methylation analysis was also performed using a robust linear model. Significant differential methylation positions (DMPs) in the epigenome were defined at FDR <0.10. Pathways enrichment analysis was conducted (FDR<0.10)

Results: Sixty-one individuals had available cancerous lung tissue samples with DNA methylation profiling. Of these 39 were female, the cohort's mean age was 67.7 years, 29 were individuals with no history of tobacco use and 15 had an EGFR mutation. The mean PM 2.5 exposure was 7.72 ug/m^3. PM 2.5exposure and EGFR status were not associated with epigenetic age acceleration in any clock. However, in individuals without an EGFR mutation, there was a trend towards significance with higher DNAmSkinBlood age increasing with higher PM 2.5 levels ($p=0.059$). Alu and Line1 methylation showed no significant hypomethylation with either EGFR or PM levels. EGFR mutation was associated with 468 DMPs and 197 (differentially methylated genes) DMGs, while PM 2.5 was associated with 223938 DMPs and 22763 DMGs. Significant pathways associated with PM 2.5 exposure were associated with cancer and aging (e.g., EGFR tyrosine kinase inhibitor resistance and mTOR signaling pathway).

Conclusions: Our findings suggest that while PM 2.5 exposure and EGFR mutation were not directly linked to age acceleration in the lung, they may still have significant epigenetic impacts on biological processes and diseases like cancer and aging. Additionally, a weaker signal was observed in individuals without the EGFR mutation suggesting that higher levels of PM 2.5 exposure may yet be associated with increased epigenetic aging. However, further research within a cohort with greater range of PM 2.5 exposure is necessary to validate these findings and deepen our understanding of the long-term effects of PM 2.5 and EGFR on epigenetic aging and lung cancer.

Keywords: Air Pollution, Epigenetic Age, Lung cancer

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.03 Determining the Role of Fine Particulate Matter (PM2.5) in Lung Cancer Initiation

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Introduction: The incidence of lung cancer occurring in people who have never smoked has been continuously rising. Outdoor air pollution, specifically PM2.5- fine particulate matter smaller than 2.5 µm in diameter- has been associated with lung cancer development in this subset of patients, yet the biological role of PM2.5 in lung cancer initiation is largely undefined. This project aimed to investigate the potential of PM2.5 to initiate malignant transformation in vitro.

Methods: Non-transformed lung epithelial cell lines (BEAS-2B and HPL1D) were exposed to PM2.5 in culture. Each PM2.5 exposure involved a 24-hour pulse period followed by recovery before a subsequent exposure was repeated for up to six weeks. A prolonged recovery period up to another six weeks was followed to allow possible mutational burden to accrue. Throughout the exposure timeline, cells were evaluated for various hallmarks of malignant transformation, which included changes in cell morphology, presence of DNA damage and stem-like features, and increase in DNA damage and anchorage independent growth. These cells were also clonally selected and sent for whole exome sequencing to understand the mutational landscape caused by PM2.5 in addition to 55 lung adenocarcinoma patients with defined levels of PM2.5 exposure.

Results: Acute PM2.5 exposures demonstrated significant DNA damage and changes in cell morphology in vitro. Long-term exposures of PM2.5 revealed a relative increase in proliferation and mutational burden as well as a significant increase in colony formation ability in soft agar assays, indicating increased anchorage independent growth. Analysis of the genome of these long-term exposure cells may demonstrate novel somatic variants or pathways altered by PM2.5 exposure.

Conclusions: Taken together, we demonstrate that PM2.5 can drive malignant transformation in normal lung epithelial cells in vitro. This work provides new insights into the role of PM2.5 in lung carcinogenesis, which has the potential to guide lung cancer screening and early detection strategies, particularly in patients who have never smoked.

Keywords: lung adenocarcinoma, pollution, transformation

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.04 Maternal Preconception Vaping of Nicotine Induces Severe Airway Remodeling in Offspring and Reduces Airway Progenitor Cells in D. Melanogaster

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Introduction: Adolescent vaping raises concerns about intergenerational respiratory health risks. Using Drosophila melanogaster, we explored how maternal preconception nicotine exposure impacts offspring airway architecture and progenitor cell function, focusing on molecular pathways linked to airway remodeling.

Methods: Virgin female flies were exposed to vaporized nicotine (e-nicotine) or control (water). F1 larval tracheae were assessed for structural defects, epithelial remodeling, and stem cell niches. mRNA sequencing of larval tracheae identified dysregulated genes.

Results: Maternal e-nicotine exposure induced severe airway malformations in F1 offspring, including shortened tracheal segments (Tr9: $p<0.001$), increased tracheal deformity rate and epithelia thickness ($p<0.0001$). Stem cell niches (tracheoblast areas) in T4/T5 segments were reduced by 35% ($p<0.0001$), with reduced PH3+ proliferating cells. mRNA sequencing revealed upregulation of genes associated with mucus production (Muc96D, Muc26B), mechanosensation (pie), Notch signaling (E(spl)mbeta-HLH), and RNA processing (Rpp30, NHP2). Additional dysregulated genes included Syb (synaptic function), hzg (cell adhesion), MAN1 (chromatin regulation), and Npc2a (lipid metabolism), suggesting broad disruption of developmental and homeostatic pathways.

Conclusions: Preconception nicotine exposure in Drosophila models triggers airway remodeling, stem cell depletion, and dysregulation of genes critical for epithelial integrity and signaling. Future studies will focus on ongoing mRNA sequencing of T4/T5 tracheoblast niches to uncover deeper molecular mechanisms linking maternal e-nicotine exposure to intergenerational airway dysfunction. These findings underscore potential intergenerational harms of adolescent vaping, warranting further investigation into nicotine's impacts on respiratory health.

Keywords: E-cigarettes, Intergenerational effects, Airway remodeling

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.05 The Effect of Lung Cancer Screening on Smoking Behaviors - No Evidence of a 'License to Smoke' Effect

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Introduction: The effect of lung cancer screening (LCS) on smoking behaviour is unclear with previous randomised studies demonstrating either increased quit rates in people screened versus unscreened controls (suggesting a teachable moment for smoking cessation at screening) or reduced quit rates in people screened (possibly suggesting a license-to-smoke effect of screening). Here we report the impact of LCS on smoking cessation service use and quit rates in the intervention vs. controls arms of the Yorkshire Lung Screening Trial (YLST).

Methods: In YLST, people aged 55-80 who had ever smoked were randomised to invitation to lung cancer risk assessment and if high-risk then LDCT screening, or control arm (no invitation to screening). LCS was not approved in the UK at the time of participant randomisation. Smoking cessation service interaction, defined as undertaking a consultation with a smoking cessation practitioner (SCP), and self-reported smoking quits were recorded during the study period. Smoking cessation services included (1) the YLST-service which was co-located with screening and available to screening attendees and (2) a local authority (LA) provided service available to all residents of Leeds (and thus available to both study arms). Differences in reporting metrics between the two services preclude direct statistical comparison of quit rates at this time although ongoing analysis is underway attempting to harmonise data and will be presented in due course.

Results: Data is presented on 43,852 people in the control arm and 43,942 people in the intervention arm (of whom 24,587 [56.0%] responded and underwent lung cancer risk assessment and 7,384 [16.8%] underwent LDCT screening). Primary care diagnostic codes suggested that 12,241 and 12,182 people in the intervention and control arms respectively were actively smoking at the time of randomisation. Overall, 5.8% (n=2,542/43,942) of the intervention arm saw an SCP compared to 1.5% (n=675/43,852) of the control arm (OR 3.92, 95%CI 3.60-4.28, p<0.0001). Self-reported quit rates are shown in Table 1. Differences in reporting metrics preclude statistical comparison but overall a higher proportion of people appear to self-report quitting in the intervention versus control arm.

	Control arm	Intervention arm
Total number of participants (irrespective of smoking code)	43,852	43,942
Number meeting with an SCP (%)	675 (1.5)	2,542 (5.8)
14-day point prevalent quits at 4 weeks with LA service (%)	264 (0.6)	198 (0.5)
7-day point prevalent quits at 4 weeks with YLST service (%)	-	471 (1.1)
7-day point prevalent quits at 12 weeks with YLST service (%)	-	613 (1.4)
Total number of participants with Primary Care smoking code suggesting active smoking at time of randomisation	12,241	12,182
Number meeting with an SCP (%)	567 (4.6)	2,212 (18.2)
14-day point prevalent quits at 4 weeks with LA service (%)	206 (1.7)	146 (1.2)
7-day point prevalent quits at 4 weeks with YLST service (%)	-	383 (3.1)
7-day point prevalent quits at 12 weeks with YLST service (%)	-	520 (4.3)

Table 1: Number of participants meeting an SCP and self-reported quits with LA and YLST services.

Conclusions: YLST is the first study to compare smoking behaviours between a whole population invited for LCS and a non-invited control population. Compared to the control population, over three times as many people in the intervention arm saw an SCP and more quits were reported. These data provide reassurance that LCS provides a teachable moment for smoking cessation with no dominant licence-to-smoke effect.

Keywords: Low dose CT screening, Smoking cessation

MA09.06 Impact of Smoking Cessation at Diagnosis on Overall Survival in Lung Cancer Patients: A Comprehensive Meta-Analysis

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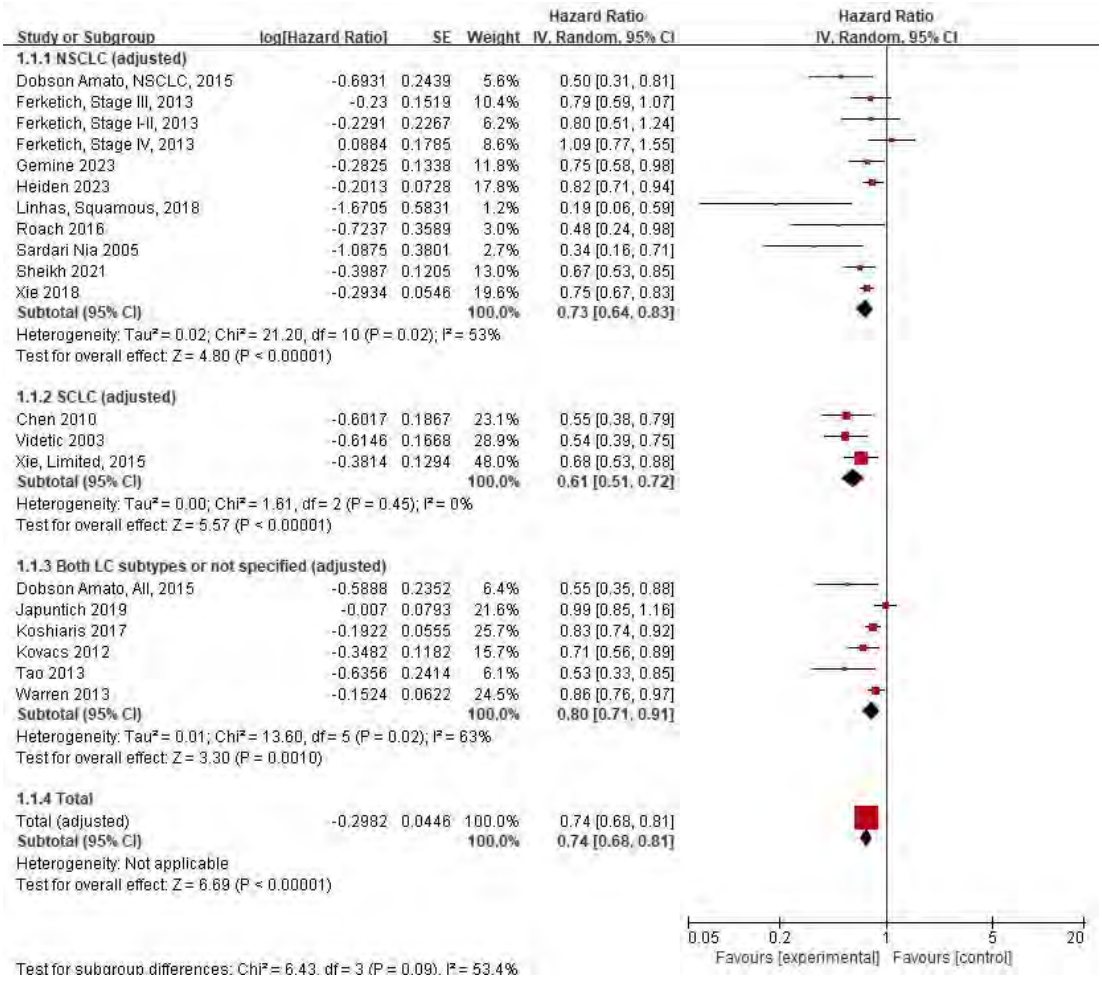
Introduction: Smoking cessation has been linked to reduced lung cancer mortality in the literature. This study aims to synthesize scientific evidence on the impact of smoking cessation at or around the time of diagnosis on survival outcomes in lung cancer patients, with a specific focus on whether the effect varies by lung cancer stage.

Methods: A systematic search was conducted in Ovid-MEDLINE, Ovid-EMBASE, Cochrane Central Register of Controlled Trials, and KoreaMed databases up to September 2024. Randomized controlled trials and cohort studies comparing smoking quitters with continued smokers at diagnosis were included. The primary outcome was overall survival (minimum follow-up of three months). The included studies were critically appraised using the Cochrane risk of bias tool and meta-analyzed.

Results: A total of 25 cohort studies including 17,584 patients were included. We found that smoking cessation at diagnosis was associated with a significant reduction in mortality risk, with an adjusted HR of 0.74 (95% CI: 0.68-0.81) for all lung cancer patients. Furthermore, in subgroup analyses, smoking cessation was associated with improved survival in both non-small cell lung cancer (adjusted HR: 0.73, 95% CI: 0.64-0.83) and small cell lung cancer (adjusted HR: 0.61, 95% CI: 0.51-0.72). Subgroup analyses showed a more pronounced benefit of smoking cessation in patients with early-stage disease (Stage I-III or limited stage, adjusted HR: 0.64, 95% CI: 0.56-0.74). In addition, active smoking cessation interventions significantly improved survival (adjusted HR: 0.55, 95% CI: 0.35-0.88). However, this impact of smoking cessation on survival needs to be further investigated as few studies objectively confirmed smoking cessation.

Conclusions: This study highlights the importance of encouraging smoking cessation at the time of lung cancer diagnosis as an integral part of patient management to improve survival outcomes. Future research should focus on identifying effective smoking cessation strategies to maximize survival benefits for lung cancer patients.



Keywords: Lung cancer, smoking cessation, survival

MA09.07 Body Roundness Index and Polygenic Risk Score Improve Lung Cancer Risk Prediction Over BMI: Prospective Analyses in the UK Biobank

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Introduction: Obesity is a well-established risk factor for multiple cancers, including lung cancer. However, traditional metrics like Body Mass Index (BMI) fail to capture body fat distribution, a critical determinant of metabolic dysregulation. The Body Roundness Index (BRI), a novel anthropometric measure derived from waist circumference and height, better reflects visceral adiposity and associated health risks. Concurrently, the polygenic risk score (PRS) quantifies genetic susceptibility to cancer. This study aims to investigate the joint associations of BRI and PRS with lung cancer incidence and mortality and compare their predictive performance against BMI in a large prospective cohort.

Methods: We utilized data from the UK Biobank to investigate the associations between the BRI and both lung cancer incidence and cancer mortality. BRI was calculated according to the following formula: BRI = $364.2 - 365.5 \times \sqrt{(1 - (\text{waist circumference} / (2\pi))^2 / (\text{height} / 2)^2)}$. PRS for lung cancer were derived using genome-wide significant SNPs ($p < 5 \times 10^{-8}$), weighted by effect sizes from prior GWAS. Participants were categorized into three groups based on BRI and PRS quintiles. Cox proportional hazards models were used to evaluate the relationships between BRI and these outcomes. To evaluate the predictive capabilities of BRI and BMI for cancer outcomes, receiver operating characteristic (ROC) analysis and area under the curve (AUC) metrics were employed. The DeLong test was used to statistically compare the AUCs of BRI and BMI.

Results: This study included 442,525 participants, among whom 4,083 lung cancer cases and 2,902 lung cancer-related deaths were identified. After adjusting for age, sex, ethnicity, education level, smoking status, alcohol consumption, and family history of cancer, individuals in third quintile (Q3: 4.58 to 23.55) had a 1.16-fold (95% CI: 1.07 - 1.26) increased risk of lung cancer incidence and a 1.13-fold (95% CI: 1.03 - 1.25) higher risk of lung cancer mortality compared to those in the lowest quintile (Q1: -1.08 to 3.36). In the high-risk PRS group, individuals in the third quintile of BRI had a 1.21-fold (95% CI: 1.06-1.37) higher risk of lung cancer incidence and a 1.17-fold (95% CI: 1.01-1.36) increased risk of lung cancer mortality compared to those in the lowest BRI quintile. ROC analysis indicated that the combination of BRI and PRS (AUC incidence= 0.58, AUC mortality= 0.58) outperformed the combination of BMI and PRS (AUC incidence = 0.51, AUC mortality= 0.51) in predicting both lung cancer incidence and mortality ($p < 0.05$).

Conclusions: BRI is a stronger predictor of lung cancer incidence and mortality than BMI, with enhanced discrimination when combined with PRS. These findings support integrating BRI and genetic risk for precision risk stratification, potentially guiding targeted prevention strategies.

Keywords: Risk factors, Body Roundness Index, Polygenic Risk Score

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.08 Germline Variants in Indian NSCLC Patients With Familial Aggregation: A Prospective Cohort Study

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Introduction: While tobacco exposure is a primary risk factor for lung cancer, not all individuals with a history of tobacco use develop the disease, and cases in individuals without such exposure are rising, highlighting the role of genetic susceptibility. Pathogenic or likely pathogenic germline variants (PGVs) in cancer predisposition genes are increasingly recognized in various cancers including lung cancer, particularly those who have familial aggregation. This study investigates the prevalence of PGVs in individuals with Indian non-small cell lung cancer (NSCLC) who have a significant family history.

Methods: A total of 750 individuals with NSCLC were screened for familial aggregation, defined as having at least one first-degree or two second-degree relatives with cancer. Of these, 112 individuals underwent next-generation sequencing (NGS) of targeted 143 cancer predisposition genes or whole exome sequencing using blood samples. Clinical, pathological, and demographic data were analyzed. Survival analysis was performed using Kaplan-Meier estimates, and statistical comparisons were conducted with the chi-square and Mann-Whitney U tests.

Results: Among 750 individuals, 137 (18.26%) had a significant family history. NGS in 112 individuals revealed PGVs in 17 participants (15.2%). These PGVs were distributed across 12 genes, with 10 genes linked to DNA damage repair pathways, including ATM (n=3), BRCA2 (n=3), BRCA1 (1) and CKEK2 (1) . Moreover, 12 individuals were identified with variants of uncertain significance (VUS), including MUC5B (n=7), and one each in POLE, PRKN, DLEC1, KRAS, ERBB2, and BRAF. Individuals with PGVs did not exhibit statistically significant differences in clinical characteristics compared to those without.

Conclusions: This study demonstrates that 15.2% of individuals with Indian NSCLC and familial aggregation harbor PGVs, predominantly in DNA repair genes. The findings underscore the need for genetic testing in individuals with lung cancer who have a strong family history, which could aid in risk assessment and personalized screening strategies.

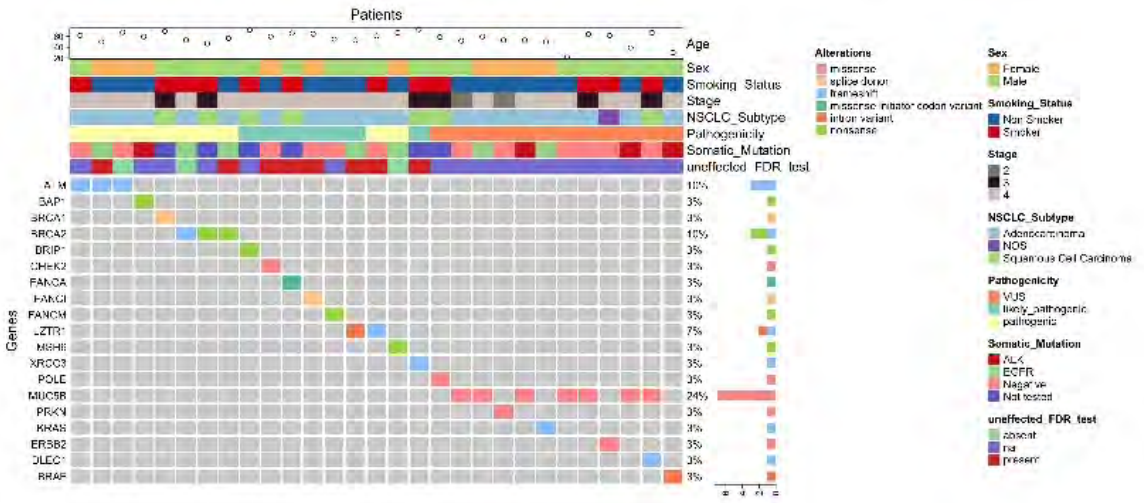

Table 1:
Clinico-pathological characteristics
Of patients with or without PGV

Keywords: Genetics, Non small cell lung cancer, grem-line variants

MA09 DIVING DEEP INTO DIVERSITY: OLD AND NEW RISKS FOR LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA09.09 Unraveling Ancestry Disparities and Intratumoral Heterogeneity in Non-Small Cell Lung Cancer

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with significant racial disparities observed in its incidence, epidemiological characteristics, molecular profiles and so on. These differences between Eastern and Western populations profoundly influence treatment strategies and patient prognosis. However, the majority of studies characterizing the molecular landscape of lung cancer have predominantly focused on Western cohorts and have often relied on single tumor region sampling, thereby overlooking racial molecular variations and intratumoral heterogeneity (ITH).

Methods: To address these gaps, we performed whole exome sequencing (WES) and RNA sequencing (RNA-seq) on 290 Chinese lung cancer patients with multiregional tumor and matched paired normal samples (called CLEVER cohort, Chinese Lung Cancer EVolution and MicroEnironment tracking under TheRapy). Systematic comparison with published data from the TRACERx cohort, comprising 365 lung tumors, revealed significant differences in the genomic and transcriptomic molecular signatures and the timing of evolutionary trajectories between Eastern and the Western lung cancer patients.

Results: The CLEVER cohort demonstrated significant epidemiological differences, including higher proportions of female patients, non-smokers, younger age at diagnosis, earlier tumor stages, and adenocarcinoma predominance. At the genomic level, CLEVER tumors exhibited elevated subclonal complexity compared to TRACERx, with significantly higher subclonal heterogeneity metrics including higher single nucleotide variation intratumor heterogeneity (SNV-ITH) and higher somatic copy number alteration ITH (SCNA-ITH) and increased subclonal whole-genome duplication (WGD) events. Comparative analysis revealed distinct clonal architectures of driver genes between two cohorts: EGFR, HMCN1, and KMT2B mutations preferentially occurred as truncal events in CLEVER, whereas KRAS mutations were predominantly subclonal. Chromosomal arm-level analysis revealed CLEVER-specific CNV patterns, including increased subclonal amplifications (5p, 8q) and deletions (3p, 9p, 19p), alongside truncal 8p deletions. Transcriptomically, the CLEVER cohort displayed reduced heterogeneity compared to TRACERx. Most transcriptional genes exhibited low intra- and intertumoral heterogeneity and were enriched in ligand-receptor interaction pathways and signal transduction cascades. Collectively, these findings demonstrate that Asian lung cancers are characterized by enhanced genomic intratumor heterogeneity driven by subclonal WGD dynamics and late-acquired drivers, and reduced transcriptional heterogeneity associated with stable signaling circuitries- a dual evolutionary paradigm distinct from Western populations.

Conclusions: These discoveries underscore the importance of population context in deciphering comprehensive molecular maps and tumor evolution for lung cancer.

Keywords: racial disparities, intratumoral heterogeneity, tumor evolution

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.01 Phase II Trial of Serplulimab Plus Bevacizumab and Chemotherapy for Treatment-Naïve Non-Squamous NSCLC with Brain Metastases (SUPER BRAIN)

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Introduction: The efficacy of immunotherapy for non-small-cell lung cancer (NSCLC) with brain metastases (BMs) remains limited. The tumor immune response property of serplulimab may be simultaneously enhanced by the blockade of vascular endothelial growth factor. This study evaluated the efficacy and safety of serplulimab combined with bevacizumab and chemotherapy as a first-line treatment for patients with NSCLC and untreated BMs.

Methods: This single-arm phase 2 clinical trial (NCT05807893) enrolled patients with advanced non-squamous NSCLC with untreated BMs that were either asymptomatic or had symptoms controlled by dehydration therapy. Patients received serplulimab combined with bevacizumab, pemetrexed, and carboplatin for four to six cycles, followed by maintenance therapy with serplulimab plus bevacizumab and pemetrexed until disease progression, unacceptable toxicity, or death, for up to two years. The primary endpoint was intracranial progression-free survival (iPFS). Intracranial outcomes were assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1.

Results: Forty patients were enrolled, and 39 had at least one postbaseline tumor assessment. As of 17 February 2025, the median follow-up duration was 13.3 months (95% confidence interval [CI]: 13.0-13.5). The median iPFS was 13.1 months (95% CI 12.7-not reached), with 6-month and 12-month iPFS rates of 91.3% (95% CI 82.3%-100.0%) and 67.1% (95% CI 51.1%-88.1%) respectively. The median PFS was 13.3 months (95% CI 11.9-not reached). Nine patients (22.5%) died due to disease progression, and the 12-month overall survival (OS) rate was 73.1% (95% CI 63.7%-92.6%). The intracranial ORR was 84.6% (33/39), with complete response (CR) in 6 patients (15.4%) and partial response (PR) in 27 patients (69.2%). The extracranial ORR was 67.7% (25/39), and the overall ORR was 71.8% (28/39). The most common treatment-related adverse events (TRAEs) of grade 3 or higher included decreased white blood cell/neutrophil count (4 patients [10.0%]), reduced platelet count (5 patients [12.5%]), and abnormal liver function (4 patients [10.0%]). No treatment-related deaths were reported.

Conclusions: Serplulimab plus bevacizumab and chemotherapy demonstrated promising intracerebral antitumor efficacy and a manageable safety profile for patients with non-squamous NSCLC with BMs in the first-line setting.

Keywords: Brain Metastases, Non-Squamous NSCLC, Immunochemotherapy

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.02 CAN-2409 With Continued Immune Checkpoint Inhibitor (ICI) in Patients With Stage III/IV NSCLC With Inadequate Response to ICI

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This abstract is under embargo until September 9 at 10:15 CET.

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.03 Efficacy and Safety of Cadonilimab Plus Pulocimab in NSCLC Patients Who Progressed Following Prior Immunotherapy: A Phase 1b/2 Study

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Introduction: PD-(L)1 inhibitors combined with chemotherapy have become the first-line standard-of-care (SOC) for advanced non-small cell lung cancer (NSCLC). This prospective, multi-center, phase 1b/2 study (NCT05142423) aims to evaluate the safety and efficacy of cadonilimab, a PD-1/CTLA-4 bispecific antibody, in combination with pulocimab, an anti-VEGFR-2 monoclonal antibody, in patients with advanced solid tumors, including those with NSCLC who have progressed after first-line SOC immunotherapy-based treatment.

Methods: This study consists of two phases: a safety run-in phase and an expansion phase. In the safety run-in phase, the safety of intravenous cadonilimab (10 mg/kg) in combination with pulocimab (10 mg/kg and 15 mg/kg),with or without chemotherapy, every 3 weeks (Q3W), were assessed in patients with advanced solid tumors who had failed standard treatments. This abstract focuses on the NSCLC cohort from the expansion phase. Patients with advanced NSCLC who had progressed after first-line immunotherapy-based SOC treatment received intravenous pulocimab (15 mg/kg) and cadonilimab (10 mg/kg), Q3W. The primary endpoints were safety and objective response rate (ORR), while secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: No dose-limiting toxicities (DLTs) were observed in the safety run-in phase (n=18). As of January13, 2025, a total of 47 NSCLC patients who had progressed on first-line immunotherapy-based SOC treatment received at least one dose of cadonilimab and pulocimab, with a median follow-up of 16.7 months (range: 8.1-19.0). All 47 patients had at least one post-baseline tumor evaluation. The ORR was 12.8% (6/47), DCR was 95.7% (45/47), median DOR was 15.2 months, median PFS was 5.8 months, and median OS was 15.6 months. Among them, 26 patients had squamous NSCLC, with an ORR of 11.5% (3/26), DCR of 96.2% (25/26), median DOR not reached, median PFS of 7.1 months, and median OS of 16.7 months, indicating a more pronounced therapeutic effect in the squamous subgroup. For the 21 non-squamous NSCLC patients, the ORR was 14.3% (3/21), DCR was 95.2% (20/21), median DOR was 8.8 months, median PFS was 5.5 months, and median OS was 12.8 months. The incidence of grade ≥3 treatment-emergent adverse events (TEAEs) was 36.2%, while the incidence of grade ≥3 treatment-related adverse events (TRAEs) was 21.3%. The most common TRAEs included elevated aspartate aminotransferase, thrombocytopenia, and proteinuria. The only Grade ≥3 TRAEs that occurred in more than two patients was hypertension. No new safety signals were identified.

Conclusions: The combination of cadonilimab and pulocimab demonstrated favorable safety profile and encouraging efficacy as second-line therapy in patients with NSCLC who progressed after prior first-line immunotherapy-based SOC treatment, with particularly notable efficacy in the squamous NSCLC subgroup. These findings suggest that this combination may overcome immunotherapy resistance and offer a potential new option for second-line treatment of NSCLC. A further phase III clinical trial is currently in planning.

Keywords: Cadonilimab, Pulocimab, NSCLC

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS , TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

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Introduction: In recent years, the first-line immunotherapy has become an essential tool in the personalized treatment of NSCLC patients. Despite a proper diagnostic procedure for qualification for the therapy, many patients do not respond to the therapy regardless of PD-L1 expression on tumor cells. This may be caused by differences in tumor heterogeneity and temporal clonal evolution. To reveal mechanisms of immunotherapy failure, we performed low-pass whole genome sequencing (lp-WGS) to investigate the dynamics of subclonal copy number alterations (CNAs) changes across primary tumors (T) and longitudinal liquid biopsies (LB).

Methods: We collected T and LB1 samples before the treatment application and further longitudinal LB samples (LB2, LB3, etc) approximately every 2-3 months during clinical follow-up until therapy completion. The lp-WGS was performed on NextSeq 550 instrument (Illumina, USA). The R package inchorCNA was used to call and asses the subclonal evolution of CNAs and GISTIC2.0 to localize the significant focal somatic CNAs. The P value of < 0.05 (Wilcoxon paired test) was considered statistically significant. This study was funded by the Polish National Centre for Research and Development (LIDER/46/0237/L-12/20/NCBR/2021).

Results: We shallowly sequenced 520 samples (93-T, 128-LB1, 89-LB2, 55-LB3, 41-LB4, 33-LB5, 25-LB6, 21-LB7, 15-LB8, 9-LB9, 9-LB10, 5-LB11) from 128 patients (73 males, 55 females; median age 67±8 years) treated with pembrolizumab in monotherapy (48) or in combination with chemotherapy (80) (median PFS: 3 months). Among them, 35 patients were long responders (PFS >12 months), while 93 were short responders (PFS ≤12 months), including 55 treated for ≤3 months, 19 for 3-6 months, and 19 for 6-12 months. Subclonal analysis revealed significant differences between T and LB1, suggesting early pre-treatment clonal selection. Long responders exhibited a gradual reduction in subclonal diversity (LB3/LB4, LB5/LB6), whereas short responders experienced rapid subclonal shifts within the first observation period (LB1/LB2, LB3/LB4), indicating early selection of resistant clones. Amplification of 3q26 was detected in T and LB1 samples across all patients, regardless of response duration. Long responders harbored also a 4q34 deletion and 12q14 amplification, while short responders exhibited a more heterogeneous CNAs profile, which included amplifications of 3q24-28, 8p11, and 19q12, or deletions of 8p23 and 9p21. LB samples obtained in long responders at the moment of progression showed persistent 3q26 amplification and newly acquired focal amplifications of 8q22 and 6q16, or 21q21 deletion.

Conclusions: Our study demonstrates that lp-WGS of longitudinal liquid biopsies reveals distinct evolutionary trajectories of clonal evolution associated with pembrolizumab response in NSCLC patients. In short responders, resistant subclones may already be present before therapy initiation, leading to rapid subclonal shifts within early treatment cycles. In contrast, long responders exhibited a gradual reduction in subclonal diversity, suggesting effective suppression of tumor heterogeneity, followed by the emergence of new CNAs potentially driving secondary resistance. The presence of 3q26 amplification across all patients suggests its role as a key driver of immunotherapy resistance in NSCLC patients.

Keywords: NSCLC, Immunotherapy, lpWGS

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.05 Phase I/II Study of Nivolumab and Ipilimumab With Concurrent Stereotactic Radiosurgery for Intracranial Metastases From NSCLC

M. Altan, T. Beckham, J. Song, J. Welsh, N. Guha-Thakurta, B. Carter, G. Blumenschein, Y. Elamin, C. Tang, A. Ghia, D. Yeboa, M.F. McAleer, C. Chung, S.L. McGovern, C. Wang, T. Martin, S. Perni, W. Jiang, B.S. De, J.S. Wefel, Y. Wang, J. Hicks, Y.S.B. Kim, J. Weinberg, T.M. Briere, X. Le, T. Cascone, M. Vailati Negrao, F. Skoulidis, R. Ferrarotto, J.V. Heymach, J. Li
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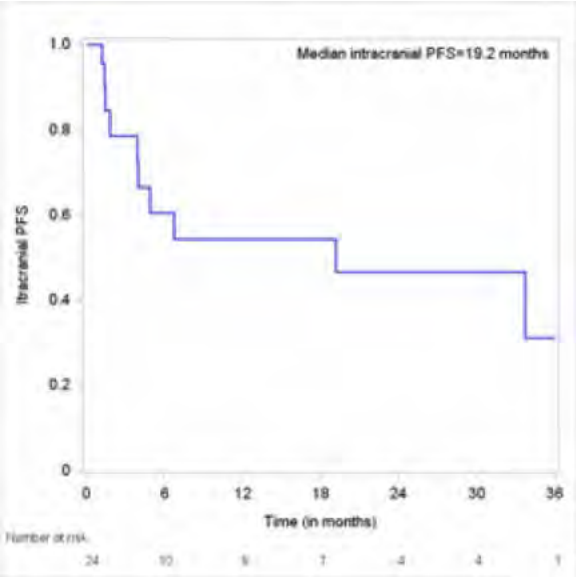
Introduction: As many as 20% of patients with non-small cell lung cancer (NSCLC) experience brain metastases (BM), for which radiation therapy, with or without surgery, remains the standard treatment. However, clinical data on the safety of combining stereotactic radiosurgery (SRS) with immune checkpoint inhibitors for BM are lacking.

Methods: We conducted a single institution, open label, phase I/II study, enrolled NSCLC patients with active brain metastases (BM) eligible for stereotactic radiosurgery (SRS). Patients received brain SRS alongside systemic therapy with nivolumab and ipilimumab within a 7-day window. The primary endpoints were safety and intracranial progression-free survival (PFS) at four months.

Results: Twenty-four patients were enrolled in the study, with a median follow-up of 41.6 months (95% CI, 36.7-53.3). The median overall survival was 20.2 months, while the median time to intracranial progression or death was 19.2 months (95% CI, 3.9-36.2). The median time to extracranial progression or death was 19.2 months (95% CI, 1.4- 36.2). No treatment failures were observed within the radiation field for brain metastases during follow up period, leading to a local control rate of 100% from SRS. The 4-, 6-, and 12-month intracranial progression-free survival (PFS) rates were 66.4%, 60.4%, and 54.3%, respectively. Only one patient experienced a predefined dose-limiting toxicity, developing cerebral edema attributed to concurrent SRS and immunotherapy, which was successfully managed and resolved with steroids.

Conclusions: In this study, concurrent brain SRS with nivolumab/ipilimumab was safe for patients with active NSCLC BM, with acceptable toxicity profile. Intracranial PFS rates (70% vs. historical ~50% at 6 months) and the median time to intracranial progression or death (19.2 months vs. historical ~ 5-10 months) compare favorably to historical data with SRS alone, highlighting the potential impact of this approach.



Keywords: brain metastasis, immunotherapy, stereotactic radiosurgery

MA10.06 IMscin002 Final Analysis: Patient Preference and Safety of Atezolizumab by Subcutaneous and Intravenous Administration

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Introduction: Atezolizumab subcutaneous (SC), a co-formulation containing atezolizumab and recombinant human hyaluronidase PH20, is approved for the same indications as atezolizumab intravenous (IV). IMscin001 (NCT03735121) showed the pharmacokinetics, efficacy, and safety of atezolizumab SC and IV were consistent. IMscin002 (NCT05171777), a phase II, randomized, open-label, cross-over trial, investigated patient preferences, healthcare professional (HCP) perceptions, and safety for atezolizumab SC versus IV in patients with non-small cell lung cancer (NSCLC); we report results from the final analysis.

Methods: Eligible adults with EGFR/ALK wildtype had PD-L1+ resected (stage II, IIIA/B; AJCC 8th edition) NSCLC and completed adjuvant chemotherapy without evidence of recurrence, or were treatment-naïve with PD-L1-high metastatic NSCLC. Patients, randomized 1:1, received atezolizumab SC (1875mg) or IV (1200mg) every 3 weeks. After Cycle 3, patients switched formulations, and after Cycle 6 patients chose an administration route for the continuation period (10 additional cycles for early-stage, or until investigator-determined loss of clinical benefit for patients with resected/metastatic NSCLC). Primary endpoint: patient preference for atezolizumab SC. Secondary endpoints included choice of administration route for the continuation period, safety, and patient-reported outcomes (PROs; captured via the EORTC QLQ-C30).

Results: At data cutoff (last patient's last visit; October 25, 2024), 179 patients were randomized; 90 to atezolizumab SC followed by IV, and 89 to atezolizumab IV followed by SC. Overall, 115 (64.2%) and 43 (24.0%) patients completed the cross-over and continuation periods, respectively. Most patients (77.4%; n=89/115) chose atezolizumab SC for the continuation period, with 22.6% (n=26/115) opting for atezolizumab IV. Median treatment duration was 10.4 months; median number of cycles initiated was 14 (range: 1-36). The safety profile of atezolizumab SC/IV was consistent with the primary analysis and established safety profile of atezolizumab; 80.6% (n=141/175) of patients experienced ≥1 adverse event (AE; 54.9% treatment-related). Nineteen (10.9%) and 4 (2.3%) patients experienced injection-site reactions and infusion-related reactions, respectively (Table). At or after 16 cycles, 44.7% (n=80/179) of patients had ongoing clinical benefit; 61.3% (n=38/62) with early-stage NSCLC and 35.9% (n=42/117) with metastatic NSCLC. During the continuation period, mean changes from baseline in PROs (global health status [GHS], physical and role functioning) aligned with the primary analysis. GHS, physical and role functioning, and symptom scales showed similar results.

Conclusions: No new or unexpected safety findings were observed. Longer term data support that most patients prefer atezolizumab SC versus IV, and that atezolizumab SC has similar efficacy, PROs, and a similar safety profile to atezolizumab IV.

Table

Patients, n (%)	Cross-over period		Continuation period		All patients (N=175)‡
	Atezolizumab IV* (n=160)	Atezolizumab SC† (n=155)	Atezolizumab IV (n=26)	Atezolizumab SC (n=89)	
≥1 AE	95 (59.4)	74 (47.7)	20 (76.9)	60 (67.4)	141 (80.6)
Injection-site reactions	0	16 (10.3)	0	3 (3.4)	19 (10.9)
Infusion-related reactions	4 (2.5)	0	0	0	4 (2.3)
Injection-related reactions	0	1 (0.6)	0	1 (1.1)	1 (0.6)
Infusion-site reactions	1 (0.6)	0	0	0	1 (0.6)
Related AE	50 (31.3)	52 (33.5)	11 (42.3)	33 (37.1)	96 (54.9)
AE with fatal outcome	1 (0.6)	4 (2.6)	1 (3.8)	3 (3.4)	9 (5.1)
Related AE with fatal outcome	0	1 (0.6)	0	0	1 (0.6)
Serious AE	15 (9.4)	13 (8.4)	6 (23.1)	12 (13.5)	45 (25.7)
Related serious AE	6 (3.8)	6 (3.9)	0	3 (3.4)	15 (8.6)
Highest grade 3–4 AE	25 (15.6)	13 (8.4)	5 (19.2)	12 (13.5)	48 (27.4)
Related highest grade 3–4 AE	7 (4.4)	5 (3.2)	2 (7.7)	5 (5.6)	19 (10.9)
AE leading to treatment discontinuation	9 (5.6)	7 (4.5)	2 (7.7)	6 (6.7)	24 (13.7)
AE leading to treatment interruption	19 (11.9)	14 (9.0)	11 (42.3)	23 (25.8)	57 (32.6)

*Received IV during Cycles 1–3 or Cycles 4–6. †Received SC during Cycles 1–3 or Cycles 4–6. ‡Safety population comprised all patients who received treatment: 4 patients enrolled on the atezolizumab SC followed by IV arm did not receive any treatment.
AE, adverse event; IV, intravenous; SC, subcutaneous.

Keywords: Atezolizumab, Subcutaneous, Intravenous

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.07 Impact of Myeloid Growth Factor Support on Outcomes in RELATIVITY-104: Insights From Clinical and Preclinical Data in NSCLC

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Introduction: Nivolumab (NIVO) plus relatlimab (RELA) with platinum-doublet chemotherapy (PDCT) is being investigated in a phase 3 study as a first-line treatment for patients with metastatic NSCLC having tumor PD-L1 expression ≥1% and non-squamous histology. Patients receiving PDCT-containing regimens often require prophylactic myeloid growth factors (MGFs; eg, G-CSF) to prevent neutropenia. However, the impact of MGFs on immunotherapy + PDCT (eg, NIVO + RELA + PDCT) outcomes is not well explored. We investigated how MGF support influences outcomes in patients receiving NIVO + RELA + PDCT in the phase 2 RELATIVITY-104 trial and performed complementary in vitro experiments to explore the immunologic effects of MGFs.

Methods: Patients in RELATIVITY-104 had untreated metastatic NSCLC. Part 1 evaluated the safety of NIVO 360mg + RELA (360mg or 720mg) + PDCT Q3W. In Part 2, patients received NIVO 360mg + RELA 360mg + PDCT or NIVO 360mg + PDCT Q3W. Based on the safety profile and observations during Part 1, prophylactic MGF was mandated in the NIVO + RELA + PDCT arm in Part 2 for patients aged ≥60 years and used therapeutically for patients aged <60 years experiencing grade ≥3 neutropenia. Prophylactic MGF was allowed but not mandatory in the NIVO + PDCT arm in Part 2 and the NIVO + RELA + PDCT arms in Part 1. Exploratory analyses included clinical outcomes by MGF use, assessment of pharmacodynamic changes of myeloid cells by flow cytometry in the context of MGF use, and the phenotypic and functional impact of MGF-treated myeloid cells on immunobiology in vitro.

Results: Data are from the Feb 15, 2024 (Part 1) and June 28, 2024 (Part 2) database locks. In the NIVO + RELA + PDCT arm of Part 1 (no prophylactic MGFs), 66% of patients experienced grade 3-4 treatment-related adverse events (TRAEs). In Part 2 (prophylactic MGFs), 54% of patients treated with NIVO + RELA + PDCT and 55% of patients treated with NIVO + PDCT experienced grade 3-4 TRAEs. Grade ≥3 treatment-related neutropenic events were observed in 42% (Part 1) and 26% (NIVO + RELA + PDCT arm in Part 2) of patients; objective response rates were 45% (Part 1) and 51% (Part 2) in all randomized patients. In vitro analyses suggested no substantial impact on the phenotype of MGF-treated myeloid-derived suppressor cells (MDSCs) and MGF-treated monocytes compared with untreated cells. MGFs did not increase MDSC suppressive activity against CD8+ T cell proliferation or IFN-γ production. Clinically, MDSC/lymphocyte or monocyte/lymphocyte ratios remained similar following prophylactic MGF use in the NIVO + RELA + PDCT arm relative to patients not treated with MGF and the NIVO + PDCT arm.

Conclusions: In patients with metastatic NSCLC treated with first-line NIVO + RELA + PDCT, prophylactic MGF did not compromise efficacy and meaningfully reduced hematologic toxicity. Taken together, these results support prophylactic MGF use with dual immunotherapy + PDCT regimens in patients with NSCLC. Use of MGFs did not appreciably modulate myeloid cell phenotype, increase their prevalence, or alter their functional effects on T cells.

Keywords: myeloid growth factor, relatlimab, in vitro

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.08 Anti-PD-1 Re-Challenge After Immune Priming by CTLA-4 Inhibition and Immune Boosting Through Radiotherapy in Advanced NSCLC: The RAD-IO Trial

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Introduction: In advanced non-small cell lung cancer (NSCLC) without targetable driver alterations, current first line standard-of-care treatment consists of PD-(L)1 inhibition with or without chemotherapy. The majority of patients does not experience durable clinical benefit from this treatment and second-line chemotherapy shows dissatisfying results. We hypothesized that immune priming by CTLA-4 inhibition followed by immune boosting through stereotactic body radiation therapy (SBRT) could reinvigorate the anti-cancer immune response in metastatic NSCLC patients previously treated with anti-PD-(L)1 therapy.

Methods: The RAD-IO trial (NCT05401786) is a phase II, single-center, single-arm trial in patients with progressive stage IV NSCLC previously treated with anti-PD-(L)1. Patients were required to have at least two separate tumor lesions: one for SBRT and one out-of-field lesion for repeat biopsies and response measurement. Patients were treated with one dose ipilimumab (1mg/kg), followed by irradiation (3x8Gy) of one to four tumor lesions seven days later. One week after SBRT completion, patients started with PD-1 inhibition (cemiplimab 350mg every three weeks) for up to two years, until disease progression or unacceptable toxicity. Response evaluation using RECIST1.1 was performed every six weeks during the first 27 weeks and every twelve weeks thereafter. The primary endpoint was clinical benefit rate defined as complete or partial response (CR or PR), or stable disease (SD) lasting six months or longer after cemiplimab initiation. Primary endpoint was reached if ≥12 patients out of 54 showed clinical benefit. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety according CTCAEv5.

Results: Between January 2023 and September 2024 we enrolled 54 patients, 35 were male (64.8%), median age was 63 years (range 43-81), 39 patients (72.2%) had adenocarcinoma, 23 patients (42.6%) had a PD-L1 negative tumor.

At data cut-off, January 31st 2025, median follow-up was 13.4 months (95%CI 8.2 - 16). The study reached its primary endpoint with clinical benefit in 13 patients (24.1%, 95%CI 13.5 - 37.6%): confirmed PR in six patients (11.1%) and SD ≥ six months in seven patients (13%). From start of cemiplimab, median PFS was 2.7 months (95%CI 1.5 - 4.2) for all 54 patients and 13.7 months (95%CI 8.6 - NA) for 13 patients with clinical benefit. Median OS was 14 months (95%CI 8.5 - NA).

Grade 3 or higher treatment-related adverse events (TRAEs) were seen in seven patients (13%). There were six grade 3 TRAEs: one patient with tracheal obstruction possibly related to SBRT, one adrenal insufficiency, one cholangitis, two lymphopenia and one ASAT/ALAT increase. There was one grade 5 acute kidney injury, probably CTLA-4 inhibition-related nephritis but without a biopsy to confirm this diagnosis.

Conclusions: In the RAD-IO trial, priming by CTLA-4 inhibition and immune boosting through SBRT followed by anti-PD-1 retreatment elicited clinical benefit in 24.1% of patients with advanced metastatic NSCLC who previously progressed on PD-(L)1 inhibition, thereby reaching the primary endpoint. No new safety signals were observed. Subgroup and translational analyses are ongoing to identify clinical and biological biomarkers in responding patients.

Keywords: Rechallenge, Immunotherapy, Radiotherapy

MA10 LONGER FOLLOW UP AND NEW IO COMBINATIONS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA10.09 Cemiplimab Plus Chemotherapy vs Chemotherapy in Advanced NSCLC: 5-Year Results from Phase3 EMPOWER-Lung 3 Part 2 Trial

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Introduction: EMPOWER-Lung 3 Part 2 (NCT03409614), a double-blind, placebo-controlled phase 3 study, demonstrated significant survival benefits with cemiplimab+chemotherapy versus chemotherapy in patients with previously untreated advanced NSCLC (aNSCLC) without EGFR/ALK/ROS1 aberrations. Cemiplimab is one of two checkpoint inhibitors with demonstrated efficacy in squamous and nonsquamous aNSCLC, both as monotherapy and with chemotherapy. Here, we report 5-year efficacy and safety outcomes.

Methods: Patients were randomized 2:1 to receive cemiplimab (350 mg every 3 weeks for up to 108 weeks) or placebo, plus 4 cycles of chemotherapy. Primary endpoint was overall survival (OS); secondary endpoints included safety, progression free survival (PFS), objective response rate (ORR), and duration of response (DOR). Patients were molecularly characterized via comprehensive genomic profiling of baseline tumor tissue or plasma.

Results: This study randomized 466 patients to cemiplimab+chemotherapy (n=312) or chemotherapy (n=154). After a median follow-up of 60.9 months, cemiplimab+chemotherapy continued to show significantly improved survival outcomes over chemotherapy. For cemiplimab+chemotherapy versus chemotherapy, respectively: median OS was 21.1 months versus 12.9 months (hazard ratio [HR]=0.662, 95% CI: 0.531-0.825, P=0.0002); median PFS was 8.2 months versus 5.5 months (HR=0.579, 95% CI: 0.467-0.718, P<0.0001); ORR was 43.6% versus 22.1%; and complete response was observed in 6.4% of patients (20/312) versus none, with median DORs of 16.4 and 7.3 months. Five-year OS probability was 19.4% (95% CI: 14.9-24.5%) for cemiplimab+chemotherapy versus 8.8% (4.8-14.4%) for chemotherapy. Efficacy was demonstrated in both histologies: for the squamous histology, median OS with cemiplimab+chemotherapy (n=133) was 22.3 months versus 13.8 months with chemotherapy (n=67; HR=0.678, 95% CI: 0.488-0.941); for non-squamous histology, median OS with cemiplimab+chemotherapy (n=179) was 19.4 months versus 12.4 months with chemotherapy (n=87; HR=0.615, 95% CI: 0.460-0.822). Among 327 (70.2%) patients with PD-L1 ≥1%, exploratory analyses showed median OS with cemiplimab+chemotherapy (n=217) was 24.0 months versus 12.1 months with chemotherapy (n=110; HR=0.537, 95% CI: 0.412-0.699). In total, 78% (362/466) of patients were mutation-evaluable; genomic profiling analysis indicated that the 3 most prevalent genes in the squamous group were TP53 (90%), CDKN2A (33%) and SOX2 (26%) and in the nonsquamous group TP53 (63%), KRAS (33%) and STK11 (24%). Of 312 patients in cemiplimab+chemotherapy arm, 66 (21.2%) completed protocol specified 2 years (108 weeks) of cemiplimab treatment and 5-year OS probability (including 2 years of treatment) for this subgroup was 56.0% (95%CI: 41.5-68.2). Grade ≥3 treatment-emergent adverse events occurred in 49.4% of patients receiving cemiplimab+chemotherapy and 32.7% receiving chemotherapy.

Conclusions: With 5-year follow-up, EMPOWER-Lung 3 continues to show durable long-term benefits with the use of cemiplimab+chemotherapy compared to chemotherapy as first-line therapy for aNSCLC. Safety profiles of cemiplimab+chemotherapy remained generally consistent with previously reported data.

Keywords: Non-small cell lung cancer, Cemiplimab, Immunotherapy

MA11 INNOVATIVE THERAPEUTIC STRATEGIES AND MOLECULAR INSIGHTS IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA11.01 Phase 1 Study of DLL3-Targeted CAR-T Cells Armored With dnTGFBR2 in Small-Cell Lung and Large-Cell Neuroendocrine Cancers

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Introduction: DLL3 is a validated target in small-cell lung cancer (SCLC) and high-grade neuroendocrine tumors. LB2102 comprises autologous DLL3-targeted CAR-T cells armored with dominant-negative TGFBR2, enabling them to overcome tumor-mediated immunosuppression. We present preliminary results from a phase 1 study of LB2102 as a one-time therapy in patients with relapsed or refractory SCLC or LCNEC.

Methods: This 3+3 dose-escalation study assesses safety, dose-limiting toxicities (DLTs), and efficacy of LB2102 across 7 dose-levels (0.3-16.0×10E6 CAR+T cells/kg) following fludarabine and cyclophosphamide lymphodepletion.

Results: As of March 5, 2025, of 17 enrolled patients, 12 (average 86% DLL3 expression at baseline) received LB2102 across 4 dose levels. Median age was 55 y (range, 20-68 y) with 2 median prior lines of therapy (range, 1-5). Ten patients had SCLC, 2 had LCNEC, and 11 received bridging therapy. Median time from apheresis to LB2102 was 87.0 days and follow up was 120.5 days. Seven patients experienced treatment (LB2102)-related adverse events (TRAEs) (2 Grade ≥3, see Table 1). Serious adverse events occurred in 5 patients after LB2102, 1 attributed to LB2102. Two patients developed Grade 1 cytokine-release syndrome. No DLTs or neurotoxicity were reported. Per RECIST1.1, median best overall change in tumor size was -19.1% (range across dose-levels, see Figure 1). Among 10 evaluable patients, the objective response rate was 20% and the disease-control rate was 70%. Pharmacokinetics suggest greater CAR-T expansion in peripheral blood at higher dose levels, with a median Cmax of 694 copies/µgDNA (range, 45.6-2260) and median Tmax of 15 days (range, 10-29) at dose level 3.

Conclusions: LB2102 was well tolerated, with no DLTs observed up to dose-level 4. A dose-dependent efficacy signal was observed; higher dose levels were associated with increased response rates, CAR-T expansion, and response duration. Evaluation at higher dose levels is warranted to assess LB2102's therapeutic potential.

Table 1: Summary of Adverse Events

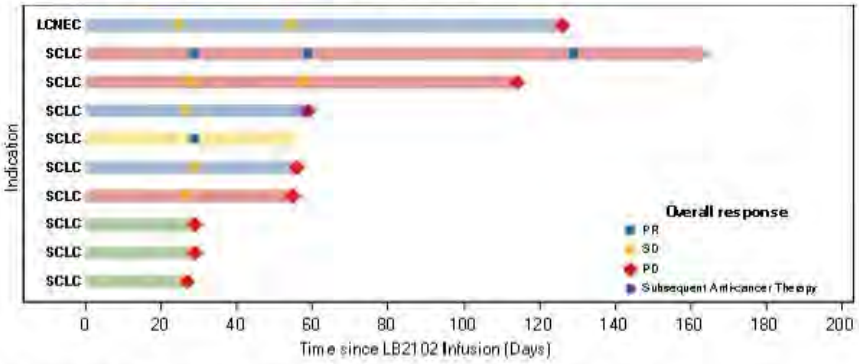
Dose levels	DL1 0.3×10⁶ CAR+T cells/kg (N=3) n (%)	DL2 1.0×10⁶ CAR+ T cells/kg (N=3) n (%)	DL3 2.0×10⁶ CAR+ T cells/kg (N=3) n (%)	DL4 4.0×10⁶ CAR+ T cells/kg (N=3) n (%)	Total (N=12) n (%)	
					Any Grade	Grade≥3
TEAE related to LB2102 (TRAE)	2 (66.7)	2 (66.7)	1 (33.3)	2 (66.7)	7 (58.3%)	2 (16.7)
Anemia	0	2 (66.7)	0	1 (33.3)	3 (25.0%)	2 (16.7)
CRS	0	0	1 (33.3)	1 (33.3)	2 (16.7%)	0
Hypotension	1 (33.3)	1 (33.3)	0	0	2 (16.7%)	0
Nausea	2 (66.7)	0 (0)	0	0	2 (16.7%)	0
Neutrophils/WBC decreased	0	2 (66.7)	0	0	2 (16.7%)	2 (16.7)
TRAEs resolved within 28 days of LB2102/total number of TRAEs (%)	1/3 (33.3%)	8/8 (100%)	2/2 (100%)	0/3 (0%)	11/16 (68.8%)	7/7 (100%)
Any serious TEAE	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	5 (41.7%)	3 (25.0)
Serious TRAEs	0	0	0	1 (33.3)	1 (8.33%)	0
CRS	0	0	0	1 (33.3)	1 (8.33%)	0
AESIs	0	0	0	0	0	0
Any DLT	0	0	0	0	0	0

AESI, adverse event of special interest (defined as CRS Grade ≥ 3, any-grade neurotoxicity, infection Grade ≥ 4, or new primary malignancy); CRS, cytokine release syndrome; DL, dose level; DLT, dose-limiting toxicity (defined as Grade ≥ 3 CRS, Grade ≥ 3 neurotoxicity, Grade ≥ 3 allergic reaction related to cell infusion, Grade 5 hematologic, or Grade ≥ 3 non-hematologic toxicity); TEAEs, treatment-emergent adverse events that started or worsened after LB2102 infusion; TRAEs, treatment-emergent adverse events deemed related to LB2102 infusion; WBC, white blood cell count

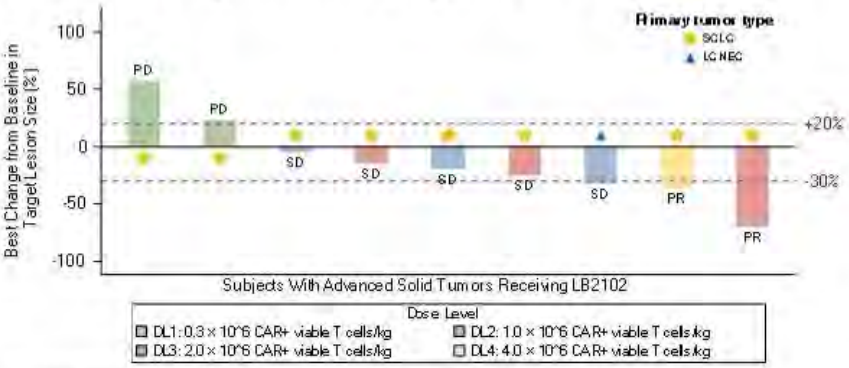
Notes: Percentages are based on the number of patients in the Safety Analysis Set (N) unless otherwise indicated. The number of patients (n) with at least 1 AE within each preferred term is presented. Only TRAEs in ≥ 2 overall patients are presented.

Figure 1: Summary of Responses and Durations

A. Response and Duration of Response by Indication



B. Best Percent Change from Baseline in Target-tumor Lesion Size



PD, progressive disease; PR, partial response; SD, stable disease

Notes: One patient who received DL1 had non-measurable disease prior to lymphodepleting chemotherapy; RECIST1.1 criteria data are pending for 2 patients.

Keywords: CAR T-cell therapy, SCLC LCNC, clinical trial phase 1

MA11.03 Tifcemalimab Plus Toripalimab and Chemotherapy as a First-Line Therapy in ES-SCLC: A Phase Ib/II Study

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Introduction: Tifcemalimab, a humanized IgG4 monoclonal antibody against B and T lymphocyte attenuator (BTLA), has shown preliminary anti-tumor activities in combination with toripalimab (anti-PD-1 antibody) as a later-line treatment for patients with lung cancer. We further conducted a multi-cohort phase Ib/II study (NCT05664971) to evaluate the safety and efficacy of tifcemalimab combined with toripalimab and chemotherapy in patients with advanced lung cancer. Here, we report the preliminary results from the extensive-stage small cell lung cancer (ES-SCLC) cohort.

Methods: Patients with ES-SCLC who had not received systemic anti-tumor therapy were administrated with tifcemalimab 200 mg in combination with toripalimab 240 mg and etoposide 100 mg/m2 plus carboplatin AUC 5 or cisplatin 75 mg/m2 intravenously every 3 weeks until disease progression, intolerable toxicity, or completion of 2-year of tifcemalimab and toripalimab. Primary endpoints included safety and objective response rate (ORR) assessed by investigators per RECIST v1.1.

Results: From Jul 12, 2023 to Dec 6, 2023, a total of 44 patients were enrolled with the median age being 63 (range 48-73) years and 84.1% (37/44) being male. The median follow-up duration was 15.28 months. Among 43 evaluable patients, 37 partial responses and 6 stable diseases were observed, the ORR and disease control rate were 86% and 100%, respectively. Median progression-free survival was 5.7 months (95% CI 4.8, 7.0). Median overall survival (OS) was not reached yet and the 15-month OS rate was 63.5%. Forty-three (97.7%) patients experienced treatment-emergent adverse events (TEAEs), grade ≥ 3 TEAEs occurred in 40 (90.9%) patients, and the most common (≥20%) grade ≥ 3 TEAEs included neutrophil count decreased (65.9%), white blood cell count decreased (25.0%), and platelet count decreased (25.0%). Three (6.8%) patients discontinued tifcemalimab due to TEAE. Twenty (45.5%) patients experienced immune-related AE (irAEs), among whom 7 (15.9%) reported grade 3 or higher irAEs. Serious adverse events occurred in 19 (43.2%) patients. TEAE leading to death occurred in 1 (2.3%) patient, which was not considered related to any treatment.

Conclusions: Tifcemalimab in combination with toripalimab and chemotherapy showed promising antitumor activities with a manageable safety profile as a first-line treatment for patients with ES-SCLC.

Keywords: Tifcemalimab, Toripalimab, ES-SCLC

MA11.04 Safety of Lurbinectedin + Atezolizumab as 1L Maintenance Treatment in ES-SCLC: Results From the Phase 3 IMforte Study

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Introduction: IMforte (NCT05091567) demonstrated significant and clinically meaningful improvements in independent review facility-assessed PFS (stratified HR, 0.54; 95% CI, 0.43-0.67) and OS (stratified HR, 0.73; 95% CI, 0.57-0.95) with lurbinectedin + atezolizumab vs atezolizumab for 1L maintenance treatment of ES-SCLC. The combination was generally well tolerated with a manageable safety profile. The incidence of all AE categories was higher in the experimental arm, which was not unexpected given the combination regimen and longer treatment exposure (median treatment duration: lurbinectedin + atezolizumab, ≈4.2 months; atezolizumab, 2.1 months). Notably, febrile neutropenia incidence was low (1.7%) in the combination arm with mandatory G-CSF prophylaxis. We present additional safety data on treatment discontinuations due to AEs and on neutropenia, further evaluating the tolerability of the combination.

Methods: Eligible patients with ES-SCLC without PD after 1L induction therapy with atezolizumab, carboplatin and etoposide were randomised 1:1 to receive maintenance treatment q3w with lurbinectedin 3.2 mg/m2 + atezolizumab 1200 mg (with G-CSF) or atezolizumab until PD, or unacceptable toxicity. Safety was assessed from start of maintenance treatment.

Results: Patients received lurbinectedin + atezolizumab (n=242) or atezolizumab (n=240; clinical cutoff: 29 July 2024). Overall, the safety profile of lurbinectedin + atezolizumab (median safety follow-up, 6.4 months) reflected the known risks of both drugs; no new safety signal was identified. In the lurbinectedin + atezolizumab arm, 12 (5.0%) and 6 patients (2.5%) discontinued lurbinectedin and atezolizumab, respectively, due to AEs; in the atezolizumab arm, AEs resulted in discontinuation in 8 patients (3.3%). The majority of treatment discontinuations due to AEs occurred within the first 3 months of treatment (Table). Most patients discontinued treatment due to PD (≳80% both arms). Rates of Grade 3/4 neutropenia were 4.5% with lurbinectedin + atezolizumab and 0.4% with atezolizumab; febrile neutropenia occurred in 1.7% (including 1 fatal event) and 0 patients, respectively. Fatal AEs occurred in 12 patients (5.0%) with lurbinectedin + atezolizumab and in 6 (2.5%) with atezolizumab.

Conclusions: Lurbinectedin + atezolizumab was generally well tolerated, with low rates of AE-related discontinuations, although higher than with atezolizumab. High-grade neutropenia and febrile neutropenia with lurbinectedin + atezolizumab occurred at lower rates than with previous clinical experience with lurbinectedin, possibly related to the primary G-CSF prophylaxis in IMforte. Although fatal AE rates were numerically higher with lurbinectedin + atezolizumab, no unexpected findings attributable to the combination regimen were identified. Overall, the combination demonstrated a manageable safety profile, with no new safety signals.

Table: AEs* resulting in discontinuation by duration

	Lurbinectedin + atezolizumab (n=242)		Atezolizumab (n=240)
Treatment duration	Lurbinectedin	Atezolizumab	Atezolizumab
Patients with AEs resulting in discontinuation, n	**12**	**6**	**8**
0 to ≤3 months, n (%)	10 (83.3)	3 (50.0)	3 (37.5)
Gastrointestinal haemorrhage	0	0	1
Nephropathy	1	1	0
Neuropathy peripheral	1	1	1
Pneumonia	0	0	1
Pneumonitis	0	1	0
Anaemia	2	0	0
Neutrophils decreased	2	0	0
Fatigue	1	0	0
Joint swelling	1	0	0
Malaise	1	0	0
Nausea	1	0	0
Peripheral swelling	1	0	0
Phlebitis	1	0	0
Platelets decreased	1	0	0
>3 to ≤6 months, n (%)	1 (8.3)	1 (16.7)	3 (37.5)
Dyspnoea	0	0	1
Immune-mediated nephritis	0	1	0
Lethargy	0	0	1
Pneumonitis	0	0	1
Psoriatic arthropathy	0	0	1
Phlebitis	1	0	0
>6 to ≤12 months, n (%)	1 (8.3)	2 (33.3)	2 (25.0)
Anaemia	0	1	0
Immune-mediated nephritis	0	1	0
Neutropenia	0	1	0
Peripheral motor neuropathy	0	0	1
Peripheral sensory neuropathy	0	0	1
Seizure	0	0	1
Thrombocytopenia	0	1	0
Trigeminal neuropathy	0	0	1
Neutrophils decreased	1	0	0
Platelets decreased	1	0	0
White blood cells decreased	1	0	0

Investigators could assign several AEs as leading to discontinuation. AEs, adverse events.

* Occurring on or after starting maintenance treatment.

Keywords: atezolizumab, lurbinectedin, ES-SCLC

MA11.05 Comparative Outcomes of Lobectomy and Sub-Lobar Resections in Pulmonary Carcinoids: A Multicentre Retrospective Cohort Study

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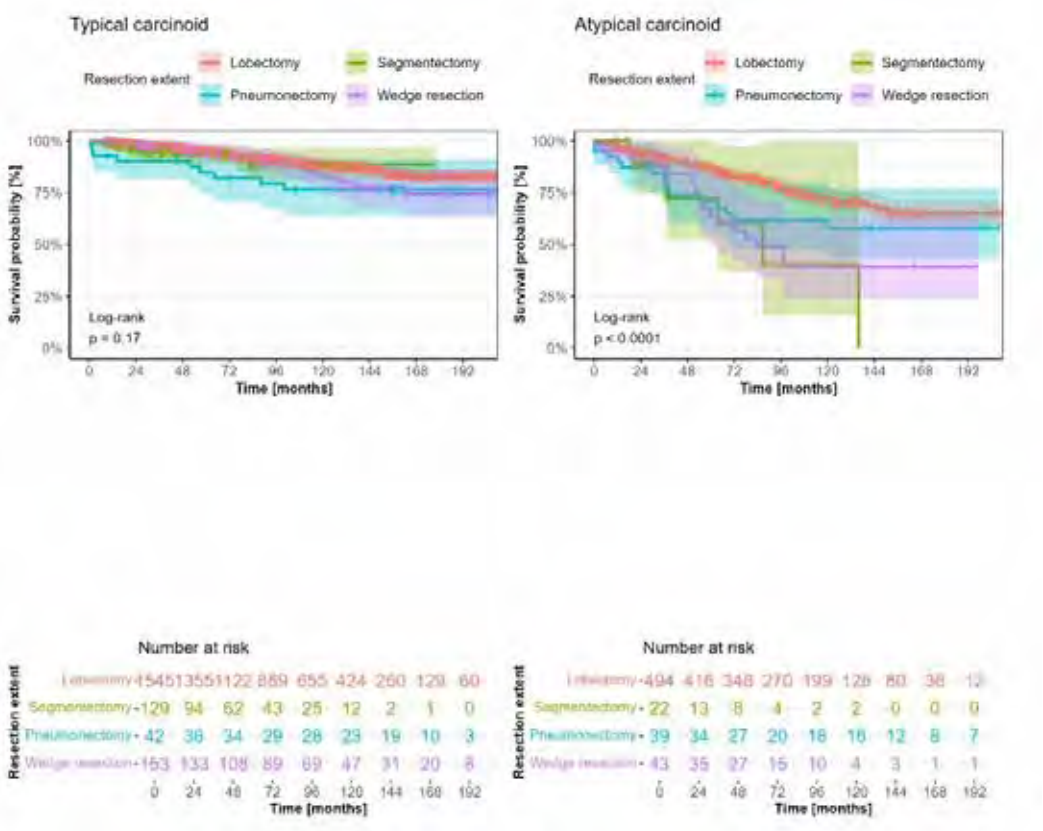
Introduction: Pulmonary carcinoids (PCs) represent a rare group of neuroendocrine tumors (NETs) occurring in the respiratory tract, distinguished by their specific biological features and clinical behavior. Despite the advancements in endobronchial therapies and immunochemotherapy, surgical resection remains the gold standard for first-line treatment. However, there is limited evidence comparing the outcomes of sub-lobar resections versus lobectomy.

Methods: The patient data was retrospectively obtained from the Polish Lung Cancer Study Group (PLCSG) database, which compiles records of surgically treated patients from nearly 30 thoracic centers throughout Poland. The study included those with typical or atypical carcinoids confirmed by histopathology who underwent radical surgical resection between 2007 and 2023 and had complete clinical data available.

Results: The study included 2467 patients. The majority were female (69.8% vs. 30.2%) and non-smokers (62.3% vs. 37.7%), with a median age of 61 years. Typical carcinoids were significantly more prevalent than atypical (75.8% vs. 24.2%). All of the patients were staged according to the 9th edition of the tumor-metastases-nodes (TNM) staging, and the most common stages were IA and IB, with 67.4% and 18.9%, respectively. The T stages were assessed, and stages pT1 (71.4%) and pT2 (22.1%) were substantially the most frequent. In the majority of the patients, lymph node involvement was absent (91.3% vs 8.7%), and among those with involvement (8.7%), stage pN1 was the most common (5.5%). Metastases were acknowledged only in 1.2%, and all of the patients were stage M1. The surgical treatment included lobectomy, wedge resection, segmentectomy, and pneumonectomy, with respective distributions of 82.7%, 7.9%, 6.1%, and 3.3%. The 5-year overall survival rates (OSR) were evaluated across the entire study population and were 93.1% (95% CI: 94.32-91.92) for lobectomy, 90.4% (95% CI: 96.13-85.00) for segmentectomy, 87.6% (95% CI: 93.06-82.49) for wedge resection, and 78.2% (95% CI: 87.95-69.50) for pneumonectomy. When the study cohort was divided into typical and atypical carcinoids, lobectomy and segmentectomy showed the highest overall survival rates in the atypical group with 86.8% and 72.4%, respectively (p<0.0001). In contrast, among patients with typical carcinoids, there were no statistically significant differences in overall survival rates between sub-lobar resections and lobectomy.

Conclusions: This retrospective multicenter study compares the efficacy of lobectomy and sub-lobar resections in the treatment of pulmonary carcinoids. The results demonstrate the superiority of lobectomy over segmentectomy, showing better 5-year OSR in the atypical carcinoid subgroup.



Keywords: Pulmonary Carcinoid, Lobectomy, Sub-Lobar Resection

MA11.06 Multiomic Profiling of Inter-Lesion Heterogeneity in Small Cell Lung Cancer: A Multicenter Rapid Research Autopsy Program

Z. Megyesfalvi[1,2,3], S. Heeke[4], L. Horvath[3], J. Gil[5], B. Szeitz[3], B.B. Morris[4], B. Ferencz[3], I. Kovacs[3], V. Teglas[2,3], J. Fillinger[2,3], M. Pozonec[2,3], S. Torok[3], E. Tatrai[3], K. Boettiger[1], B. Ernhofer[1], K. Bogos[3], M. Malumbres[6,7,8], F. Renyi-Vamos[2,3], C. Aigner[1], K. Schelch[1], C.M. Gay[4], J. Zhang[4], L.A. Byers[4], L. Paz-Ares[8,9], P. Van Loo[4], G. Marko-Varga[5], J.V. Heymach[4], B. Dome[1,2,3,5]
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Introduction: To gain insights into the evolutionary processes of small cell lung cancer (SCLC), it is important to analyze the primary tumor and multiple metastatic lesions in different organs from the same patient. This is particularly relevant, as therapeutic resistance may be associated with increased tumor heterogeneity and subtype plasticity. Nevertheless, acquiring representative tumor tissue specimens remains difficult in SCLC, and performing multiple biopsies is invasive and often clinically impractical. Here, we investigated inter-lesion SCLC heterogeneity and plasticity with regard to protein expression landscape and molecular subtypes, identifying stably expressed therapeutic targets across distinct metastatic sites.

Methods: Representative tissue samples from primary tumors, metastatic lesions, and corresponding non-tumorous control samples, were obtained through our multicenter SCLC rapid research autopsy (RRA) program. All RRAs were conducted within four hours of the patient's death by a dedicated multidisciplinary team. The number of tumorous specimens retrieved from distinct sites per a single patient ranged from 6 to 14. Multiomic profiling of the acquired fresh, snap-frozen, and formalin-fixed specimens was achieved by mass spectrometry (MS)-based proteomics (nLC-MS/MS), RNAseq (KAPA Hyper RNA with Riboerase) and immunohistochemistry (IHC). Specific pathways linked to tumor content differences were analyzed, confirming the histological pattern of the samples. Biostatistical and bioinformatics approaches were applied to evaluate inter-lesion tumor heterogeneity and to identify differentially and stably expressed molecules, as well as metastasis site-specific alterations.

Results: We collected 194 tumor specimens and 60 matched non-tumorous controls from 23 SCLC patients. Tumor sites included lung, brain, brainstem, cerebellum, liver, adrenal glands, peritoneum, pleura, pericardium, skin, spleen, and lymph nodes. On average, 19354 transcripts (TPM>0) and 7786 protein groups were quantified per sample. In general, clinically relevant SCLC-related proteins and therapeutic targets exhibited a moderate to high degree of inter-lesion heterogeneity. Subsequent IHC analyses validated the observed high inter-lesion proteomic heterogeneity. We identified 27 stably expressed novel therapeutic targets showing tumor-specificity (adj.p<0.05 & FC>1.5) and a low degree of inter-lesion variability (pooled MAD < 15%) in their expression pattern. Besides SCLC-A, -N, -AN, -P, and -QN, IHC analyses distinguished a unique subtype with high ASCL1 expression and an inflamed phenotype (SCLC-A-inflamed). In 85% of the examined patients, the dominant molecular subtype differed across metastatic sites, as per IHC. Notably, significant subtype intra-tumoral heterogeneity (intralesion spatial sectioning distance: 40 µm) was identified in 59% of examined cases.

Conclusions: Several known clinically relevant proteins and therapeutic targets have heterogeneous expression profiles across tumor sites within a SCLC patient. Molecular subtypes show both intratumoral and inter-lesion variability. The newly identified stably expressed proteins are potential novel therapeutic targets that warrant further therapeutic validation.

Keywords: small cell lung cancer, tumor heterogeneity, therapeutic targets

MA11 INNOVATIVE THERAPEUTIC STRATEGIES AND MOLECULAR INSIGHTS IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA11.08 Longitudinal Circulating Tumor DNA Dynamics Predict Therapeutic Efficacy in ES-SCLC Treated With Immunotherapy

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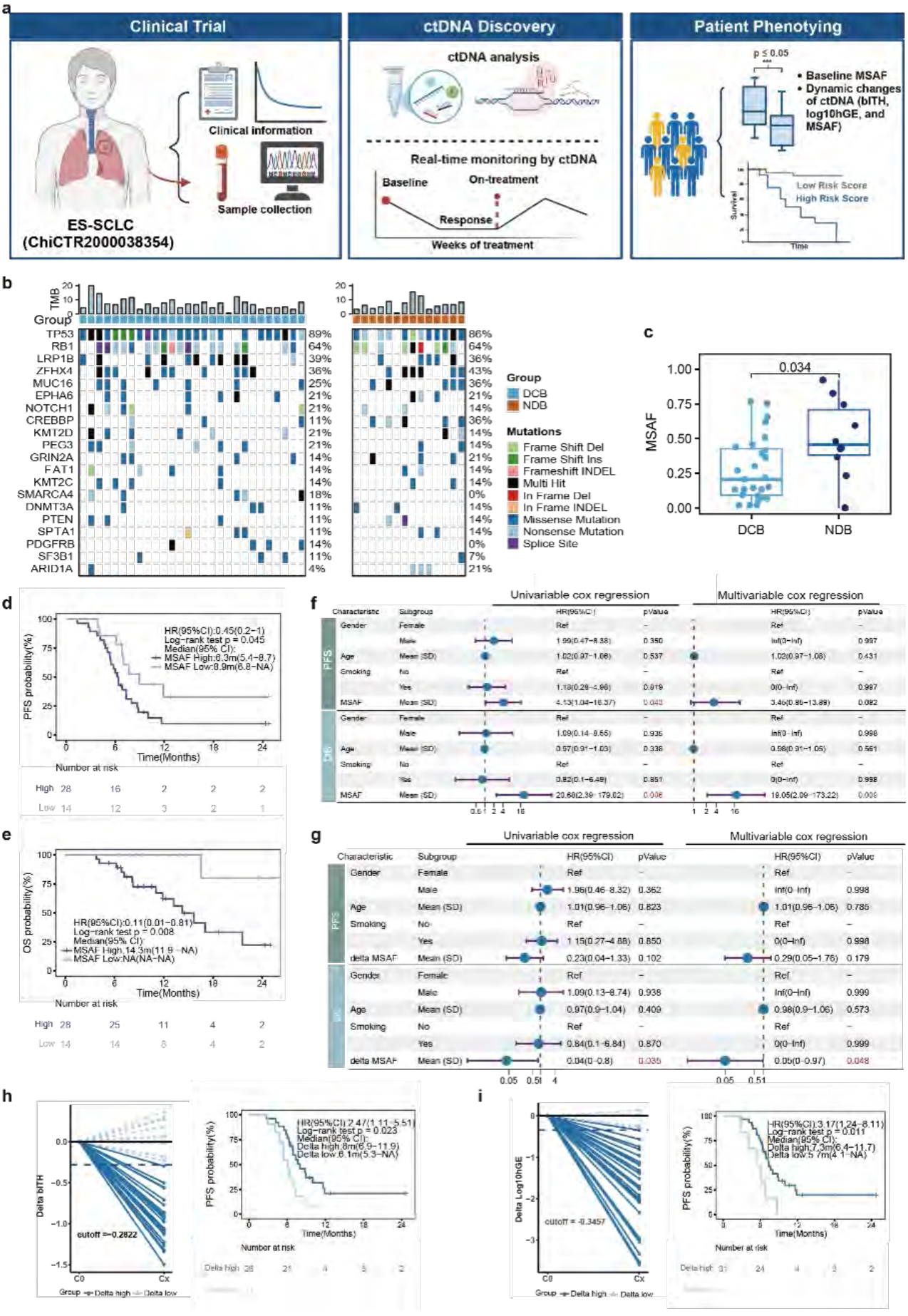
Introduction: While immune checkpoint inhibitors (ICIs) combined with platinum-etoposide chemotherapy improve outcomes in extensive-stage small-cell lung cancer (ES-SCLC), the prognostic role of longitudinal circulating tumor DNA (ctDNA) dynamics remains underexplored. This phase II trial investigates ctDNA's association with therapeutic response.

Methods: In this single-arm prospective study (ChiCTR2000038354), treatment-naïve ES-SCLC patients received sintilimab plus chemotherapy. Serial plasma samples were collected for ctDNA analysis using next-generation sequencing. Maximum somatic allele frequency (MSAF), blood intratumor heterogeneity (bITH), and log10-transformed haploid genome equivalents/mL (log10hGE) were correlated with progression-free survival (PFS) and overall survival (OS).

Results: This study included 43 patients who were evaluable for treatment response, with 42 baseline blood samples and 37 longitudinal on-treatment blood samples collected. Patients were stratified into durable clinical benefit (DCB) and non-durable benefit (NDB) groups based on PFS exceeding 6 months. The NDB group demonstrated higher maximum somatic allele frequency (MSAF). Patients with lower baseline MSAF demonstrated significantly improved progression-free survival (PFS: HR=0.45, 95%CI 0.2-1, p=0.045) and overall survival (OS: HR=0.11, 95%CI 0.01-0.81, p=0.008). Univariate and Multivariate Cox regression confirmed baseline MSAF as an independent prognostic factor for both PFS and OS. Longitudinal analysis revealed dynamic ctDNA changes predictive of therapeutic outcomes: ΔMSAF independently correlated with OS in multivariate analysis (HR=0.05, 95%CI 0-0.97, p=0.048). Post-treatment reductions in blood intratumor heterogeneity (ΔbITH) and log10-transformed haploid genome equivalents/mL (Δlog10hGE) further stratified clinical outcomes. Patients with greater ΔbITH reduction showed extended PFS (8 vs 6.1 months; HR=2.47, p=0.023), and those with higher Δlog10hGE decreases achieved longer PFS (7.3 vs 5.7 months; HR=3.17, p=0.011). Both bITH and log10hGE metrics exhibited progressive decline during treatment, mirroring therapeutic response.

Conclusions: This study identifies ctDNA dynamics as pivotal biomarkers for sintilimab-chemotherapy in ES-SCLC. Baseline MSAF independently predicts survival, with lower values indicating superior PFS and OS. Early reductions in ΔMSAF, ΔbITH, and Δlog10hGE stratify therapeutic response, while progressive declines in bITH and ctDNA load (log10hGE) reflect clinical benefit. Our results bridge ctDNA dynamics with clinical outcomes, offering a non-invasive approach to optimize SCLC immunotherapy management. Randomized trials are needed to validate these biomarkers' utility.



Keywords: Small cell lung cancer, Immunotherapy, ctDNA

MA11 INNOVATIVE THERAPEUTIC STRATEGIES AND MOLECULAR INSIGHTS IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA11.09 Circulating Tumor DNA Refines Consolidation Immunotherapy for Limited-Stage SCLC

N. Bi[1], Y. Yang[1], Y. Wu[1], J. Zhao[1], X. Zhao[2], Z. Wang[1], L. Wang[3]
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This abstract is under embargo until September 9 at 10:15 CET.

MA11 INNOVATIVE THERAPEUTIC STRATEGIES AND MOLECULAR INSIGHTS IN SCLC AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 13:00 - 14:15

MA11.10 IFITM3 Enhances Immunotherapy Sensitivity Through MHC-I Regulation in Small Cell Lung Cancer

Y. Cui[1], S. Ren[1], H. Zhang[2], T. Qiu[1], J. Wang[1], X. Liu[1], L. Luo[1], C. Wu[1], Z. Zhao[1]
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This abstract is under embargo until September 9 at 13:00 CET.

04 | POSTER TOUR

PT1.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.01.01 Large Language Models to Extract Smoking History From Clinical Notes in EHR to Evaluate Lung Cancer Surveillance Strategies

I. Luo[1], A. Graber-Naidich[1], R. Kaushik[1], G.M. Nieda[1], E. Choi[2], V.Y. Ding[1], F. Gunturkun[1], M. Satoyoshi[1], A. Bhat[1], T. Chen[3], M. Zhang[1], T. Lee[1], C.C. Su[1], T.J. Ellis-Caleo[1], A.S. Henry[1], M. Desai[1], L.M. Backhus[1], N.S. Lui[1], A. Leung[1], J.W. Neal[1], A.W. Kurian[1], C.P. Langlotz[1], H.A. Wakelee[1], S-Y. Liang[3], A. Kahn[4], S.S. Han[1]
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Introduction: Accurate smoking documentation in electronic health records (EHRs) is essential for lung cancer (LC) risk assessment, screening, and monitoring. However, smoking data are often missing or inconsistently recorded due to recall bias and reporting errors. Large language models (LLMs) offer a promising solution for interpreting clinical narratives, yet their effectiveness in extracting detailed smoking data remains unexplored. This study aimed to develop a framework leveraging LLMs and rule-based smoothing to extract and harmonize longitudinal smoking data, with applications in LC surveillance.

Methods: We evaluated three generative AI models (Gemini-1.5-Flash, PaLM-2 Text-Bison, GPT-4) against encoder-based models (ClinicalBERT, BlueBERT) using 1,683 manually-annotated clinical notes from 500 patients across academic (Stanford) and community (Sutter Health) healthcare systems. Models extracted seven smoking variables, including status, duration, quit date, and pack-years. To curate comprehensive longitudinal smoking data, the best-performing model (Gemini-1.5-Flash) was deployed on an independent set of 80,037 notes from 4,988 Stanford LC patients. Rule-based smoothing integrated the AI-extracted variables with structured EHRs. We assessed the clinical utility of the curated smoking data by evaluating various post-diagnosis surveillance strategies in these patients.

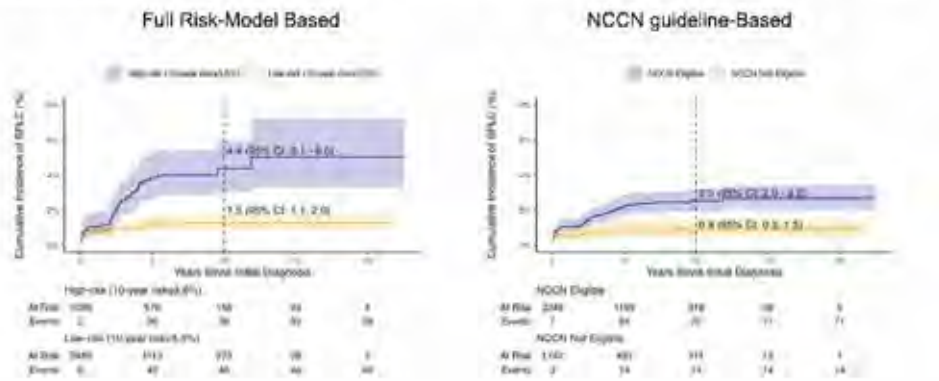
Results: Generative AI models outperformed encoder models in extracting smoking status from notes (accuracy on hold-out set: 95.6%-97.5% vs. 69.5%-74.2%). Among generative models, Gemini-1.5-Flash achieved the highest average accuracy across 7 variables (Table-1), ranging from 94.1% for packs-per-day to 99.6% for cessation-age. External validation (500 notes) in Sutter confirmed Gemini-1.5-Flash's generalizability with 98.3% average accuracy across variables. Analysis of the curated smoking data showed that a comprehensive risk-model-based surveillance strategy utilizing both smoking and clinical data outperformed NCCN guidelines based solely on clinical data in identifying second malignancies (Figure-1).

Conclusions: This study highlights the potential of generative AI to improve the quality and utility of smoking documentation in EHRs, facilitating evaluation of effective LC surveillance and broader clinical applications.

Table-1. Comparative performance of three generative AI models for smoking variable extraction using Stanford hold-out test set (236 notes) and Sutter Health external validation cohort (500 notes). Shading represents relative model performance: green for high accuracy, white for moderate, and red for low.

	Model	Overall	Smoking Status	Duration	Age at cessation	Year of cessation	Years since cessation	Pack year	Pack per day
Stanford	Gemini 1.5 Flash	96.5%	95.6%	94.9%	99.6%	97.9%	95.4%	97.9%	94.1%
	GPT-4	96.1%	97.5%	93.2%	97.9%	96.9%	92.4%	96.3%	97.0%
	PaLM 2 Text Bison	88.9%	96.6%	84.0%	78.9%	87.8%	83.2%	86.9%	92.4%
Sutter Health	Gemini 1.5 Flash	98.3%	98.9%	97.6%	100.0%	99.6%	94.0%	98.4%	99.6%
	GPT-4	98.8%	97.2%	99.2%	99.2%	99.0%	98.6%	98.8%	99.2%
	PaLM 2 Text Bison	97.9%	98.4%	92.6%	98.8%	99.2%	98.4%	97.8%	99.0%

Figure-1. Comparison of Post-Diagnosis Surveillance Strategies for Second Primary Lung Cancer (SPLC) in LC patients: risk model-based vs. NCCN guidelines. The risk model includes smoking history, tumor characteristics (histology, stage), treatment, and past history of cancer, and NCCN guidelines are based on histology, stage, and treatment.



Keywords: Smoking, Large Language Models, Post-Treatment Surveillance

PT1.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.01.02 Temporal Analysis of Smoking Profiles in Brazil Among Lung Cancer Patients and the Impact of 25 Years of Public Policies

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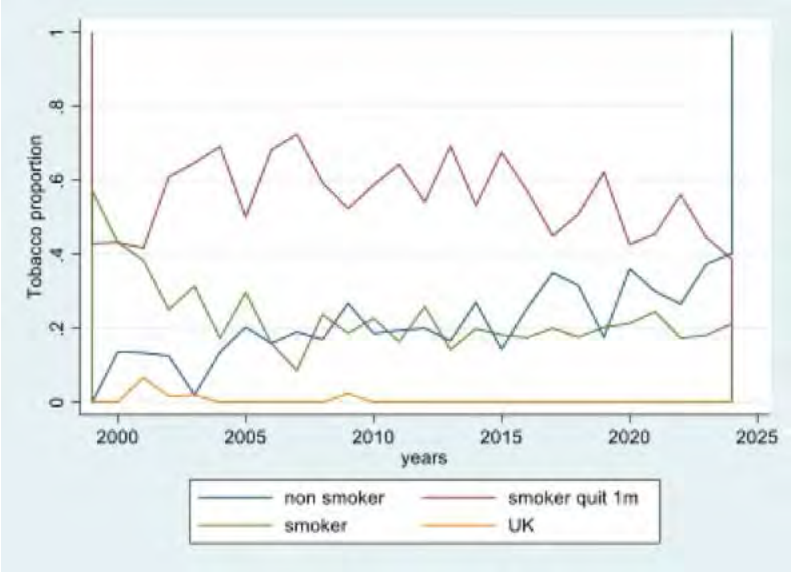
Introduction: Smoking is the main risk factor for lung cancer. Studies indicate that if the current pattern of tobacco consumption in Brazil persists, lung cancer cases are expected to increase by 65% and mortality by 74% by 2040. Over the past 40 years, Brazil has invested in public policies aimed at smoking cessation. This study aims to analyze temporal changes in the Brazilian smoking profile over the past 25 years and the impact of public measures implemented in the last 40 years.

Methods: This is a retrospective cohort study of 2,488 lung cancer patients from three hospital institutions in São Paulo, between 1999 and 2024. Variables analyzed included sex and smoking status. Statistical tests were applied according to data type and distribution (Wilcoxon, Shapiro-Wilk, Kruskal-Wallis, chi-square, and Cochran-Armitage trend tests).

Results: In 1999, the probability of having lung cancer and being an active smoker was 50.91%, decreasing to 20% in 2016 and 12.33% in 2024. The probability of a person having lung cancer and being a non-smoker increased from 6.34% (1999) to 34.24% in 2024. There was a gradual increase, with significant jumps in the years 2004 (19.82%), 2007 (26.52%), 2020 (30.57%), 2023 (33.45%), and 2024 (34.24%), with a peak in smoking cessation observed in 2006 (57.11%). The probability of having lung cancer and being a former smoker rose from 41.25% (1999) to 53.24% (2024). The percentage of active smokers among lung cancer patients was similar between sexes (21.30% in men vs. 20.19% in women). However, among non-smokers, females predominated (37.32% vs. 12.88% in men). Among those who quit smoking after diagnosis, men were the majority (65.32%). The distribution of smoking status between sexes was statistically different ($p < 0.0001$), indicating that smoking patterns vary between men and women. In 1999, the probability of being a non-smoking man with lung cancer was only 2.78% ($p = 0.03$). In 2024, this probability increased to 28.10% ($p = 0.001$). In women, this trend was not statistically significant.

Conclusions: Among lung cancer patients, there has been a decrease in the number of active smokers over time. The probability of being a lung cancer patient who does not smoke has increased. There has also been an increase in the likelihood of quitting smoking after diagnosis.

Women with lung cancer tend to be non-smokers more often than men. However, among smokers, men are more likely to quit smoking after diagnosis than women.



Keywords: tobacco trends, tobacco Brazil, lund cancer and tobacco

PT1.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.01.03 IMPRINT-Lung: Single-Arm, Multi-Center Phase II Trial of Immunotherapy With Pembrolizumab for Interception of High-Risk Lung Nodules

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Introduction: The widespread implementation of lung cancer screening and the advent of high-resolution CT for diagnostic imaging have led to a significant increase in the detection of indeterminate pulmonary nodules (IPNs). If persistent, many of these IPNs are lung cancer precursors. While some IPNs can be resected with minimal morbidity, the cost-effectiveness and necessity of surgical resection remain subjects of debate. Additionally, multifocality is a common occurrence, further complicating surgical management. Previous studies have demonstrated that lung cancer precursors exhibit a simpler molecular landscape and a more intact immune response than invasive lung cancer. Furthermore, adaptive immune evasion—such as PD-L1 upregulation—emerges at the precursor stage. These findings led to the development of the IMPRINT-Lung trial, a single-arm, multi-center phase II study evaluating anti-PD-1 pembrolizumab for the interception of high-risk lung nodules.

Methods: Patients with persistent high-risk pulmonary nodules—defined as nodules that show no evidence of regression on at least two CT scans taken three months apart, with a predicted malignancy risk >10% based on the Brock model for those without a personal history of lung cancer, or >5% for those with localized lung cancer who have completed standard-of-care therapy—are eligible to receive pembrolizumab at a dose of 200 mg intravenously every three weeks for up to four doses. CT scans are performed at 6 weeks, 12 weeks, and 6 months to assess treatment response. The primary endpoint is therapeutic outcomes at 6 months post-pembrolizumab treatment, evaluated using modified RECIST (mRECIST) criteria, which account for both solid and ground-glass opacity components. Additionally, radiologic images undergo 3D volumetric analysis, and peripheral blood samples collected at baseline (prior to treatment initiation), 3 weeks, and 6 months after the first dose of pembrolizumab undergo T cell receptor (TCR) sequencing, cytokine profiling, single-cell RNA sequencing (scRNA-seq), and plasma cell-free DNA (cfDNA) methylation profiling using the TEEM-seq methodology.

Results: A total of 40 patients received at least one dose of pembrolizumab and all patients have completed 6 months follow up. The treatment was generally well tolerated. Two patients experienced Grade 3 toxicities unrelated to pembrolizumab (retinal detachment, n=1; hypertension, n=1), while three patients developed Grade 2 toxicities that were either possibly related or related to pembrolizumab (pruritus, n=1; hypothyroidism, n=2). All remaining toxicities were Grade 1. At the 6-month post-treatment time point, 36 patients were evaluable. Two patients had progressive disease due to the emergence of new pulmonary nodules. Among the remaining 34 patients, only one met the criteria for partial response (-34% from baseline) per mRECIST criteria. However, 18 patients exhibited some degree of lung nodule shrinkage, with a median reduction of -3% and an average reduction of -5%. Notably, all 40 patients had experienced nodule enlargement before pembrolizumab treatment. Radiomics analysis and peripheral blood biomarker profiling are currently ongoing.

Conclusions: Pembrolizumab has demonstrated a favorable safety profile and preliminary evidence of efficacy in treating patients with persistent high-risk lung nodules. Intercepting precancerous high-risk lung nodules by reprogramming the tumor immune microenvironment remains a promising strategy for lung cancer prevention.

Keywords: Precancer, Interception, Immunotherapy

PT1.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.02.01 Targeting NOX1/4-YAP/TEAD-CD47 Axis Promotes Macrophage Phagocytosis and Potentiates Radiotherapy Antitumor Efficacy in NSCLC

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Introduction: Radiotherapy, as a crucial treatment style of non-small cell lung cancer (NSCLC), could lead to form immunosuppressive microenvironment by regulating the expression of immune molecules, such as phagocytosis checkpoints. Anti-phagocytosis checkpoint CD47 universally expresses on tumor cells. Although anti-CD47 treatment is a promising immunotherapy manner, the treatment has serious blood toxicity because that normal blood cells also express CD47. Therefore, targeting specially CD47 on tumor cells without on normal blood cells can promote phagocytosis function of macrophages and enhance radiosensitivity.

Methods: A drug array was used to recognize compounds that can suppress radiotherapy-induced CD47 expression in NSCLC via flow cytometry assay. THP-1-derived macrophages were co-cultured with lung tumor cells treated with NOX1/NOX4 inhibitor (GKT137831, GKT). The tumor-bearing mouse models were treated with GKT and radiotherapy to further analysis tumor environment by flow cytometry.

Results: Radiotherapy increases CD47 expression on lung cancer cells by radiation dose and time dependent style. The drug screenings identified NOX1/NOX4 inhibitor GKT137831 could inhibit baseline expression of CD47 and radiation-induced CD47 upregulation in NSCLC. Knockdown of NOX1 and NOX4 respectively could downregulate CD47. Moreover, both knockdown of NOX1 and NOX4 has the strongest inhibition effect. The co-culture experiment suggested that GKT could promote macrophages to phagocytose lung cancer cells and also enhanced radiotherapy-induced phagocytic impairment. The mechanism analysis of RNA-seq data revealed that tumor cells treated with GKT is associated with YAP1/TEAD4 hippo signal pathway to inhibit CD47 expression. In mouse models, GKT enhance radiosensitivity through a macrophages-dependent mechanism without increasing blood toxicities.

Conclusions: This study unveils a novel mechanism which regulates basal CD47 expression and radiotherapy-induced CD47 upregulation in tumor cells. Targeting NOX1/NOX4-YAP1/TEAD4 signaling could suppress CD47 expression, resulting in promoting phagocytosis function of macrophages without blood toxicity and improving the anti-tumor efficacy of radiotherapy in NSCLC.

Keywords: CD47, Radiotherapy, NSCLC

PT1.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.02.02 Novel Organoid Models of Patient-Derived Lung Cancer in Decellularized Mouse Lung Tissue

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Introduction: The extracellular matrix (ECM) plays a crucial role in cancer biology, including tumor progression and response to therapeutics. Current organoid models mostly rely on Matrigel, a mouse tumor cell-derived matrix, which may not accurately represent the ECM of patient tumors. Therefore, there is a strong rationale for developing additional three-dimensional (3D) ex vivo models for cancer research. This study focuses on developing such a model for lung cancer research using decellularized lungs from normal mice (DCL).

Methods: Cellular compartments of C57/Bl6 mouse lungs were removed through a decellularization procedure. To model different experimental scenarios, we generated four distinct decellularized lung models by seeding: (1) established lung (A549) and breast (MCF7, MDA-MB231) cancer cell lines (CL); (2) total and EpCAM sorted cell population isolated from patient-derived xenografts (PDX) (XDC); (3) organoids established from PDX models (XDO); and (4) total cell population obtained from resected primary lung cancer tumors (PLC). Seeded DCL samples were maintained in culture for 30 days. Tumor growth was represented by 2-dimensional (D) surface coverage area of DCL sections measured by the HALO software (Indica Labs, Albuquerque, NM). Tumor cells were labeled with mCherry to quantify growth rates. To compare XDC models with their corresponding PDX tumors, RNA sequencing data was analyzed alongside proteomics data from 18 PDX models to identify target genes and proteins associated with successful growth in XDC model.

Results: Tumor cell establishment rates in DCL models were: 100% (4/4) for CL, XDC (EpCAM sorted cells) and XDO groups, 57% (16/28) for XDC (total cells), and 18.7% (6/32) for PLC. Growth analysis of two non-small cell lung cancer (NSCLC) XDO models expressing mCherry (XDO344mCh and XDO377mCh) demonstrated significant proliferation over 30 days ($P = 0.006$ and $P = 0.0018$, respectively). Histological analysis of successful models revealed ECM deposition, with new eosinophilic collagen-like material in DCL, suggesting new ECM production by tumor cells. Growth rates were highest in CL, XDC (EpCAM sorted cells) and XDO models, likely due to the purity of tumor cells derived from cell lines and PDX tumors, as well as reduced abundance of non-tumor cell populations. We also used the XDC137 (EpCAM sorted cells) model generated from PHLC137 lung PDX with EGFR exon 19 deletion to investigate drug response. The tumor cells in the 3D-XDC model recapitulated the corresponding PDX137's sensitivity to EGFR tyrosine kinase inhibitors. Ongoing studies aim to identify XDC derived proteins to elucidate their roles in tumor growth within DCL models.

Conclusions: Decellularized mouse lung tissue provides a microenvironment that supports the growth of primary NSCLC cells in 3D matrix as scaffold. This new platform may complement existing organoid platform to study lung cancer in matrix stroma that more closely mimic the patient tumors.

Keywords: Extracellular matrix, decellularized mouse lung, ex-vivo model

PT1.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.02.03 GBC-11004: An AI-Driven Novel Kinase Target With Potential to Overcome Osimertinib Resistance in NSCLC

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Introduction: Osimertinib resistance in non-small cell lung cancer (NSCLC) presents a significant clinical challenge, driven by a variety of mechanisms that complicate patient outcomes. Conventional next-generation sequencing (NGS) analysis methods often fall short in identifying effective therapeutic targets due to the complexity and heterogeneity of resistance mechanisms.

Methods: We have developed an artificial intelligence (AI)-driven target discovery platform designed to identify novel and effective drug target genes capable of overcoming Osimertinib resistance in NSCLC, surpassing the constraints of conventional NGS analysis. This platform integrates three key components: deep learning (G-TAC), statistical significance testing (G-SET), and a large language model (G-LAT). G-TAC and G-SET work together to identify and stratify genes based on their responsiveness to Osimertinib and tumor-specific expression profiles. G-LAT assesses these genes based on publications and clinical trials to ensure novelty and efficacy of the identified targets.

Results: A novel kinase target, designated GBC-11004, emerged as one of the top-ranked candidates, exhibiting overexpression in patient-derived organoids (PDOs) resistant to Osimertinib. To assess the functional relevance of GBC-11004, target validation was conducted using PDOs and CRISPR/Cas9-based gene editing. Gene editing in Osimertinib-resistant PDOs resulted in a significant reduction in cell viability, which correlated with an increased indel frequency. Furthermore, preliminary IC50 analyses of compounds targeting GBC-11004 were performed to optimize lead compounds. Notably, combination therapy (Osimertinib + GBC-11004 inhibitor) demonstrated significantly improved sensitivity compared to Osimertinib monotherapy in multiple resistant PDO models.

Conclusions: These findings highlight the potential of GBC-11004 as a novel therapeutic target for overcoming Osimertinib resistance in NSCLC, reinforcing the robustness of the PDO-based AI-driven platform for target discovery in identifying high-priority, novel therapeutic targets.

Keywords: Osimertinib, NSCLC, Target discovery

PT1.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.02.04 Mapping Gene-Environment Interactions Driving Small Cell Lung Cancer (SCLC) Initiation in Human Airway Organoids

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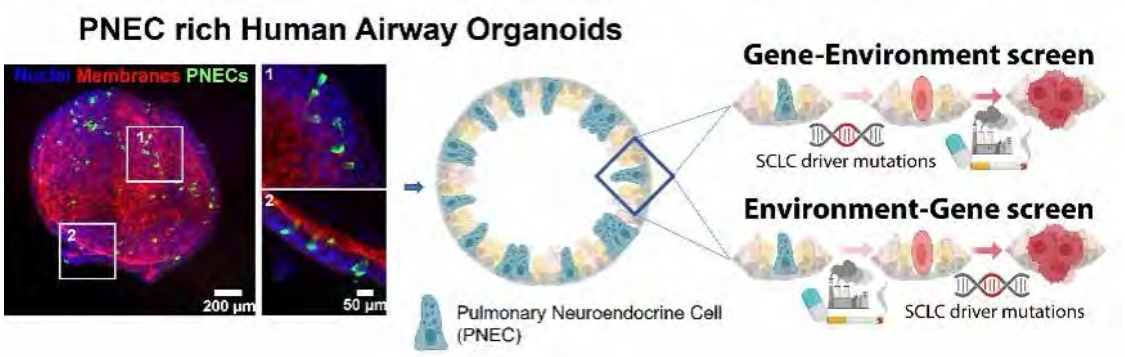
[1]EMBL, Barcelona/ES ,[2]Columbia University Biomedical Engineering, New York/NY/USA

Introduction: Small cell lung cancer (SCLC) accounts for up to 15% of all lung cancers and is the most fatal type, with a 5-year overall survival of ~6%. SCLC's etiology involves genetic alterations, such as the near-universal loss of TP53 and RB1, and environmental exposures like smoking or air pollution. Patients with SCLC often present with metastasized disease, preventing the use of human samples to study the early stages of the disease. Therefore, it is not well understood how genetic and environmental factors can drive the malignant transformation of pulmonary neuroendocrine cells (PNECs) into poorly differentiated cells with fast growth and rapid metastatic spread.

Methods: To overcome the lack of human models of SCLC initiation, we developed a novel airway organoid model that, for the first time, supports the culture of human airway cells alongside PNECs. Multicellular complexity of the organoids was characterised by scRNA-seq. Additionally, we established protocols for genetically engineering organoids with SCLC driver mutations and for quantitative imaging of the PNEC population.

Results: Our methods provide a versatile platform to monitor wildtype and mutant PNECs in response to various environmental cancer risk factors added to the organoid culture. We plan to screen for environmental carcinogens that induce malignant transformation of PNECs within these organoids.

Conclusions: On balance, our goal is to establish the first human model of lung neuroendocrine cancer initiation that integrates both genetic and environmental drivers. The models and experimental protocols we generate will offer a valuable toolkit for elucidating the mechanisms underlying the pathogenesis of lung neuroendocrine cancers and will help identify novel strategies for early detection and treatment



Keywords: SCLC Initiation, Human Airway Organoids, Genetic and Environmental Cancer Risk Factors

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.01 Precision Medicine Platform to Guide the Treatment of NSCLC

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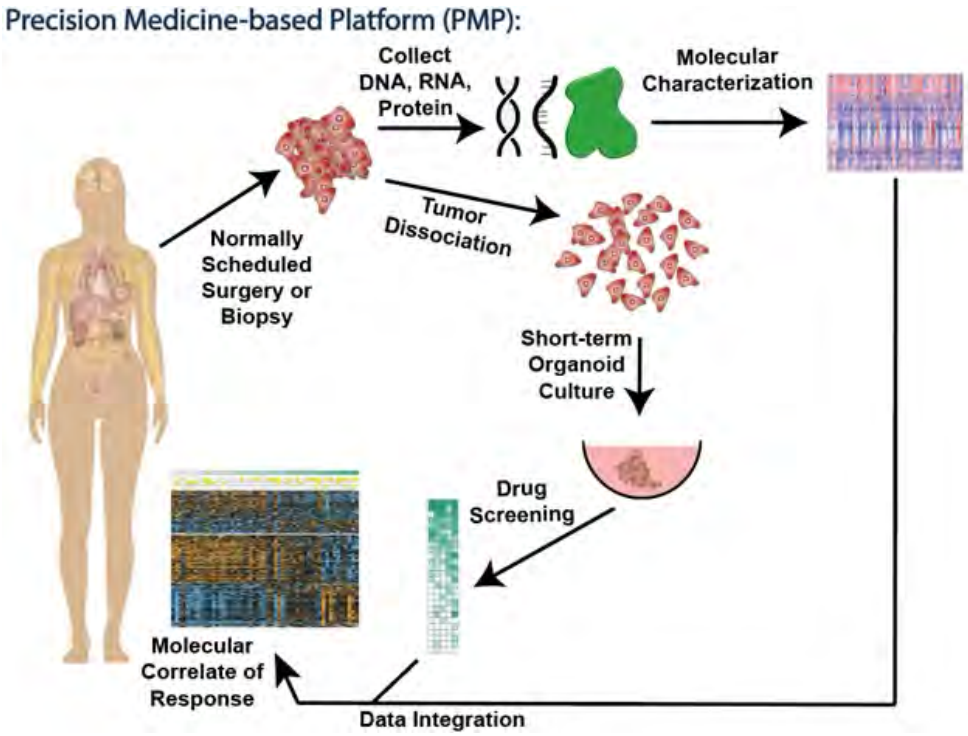
Introduction: Lung cancer (LC) remains the top cause of cancer-associated mortality worldwide, with a 10-year overall survival rate of only 5%. While most LCs are smoking related, 25% of non-small cell LC (NSCLC) are diagnosed in patients with little or no smoking history. Fusions involving anaplastic lymphoma kinase (ALK) are the oncogenic driver in ~3-7% of NSCLC. While inhibitors targeting the kinase domain of ALK have proven effective, inevitably, resistance develops with limited subsequent efficacious options. We aimed to integrate multiomic characterization and drug sensitivity testing of minimally cultured NSCLC samples to provide a ranked list of most effective drugs for each patient.

Methods: We developed a precision medicine platform (PMP) to screen patient-derived material (PDM) directly from the operating room with curated panels of drugs. PDM collected during clinically indicated procedures is plated in 3D-culture to generate patient-derived organoids (PDOs). PDOs are screened at therapeutically relevant doses, drawing from pharmacokinetic data for each drug. We have optimized an assay to rapidly screen for EML4-ALK fusions and can perform next-generation sequencing in ~7 days to integrate with drug screening results.

Results: To date, we have screened and molecularly characterized 77 NSCLC PDOs. Our cohort prioritized collection of EML4-ALK LC, resulting in 14 distinct ALK+ cases, with 13 patients having progressed on 2+ lines of therapy. While our dataset is enriched in non-smokers (32/80 screened models), we observed only 4 cases of LC with mutations in EGFR. Twelve models have mutations in KRAS, ¼ of those occurring in never-smokers. We demonstrate high quality drug screening data from low input samples (biopsies). In one case of EML4-ALK NSCLC, we collected PDM from two distinct anatomic spaces (pleural effusion and peritoneal fluid) and the screens yielded nearly identical results, highlighting the consistency of our assay. Our results recapitulate known resistance in samples previously exposed to therapy, demonstrating a strong negative predictive value. Sequencing identified diverse driver mutations in populations of both smokers and non-smokers.

Conclusions: Our PMP captures robust results that are consistent with known clinical pathogenesis. Prioritization of drug screening using compounds with diverse targets is critical when driver mutations are unknown to ensure we screened the most clinically relevant drugs for each tumor. We are currently collecting longitudinal data from enrolled patients in parallel with clinical trials to demonstrate the positive predictive value of our PMP. We additionally strive to demonstrate reproducibility to obtain Clinical Laboratory Improvement Amendments approval.



Keywords: Organoids, Drug Sensitivity, Multiomics

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.02 Single-Cell Profiling of Tumor Lineage Plasticity and the Immune Microenvironment in Transformed Small Cell Lung Cancer

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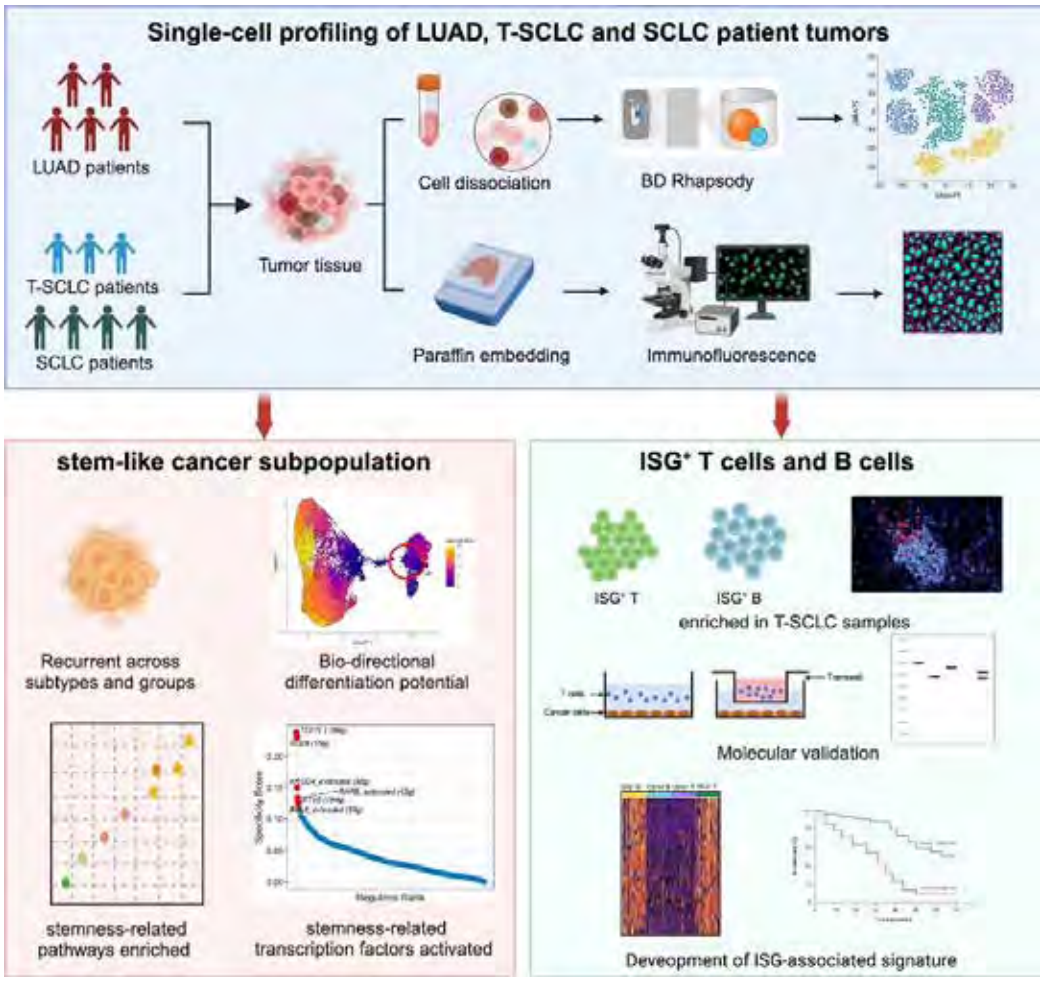
Introduction: The transformation of non-small cell lung cancer (NSCLC) into small cell lung cancer (SCLC) is a recognized resistance mechanism of target-therapy, most often arising from EGFR-mutant lung adenocarcinoma (LUAD). However, the underlying molecular mechanisms of transformation remain poorly understood.

Methods: Single-cell RNA sequencing was employed to analyze the tumor cell heterogeneity and to map the intratumoral immune cell landscape of 73,195 cells from five LUAD, three transformed small cell lung cancer (T-SCLC) and four SCLC patients. Multiplex immunofluorescence (mIF) staining and in vitro studies were conducted to validate the stem-like feature of a malignant cell cluster and the enrichment and the function of interferon-stimulated gene-positive (ISG+) lymphocytes in transformation. Moreover, western blotting analyses further performed to detect the expression of neuroendocrine markers in LUAD cells after co-culture with MX1OE T cells, representing ISG+T cells,.

Results: Although increase intratumoral heterogeneity was observed upon SCLC transformation, a stem-like malignant cell subpopulation was identified to recur across subtypes and groups as the pioneering force of lineage plasticity for SCLC transformation. Further mIF staining and transcription factor analyses validated the stem-like feature of this cell cluster. Additionally, ISG+ T cells and B cells were enriched in T-SCLC, and further cell co-culture experiments disclosed that ISG+ lymphocytes promote neuroendocrine phenotypic shift in LUAD cells via type I interferons (IFN-Is). Deciphering cell-cell interactions revealed that the stem-like malignant cells could activated and attract ISG+ T cells. Finally, we developed an ISG-associated gene signature that significantly correlates with poor prognosis in LUAD patients.

Conclusions: Our findings provide a comprehensive understanding of the lineage plasticity and the immune landscape in T-SCLC, highlighting the crucial role of the stem-like cell cluster and ISG+ lymphocytes in LUAD-to-SCLC transformation.



Keywords: SCLC transformation, stem-like cells, ISG+ lymphocytes

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.03 Drug Repurposing for Metastatic Lung Adenocarcinoma Therapy Using AI-Guided Single-Cell Gene Expression Profiles

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Introduction: Metastasis is the leading cause of cancer-related deaths, mainly due to therapeutic resistance. Drug repurposing offers a promising strategy for metastatic lung adenocarcinoma by identifying antineoplastic properties in existing drugs. Advances in single-cell RNA sequencing (scRNA-seq) enable high-resolution characterization of malignant cells, providing insights into transcriptional changes in metastasis. By integrating AI-driven network-based and machine-learning algorithms with scRNA-seq data, gene signatures of metastatic cells can be compared to drug-induced expression profiles, facilitating the identification of candidate drugs capable of reversing oncogenic programs. Despite the growing interest in this strategy, its application to metastatic lung adenocarcinoma remains limited. In this study, we applied scRNA-seq data and AI-based computational methods to identify candidate drugs capable of reversing gene expression signatures. By analyzing gene expression profiles from metastatic malignant cells in both smokers and never-smokers, we aimed to uncover novel therapeutic opportunities for drug repurposing.

Methods: We preprocessed and analyzed scRNA-seq data from 63 lung adenocarcinoma patients with brain and lymph node metastases, including samples from smokers and never-smokers, totaling 164,857 single cells from the Gene Expression Omnibus repository (GSE131907 and GSE123904) using Seurat v5.0.2. Differentially expressed genes between metastatic malignant and non-malignant cells were identified using the Seurat v5.0.2 FindMarkers function. Pathway enrichment analysis was performed with EnrichR, while drug prediction was conducted using the L1000FWD platform, which applies machine learning and network-based gene signature concordance analysis.

Results: Malignant cells were most abundant in brain metastases (39.7%), B lymphocytes in lymph node metastases (34.95%), and T lymphocytes dominated lung primary tumor (47%) and adjacent normal tissues in lung (30.02%) and lymph node (66.84%). Pathway enrichment analysis revealed key mechanisms driving tumor progression and metastatic adaptation. Common pathways across all sites included metabolic reprogramming, with a strong enrichment in glycolysis-related pathways, highlighting the tumor's dependence on this energy source. Kinase regulation and VEGFA-VEGFR2 signaling were also consistently enriched, reinforcing their roles in tumor progression and angiogenesis. Site-specific signatures were also detected: (i) primary lung tumors exhibited kinase activation; (ii) brain metastases displayed metabolic shifts characterized by mTOR signaling activation via fatty acid and glucose metabolism; and (iii) lymph node metastases showed activation of the p53 pathway and epithelial-mesenchymal transition (EMT), indicating increased plasticity and aggressiveness. Drug prediction analysis revealed both shared and site-specific pharmacological candidates, presenting new opportunities for drug repurposing. Cardiotonic glycosides were common across all tumor sites, while mTOR inhibitors and immunosuppressants were shared between metastatic and primary tumors. Corticosteroids and selective serotonin reuptake inhibitors (SSRIs) were specific to lymph node metastases, whereas histone deacetylase (HDAC) inhibitors and selective estrogen receptor modulators (SERMs) were unique to primary lung tumors.

Conclusions: These findings offer important insights into the molecular landscape of metastatic lung adenocarcinoma, revealing key pathways driving tumor progression. We identified promising therapeutic candidates, including site-specific drugs, by integrating pathway enrichment and drug repurposing analyses. Future "in vitro" assays using cell culture models will be conducted to validate these drug candidates for repurposing.

Keywords: Brain Metastases, Lung Adenocarcinoma, Drug Repurposing

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.04 VIKTOR - the Virtual International Knowledgebase for Thoracic Oncology Research of the IASLC

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Introduction: Preclinical cancer models are crucial for advancing knowledge, research, and treatments in thoracic oncology. No resource is currently available to access preclinical cancer models focusing specifically on the requirements of the thoracic oncology community. The Virtual International Knowledgebase for Thoracic Oncology Research (VIKTOR) is a digital platform addressing this critical unmet need. VIKTOR's goal is to center the information from curated cancer model knowledge bases and single institutes toward the questions, priorities and needs of the researcher in thoracic oncology. VIKTOR will facilitate and accelerate research and collaborations among scientists, clinicians, and industry partners, fostering participation in identifying research priorities for the thoracic oncology community and the benefit of our patients.

Methods: Semantic search is used to retrieve information from open accessible and curated knowledge bases. Currently, data from Cellosaurus, PharmacoDB and UniProt/neXtProt are converted into RDF statements and stored in a triple store enabling SPARQL-based queries. Queries submission and retrieval of results in CSV files format are supported by a web interface. Knowledge from single institutes of the community will be integrated. VIKTOR supports the active participation of the scientists in prioritizing the research questions.

Results: VIKTOR is a searchable digital platform that permits to identify and retrieve information on preclinical cancer models tailored to the needs of researchers in thoracic oncology. Specific research questions can be addressed such as: "which lung cancer cell lines harbor ROS1 fusion genes?", "which cell lines have been modified to express a mutated gene X of interest?" or "which lung cancer cell lines have undergone sensitivity screenings for drug Y ". A list of available cell lines from open-access knowledge bases is then reported linked to relevant biological data such as omics profiles or drug sensitivity results. The reports are user-friendly and will incorporate a scoring system to help researchers selecting the most suitable preclinical models.

Conclusions: VIKTOR is an ongoing project of the Basic and Translational Science Committee (BaTS) of IASLC that supports researchers in accessing and querying data about preclinical cancer model systems. It retrieves data from open access resources and will integrate knowledge from single institutes of the community. The platform is centered toward the research priorities identified by the IASLC thoracic oncology community in order to facilitate rapid dissemination of information and collaboration. Presented on behalf of the Basic and Translational Science Committee of the IASLC

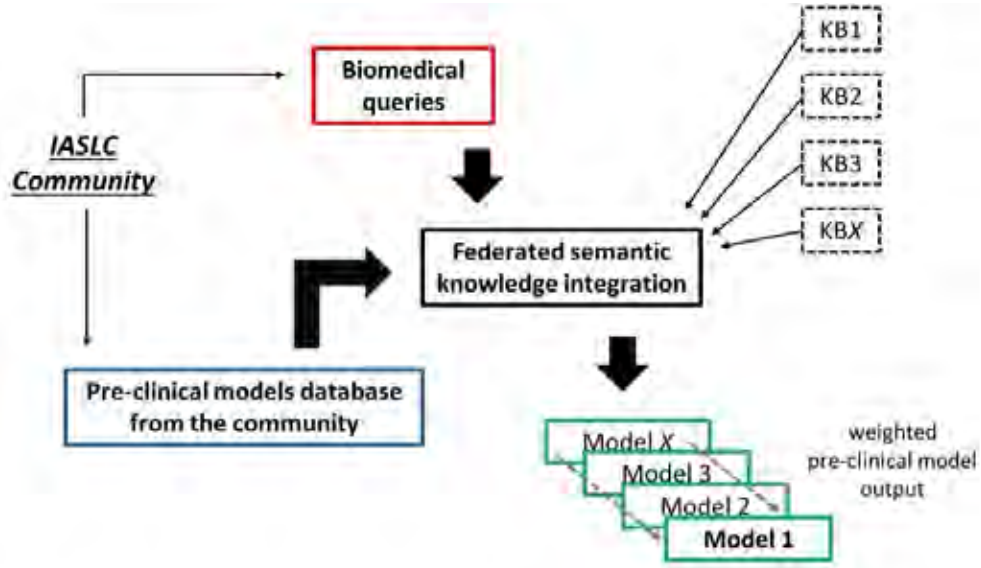

Figure 1 VIKTOR: schematic overview of the main components of the platform; KB = knowledge base

Keywords: cancer model system, knowledge base, cell lines

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.05 An Ai-Based Predictive Tool for Druggable Mutations in Lung Cancer Using Nationwide Comprehensive Genomic Profiling Data

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Introduction: Comprehensive genomic profiling (CGP) plays a pivotal role in precision medicine. However, the low probability of discovering mutation-based treatments, despite the financial and time burden, may prevent eligible patients from undergoing CGP. To enhance the efficiency and efficacy of cancer precision medicine, it is critical to identify patients who are likely to benefit from CGP. This study aims to identify patient characteristics associated with the discovery of mutation-based treatments through CGP and to develop an intuitive AI tool to predict the probability of identifying druggable mutations.

Methods: To train a predictive AI model, we used clinical data from 3,470 lung cancer patients (Cohort 1) who underwent CGP between Jun 2019 and Nov 2023 and were registered in the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database, which covers 99.7% of CGP performed in Japan. Using clinical information available prior to CGP, we developed an eXtreme Gradient Boosting (XGBoost) model to predict the detection of druggable mutations. SHapley Additive exPlanations (SHAP) was employed to extract features that contribute to the model prediction. Using the identified clinical factors as input, another AI model was built and deployed as a smartphone and web-based application to predict the probability of identifying druggable mutations. The app's performance was tested on clinical data from 1,307 lung cancer patients (Cohort 2) who underwent CGP between Dec 2023 and Nov 2024.

Results: The predictive AI model trained on Cohort 1 achieved an AUROC of 0.85 (95% confidence interval [CI]: 0.82-0.89, sensitivity: 0.82, specificity: 0.73). A separate model, excluding patients with at least one druggable mutation detected by small companion diagnostic tests before CGP, showed an AUROC of 0.79 (0.74-0.84). Positive SHAP values were associated with adenocarcinoma and the number of metastatic sites, while negative SHAP values were with male sex and smoking history. These relationships were consistent across tissue and liquid CGP cases. Notably, among tissue CGP cases, patients with bone or lung metastases exhibited a significantly higher rate of druggable mutation detection compared to those without (bone: $p = 0.011$; lung: $p < 0.001$). A streamlined AI model was retrained using the most influential clinical factors and deployed as a smartphone and web-based application. When tested on Cohort 2, the app demonstrated predictive accuracy with an AUROC of 0.77 (0.74-0.79) and a Brier score of 0.19.

Conclusions: We developed an AI model that predicts the probability of identifying druggable mutations by using pre-CGP clinical data. We also identified key clinical factors predictive of druggable mutation detection in lung cancer through explainable AI analysis of nationwide CGP data. Based on these findings, an easy-to-use smartphone and web-based application was developed to predict the probability of identifying druggable mutations. This model could expand access to targeted therapies by facilitating broader utilization of CGP tests.

Keywords: Comprehensive genomic profiling, Artificial intelligence, Clinical decision support

PT1.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.03.06 Mechanisms of Acquired Resistance to First-Line Amivantamab Plus Lazertinib Vs Osimertinib: Updated Analysis from MARIPOSA

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Introduction: Amivantamab, an EGFR-MET bispecific antibody, plus lazertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), is approved for first-line treatment of EGFR-mutated advanced NSCLC. In the protocol-specified final overall survival (OS) analysis (median follow-up, 37.8 months), amivantamab-lazertinib demonstrated a statistically significant and clinically meaningful improvement in OS versus osimertinib (HR, 0.75; P<0.005), with the median OS benefit projected to exceed 1 year (Yang ELCC 2025). One key rationale for combining amivantamab with lazertinib was to proactively address acquired resistance mechanisms to third-generation TKIs. An early analysis showed that first-line amivantamab-lazertinib significantly reduced acquired EGFR-based and MET-based alterations (P<0.05 versus osimertinib), without significant increases in other known pathways (Besse ESMO 2024). Here we report updated acquired resistance mechanism data.

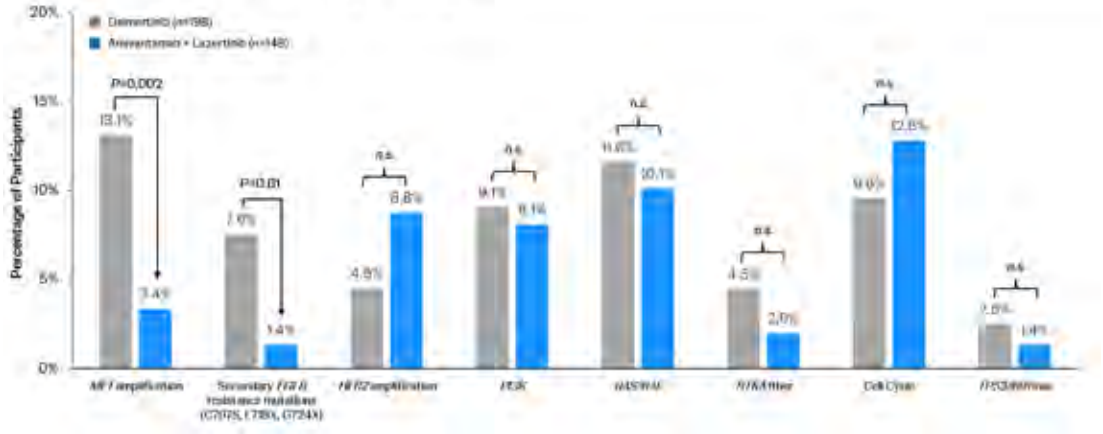
Methods: Participants with previously untreated EGFR-mutated (Ex19del/L858R) advanced NSCLC were randomized 1:1 to receive amivantamab-lazertinib (n=429) or osimertinib (n=429). Next-generation sequencing (Guardant 360 CDx) was used to analyze detectable circulating tumor DNA in paired blood samples collected at baseline and end of treatment (EOT; defined as at disease progression or at/within 90 days of treatment discontinuation). Mutational heterogeneity was quantified using the Shannon Diversity Index (Oh et al. Sci Reports 2019;9:4542). All P-values are nominal.

Results: Among participants who discontinued treatment and had baseline ctDNA data, 148/187 (79%) in the amivantamab-lazertinib arm and 198/218 (91%) in the osimertinib arm had matched EOT ctDNA data. MET amplification was significantly reduced in participants receiving amivantamab-lazertinib versus osimertinib (3.4% vs 13.1%; P=0.002). Further, MET amplifications were enriched among osimertinib-treated participants who experienced early disease progression (≤6 months post-randomization); there were too few MET amplifications to draw conclusions for amivantamab-lazertinib. Secondary EGFR mutations (eg, C797S) were also significantly lower in the amivantamab-lazertinib versus osimertinib arm (1.4% vs 7.6%; P=0.01). The 2 participants in the amivantamab-lazertinib arm with acquired EGFR mutations only received amivantamab for one cycle and continued on lazertinib. Differences between arms for other known resistance pathways were not significant (Figure).

Compared to amivantamab-lazertinib, mutational heterogeneity was significantly increased after osimertinib treatment (P<0.05); this difference was most pronounced among participants with acquired EGFR- and MET-based alterations. Additional details, including data on outcomes, will be presented at the meeting.

Conclusions: In this updated analysis, significantly lower rates of EGFR and MET resistance alterations were seen in the amivantamab-lazertinib arm vs osimertinib. These findings further suggest that amivantamab-lazertinib, with its statistically significant and clinically meaningful survival benefit over osimertinib, is changing the underlying biology of EGFR-mutant disease.

Figure: Mechanisms of Resistance by Pathway



Keywords: Non-small cell lung cancer, EGFR mutation, amivantamab

PT1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.04.01 Incidental Pulmonary Nodule Programs (IPN) Working Together With LDCT Scans and Artificial Intelligence (AI) Increase Lung Cancer Detection

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Introduction: Low-Dose CT (LDCT) scan is considered standard for lung cancer screening (LCS) in high-risk populations, but significant barriers remain, and screening rates are low. Social determinants of health create barriers to screen underserved populations and current eligibility criteria do not include never-smokers and younger populations. Incidental Pulmonary Nodule Programs (IPN) programs use artificial intelligence (AI) driven tools to identify patients who have pulmonary nodules detected on imaging studies done for other reasons. These tools facilitate identification, classification, and management of pulmonary nodules. Preliminary comparisons like the DELUGE trial in Mississippi have shown that IPN programs can detect more lung cancers than traditional LDCT programs.

Methods: We created an IPN program at Memorial Cancer Institute/Memorial Healthcare System in Broward, Florida to complement our LDCT program. The goal was to identify lung cancers in individuals with limited access to or not covered by screening and thus eliminate disparities. Large healthcare systems like us perform thousands of CT scans every month, making manual review of results impossible for nodule identification. To address this challenge, we used an AI solution called ILUMINATE to interact with our electronic medical records (EMR) EPIC system to detect and triage lung nodules (high, intermediate or low risk). The system reviewed results from all CT scans that included portions or the lung, such as CT chest, abdomen, spine, and calcium score scans from all five of our hospitals. A nurse navigator managed the program, reviewing reports from the AI system and presenting cases to a weekly lung nodule review group that included pulmonologists and thoracic surgeons. Each case was recommended either for workup (e.g. short interval CT, PET scan, biopsy, surgery), or continued follow-up in the LCS program. Here we compare results from the first 20 months of the IPN program with results from same period of the LDCT program.

Results: From May 2023 to January 2025 2,423 individuals were screened in the LDCT group of which 781 (33%) had follow-up scans. A slight majority (51%; 1,246) were female and non-Hispanic whites (NHW) were 1453 (60%). Median age was 71y (25-99y). Ten patients (0.4%) were diagnosed with lung cancer. In the IPN program 205,022 radiology reports were screened by the AI and 6,685 individuals were identified for follow up. Most were female (58%; 3,877) and NHW 4010 (60%). Median age was 70y (20-100y). From this IPN group 817 patients (17%) were enrolled in the LCS program for follow up and 127 (1.9%) were diagnosed with lung cancer. Most of the patients in the LDCT group and IPN group were diagnosed with early stage (I/II) NSCLC

Conclusions: Our IPN program significantly improves lung cancer detection, detecting more lung cancers than the LDCT program over the same period. There were no significant differences in age, gender or race between these two groups. AI tools made it possible to review the large number of studies generated in a health care system, leveraging limited human resources to address a large unmet need. Longer follow up will allow us to present survival data.

Keywords: LDCT, IPN, lung screening

PT1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.04.02 Performance of Lung Nodule and Cancer Risk Calculators in Identifying Primary Lung Cancer Across Screening and Incidental Nodule Populations

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Introduction: Pulmonary risk calculators support decision-making in nodule management. Nodule-based models use imaging characteristics, while lung cancer risk models rely on demographic-clinical data. This study compared the performance of these tools in distinguishing confirmed primary lung cancer from non-investigated nodules in a combined screening and incidental cohort, with subgroup analyses by tobacco exposure.

Methods:

We retrospectively analyzed 290 individuals evaluated between 2023 and 2024 in a multidisciplinary program. A total of 74 cases of primary lung cancer were histologically confirmed. Five nodule-based calculators - Brock University cancer prediction equation (Brock Model), Mayo Clinic Model, Herder Model, Veterans Affairs (VA) Model, and Cleveland Model and three lung cancer risk models: Liverpool Lung Project risk (LLP) Model, PLCOm2012, Simplified PLCOm2012. Risk scores were compared between cancer cases and nodules without histologic investigation using Mann-Whitney U tests. Subgroup analyses included individuals with incidental nodules (n=195) and those without a history of tobacco exposure (n=116). Significance was set at $p<0.05$.

Results: In the overall cohort, four nodule-based calculators (Brock Model, Mayo Clinic Model, Herder Model, VA) significantly differentiated cancer cases from nodules without diagnosis ($p<0.05$ for all). The VA Model demonstrated the highest discrimination (mean 86.3 vs. 43.1, $p<0.001$). The Cleveland model showed no significant difference ($p=0.850$). Lung cancer risk models—Liverpool, PLCOm2012, and Simplified PLCOm2012—did not distinguish between groups ($p>0.19$ for all).In the incidental subgroup, the VA model again had the best performance (86.8 vs. 37.8, $p<0.001$). Brock Model (27.2 vs. 13.1, $p<0.001$), Mayo Clinic Model (41.1 vs. 15.9, $p=0.012$), and Herder Model (63.1 vs. 45.8, $p=0.015$) were also significant. Cleveland Model was not ($p=0.490$). Among cancer risk models, only LLP Model was statistically significant (2.66 vs. 1.24, $p=0.025$); Simplified PLCOm2012 showed a trend ($p=0.094$).In individuals without tobacco exposure, the VA model was the only significant tool ($p<0.001$), indicating robustness beyond smoking-related populations. Brock model showed a non-significant trend ($p=0.130$), while Mayo Clinic Model, Herder Model, Cleveland Model, and all cancer risk models lacked discriminatory capacity.

Conclusions: Nodule-based calculators, especially the VA model, outperformed lung cancer risk models in identifying primary lung cancer. The VA model consistently demonstrated robust performance across all subgroups, including individuals without tobacco exposure. Notably, the LLP Model was the only lung cancer risk calculator to show discriminatory capacity in individuals with incidental nodules. These findings support the integration of imaging-based models, particularly VA Model, alongside selective use of clinical-demographic tools like LLP Model, in multidisciplinary pulmonary nodule programs.

Variable/Calculator	Screening and Incidental Nodule Program (n=288)	Incidental Nodule Program (n=194)	Person who never smoked and incidental nodule (n=116)	
Gender				
Male	129 (44,8%)	89 (45,9%)	40 (34,5%)	
Female	159 (55,2%)	105 (54,1%)	76 (65,5%)	
Age – mean (years)	68,7	69,4	70,5	
Lesion Size				
<6 mm	27 (9,4%)	5 (2,6%)	3 (2,6%)	
6–8 mm	44 (15,2%)	28 (14,5%)	19 (16,5%)	
9–14 mm	81 (28,3%)	59 (30,6%)	40 (34,8%)	
15–29 mm	93 (32,3%)	68 (35,2%)	36 (31,3%)	
≥30 mm	43 (14,8%)	33 (17,1%)	17 (14,8%)	
Lung cancer	74 (25,7%)	72 (37,1%)	32 (27,6%)	
Person who never smoked	116 (40,3%)	116 (59,8%)	116 (100%)	
Patient with active tobacco use	172 (59,7%)	78 (40,2%)	0 (0%)	
Brock University cancer prediction equation	27,64	27,2	51,76	mean (primary malignance)
	13,59	13,11	41,83	mean (Not investigated)
	< 0,001	< 0,001	0,130	p*
Mayo Clinic Model	41,11	41,11	31,33	mean (primary malignance)
	16,17	15,91	28,16	mean (Not investigated)
	0,013	0,012	0,652	p*
Herder Model	63,38	63,09	24,93	mean (primary malignance)
	45,35	45,77	20,07	mean (Not investigated)
	0,003	0,015	0,209	p*
Veterans Affairs Model	86,33	86,76	66,02	mean (primary malignance)
	43,08	37,85	43,22	mean (Not investigated)
	< 0,001	< 0,001	< 0,001	p*
Cleveland Clinic Model	62,02	61,14	48,19	mean (primary malignance)
	60,68	57,93	50,00	mean (Not investigated)
	0,850	0,490	0,778	p*
Liverpool Lung Project (LLP) risk model	2,64	2,66	37,7	mean (primary malignance)
	1,81	1,24	35,33	mean (Not investigated)
	0,660	0,025	0,664	p*
Simplified $PLCO_{M2012}$	4,14	4,23	12,70	mean (primary malignance)
	2,84	2,42	9,04	mean (Not investigated)
	0,197	0,094	0,211	p*
$PLCO_{M2012}$	6,87	7,10	1,5	mean (primary malignance)
	4,70	4,87	5,0	mean (Not investigated)
	0,637	0,735	0,053	p*

* Mann–Whitney test

Keywords: Pulmonary Nodule Risk Assessment, Incidental Pulmonary Nodules, Lung Cancer

PT1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.04.03 The LEAP Study: A Biospecimen Bank for Validation of Liquid Biomarkers in a Lung Cancer Screening Cohort

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Introduction: Liquid biomarkers could improve the effectiveness of lung cancer screening (LCS) by low-dose computed tomography (LDCT) through more accurate lung cancer (LC) risk stratification and nodule malignancy risk assessment. The LEAP study aims to establish a reference set to validate the most promising cancer biomarkers in the context of LCS.

Methods: This study is a prospective international cohort (USA, France, Spain) enrolling active or former smokers at high LC risk based on National Comprehensive Cancer Network Guidelines (v1.2014) into an LCS program. Participants underwent three annual rounds of LDCT-LCS with blood specimens collected at each screening timepoint. Questionnaires and medical chart reviews were utilized to determine who was later diagnosed with lung and/or other cancers.

Results: Between 2014 and 2019, 2,846 participants enrolled who underwent LDCT: 2,842 at baseline, 2,097 at year 1 (73%) and 1,779 at year 2 (62%). The rates at baseline, year 1, and year 2 were as follows: positive scans (13%, 7.5%, 7.5%), false-positive (12%, 6.6%, 6.9%) and screen-detected LC (1.1%, 0.8%, 0.7%). After 5 years of follow-up, 72 LC were detected: 56% stage I, 13% stage II, 17% stage III and 14% stage IV. The LEAP biobank collected 6,188 blood specimens, including 126 pre-diagnostic for LC (within 5 years before diagnosis) and 201 pre-diagnostic for other cancers.

Conclusions: The LEAP cohort is a valuable longitudinal database of subject data, LDCT imaging, and matched blood specimens for biomarker validation, aiming to address unmet clinical needs in the context of LCS.

Keywords: lung cancer screening, blood biomarkers, low dose CT scanning

PT1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.04.04 Biomarker-Based Eligibility for Lung Cancer Screening - Validation of Protein-Based INTEGRAL-Risk Model in the LC3 Consortium

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Introduction: Current eligibility criteria for lung cancer screening by LDCT exclude approximately 50% of lung cancer cases whilst including many individuals at low risk who may not benefit from screening. Biomarkers have the potential to enhance smoking-based risk assessment tools. We previously developed a fit-for-purpose protein biomarker panel (INTEGRAL panel) comprising 21 proteins selected to inform lung cancer screening. We aimed to develop a biomarker-based risk model for use in LDCT-screening using a robust study design in the target population.

Methods: The Lung Cancer Cohort Consortium (LC3) involves 25 population cohorts from around the world with pre-diagnostic blood and risk factor information on up to 3,000,000 study participants, including 70,000 incident lung cancer cases. We designed 14 independent case-cohorts in LC3, including 2,305 randomly sampled sub-cohort participants and 1,390 incident lung cancer cases. All participants had a history of smoking, and cases were diagnosed within three years of blood collection. We developed the protein-based INTEGRAL-Risk model using data from seven case-cohorts, incorporating age, smoking history, and absolute concentrations of 13 proteins. Model testing was performed in seven independent cohorts by assessing model calibration and discrimination and comparing performance with existing risk assessment tools.

Results: In the testing set (1,161 sub-cohort participants and 583 lung cancer cases), the INTEGRAL-Risk model demonstrated superior discrimination for lung cancer incidence over one year compared to the smoking-based PLCOm2012 model (AUC: 0.88 [95% CI: 0.85-0.90] vs. 0.79 [95% CI: 0.75-0.83]; p<0.001). The model was well-calibrated for one-year lung cancer risk prediction (expected/observed ratio: 0.86 [95% CI: 0.61-1.25]). The USPSTF screening criteria identified 25% of individuals with smoking exposure as eligible for LDCT screening, capturing 63% of lung cancer cases within one year. Using a risk threshold that selected an equivalent 25% of participants, the INTEGRAL-Risk model identified 85% of lung cancers as eligible for screening (Figure 1). Stratified analyses by race/ethnicity demonstrated consistent model performance across white (AUC: 0.88 [95% CI: 0.84-0.92]), black (AUC: 0.90 [95% CI: 0.81-0.97]), and Asian (AUC: 0.88 [95% CI: 0.82-0.93]) participants.

Conclusions: This study represents a major effort from an international consortium to develop a biomarker-based risk prediction tool for use in LDCT screening. The protein-based INTEGRAL-Risk model improves upon existing risk assessment tools for identifying high-risk individuals with a history of smoking. These findings underscore the potential of biomarker-based risk models to enhance LDCT screening efficiency by better targeting individuals likely to benefit.

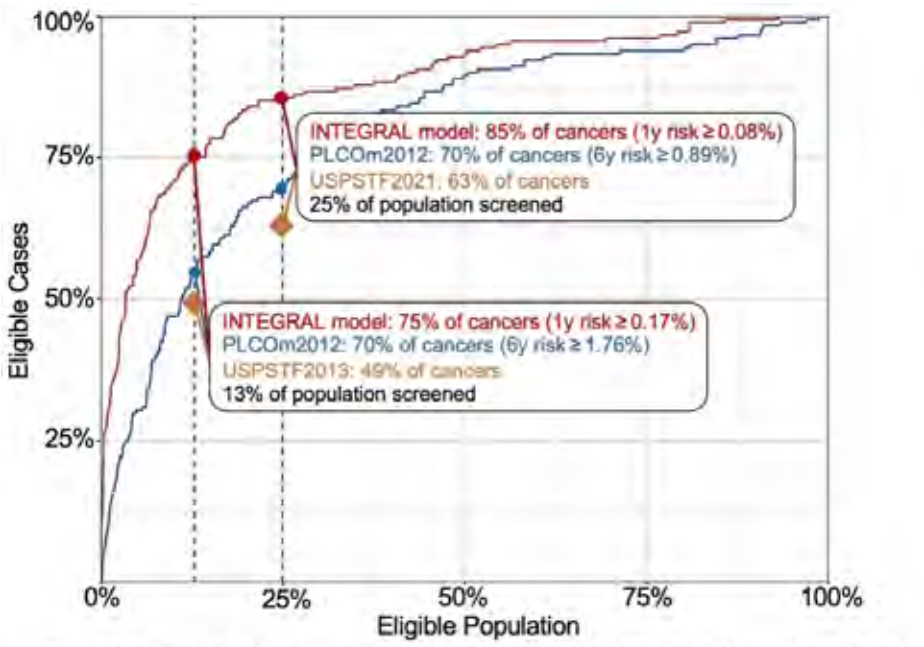

Figure 1. *Overview of the study design (a) cohorts participating in the INTEGRAL study of risk biomarkers (b). Cohorts marked in grey were included in the discovery phase to design the INTEGRAL protein panel. Cohorts marked in purple were used to train the protein-based INTEGRAL-Risk model, and cohorts marked in green were used to test the INTEGRAL-Risk model*

Keywords: Lung cancer, Screening eligibility, biomarkers

PT1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.04.05 Subclassification of Abnormal Cells Into Precancerous and Malignant Categories Based on 3D Cellular Imaging

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Introduction: VisionGate's Cell-CTTM platform captures 3D images of cells in isometric, sub-micron resolution and measures >500 orientation-invariant 3D features in each cell. The LuCED® assay uses home-collected sputum to detect early-stage lung cancer through AI discovery of abnormal cells across the cytologic categories of atypia through to malignancy. Results show that early-stage lung cancer is detected with sensitivity and specificity both exceeding 90%, and the sensitivity to biopsy-confirmed stage 1 NSCLC was 93.8%. In this context, we hypothesize that the abnormal cell population may be sub-classified into malignant and pre-cancer categories. This application will broaden the clinical scope of the LuCED assay to prioritize patient triage in cases where frankly cancerous cells are detected. Cases without malignant cells would default to standard protocols of vigilance with a likelihood of pre-cancer.

Methods: Abnormal cells detected with LuCED were further classified into cancer and pre-cancer categories using an AI-supervised learning process involving cytologically defined cells in classes of pre-cancer (N=623) and malignancy (N=374). The Cell-CT measured 503 3D features for each cell and adaptively boosted logistic regression separated the two classes. Ten-fold cross-validation ensured that the resulting classifier was not overtrained.

Results: A model involving six features emerged from the training process, producing an area under the ROC of 0.81. A potential operating point produced these results: 70% detection of malignant cells, with 30% of malignant cells called pre-cancer; 80% detection of pre-cancer cells, with 20% of pre-cancer cells called malignant; None of the abnormal cells were called normal.

Conclusions: These results demonstrate the efficacy of 3D cell analysis in characterizing subtle aspects of abnormal cell morphology to assess whether a malignant process is likely to be present. This new AI classifier may find application in the COPD patient population and in improving the management of IPNs. In such populations, a clear indication of malignancy is urgently needed to initiate curative/lifesaving therapy, particularly in early-stage disease, where such treatments will be most effective.

Keywords: Lung Cancer Detection, Early stage, 3D cell imaging

PT1.05 PULMONOLOGY AND STAGING
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.05.01 Impact of Endobronchial Ultrasound-Guided Intranodal Forceps Biopsy on Next-Generation Sequencing

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Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) offers high diagnostic accuracy and provides specimens well-suited for next-generation sequencing (NGS). The success rate of NGS has been reported to correlate with the number of punctures and core tissues obtained. However, since obtaining sufficient samples from tumors in TBNA is sometimes difficult, we have actively incorporated standard-sized intranodal forceps biopsy (IFB) as an adjunct. The advantage of IFB over TBNA is that it allows the collection of tissue specimens rather than cytological specimens, and using standard-sized forceps enables the collection of larger, higher-quality specimens than conventional mini-forceps. In this study, we aimed to evaluate the impact of adding IFB to TBNA on NGS.

Methods: We retrospectively collected consecutive patients diagnosed with non-small cell lung cancer (NSCLC) via EBUS-TBNA from metastatic hilar/mediastinal lymph nodes (LNs) at our institution between April 2020 and March 2024. Of them, cases submitted to the amplicon-based NGS targeting 46 gene aberrations using those specimens were extracted. Cases in which a sufficient number of core tissues could be obtained by TBNA (i.e., 5 or more) were excluded. The remaining cases were divided into those with IFB (combined group) and those without (TBNA group), and the results of the NGS were compared between the two groups. NGS was defined as successfully analyzed if any driver oncogene or a negative result for all actionable genetic alterations (i.e., EGFR, ALK, ROS1, BRAF, RET, MET, KRAS, and HER2) with approved drugs was detected.

Results: Of the total 1,414 EBUS-TBNA procedures, 1,163 targeted LNs of NSCLC and NGS were submitted in 436. Ultimately, 325 patients met the selection criteria, with 275 (84.6%) in the combined group and 50 (15.4%) in the TBNA group. The median age was 69 years (range 25-89), 215 patients (66.2%) were male, and 208 (64.0%) had adenocarcinoma. The median short axis size of the LNs was 14.2 mm (range, 3.8-46.3), and 253 (77.8%) targeted mediastinal LNs. The TBNA group had more male patients and cases in stages I to III, but the other factors were comparable between the two groups. The overall NGS success rate was 86.2%, and the most common gene aberration was EGFR in 58 (17.8%), followed by KRAS in 35 (10.8%), ALK in 18 (5.5%), and others in 58 (17.8%) at various frequencies. Univariable analysis demonstrated that the combined group showed a significantly higher NGS success rate than the TBNA group (88.0% vs. 76.0%, p = 0.042). Multivariable analysis revealed that only the combined group was significantly associated with a higher NGS success rate (adjusted odds ratio 2.35; 95% confidence interval 1.06-4.99; p = 0.035).

Conclusions: Our results suggest that IFB complements the success of NGS when added to TBNA. IFB is a valuable alternative if TBNA cannot obtain sufficient samples.

Keywords: Intranodal Forceps Biopsy, EBUS-TBNA, Next-generation Sequencing

PT1.05 PULMONOLOGY AND STAGING
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.05.02 Development of an AI Image Analysis System for Malignancy Classification in Rapid On-Site Cytologic Evaluation of Lung Cancer

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Introduction: Rapid on-site cytologic evaluation (ROSE) during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) reduces the need for repeated puncture procedures and the complication rate of bronchoscopy. However, ROSE is not widely utilized due to limited human resources, particularly the availability of staff to classify malignant and benign cells. This study aims to develop an artificial intelligence (AI) image analysis system to classify individual cells observed in ROSE during EBUS-TBNA as malignant or benign.

Methods: Patients suspected of having lymph node metastasis from lung cancer who underwent EBUS-TBNA were prospectively enrolled at five hospitals in Japan. Pathological slides using the Diff-Quik staining method were obtained from each patient, and images were captured using a microscope with a 40x objective lens. Cytotechnologists classified the individual cells observed into five types of benign cells (endothelial cell, inflammatory endothelial cell, macrophage, lymph cell, white blood cell) and four types of malignant cells (small cell carcinoma, adenocarcinoma, squamous cell carcinoma, other non-small cell lung cancers). A deep learning AI image analysis system was developed, and its performance was evaluated. This study was conducted in collaboration with NEC.

Results: Between August 2023 and September 2024, 128 patients were enrolled in this study. Of these, 108 cases were analyzed after excluding those with low-quality specimen images or without prepared pathology slides. The final diagnoses of the punctured lymph nodes included adenocarcinoma in 38 cases, squamous cell carcinoma in 13 cases, non-small cell lung cancer not otherwise specified in 18 cases, small cell carcinoma in 22 cases, and benign in 17 cases. Among them, 8184 cells were selected, with 2200 cells categorized as benign and 5984 cells categorized as malignant. The cases were divided into a training set (74 cases, 4763 cells), a validation set (15 cases, 1590 cells), and a test set (19 cases, 1831 cells). The training and validation sets were used for AI development, while the test set was used for performance evaluation. The AI's sensitivity for diagnosing malignancy in individual cells in the test set was 0.73 (95% confidence interval, 0.71-0.75), specificity was 0.97 (95% CI, 0.94-0.98), and positive predictive value was 0.99 (95% CI, 0.98-0.99).

Conclusions: The AI developed in this study demonstrated high specificity in determining whether individual cells observed in ROSE of lung cancer are malignant or benign. This system could assist in diagnosis during ROSE, improving diagnostic efficiency.

Keywords: ROSE, AI, Lung cancer

PT1.05 PULMONOLOGY AND STAGING
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.05.03 Comparison Between Lymph Node Station- and Zone-Based Classification: Analysis With the 9th IASLC Node Descriptors in Surgically Resected NSCLC

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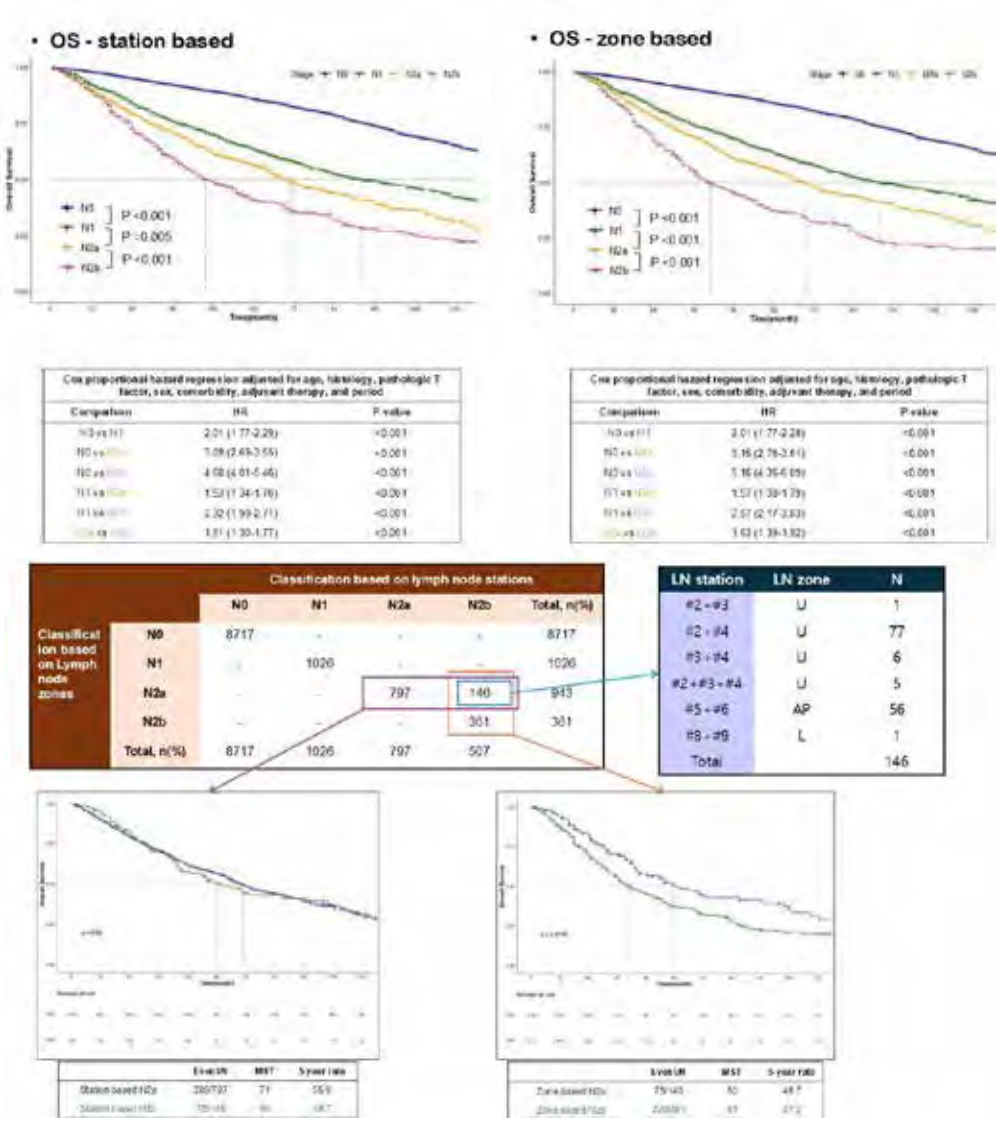
Introduction: The International Association for the Study of Lung Cancer (IASLC) has introduced a 9th staging, dividing pN2 into pN2a and pN2b. We adopted the newly subdivided N descriptors to reclassify based on the involved lymph node (LN) zones or LN stations and then compared the discriminative abilities of these classifications.

Methods: A retrospective analysis was conducted on patients who underwent complete resection with systematic LN dissection for non-small cell lung cancer (NSCLC) diagnosed as pathological stages I-III, between 2005 and 2022. The N classification was divided into four categories according to 9th TNM staging: N0, N1, N2a, and N2b. LN zones were defined by grouping the LN stations: peripheral or hilar for N1 nodes, and upper mediastinal, lower mediastinal, aortopulmonary, and subcarinal for N2 nodes. The concordance index (C-index), Akaike Information Criterion (AIC), and R2 were calculated to assess the discriminatory power of the two classification systems.

Results: A total of 11,047 patients (6112 male; median age: 62.9 years) were analyzed. The median follow-up was 57.0 months. Multivariable analysis revealed that the subdivided N descriptors, based on both lymph node stations and zones, independently predicted overall survival(OS) and freedom from recurrence (FFR). When classified using the zone-based method, the N2a and N2b groups exhibited lower 5-year survival rates and higher hazard ratios (HRs). The zone-based classification demonstrated a discrimination ability comparable to that of the station-based classification as evidenced by a similar C-index (0.7679 vs. 0.7679), lower AIC (43,235 vs. 43,241), and higher R2 (0.167 vs. 0.166) values.

Conclusions: The discrimination ability was not significantly different between station-based and zone-based N descriptors. The new concept of N classifications could be considered for future revisions of N descriptor for Lung cancer.



Keywords: lymph node descriptor, 9th IASLC, zone based classification

PT1.05 PULMONOLOGY AND STAGING
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.05.04 Use of an Ultrathin Bronchoscope With a Larger Working Channel Enhances Diagnostic Yield in Cone-Beam CT-Guided Transbronchial Biopsy

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Introduction: Cone-beam computed tomography (CBCT)-guided transbronchial biopsy (TBB) using an ultrathin bronchoscopy (UTB) may be useful for diagnosing peripheral lung lesions. Commercially available UTBs have working channel diameters of 1.2 mm (small channel; SC-UTB) and 1.7 mm (large channel; LC-UTB). The latter can be used in combination with (radial endobronchial ultrasound (R-EBUS), which may be even more useful. This study aimed to compare the outcomes of SC-UTB and LC-UTB with R-EBUS in CBCT-guided TBB.

Methods: This study retrospectively included patients with pulmonary lesions ≤30 mm who underwent CBCT-guided TBB using UTB between October 2016 and November 2024. The UTB and biopsy forceps were advanced to the target bronchus under virtual bronchoscopic navigation and 2D-fluoroscopy. For cases using SC-UTB, CBCT was performed with forceps inserted. In cases using LC-UTB, CBCT was performed with forceps inserted after inserting the R-EBUS probe. We used inverse probability weighting to adjust for confounding variables and the outcomes were compared between SC-UTB group and LC-UTB with R-EBUS group.

Results: SC-UTB was used in 89 patients, and LC-UTB with R-EBUS in 76 patients. The inverse probability-weighted cohort represent 306 weighted patient cases (SC-UTB ,154; LC-UTB, 152). In the weighted cohort the diagnostic yield was 64.9% and 75.7% in cases using SC-UTB and LC-UTB with R-EBUS, respectively, showing a significantly higher diagnostic yield with the latter (p=0.040). The proportion of re-navigation after the primary CBCT decreased (47.4% vs. 26.1%; p<0.001) and reduced number of CBCT scans during examination (mean 1.8 times vs. 1.1 times; p<0.001)) in the LC-UTB with R-EBUS group.

Conclusions: In CBCT-guided TBB using UTB for peripheral pulmonary lesions, the use of LC-UTB allows the use of R-EBUS, which is expected to result in a higher diagnostic yield and a reduced number of CBCT scans compared with the use of SC-UTB.

Keywords: Cone-beam computed tomography, ultrathin bronchoscopy, radial endobronchial ultrasound

PT1.06 PATHOLOGY AND BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.06.01 ERBB2 (HER2) Fusions in Lung Cancer Are Targetable by Anti-HER2 Small Molecules and Antibody-Drug Conjugates

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Introduction: ERBB2 (HER2) Fusions in Lung Cancer are Targetable by Anti-HER2 Small Molecules and Antibody-Drug Conjugates Juan Luis Gomez Marti1,2, Tom Zhang1,3, Rohan Masters1,3 , Ryan Cheng1,3, Marissa Mattar1, Leo Gili1, Christopher A Febres-Aldana1,2, Romel Somwar1,2 and Marc Ladanyi1,2 Affiliations:1 Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering CancerCenter, New York, NY, 10065, USA2 Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, 100653 Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065 Background: ERBB2 amplification and ERBB2 activating mutations are predictive biomarkers for targeted therapies including the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) and small molecule kinase inhibitors such as tucatinib. However, gene rearrangements involving ERBB2 remain understudied, especially in lung cancers. Here we performed a comprehensive pan-cancer analysis of the landscape of ERBB2 fusions and performed functional in vitro studies of a representative ERBB2 fusion.

Methods: A large institutional tumor cohort, prospectively profiled using MSK-IMPACT (genomic DNA) and MSK Solid Fusion (RNA) next-generation sequencing platforms, was interrogated for ERBB2 fusions. All structural variants (SV) involving ERBB2 were reviewed using Integrative Genome Viewer. Putative oncogenic ERBB2 fusions were defined as intergenic SVs preserving its tyrosine kinase domain (TKD, exons 18 to 24). Total or partial TKD truncation was considered as loss-of-function. Reading frame status, partner position in the chimeric transcript (5' or 3'), mechanism of SV formation (translocation or intrachromosomal rearrangement), and co-occurrence with ERBB2 amplification were annotated. Oncogenicity was assessed by interleukin 3-withdrawal assays in murine Ba/F3 cells or growth of transfected human bronchiolar epithelial (HBEC) cells in immunocompromised mice.

Results: Ninety-eight ERBB2 SV were detected amongst 87,266 profiled tumors (including 19,980 non-small cell lung cancers) with 33 (34%) retaining an intact TKD. Two fusion topologies were identified: 1) fusions involving upstream/5' partners fused to ERBB2 TKD (21/33, 64%) recapitulated the structure of known kinase fusions with the fusion partner contributing dimerization domains and/or aberrant high expression; 2) fusions of ERBB2 including TKD to downstream/3' partners (12/33, 36%) consistently replaced the C-terminal domain of ERBB2 (which contains its ubiquitination site at residue 1091) and recurrently involved signaling adapters as partners, e.g. ERBB2::GRB7 and ERBB2::SHC1. Both of these fusions retained the trastuzumab binding site and were associated with focal ERBB2 amplification/gains (22/33, 66%). The majority of ERBB2 fusions in the context of amplification were the result of intrachromosomal rearrangements (15/22, 68%) involving copies of the amplified ERBB2 allele fused to neighboring genes at 17q12 (IKZF3, STARD3, GRB7, TCAP). The ERBB2::SHC1 translocation involvingSHC1 at 1q21 (n=2, 0.01%) was the most common ERBB2 fusion in lung cancers lacking RTK/RAS/RAF canonical drivers, including ERBB2 amplification. Expression of ERBB2::SHC1 transformed Ba/F3 and HBEC cells. ERBB2::SHC1 was proficient at activating common growth and survival pathways in HBEC cells. Treatment of tumorigenic lung cells expressing ERBB2::SHC1 with afatinib, tucatinib, or T-DXd blocked cell growth and induced apoptosis.

Conclusions: ERBB2/HER2 fusions are rare oncogenic drivers in lung cancer. These tumors are candidates for therapy with FDA-approved HER2 antagonists. The subset of recurrent ERBB2 fusions with C-terminal/3' partners may represent an alternative mechanism of fusion oncogenicity.

PT1.06 PATHOLOGY AND BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.06.02 Distinct Bronchoalveolar Lavage Fluid Microbiome and Metabolome Profiles in EGFR-Mutated and Wild-Type Non-Small Cell Lung Cancer

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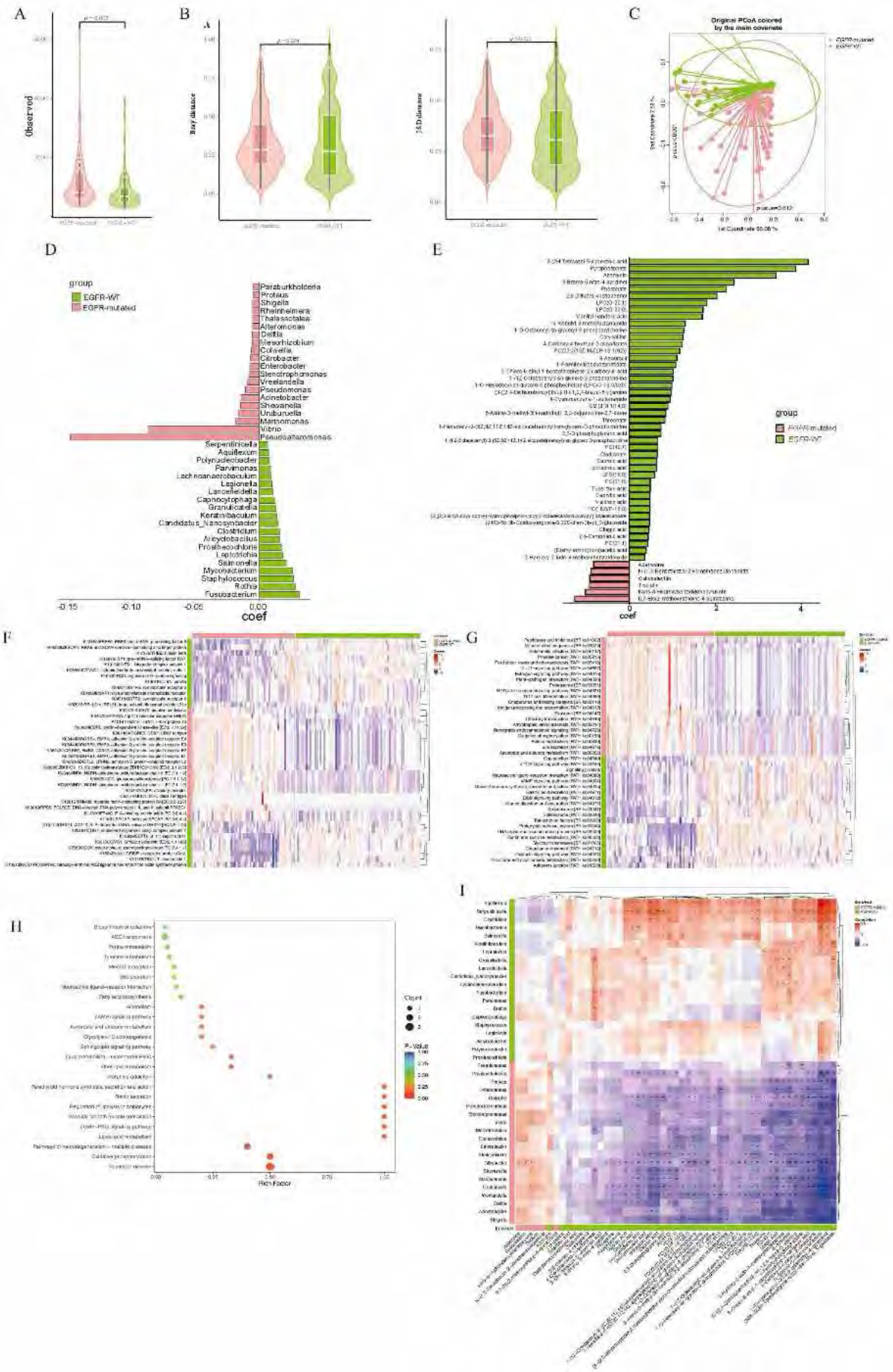
Introduction: Substantial differences exist in the tumor immune microenvironment between EGFR-mutated and wild-type lung cancer patients. Emerging researches indicates that bronchoalveolar lavage fluid (BALF) microbiota modulate lung local immune responses and contribute critically tumor initiation, progression and therapeutic outcomes. However, no studies to date have systematically characterized the BALF microbiota and metabolome profiles in NSCLC patients stratified by EGFR mutation status.

Methods: 131 treatment-naïve NSCLC patients from Guangdong, China was enrolled prospectively and BALF at initial diagnosis (59 EGFR-mutated and 72 wild-type cases) was collected. DNA was extracted for shotgun metagenomic sequencing. Alpha diversity was assessed using Observed Species and β-diversity was assessed using Bray-Curtis dissimilarity and Jensen-Shannon divergence (JSD), followed by Principal Coordinate analysis (PCoA). This was followed by KEGG Orthology (KO) and KEGG pathway enrichment analyses of differential species and metabolites. Spearman's rank correlation analysis was performed to evaluate associations between differential abundant microbial taxa and metabolites.

Results: EGFR-mutated cohort demonstrated significantly elevated α-diversity (Observed Species, $p = 0.007$) and β-diversity metrics (Bray-Curtis dissimilarity: $p = 0.004$; Jensen-Shannon divergence: $p < 0.001$) as well as in PCoA analysis compared to wild-type patients. In EGFR-mutated cohort, the significantly enriched($p<0.05$) genera were Pseudoalteromonas and Vibrio, whereas Fusobacterium and Rothia showed enrichment in wild-type cohort. Among tumor-immunity-related metabolites, adenosine was significantly enriched($p<0.05$) in EGFR-mutated cohort, whereas ellagic acid and valproic acid was accumulated in wild-type cohort. We summarized the top 20 differential genera and 51 differential metabolites between two cohorts. KO enrichment analysis of differential species($p<0.05$) showed that EGFR-mutated cohort were significantly enriched in proteins including hypoxia-inducible factor 1 (HIF-1) and inhibitor of apoptosis proteins (IAPs). In contrast, wild-type cohort exhibited enrichment($p<0.05$) in microtubule-related processes and mRNA splicing machinery. KEGG pathway analysis demonstrated significant enrichment($p<0.05$) of the prostate cancer pathway (PATH:ko05215) and NOD-like receptor signaling pathway (PATH:ko04621) in EGFR-mutated cohort whereas wild-type cohort indicated enrichment in ascorbate metabolism (PATH:ko00053) and spliceosome pathways (PATH:ko03040). KEGG enrichment analysis of differentially abundant metabolites($p<0.05$) revealed significant enrichment in pathways associated with Parkinson's disease, oxidative phosphorylation and neurodegenerative disorders. Notably, correlation analysis revealed positive associations($p<0.05$) between EGFR mutation-enriched genera and mutant-associated metabolites while negative correlations were observed($p<0.05$) with wild-type-associated metabolites.

Conclusions: To our knowledge, this is the first study to systematically analyze the BALF microbiota and metabolome profiles between EGFR-mutated and wild-type NSCLC patients. We identified differentially abundant microbial taxa and discriminatory metabolites, their mutation-specific enriched pathways and correlations.



Keywords: Bronchoalveolar Lavage Fluid (BALF), Microbiome and Metabolome, Lung Cancer

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PT1.06 PATHOLOGY AND BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.06.03 Loss of MTAP Expression in Thymic Carcinomas: Insights From a Retrospective Multi-Institutional, Global Study

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Introduction: Due to the rarity of thymic carcinomas our understanding of molecular alterations is limited. While tumor mutational burden is low in many thymic carcinomas, various promising molecular alterations are increasingly reported. Identifying these molecular alterations could facilitate the development of targeted therapies, potentially expanding treatment options for patients. Recently a second-generation protein arginine methyltransferase 5 (PRMT5) inhibitor has shown promising activity in solid tumors with Methylthioadenosine Phosphorylase (MTAP) deficiency. MTAP-deficient tumors may also be susceptible to antifolates targeting de novo purine synthesis. Furthermore, in non-small cell lung cancer, loss of MTAP expression negatively predicts response to immune checkpoint inhibitors. Loss of MTAP expression and homozygous CDKN2A deletion, frequently observed in mesotheliomas and other neoplasms, have been identified in a subset of thymic carcinomas in a single institution study. We aimed to identify the prevalence of loss of MTAP expression and molecular alterations in thymic carcinomas in a global, multi-institutional study.

Methods: Institutional databases of members of the Rare Tumor Committee of the International Association for the Study of Lung Cancer (IASLC) were searched for thymic carcinomas. A representative tissue section was stained with the locally available immunohistochemical tests for MTAP (clones: 2G4, 1813, EPR 22570-76, 42-T, RBT-MTAP). A subset of cases stained with MTAP has been previously published. A subset of cases underwent molecular testing (Foundation One or a laboratory developed next generation sequencing test). Medical records were reviewed for demographics and outcome data which were recorded as deidentified information in a common spreadsheet. Institutional IRB-approvals were obtained.

Results: Sixty-four thymic carcinomas were included. Fifty-three patients with available medical history had a median age of 59.6 years (range, 28-84), 31 (58.5%) were male. Eight (of 64, 12.5%) thymic carcinomas showed loss of expression of MTAP, 5 (7.8%) additional thymic carcinomas revealed subclonal loss of MTAP expression. Details of MTAP expression and results of molecular testing (n=6) by thymic carcinoma subtype are summarized in Table 1.

Thymic Carcinoma Subtype	N=64 (%)	Complete Loss of Expression of MTAP n (%)	Subclonal Loss of Expression of MTAP n (%)	Preserved Expression of MTAP n (%)	Molecular Alterations[a]	TMB (mutations/ Mbp) Median (range)
Squamous cell carcinoma	29 (45.3)	4	0	25	3 (of 5, 60%) with molecular alterations[b]; *CDKN2A/B* (n=2), *TP53* (n=2), *FGFR3*, *BAP1*, *CREBBP*, loss of *CDKN2C*	2.5 (0-9)
Thymic Carcinoma, NOS	21 (35.6)	2	3	16		
Adenocarcinoma, NOS	3 (5.1)	0	2	1		
Small Cell Carcinoma	3 (5.1)	0	0	3		
Mucoepidermoid Carcinoma	2 (3.4)	0	0	2		
Adenosquamous Carcinoma	1 (1.7)	1	0	0		
Sarcomatoid carcinoma	2 (3.1)	1	0	1	1 (of 1, 100%) with molecular alterations, *EGFR* amplification, *ERBB2* amplification, *SETD2*	5
Undifferentiated Carcinoma	1 (1.7)	0	0	1		
Lymphoepithelial Carcinoma	1 (1.7)	0	0	1		
Typical carcinoid	1 (1.7)	0	0	1		

NOS, Not otherwise specified; Mbp, Megabase pair; [a]Molecular testing performed in 6 cases; [b]*MTAP* was not included in the molecular analysis of 1 case

In one case of thymic carcinoma with loss of MTAP expression no mutation of MTAP was found.

Conclusions: Our study suggests that 20% of patients with thymic carcinoma including squamous cell carcinomas, adenosquamous carcinomas, and sarcomatoid carcinomas, could potentially benefit from PRMT5 inhibitors or antifolate therapy. Loss of MTAP expression in thymic carcinomas may occur due to mechanisms other than mutation in the MTAP gene. Future studies will investigate whether loss of expression of MTAP may be associated with outcome.

Keywords: MTAP, Thymic carcinoma, PRMT5 inhibitor

PT1.06 PATHOLOGY AND BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.06.04 Signatures of Functional CD8 T, Marginal Zone/Memory B and NK Cells in PBMCpredict Survivalin NSCLC Patients Receiving Chemoimmunotherapy

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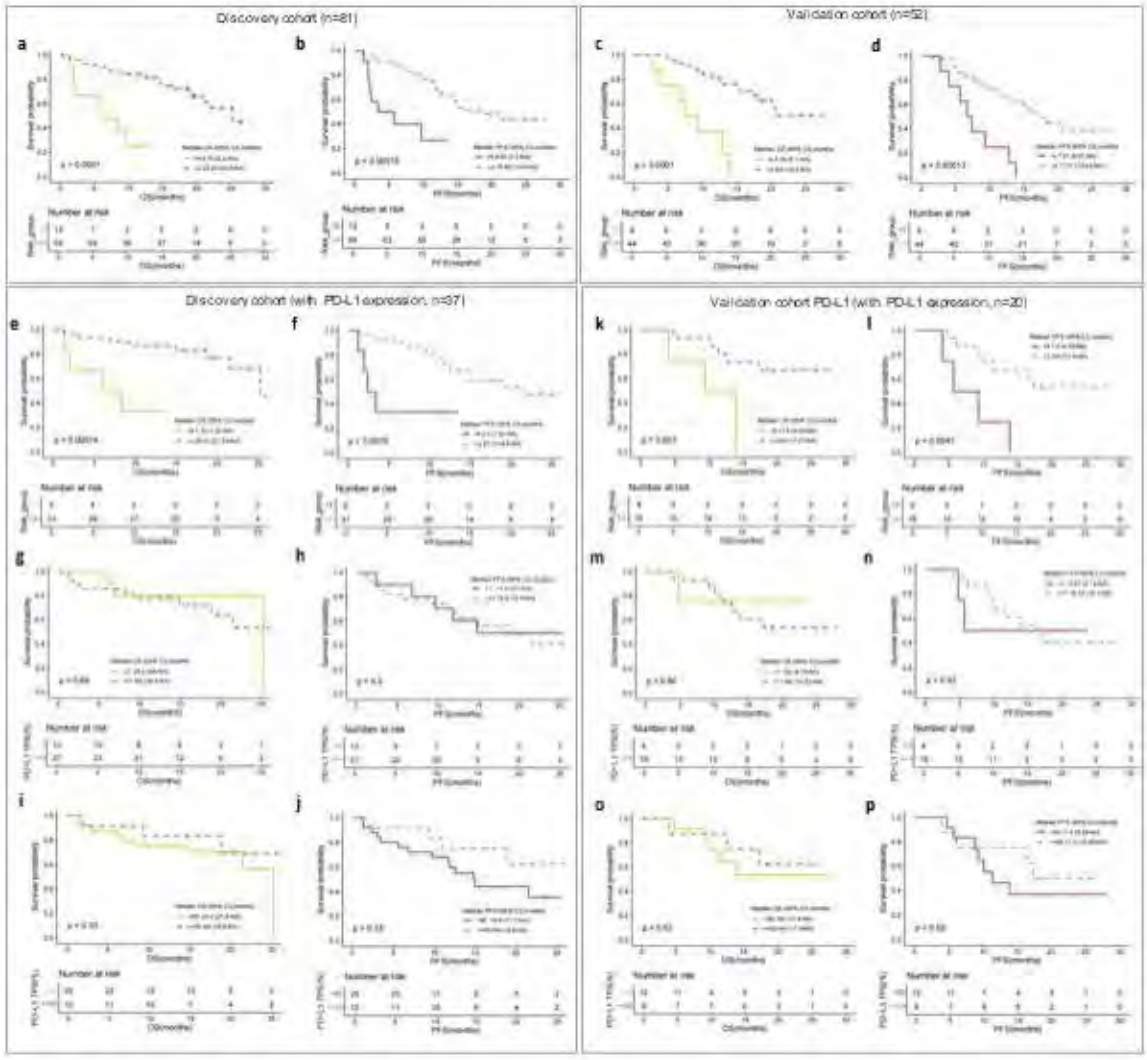
Introduction: Despite chemoimmunotherapy overcoming biomarker-based patient selection limitations, clinical evidence suggests variable treatment benefits. This study aimed to identify novel immune signatures derived from peripheral blood mononuclear cells (PBMCs) to predict survival in advanced non-small cell lung cancer (NSCLC) patients receiving chemoimmunotherapy.

Methods: We enrolled 133 treatment-naïve patients with advanced NSCLC who underwent first-line chemoimmunotherapy. Pre-treatment PBMC transcriptome sequencing was performed, and patients were randomly divided into discovery (n=81) and validation (n=52) cohorts. Using single-sample gene set enrichment analysis (ssGSEA) and Cox proportional hazards regression, we identified immune cell characteristics associated with prognosis and constructed a predictive model.

Results: Gene set analyses revealed significant associations between pre-treatment immune cell compositions and progression-free survival (PFS) and overall survival (OS) (P<0.05). CD8+ effector memory T cells, marginal zone B cells/activated memory B cells, adaptive natural killer cells-related genes expression were associated with improved PFS and OS. By integrating these T-cell, B-cell, and NK-cell module signatures, our comprehensive model effectively stratified patients into high- and low-risk groups with significant differences in survival outcomes. In the discovery cohort, median OS was significantly longer in the low-risk group (25.23 vs. 6.06 months, P<0.0001), as was median PFS (18.83 vs. 4.55 months, P=0.00015) (Fig 1a, b). These findings were confirmed in the validation cohort, with median OS (not reached vs. 8.36 months, P<0.0001) and median PFS (17.27 vs. 7.07 months, P=0.00013) (Fig 1c, d). Notably, our model demonstrated superior predictive performance compared to conventional PD-L1 expression thresholds (1% and 50%) for both PFS and OS (Fig 1e-p).

Conclusions: This novel PBMC-based immune signature model provides a robust, non-invasive approach for prognosticating outcomes in advanced NSCLC patients receiving first-line chemoimmunotherapy.



Keywords: NSCLC, Chemoimmunotherapy, Biomarker

PT1.06 PATHOLOGY AND BIOMARKERS
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.06.05 Enhancing Spread Through Air Spaces Diagnosis Using AI Diagnostician: A Multi-Center Study

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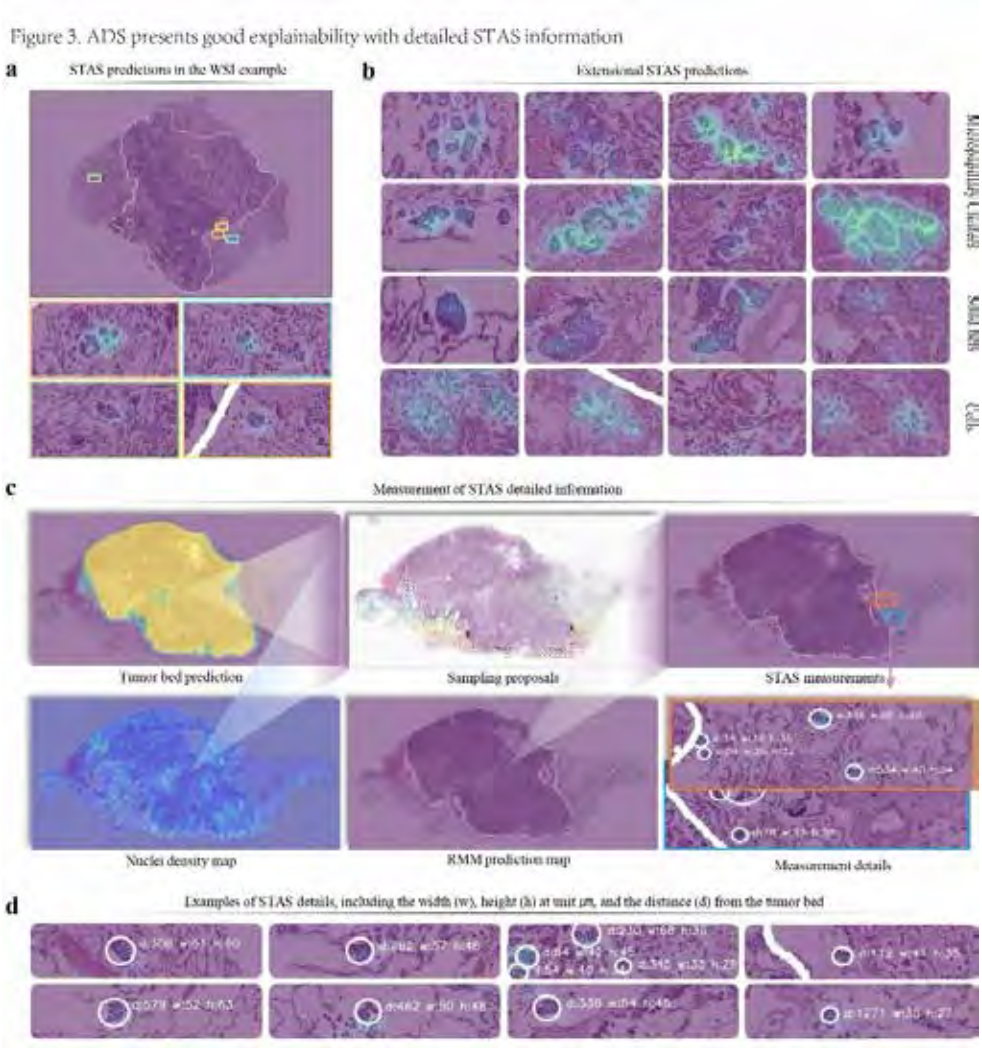
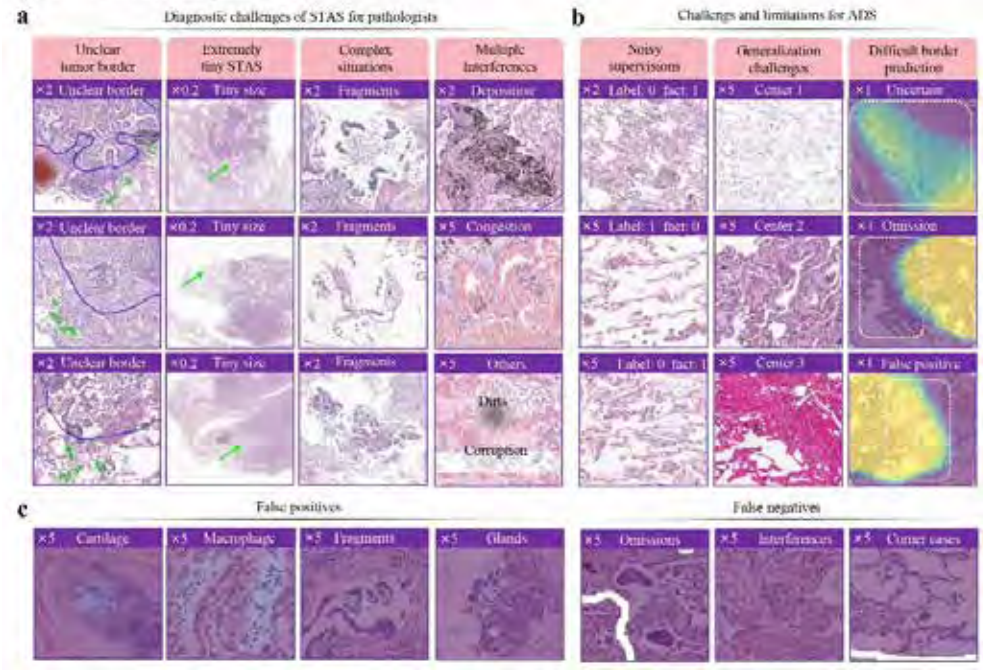
Introduction: Spread Through Air Spaces (STAS) is closely related to the postoperative recurrence and prognosis of lung cancer, playing a pivotal role in guiding the selection of clinical treatments for early-stage lung cancer. However, the accurate pathological diagnosis of STAS remains challenging, hindered by the variety of STAS forms, limited specialized training among pathologists, and a global shortage of pathologists.

Methods: To address these challenges, we established the largest STAS datasets to date sourced from seven medical centers, and developed an innovative AI solution named AI Diagnostician for STAS (ADS).

Results: Leveraging 210 million pathological tiles from 1,586 whole-slide images (WSI), ADS demonstrates remarkable performance in identifying this unique and challenging tumor invasion pattern in clinical settings. Across the medical centers involved, ADS significantly outperforms conventional methods, achieving improvements in Area Under the Curve (AUC) ranging from 13.96% to 21.51% under fair settings. Moreover, ADS enhances the diagnosis sensitivity of junior pathologists by an average of 10.44%, while simultaneously reducing the average review time by 50.66%.

Conclusions: By augmenting diagnostic accuracy and efficiency in clinical practice for multicenter, ADS holds promise for enhancing the accurate diagnosis and treatment of lung cancer, ultimately improving patient outcomes.





Keywords: Spread Through Air Spaces, lung cancer, AI Diagnostician

PT1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.07.01 IASLC Multidisciplinary Recommendations for Pathological Response Evaluation of Resected Lymph Nodes After Neoadjuvant Therapy in NSCLC

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Introduction: Pathologic response has become a surrogate of long-term outcomes following neoadjuvant chemotherapy, and most recently either the primary or secondary endpoint in phase II and III neoadjuvant immunotherapy clinical trials in non-small cell lung carcinoma (NSCLC). Although several recent retrospective studies have demonstrated the prognostic value of treatment response in lymph node metastases following neoadjuvant therapy, there remains no standardized or widely accepted guidance on how to evaluate pathologic response in resected lymph node specimens—either in clinical trials or routine clinical practice. In 2020, the International Association for the Study of Lung Cancer (IASLC) published detailed multidisciplinary consensus recommendations for standardization of gross processing and pathologic evaluation of surgically resected lung cancers treated with any type of neoadjuvant therapy. This recommendation provided a detailed guidance for the assessment of pathologic response in the primary tumor. The aim of the current project is to provide equally detailed guidelines on the evaluation of treatment response in the regional lymph nodes.

Methods: The IASLC Pathology Committee is conducting an interdisciplinary Delphi study, with broad representation from medical oncologists, thoracic surgeons, radiologists, and pathologists. The Delphi-Process is applied for the generation of the recommendations. A core group of pathologists has designed the questions to be answered and has drafted recommendations for voting by a large interdisciplinary project team. Feedback loops after voting ensure adaptation of the recommendations to gain final consent. Two to three rounds of voting are anticipated. According to the Delphi-SOP issued by the IASLC, consensus is defined as agreement of at least 85%.

Results: The core team has drafted 35 initial questions and has condensed them to 13 final recommendations for Delphi voting (see table). Those recommendations focus on interdisciplinary aspects, the definition of complete and major pathologic response (CPR, MPR) and application of TNM-staging when it comes to lymph node evaluation after neoadjuvant therapy, specificities of macroscopic and histological evaluation including slide preparation and the usage of immunohistochistry. The Delphi voting methodology is currently being executed.

Conclusions: The final IASLC interdisciplinary recommendations on the evaluation of lymph nodes resected after neoadjuvant therapy in NSCLC will be reported at the WCLC 2025. The proposed recommendations are intended to be practice-changing, providing a harmonized framework for evaluating regional lymph nodes that can be adopted in both clinical trials and real-world settings. Areas where consensus failed to be reached will equally be discussed, in order to stimulate future research.

Table: Recommendations for pathological response evaluation of resected lymph nodes after neoadjuvant therapy in NSCLC drafted for Delphi-voting.

Interdisciplinary Aspect	The surgical team should provide information about neoadjuvant therapy to the pathology laboratory to ensure proper processing and evaluation of the resection specimen.
Definitions of CPR and MPR	The term "Complete Pathologic Response (CPR)" is defined as no residual viable tumor in both the lung and the lymph nodes. Any viable tumor in lymph nodes precludes designation of CPR, even if the primary tumor shows no viable tumor cells.
	The term "Major Pathologic Response (MPR)" is defined as a treatment response of ≤10% viable tumor cells in the primary tumor. MPR can also be classified for the lung primary in the setting where the lung primary shows little or no viable tumor, but lymph nodes show viable metastatic carcinoma (ypT0, N1, 2, or 3).
Histologic Evaluation of Treatment Response in Lymph Nodes	For all patients who have undergone neoadjuvant therapy (regardless of regimen type), treatment response should be assessed across all sampled lymph nodes together using the IASLC-criteria established for the primary tumor and should be recorded separately to treatment response in the primary tumor. This involves estimating the percentages of viable tumor, stroma and necrosis within the tumor bed.
	If the tumor bed cannot be clearly identified, this limitation should be documented in the pathology report.
	Unweighted ("eyeball") estimation is acceptable for assessing treatment response in the lymph nodes.
	Whenever possible, the size of the largest metastatic deposit for each lymph node station should be reported.
	The presence of psammoma bodies or acellular mucin without viable tumor cells should not be regarded as viable tumor.
Staging	The general TNM staging, and R status assessment principles should continue to be applied.
	Treatment response in cases where the primary tumor directly extends into lymph nodes should be included in the evaluation of the primary tumor bed but staged as lymph node metastases in accordance with TNM general principles.
Macroscopic Aspects and Slide Preparation	All intraparenchymal lymph nodes in the main lung resection specimen as well as separately submitted lymph node stations should be entirely submitted for histologic evaluation. Exceptionally, if there is a very large metastasis (> 2 cm), the lymph node can be bisected and the central slice through the tumor can be submitted in designated cassettes.
	If a tumor bed is suspected but no viable tumor cells are detected in the initial histologic sections, deeper levels may be considered for further evaluation.
Use of IHC in Lymph Node Evaluation	Routine immunohistochemistry (IHC) in cases lacking morphological evidence of viable tumor cells is not recommended. In selected cases, however, immunohistochemistry (e.g., cytokeratin) may be used to confirm the presence of viable tumor cells suspected on H&E slides.

Keywords: neoadjuvant Therapy, Lymph node regression grading in NSCLC, IASLC interdisciplinary recommendations

PT1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.07.02 Neoadjuvant Ensartinib for ALK-Positive (ALK+) Non-Small Cell Lung Cancer (NSCLC): A Multicenter, Real-World Study

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Introduction: Neoadjuvant-targeted therapies provided more opportunities for achieving a cure in patients with NSCLC. Notably, anaplastic lymphoma kinase (ALK) inhibitors in the neoadjuvant setting for ALK+ NSCLC have demonstrated promising efficacy and favorable tolerability profiles. Ensartinib is a novel, potent, and highly selective ALK inhibitor that has been approved for first-/second-line treatment of advanced ALK+ NSCLC. However, its application as a neoadjuvant therapy is supported by limited studies. This study aims to evaluate the efficacy and safety of ensartinib as neoadjuvant therapy for ALK+ NSCLC in a real-world setting. Herein, we primarily reported the outcomes of the retrospective cohort.

Methods: This study included patients aged ≥18 years with histologically confirmed resectable, stage II-III NSCLC who were ALK+, and had previously received neoadjuvant treatment with ensartinib, either as monotherapy or in combination with chemotherapy. Outcomes included major pathologic response (MPR), pathological complete response (pCR), objective response rate (ORR), disease-free survival (DFS), 2-year DFS rate, overall survival (OS), and safety.

Results: A total of 9 patients (median age, 61 years [range, 36-74]) with ALK+ NSCLC were included in this study; of whom, the majority were male (66.7%), diagnosed with lung adenocarcinoma (88.9%), and had an ECOG PS of 0 (55.6%). All patients (100.0%) underwent R0 resection. MPR and pCR rates were 66.7% (95% CI, 29.9%-92.5%) and 44.4% (95% CI, 13.7%-78.8%), respectively. No complete responses were observed, 7 patients (77.8%) achieved partial response, resulting in an ORR of 77.8% (95% CI, 40.0%-97.2%). Adverse events (AEs) occurred in 7 patients (77.8%), including rash (77.8%), white-cell count decreased (22.2%), dysgeusia (11.1%), and pruritus (11.1%). Only one patient (11.1%) experienced a grade ≥ 3 white-cell count decreased. No patients had grade ≥ 3 treatment-related AEs.

Conclusions: Neoadjuvant ensartinib demonstrated a promising antitumor activity in ALK+ NSCLC with high rates of MPR, pCR, and ORR, along with acceptable tolerability.

Keywords: Ensartinib, NSCLC, Neoadjuvant Therapy

PT1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.07.03 Adjuvant Osimertinib in IB-IIIB NSCLC with Uncommon EGFR Mutations (Admin): Mutation Profile and ctDNA Dynamics

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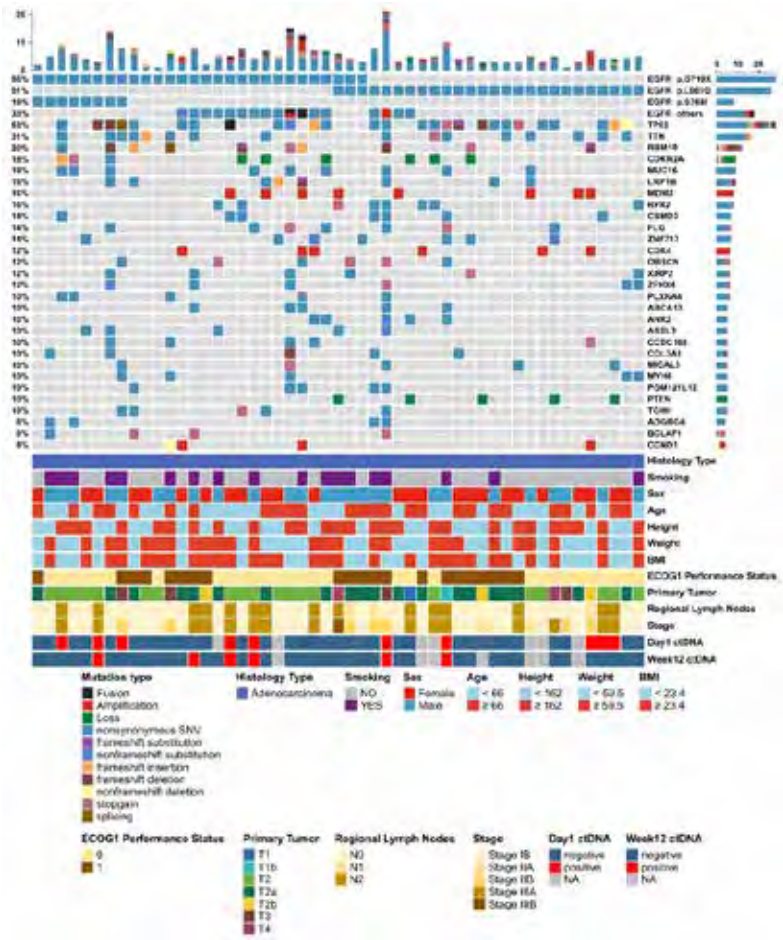
Introduction: Uncommon epidermal growth factor receptor mutations (EGFRm) constitute a heterogeneous group of mutations within exons 18 to 21, comprising approximately 10% to 20% of all EGFRm. Although osimertinib has demonstrated impressive efficacy in treating common EGFRm NSCLC, its efficacy in uncommon EGFRm NSCLC remains incompletely characterized. ctDNA monitoring could detect the molecular dynamics in uncommon EGFRm NSCLC.

Methods: The ADMIN study (NCT05546866) is an open-label, prospective, multicenter, single-arm trial that enrolled patients with stage IB-IIIB NSCLC harboring uncommon EGFRm (G719X, S768I, L861Q, or de novo T790M), who received adjuvant osimertinib (80 mg once daily) with or without prior adjuvant chemotherapy. Whole-exome sequencing (WES) was performed on primary tumor tissue to identify somatic mutations, and a personalized, tumor-informed ctDNA assay was utilized to monitor molecular residual disease (MRD) dynamics at baseline (before adjuvant osimertinib, D1) and after 12 weeks (wk-12) of adjuvant osimertinib. Quantitative analysis of MRD was conducted by measuring the concentration of haploid genome equivalents per milliliter (hGE/mL).

Results: A total of 51 NSCLC patients with uncommon EGFRm were enrolled. The mutation profile and relevant characteristics were presented in Figure 1. 43 pts had evaluable plasma ctDNA status at both D1 and wk-12 time point, comprising 23 males and 20 females with a median age of 66 years old. MRD positive rate was 23.3% (10/43) and mean level of ctDNA was 1.81 hGE/mL at D1 and reduced to 13.9% (6/43) and 0.05 hGE/mL at wk-12. 50% (5/10) of patients had ctDNA clearance (MRD positive to negative) after 12 weeks osimertinib treatment. 18.6%(8/43)of patients were plasma EGFRm positive at baseline. Plasma EGFRm clearance was observed in 62.5% (5/8) patients. In three patients without EGFRm clearance, variant allele frequency (VAF) of EGFRm was also largely decreased.

Conclusions: 12 weeks of osimertinib treatment could facilitate ctDNA clearance in stage IB-IIIB NSCLC with uncommon EGFRm. Long-term follow-up is ongoing to further investigate the association between ctDNA status and recurrence.



Keywords: ctDNA, uncommon EGFRm, Osimertinib

PT1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.07.04 Radiomics Model Based on Synthesized PET for Predicting Neoadjuvant Therapy Pathologic Response in NSCLC (CPT-LC-NEO Trial)

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Introduction: Neoadjuvant immunochemotherapy has become a cornerstone in lung cancer treatment, significantly improving patient prognoses. However, substantial inter-individual variability in therapeutic response and limitations in PET imaging hinder accurate pathological response prediction. To overcome these challenges, we propose a GAN-based framework that integrates cross-modal image synthesis and multimodal feature fusion, addressing incomplete clinical imaging data and single-modality limitations to establish a novel predictive paradigm for NSCLC neoadjuvant therapy.

Methods: A total of 729 NSCLC patients were enrolled and stratified into a source domain pre-training group (SDPG) and a target domain fine-tuning group (TDFG). An enhanced Pix2PixHD GAN was utilized to develop a CT-to-PET synthesis model (CPT-NeoIO). In the TDFG cohort, various machine learning models were employed to construct and validate single-modality and multimodal pathological response prediction models based on synthetic PET images. Subsequently, synthetic PET images were generated for 91 resectable NSCLC patients with only pre-treatment CT data, and an XGBoost-based predictive model was established to assess the impact of cross-modal PET generation and multimodal fusion on predictive performance (Figure 1.A).

Results: The CPT-NeoIO model generated PET images with high structural fidelity (SSIM = 0.946) and minimal reconstruction error (MSE = 0.017, IQR: 0.012-0.021). A Turing test demonstrated that 73% of the synthesized images were rated as high quality by clinical physicians. In predicting neoadjuvant therapy response, synthetic PET images achieved performance comparable to conventional imaging, and the multimodal fusion model outperformed single-modality models. Notably, the predictive efficacy of the multimodal model based on synthetic PET/CT closely matched that of real PET/CT (AUC = 0.796 vs. 0.791, p = 0.589) (Figure 1.B). Furthermore, in the validation cohort, incorporating synthetic PET into the multimodal model enhanced predictive accuracy (AUC increase from 0.57 to 0.72, Δ = 0.15, p = 0.002), demonstrating the efficacy of cross-modal synthesis and feature integration (Figure 1.C).

Conclusions: Our findings underscore the potential of GAN-based CT-to-PET synthesis in addressing PET imaging limitations while significantly improving the prediction of pathological response to neoadjuvant therapy in NSCLC through multimodal feature fusion. This approach holds substantial clinical translational value, offering a non-invasive, cost-effective, and accessible alternative for treatment stratification.

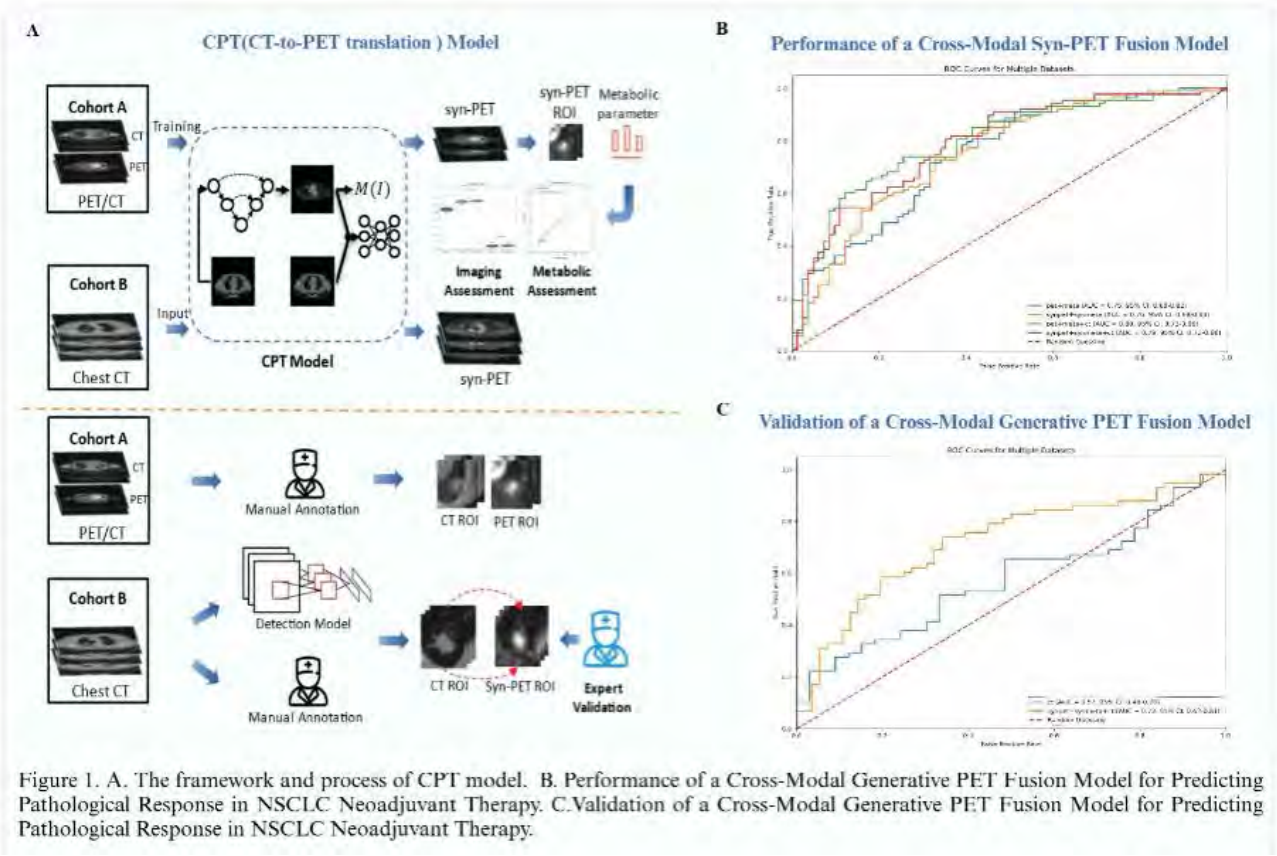

Figure 1. A. The framework and process of CPT model. B. Performance of a Cross-Modal Generative PET Fusion Model for Predicting Pathological Response in NSCLC Neoadjuvant Therapy. C.Validation of a Cross-Modal Generative PET Fusion Model for Predicting Pathological Response in NSCLC Neoadjuvant Therapy.

Keywords: Non-Small Cell Lung Cancer, Neoadjuvant Therapy, Cross-Modal Image Synthesis

PT1.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.08.01 Neoadjuvant Almonertinib Followed by Chemo-Immunotherapy in II-IIIB EGFR-TKI, Interim Analysis of a Single Arm, Phase II Study (NEOVADE)

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Introduction: Neoadjuvant EGFR-TKIs has revealed superior efficacy and disease-free survival (DFS) in resectable II-IIIB NSCLC, however, unmet needs remained in major pathological response (MPR) and overall survival (OS). This study aimed to explore the efficacy and mechanisms of neoadjuvant almonertinib followed by combination of immunotherapy and chemotherapy in II-IIIB NSCLC.

Methods: In this single arm, phase II study (NCT06300424), we tend to enroll 32 patients with untreated II-IIIB NSCLC to receive 110mg of almonertinib, followed by adebrelimab and chemotherapy every 3 weeks for 3 cycles before surgery. Primary end point was MPR.

Results: This study has enrolled 23 patients at the time of March 31, 2025, and 13 patients has undergone surgery, 1 patient discontinued 3rd chemo-immunotherapy and surgery. Overall response rate was 64.3% (9/14). MPR rate was 35.7% (5/14), including 2 (14.3%) patients with complete pathological response (CPR), N downstage was found in 50.0% (7/14) of patients. Twenty-one patients will finish neoadjuvant therapy and surgery as of July 30, 2025, further updated data will be presented at the Conference.

Conclusions: Neoadjuvant almonertinib followed by chemo-immunotherapy maybe a potential efficacious treatment for II-IIIB EGFR-NSCLC.

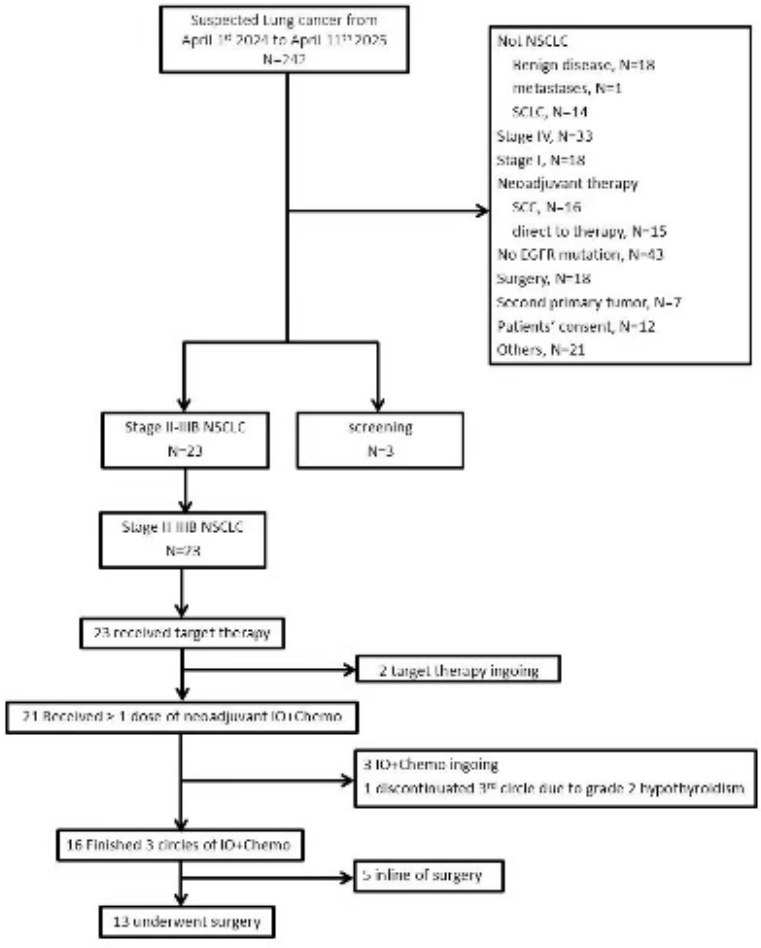

Figure 1. Study flowchart

Date cutoff: April 12th, 2025

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-treat Population).

Characteristic	Number
Age	
Median (range, yrs)	59 (39-73)
Gender	
Male	3
Female	11
ECOG performance status score	
0	5
1	9
Smoking status	
Smoker	3
Never smoker	11
Baseline stage	
II	4
III	10
Tumor stage	
T1	4
T2	5
T3	4
T4	1
Node stage	
N1	6
N2	7
N3	1
Histology	
Squamous	0
Nonsquamous	14
PD-L1 tumor proportion score	
<1%	6
1–49%	4
≥50%	4
EGFR	
19del	7
L858R	6
Uncommon mutation	1

Table 2. Primary and Secondary Outcomes as of April 12, 2025

Outcomes	TKI+IO
Major pathological response rate	35.7% (5/14)
Complete pathological response rate	14.3% (2/14)
Tumor response rate after receiving neoadjuvant TKI	
Objective response	42.9% (6/14)
Disease control	100.0% (14/14)
Tumor response rate after receiving neoadjuvant TKI+IO	
Objective response	64.3% (9/14)
Disease control	100.0% (14/14)

Keywords: non small cell lung cancer, neoadjuvant immunotherapy, EGFR

PT1.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.08.02 5-Y Outcomes of Stereotactic Ablative Radiotherapy in 101 Unresectable La-Nsclc Patients:The START-NEW-ERA Phase II Trial

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Introduction: In the early analysis of START-NEW-ERA phase II trial (Clinical trials.gov NCT05291780), stereotactic ablative radiotherapy (SAbR) had optimal local control (LC) and promising OS without ≥G3 toxicity in 50 unresectable LA-NSCLC patients unfit for concurrent chemo-radiotherapy (1). Here we report the 5-year outcomes of SAbR in 101 unresectable LA-NSCLC.

Methods: SAbR was delivered by V-MAT to primary tumor (T) and regional nodes (N) based on PET-CT. Simultaneous integrated boost (SIB) was optimized to differentiate the dose for T and N. Moreover, when target volume overlapped organs at risk (OAR) the simultaneous integrated protection (SIP) technique was implemented to lower the dose to the part of planning target volume closest to the critical OAR. Neoadjuvant ChT was prescribed in fit patients. After PACIFIC trial publication PD-L1 ≥1% received durvalumab after SAbR. The co-primary study endpoints were LC and safety. Hepilor gel and Kariosyte mouthwash were recommended in order to prevent dysphagia and esophagitis.

Results: Between December 2015 and August 2024, 101 unresectable LA-NSCLC patients unfit for concurrent ChT-RT were enrolled. Median age was 73 years (45-90). Histology was adenocarcinoma in 66% and squamous cell carcinoma in 34%. The stage was IIB, IIIA, IIIB and IIIC in 12%,41%,33% and 14%. 55% had multiple nodes, 84% was had central/ultracentral T and 96% had T and/or N overlapping organs at risk (OAR). 44%, 31% and 26% received SAbR alone, ChT followed by SAbR and ChT followed by SAbR followed by durvalumab. Median dose was 45 Gy (35-60) and 40 Gy (35-50) in 5 daily fractions to T and N, respectively. After a median follow-up of 55 months (95% CI, 38 to 76) range (10-119 months), the median local recurrence (LR) free survival (FS) was not reached (95% CI, 8 to not reached). The 1-, 3- and 5- year LR-FS rates were 88 ± 3%, 69 ± 5% and 69 ± 5%, respectively. The median thoracic nodal recurrence (TNR)-FS was not reached (95% CI, to not reached). The 1-, 3- and 5- year TNR-FS rates were 83 ±4%, 63 ±5% and 63 ± 5%, respectively. The median distant progression-FS (d-PFS) was 54 months (95% CI, 20 months to 65). The 1-, 3- and 5- year d-PFS rates were 79 ±4%, 50± 5% and 47± 6%, respectively. The median PFS was 14 months (95% CI, 13 to 20). The 1-, 3- and 5- year PFS rates were 62±5%, 31±5% and 28 ±6%, respectively. The median OS was 50 months (95% CI, 42 to 73). The 1, 3, and 5-year OS rates were 88 ± 3%, 65 ± 5% and 41 ± 6%, respectively. 2% and 2% patients had experienced G3 lung and esophageal toxicity, respectively.

Conclusions: To our knowledge the START-NEW-ERA is the trial with more patients and longer follow-up investigating SAbR in LA-NSCLC. The 5-year outcomes confirm robust and sustained benefit in terms of safety and effectiveness suggesting SAbR as a great alternative in LA-NSCLC patients unfit for concurrent chemo-radiotherapy.1. Int J Radiat Oncol Biol Phys 2023;115(4):886-896. doi: 10.1016/j.ijrobp.2022.10.025.

Keywords: stereotactica ablative radiotherapy (SAbR), locally advanced non-small cell lung cancer, immunotherapy

PT1.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.08.03 Chemoradiation/Immunotherapy(IO) for Stageiii NSCLC: Timing of IO, and the Benefits/ Selection in Elderly & Black Patients

H. Eldib[1], R. Voland[1], J. Flickinger[2], M. DeCamp[3], M. Jamil[1], N. Chowdhury[1], J. Bastidas[1], M. Shenouda[1], Y. Shweihat[1], M. Valsecchi[4], A. Bir[1], T. Pacioles[1], D. Silbermins[1], M. Legenza[1], J. Varlotto[1]
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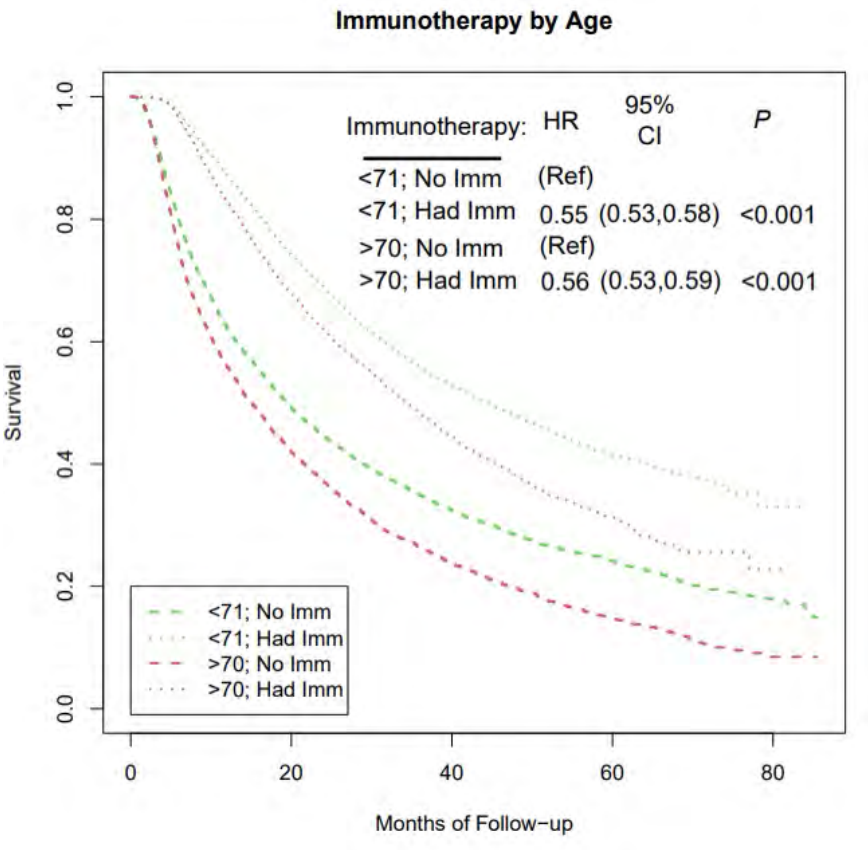
Introduction: Durvalumab was FDA approved as consolidation immunotherapy(IO) after concurrent chemo/radiation(CRT) in 2018 for the treatment of Non-small cell lung cancer(NSCLC). Our study investigates the timing of IO's association with OS, the % of patients receiving IO for each year, and whether IO affects prognostic factors as compared to the years prior to its approval.

Methods: The NCDB was queried for Stage III NSCLC patients (2016-2022) undergoing CRT (54-66Gy) +/- IO. Patients were grouped based on IO timing after CRT (0-14, 15-28, 29-42, >42 days), assuming a 45-day course of CRT. Propensity score matching compared OS between early (0-14 days) and late IO administration and age-adjusted OS. ANOVA and multivariable analyses assessed OS factors for CRT alone (2016/2017, N=13,034, B years) vs. CRT + IO (2018-2021, N=29,974, A years) and IO selection factors (2018-2022, N=36,519). Ages were divided into quintiles for analysis.

Results: Median follow-up was 42 months. IO use increased from 47.8% to 58.3% from 2018-2022. Significant favorable OS factors in the B years include the youngest age quintile, academic facility treatment, and lower cT stage. In the A years, significant favorable factors include the youngest age quintile, Black race, academic facility treatment, 0 Charlson Deyo Score (CDCC), and adenocarcinoma. In 2018-2022, factors associated significantly with less IO use were the oldest two age quintiles, community programs, CDCC 3, Black/White Hispanic race, and non-adenocarcinoma histology. Compared to early IO, the HR for OS for those receiving IO at 15-28, 29-42, and >42 days were 0.94 (0.87-1.01), 1.02 (0.94-1.10), and 1.01 (0.94-1.01), respectively with median OS ranging from 39.1- 42.6 months. Patients aged 71+ benefitted just as much from IO as those < 70 with HRs = 0.56(0.53 -0.59), 0.55(0.53-0.58), respectively.

Conclusions: Consolidative IO remains underutilized with only 58.3% receiving it in 2022 despite its known ability to increase OS/PFS. The timing of IO administration had no effect on OS, but IO positively affected OS even in those who receiving IO at times greater than allowed in the Pacific trial(> 42 days post CRT, median 61 days). Those greater than 70 benefit equally from IO as those younger and Blacks benefit more from IO than other races despites significantly less IO use in these groups. There needs to be increased IO usage, especially in Black and elderly patients.



Keywords: Immunotherapy(IO), concurrent chemo/radiation(CRT), Non-small cell lung cancer (NSCLC)

PT1.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.08.04 Cachexia in Patients With Unresectable Stage III NSCLC

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Introduction: Cachexia is a wasting condition that negatively impacts survival outcomes and quality of life. Across solid tumors, cachexia is highly prevalent, accounting for about half of patients with advanced cancer, including lung cancer. Nevertheless, cancer-associated cachexia is not captured by the national cancer statistics in any country and is seldom listed as the cause of death. It is mainly associated with advanced disease but can also occur in curable setting and might be reversed by successful treatment of the underlying cancer. We hypothesize that evaluating circulating non-invasive markers, such as cytokines, could help better understand the cachexia phenotype and identify potential interventions to improve the clinical management of these patients.

Methods: We conducted a prospective study that included 51 patients with stage III unresectable non-small cell lung cancer (NSCLC) that underwent concurrent chemoradiotherapy followed by immunotherapy. Body composition, metabolic parameters have been prospectively assessed, and blood was collected before and after completing chemoradiation. Patients were classified based on their cachexia status. Cachexia was defined as weight loss greater than 5%, or weight loss greater than 2% in individuals with body mass index (BMI) <20 kg/m2 or low skeletal muscle mass (Fearon criteria). Then, metabolic parameters, body composition metrics and the circulating levels of different cytokines were compared between the two groups.

Results: 27 patients (53 %) with stage III unresectable NSCLC had cachexia based on Fearon's criteria. Almost all women included in the study displayed cachexia, whereas men were evenly distributed across groups. The cachectic phenotype was significantly enriched in patients with poorer ECOG performance status, higher tumor stage, lower BMI values, higher reactive C protein blood levels, moderate to severe malnutrition, decreased caloric intake and decreased physical strength, based on dynamometer test. Patients with cachexia had worse PFS compared with those without (univariate HR (95%-CI) = 3.1 (0.9 - 10.9), p = 0.08). Regarding body composition, cachexia-classified patients showed less adipose tissue (i.e., lower subcutaneous, visceral and total adipose tissue index) and lower skeletal muscle index. We identified several cytokines that were elevated in the blood of patients with cachexia compared with their counterparts, such as CCL23, IL6, IL11, OSM or AGRP.

Conclusions: Cancer cachexia is frequent in stage III unresectable NSCLC and is associated with shorter PFS. We identified novel cytokines associated with cancer cachexia that might become new potential targets to overcome this debilitating condition.

Keywords: cachexia, stage III NSCLC, biomarkers

PT1.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.08.05 Radioresistance of NSCLC Tumors Is Mediated by Immunosuppressive Cell Populations. Strategies to Sensitize Tumors by Targeting Innate Immunity

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Introduction: Standard treatment for inoperable or unresectable stage I-III NSCLC includes stereotactic ablative radiotherapy (SABR) and concurrent chemo and radiotherapy, but locoregional recurrence occurs in 10%-30% of the patients. In the absence of distant metastasis, re-irradiation is the main curative-intent treatment option available for these patients. The tumor microenvironment (TME) plays a role in supporting tumor growth and resistance to cancer therapies. However, scarcity of immunocompetent lung cancer models to assess radioresistance in the context of re-irradiated tumors has hindered the study of the relevance of the TME in this process. In the present study, we have developed and characterized two murine lung adenocarcinoma models of radiation resistance in immunocompetent mice and evaluated the role of TME cell in radioresistance.

Methods: Two lung adenocarcinoma cell lines (Lacun3 and CMT167) were subjected to several rounds of irradiation (in vivo and in vitro) to generate their corresponding radioresistant cell lines (Lacun3 RR and CMT167 RR from now on). Resistance to radiation was tested in vivo and TME was analyzed with flow cytometry, in situ immunophenotyping, RNA sequencing (seq) and immune depletion experiments.

Results: We have successfully generated and characterized the Lacun3 RR and CMT167 RR models. Clonogenic and apoptotic assays confirmed that both Lacun3 RR and CMT167 RR were more resistant to radiotherapy than their parental cell lines. Downstream signaling cascades revealed increased pATR, pP38 and pP70-S6K levels in these cells, with higher sensitivity to pATR-targeting drugs. To validate the phenotype in vivo, different radiation schedules were tested for both models (3 x 8 Gy for Lacun3 RR; 5 x 5 Gy for CMT167 RR). In both cases we found that immunocompetent mice bearing radioresistant tumors were completely refractory to irradiation, unlike controls. RNAseq showed downregulation of STING, IFNα/β and IFNγ signaling, as well as reduced expression of proinflammatory cytokines, in irradiated Lacun3 RR tumors. Flow cytometry and/or in situ localization revealed decreased tumor infiltration of CD4+, CD8+, CD8+/PD-1+ and macrophages, as well as increase in T regulatory (Treg) cells and PMN-MDSC cells, in irradiated Lacun3 RR tumors. In irradiated CMT167 RR tumors, reduction in NK cells, CD4+ cells and macrophages, together with increase in Treg cells was observed. Depletion of CSFR1+ cells, Gr1+ cells or the STING/IFNα/β/γ axis with poly(I:C) + resiquimod in radioresistant tumors led to re-sensitization to radiotherapy. Co-depletion of CD8+/CD4+ lymphocytes led to resistance to radiotherapy in parental tumors. Injection of Lacun3 RR and CMT167 RR tumors in athymic nude mice (immunodeficient) resulted in radiotherapy sensitivity, similar to the one found for the parental tumors, thus stressing the role of the immune system in radioresistance.

Conclusions: Our results demonstrate that the immune system plays a key role in radioresistance, in the two immunocompetent mouse models that we have generated. Each radioresistant model has their own particular TME, suggesting that, depending on the TME, radioresistance can be mediated by different immune populations. Moreover, targeting the immunosuppressive myeloid population or restoring innate immunity can revert resistance to radiotherapy in NSCLC.

Keywords: NSCLC, Radioresistance, Re-Sensitization Therapies

PT1.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.09.01 Chemoradiotherapy Plus Tislelizumab in Advanced or Metastatic NSCLC: A Prospective, Multicenter, Phase II Study

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Introduction: In recent years, the combination of chemotherapy and immune checkpoint inhibitors (ICIs) has significantly improved survival outcomes in patients with advanced non-small cell lung cancer (NSCLC). However, 30%-50% of patients still fail to benefit from this approach in clinical practice. Emerging evidence suggests that radiotherapy can synergize with chemotherapy and ICIs by modulating the tumor immune microenvironment (TIME). This triple-combination strategy may overcome current therapeutic limitations and expand the population responsive to immunotherapy.

Methods: We conducted a phase II study to evaluate the efficacy and safety of chemoradiotherapy plus tislelizumab in advanced or metastatic NSCLC. Thirty eligible patients were enrolled and received induction therapy consisting of:4 cycles of tislelizumab (200 mg Q3W), platinum-based doublet chemotherapy, Stereotactic body radiotherapy (SBRT, 40-50 Gy/3-5 f)or hypo-fractionated radiotherapy (HFRT, 30 Gy/1 f) The first cycle of chemotherapy and immunotherapy was administered 3-7 days after radiotherapy. Patients then received maintenance tislelizumab until disease progression or intolerable toxicity. Primary endpoint: 1-year progression-free survival (PFS) rate. Secondary endpoints: objective response rate (ORR), PFS, overall survival (OS), safety, tolerability, and exploratory biomarker analysis.

Results: As of March 2025, 30 patients had been enrolled. Key efficacy outcomes included:1-year PFS rate:53.0%,ORR:39.7%,Disease control rate (DCR):61.4%,Median PFS and OS data remain immature. Safety profile: Grade 3-4 adverse events (AEs): 2 patients (6.7%), including immune-related pneumonitis (3.3%) and immune-related heart failure (3.3%). Grade 1-2 AEs:19 patients (63.3%), most commonly hepatic dysfunction and granulocytopenia. Preliminary findings suggest that in bone metastasis patients treated with SBRT plus tislelizumab, elevated serum urea (Urea)and alkaline phosphatase (ALP) levels may serve as biomarkers for poor prognosis.

Conclusions: This study suggests that the triple-combination strategy (chemoradiotherapy plus immune checkpoint inhibitors) may represent a promising therapeutic approach for advanced NSCLC patients.

Keywords: radiotherapy, immunotherapy, advanced non-small cell lung cancer

PT1.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.09.02 Double Lung Transplantation in Patients With Metastatic Lung-Limited Non-Small Cell Lung Carcinoma (NSCLC): A Case Series

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Introduction: The role of double lung transplantation (DLT) in patients with advanced bilateral lung-limited non-small cell lung cancer (NSCLC) has been a subject of debate. We present a prospective study involving patients who underwent DLT for this indication.

Methods: Patients treated with DLT for advanced bilateral lung-limited NSCLC were identified between September 2021 and December 2024 at Northwestern Memorial Hospital. All patients were enrolled in the DLT registry for lung-limited malignancies (DREAM) study cohort A (NCT05671887). Exclusion criteria included the presence of extrapulmonary disease. The indication for DLT was cancer refractory to available systemic treatments, with or without respiratory failure.

Results: Eleven patients with advanced bilateral lung-limited NSCLC were included; the median age was 62 years (range 37-71). Two patients (18%) were Asian, eight (73%) were White, one was Black (9%), Six (55%) were female, and three (27%) had a history of smoking. Seven patients (64%) had invasive mucinous adenocarcinoma, and four patients (36%) had invasive non-mucinous adenocarcinoma histology. The median number of pretransplant treatment lines was 3 (range 1-8). All patients experienced disease progression on standard-of-care treatments, with or without participation in clinical trials. The median duration of the waitlist for DLT was 18 days (range 5-414). There was no 30-day mortality. Only one patient experienced a recurrence at 18 months post-DLT, presenting with a 1 cm solid nodule, successfully treated with stereotactic body radiotherapy. Furthermore, the explant pathology revealed malignant cells in the mediastinal and hilar lymph nodes in two patients. With a median follow-up of 16 months (range 1-39), there were no cases of rejection, no patients required oxygen therapy, and all patients remained alive at the time of reporting.

Conclusions: Eleven patients with NSCLC underwent DLT successfully without experiencing any significant complications. All patients have survived, with one patient receiving curative treatment after a recurrence, while the remaining patients are currently under observation.

Keywords: double lung transplant, lung cancer, dream study

PT1.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.09.03 Dormant Tumor Maintenance and Immune Evasion in Induced Oligometastatic Lung Cancer

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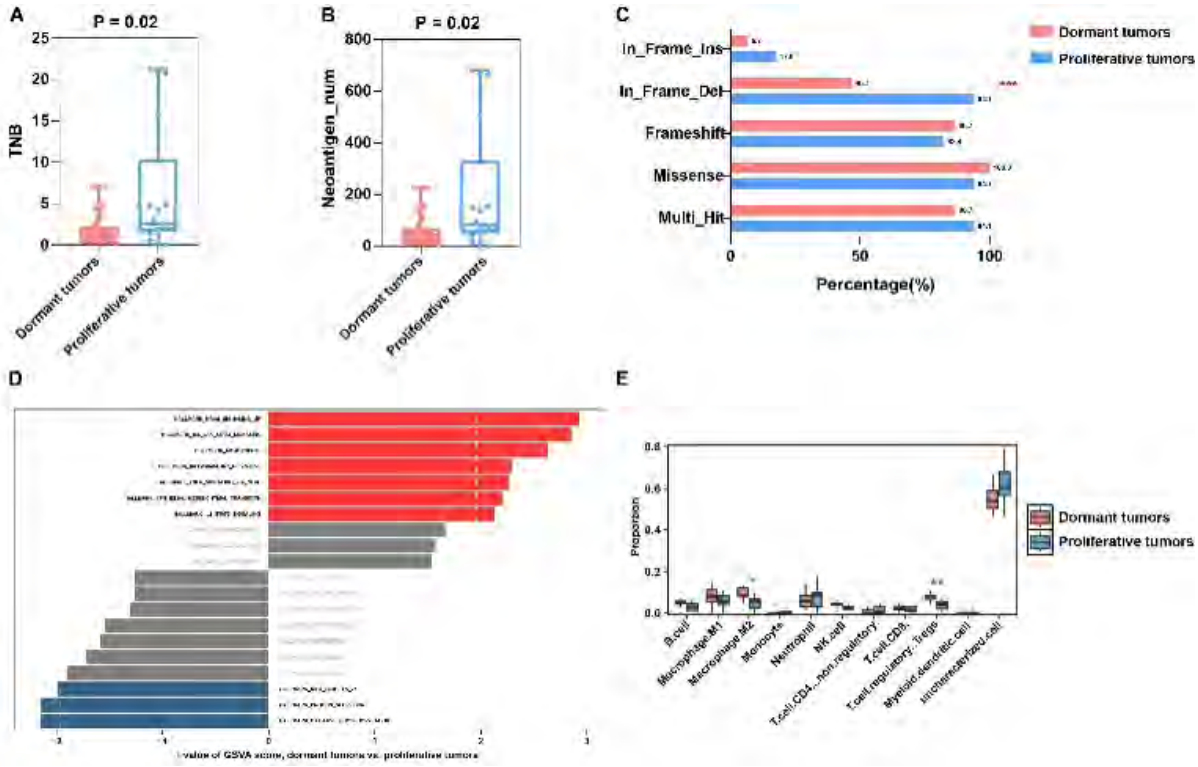
Introduction: Cancer cell dormancy is a major contributor to cancer recurrence and therapeutic failure, as dormant cells evade both anticancer drugs and the host immune system. Although substantial progress has been made in understanding the mechanisms underlying dormancy, critical knowledge gaps remain. Recent studies have highlighted circulating tumor DNA (ctDNA) as a potential diagnostic tool for tumor dormancy. This study elucidates the dormancy characteristics of oligometastatic lung cancer across varying ctDNA statuses.

Methods: We conducted whole-exome and whole-transcriptome sequencing on primary tumor samples from 21 patients with induced-oligometastatic lung cancer, all of whom had undergone surgical resection following first-line systemic therapy with pathologically confirmed residual viable tumor cells exceeding 30%. High-depth ctDNA analysis was performed on matched blood samples. Tumors from patients with preoperative ctDNA-negative status were classified as dormant, whereas those with ctDNA-positive status were deemed proliferative.

Results: Compared to proliferative tumors, dormant tumors exhibited lower neoantigen numbers (P = 0.02) and neoantigen burden (P = 0.02). In all tumors, the incidence of neoantigen-related gene in-frame deletions in dormant tumors was significantly lower than in proliferative tumors (P = 0.001). Particularly, candidate neoantigen IKTSPKANK generated by EGFR Ex19 del (in-frame deletion in exon 19 mutation) in dormant tumors was selectively reduced. Furthermore, genes related to cell division pathway were significantly downregulated in dormant tumors. Finally, dormant tumors had a more immunosuppressive tumor microenvironment, including higher levels of M2 macrophages (P = 0.01) and regulatory T cells (P = 0.003) compared with proliferative tumors.

Conclusions: Oligometastatic lung cancer patients with pre-local treatment ctDNA-negative status exhibited dormant features, characterized by downregulated antigen presentation, dysregulated cell division, and a tumor microenvironment that suppresses immune effector functions. These findings provide critical insights for refining therapeutic strategies in the management of oligometastatic lung cancer.



Keywords: oligometastatic lung cancer, ctDNA, tumor dormancy

PT1.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.09.04 Incomplete Cryoablation Promotes Recurrence and Progression of KRAS-Driven Lung Adenocarcinoma via the NF?B-CCL20-MAPK/MEK/ERK Axis

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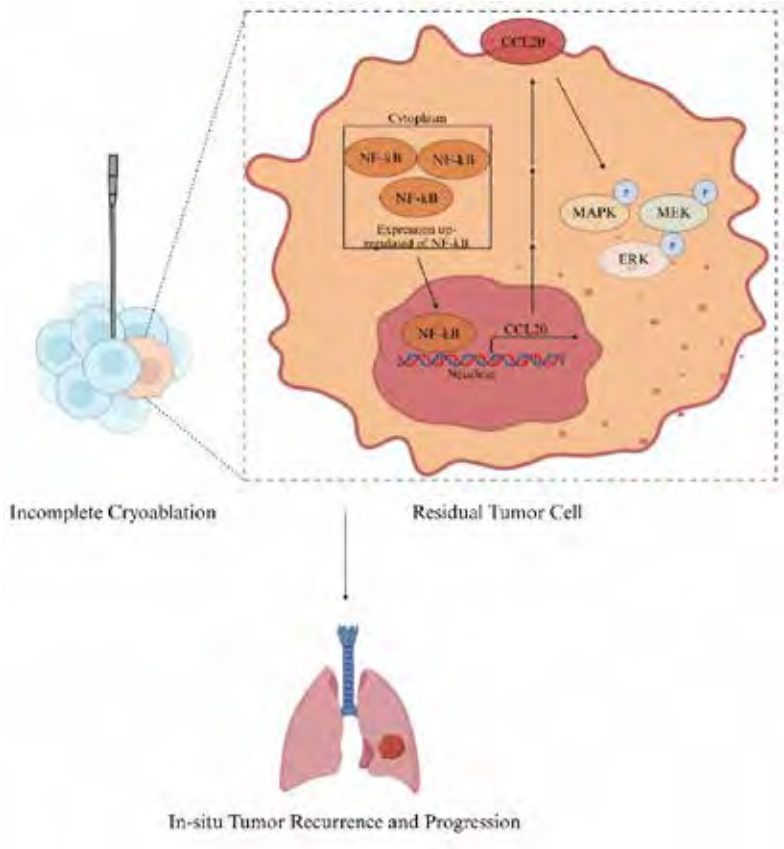
Introduction: Cryoablation (CA) can serve as an alternative treatment for high-risk patients with KRAS-driven lung adenocarcinoma (LUAD) who are ineligible for surgical resection. However, incomplete CA and high postoperative local recurrence rates remain major challenges limiting its clinical application. The C-C motif chemokine ligand 20 (CCL20) is involved in LUAD processes such as epithelial-mesenchymal transition (EMT), cell proliferation, and migration. Nevertheless, whether CCL20 mediates the recurrence and progression of KRAS-driven LUAD after incomplete CA, as well as the underlying molecular mechanisms, remains unclear. This study constructs in vitro and in vivo models of incomplete cryoablation to demonstrate that incomplete ablation upregulates CCL20 expression in residual KRAS-driven LUAD cells, thereby activating the MAPK/MEK/ERK pathway and promoting tumor recurrence and metastasis. The findings may reveal novel therapeutic targets for combination therapy with cryoablation, offering new strategies for post-CA management.

Methods: Orthotopic KRAS-driven LUAD xenografts and primary cell lines were subjected to incomplete cryoablation using a clinical-grade cryoablation device (in vivo) and a controlled liquid nitrogen spray system (in vitro), respectively. RNA-seq of residual tumors/cells revealed the conserved dysregulated gene and pathways. Potential key dysregulated genes were subjected to transcription factor and binding site prediction using UCSC and JASPAR databases, followed by dual-luciferase reporter assay, functional validation through loss-of-function analysis (siRNA/ CRISPR-Cas9-based editing), downstream signaling analysis (RT-qPCR/Western Blot/ Immunofluorescence) and Functional characterization of cells and mouse xenografts.

Results: Following incomplete ablation, residual KRAS-driven LUAD cells exhibited significantly enhanced proliferation and migration capabilities. Correspondingly, KRAS-driven LUAD mouse xenografts showed post-CA recurrence, progression, and metastasis. Integrated analysis combining whole-transcriptome sequencing of residual tumor cells and transcription factor prediction via the JASPAR and UCSC databases identified NF-κB and CCL20 as significantly upregulated molecules after incomplete cryoablation. Additionally, NF-κB was predicted to transcriptionally regulate CCL20 expression after incomplete CA, which was further confirmed by dual-luciferase reporter assays. Through NF-κB siRNA transfection, NF-κB knockout and overexpression stable cell lines, and functional validation, we demonstrated that NF-κB upregulates CCL20 expression post-incomplete CA, and CCL20 subsequently activates the cytoplasmic MAPK/MEK/ERK signaling cascade via phosphorylation, promoting tumor proliferation, migration, and clonal survival. Ultimately, the NF-κB-CCL20-MAPK/MEK/ERK axis drives local recurrence, disease progression, and lung metastasis in mouse models.

Conclusions: We establish that incomplete cryoablation drives KRAS-driven LUAD recurrence and metastasis via CCL20-mediated MAPK/MEK/ERK activation, revealing a targetable mechanism for post-procedural combination therapies.



Keywords: Incomplete Cryoablation, KRAS-driven LUAD, Recurrence

PT1.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
SUNDAY, SEPTEMBER 7, 2025 - 14:15 - 15:00

PT1.09.05 Preclinical Safety Assessment of a Conformable Electrode for Bronchoscopy-Guided Radiofrequency Ablation

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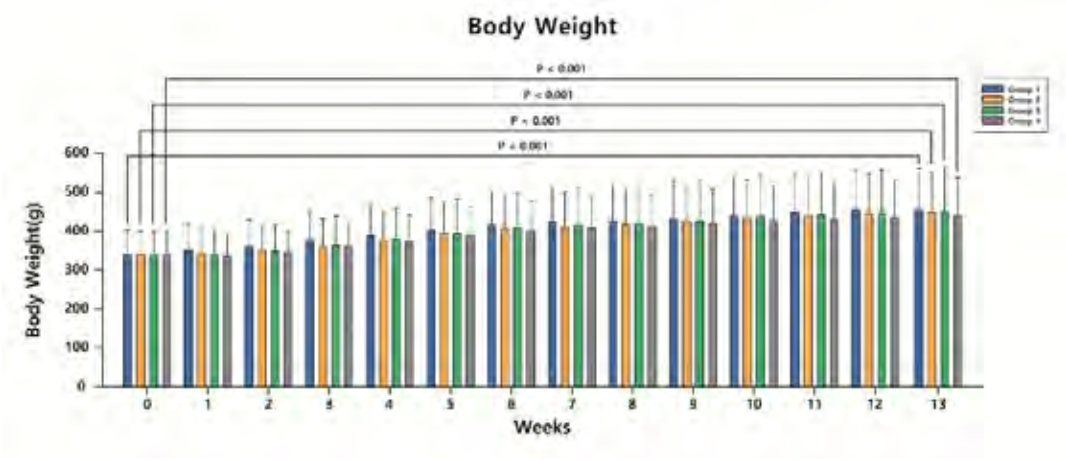
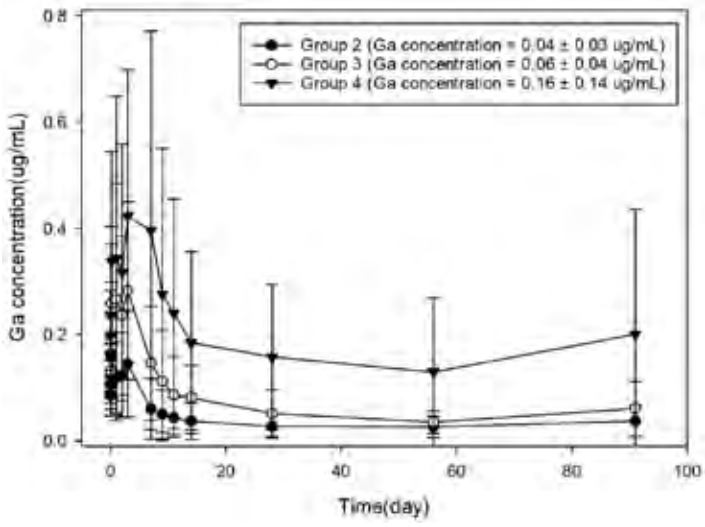
Introduction: The Conforming Ablation of Radiofrequency Out of a Liquid Metal (CAROL) technique is a novel bronchoscopic treatment for peripheral lung tumors using a conformable liquid metal electrode. We aimed to evaluate its toxicological safety for bronchoscopy-guided endobronchial radiofrequency ablation in a preclinical animal model.

Methods: The liquid metal electrode (75% gallium, 25% indium; E-GaIn) was administered via the CAROL system and evaluated in Sprague-Dawley rats. Body weight, CBC, blood chemistry, and serum levels of gallium (Ga) and indium (In) were assessed over 13 weeks. Subjects were classified into four groups: control, low, medium, and high dose (5×, 7.5×, 10× human-equivalent dose, respectively).

Results: A total of 48 rats were assigned to each group (12 per group; 6 males and 6 females). All animals showed consistent body weight increases with no significant differences between groups (control: 445.24±106.82 g; low dose:447.89±105.91 g; medium dose:450.27±115.55 g; high dose:439.72±97.87 g, P = 0.737) (Figure 1). CBC and blood chemistry parameters remained within normal physiological ranges. Serum Ga and In increased dose-dependently, but remained negligible in terms of safety. The AUC values for Ga and In were as follows: low dose, 0.04±0.03 μg/mL and 0.00032±0.00065 μg/mL; medium dose, 0.06±0.4 μg/mL and 0.00103±0.00183 μg/mL; high dose, 0.16±0.14 μg/mL and 0.00253±0.00306 μg/mL (Figure 2). Additionally, further tissue distribution analysis showed that gallium was detected in major organs in a dose-dependent manner, with the highest concentration in the lungs, followed by the spleen, and no toxic responses were observed in any organs.

Conclusions: Our preclinical study demonstrated that direct endobronchial administration of the conformable liquid metal electrode (E-GaIn) had no adverse effects on growth, with E-GaIn detected at negligible systemic levels without any toxic responses. These findings support the CAROL technique as a promising and safe bronchoscopic treatment for peripheral lung tumors.





Keywords: CAROL ablation, Liquid metal electrode, Safety

PT2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.10.01 Incidence and Severity of Interstitial Lung Disease Associated With Antibody-Drug Conjugates in NSCLC and SCLC: A Meta-Analysis

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Introduction: Antibody-drug conjugates (ADCs) have transformed the treatment landscape of multiple malignancies, including non-small cell lung cancer (NSCLC) and Small Cell Lung Cancer (SCLC). However, pulmonary toxicity, particularly interstitial lung disease (ILD), has emerged as a clinically significant adverse event. While clinical trials often exclude patients with preexisting pulmonary comorbidities, real-world populations with NSCLC and SCLC frequently carry risk factors such as smoking history and prior lung injury. To better quantify the pulmonary safety profile of ADCs in lung cancer, we conducted a meta-analysis of ILD incidence, severity, and treatment discontinuation due to ILD.

Methods: We performed a systematic literature review and meta-analysis following PRISMA guidelines, including phase I-III clinical trials of ADCs in patients with NSCLC and SCLC. Databases searched included MEDLINE, Embase, and Cochrane CENTRAL. Eligible studies reported the incidence of ILD (any grade, grade ≥3, and treatment discontinuation due to ILD) using CTCAE criteria. Pooled incidence estimates and 95% confidence intervals (CI) were calculated using a random-effects model with logit transformation. Heterogeneity was assessed via the I^2 statistic and τ^2. Subgroup analyses were performed by ADC agent and payload type. Meta-regression was used to evaluate the independent contributions of payload versus ADC.

Results: We identified 18 clinical trials in NSCLC (N = 2,123 patients) and 5 trials in SCLC (N = 555 patients) evaluating the safety of ADCs with respect to ILD. In NSCLC, the highest pooled incidence of any-grade ILD was seen with patritumab deruxtecan (23%) and trastuzumab deruxtecan (22%), followed by datopotamab deruxtecan (9%), telisotuzumab vedotin (7%), and sacituzumab govitecan (1%). For grade ≥3 ILD, trastuzumab and patritumab deruxtecan again demonstrated the highest pooled rates at 6-7%, whereas other ADCs ranged from 0-3%. Treatment discontinuation due to ILD in NSCLC was highest with telisotuzumab vedotin combined with erlotinib (36%), followed by trastuzumab deruxtecan (9%) and patritumab deruxtecan (7%). In contrast, datopotamab deruxtecan (4%) and sacituzumab govitecan (0%) showed lower discontinuation rates. In SCLC, any-grade ILD incidence was 8% with rovalpituzumab tesirine, with no reported grade ≥3 ILD events. No ILD-related treatment discontinuations were reported in the included SCLC trials. Meta-regression indicated that ADC agent explained a larger proportion of between-study variance in ILD incidence (R^2 = 74%, p = 0.006) compared to payload type (R^2 = 26%, p = 0.007). In a combined model, ADC identity remained the only independent predictor of ILD risk.

Conclusions: ILD is an important adverse event associated with ADC therapy in lung cancer, with risk varying considerably by agent. HER2/HER3-targeted, deruxtecan-containing ADCs demonstrated the highest ILD rates, while other ADCs such as sacituzumab govitecan had minimal reported toxicity. These findings highlight the need for agent-specific ILD monitoring and support the consideration of ADC design, including target and payload, when evaluating pulmonary safety and guiding clinical decision-making.

Keywords: Antibody-Drug Conjugates (ADCs), Non-Small Cell Lung Cancer (NSCLC), Interstitial Lung Disease (ILD)

PT2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.10.02 Peripheral Neuropathy and Efficacy of Telisotuzumab Vedotin in c-Met Protein-Overexpressing NSCLC: LUMINOSITY Study

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Introduction: The first-in-class c-Met (also known as MET) protein-directed antibody-drug conjugate (ADC) telisotuzumab vedotin (Teliso-V) is composed of the monoclonal antibody telisotuzumab conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE). Peripheral neuropathy (PN) is a known cumulative toxicity associated with MMAE ADCs. In the phase 2 LUMINOSITY trial (NCT03539536), PN was observed in patients treated with Teliso-V. We present data from LUMINOSITY on PN occurrence and severity, and efficacy outcomes in patients who developed PN.

Methods: Patients (≥18 years) with locally advanced/metastatic c-Met protein-overexpressing EGFR-wildtype non-squamous NSCLC who received prior therapy were treated with 1.9 mg/kg Teliso-V every 2 weeks. c-Met protein overexpression (by immunohistochemistry clinical trial assay for MET [SP44] [Roche]) was defined as ≥25% tumor cells with 3+ staining intensity (c-Met intermediate: 25-<50% 3+; c-Met high: ≥50% 3+). The primary endpoint was overall response rate by independent central review per RECIST v1.1. Adverse events were reported using MedDRA Preferred Terms; analyses are presented on PN summarized on the basis of standardized MedDRA queries (SMQ narrow).

Results: A total of 168 patients who received Teliso-V at 1.9 mg/kg every 2 weeks were included in the analyses (data cutoff: 21 February 2024). Overall, 74 (44.0%) patients experienced any-grade PN and 17 (10.1%) had grade ≥3 PN (treatment-related PN per investigator: any grade in 69 [41.1%]; grade ≥3 in 16 [9.5%] patients). Median time to PN onset was 103 days (range: 1-472). For 20 (11.9%) patients, PN led to treatment discontinuation. PN events leading to discontinuation occurred at a median 238.5 days (range: 57-519). Median exposure to Teliso-V was longer for patients with PN grade ≥3 (8.3 months, range: 1.4-11.3) versus patients without PN grade ≥3 (4.2 months, range: 0.03-28.8). Efficacy outcomes for patients with and without PN grade ≥3 are in the Table.

Conclusions: Although a common event in patients treated with Teliso-V, PN is a cumulative toxicity, as evidenced by the late onset of these events (median time to PN events leading to discontinuation of nearly 8 months). Patients with grade ≥3 PN (n=17) had a longer median duration of treatment and improved efficacy outcomes compared with those without grade ≥3 events (n=151). Although the number of patients with grade ≥3 PN was limited, these findings suggest that patients who develop these events are generally patients who remain on treatment for an extended time, indicating they are deriving benefit from Teliso-V.

Table. Efficacy outcomes in patients with and without grade ≥3 peripheral neuropathy

	c-Met OE Total N=168		c-Met OE High n=84		c-Met OE Intermediate n=84	
	No PN ≥3 n=151	PN ≥3 n=17	No PN ≥3 n=77	PN ≥3 n=7	No PN ≥3 n=74	PN ≥3 n=10
ORR, %	26.5	52.9	31.2	71.4	21.6	40.0
Median DOR[a], months	6.9	13.0	6.9	13.0	6.9	7.2
DOR[a] ≥6 months, %	47.5	77.8	54.2	80.0	37.5	75.0
Median PFS, months	5.3	14.3	4.6	14.3	5.5	8.5
Median OS, months	12.6	20.2	12.3	25.9	12.6	16.3

[a]40 CR/PR in no PN ≥3 group and 9 CR/PR in PN ≥3 group.
CR, complete response; DOR, duration of response; OE, overexpression; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response.

Keywords: NSCLC, Teliso-V, peripheral neuropathy

PT2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.10.03 Safety, Tolerability and Preliminary Efficacy of Anti-PD-L1 ADC HLX43 in Advanced/Metastatic Solid Tumors: A Phase I Study

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Introduction: HLX43, a novel PD-L1-targeted antibody-drug conjugate (ADC), exhibits dual mechanisms: immune checkpoint blockade and payload-mediated cytotoxicity. Preclinical data showed tumor regression of HLX43 in PD-(L)1 inhibitor-resistant non-small cell lung cancer (NSCLC) and esophageal squamous cell carcinoma models. This study aims to evaluate the safety, tolerability, and preliminary efficacy of HLX43 in patients with advanced solid tumors who have failed standard therapies.

Methods: This multicenter Phase I study evaluated HLX43 in two parts: the dose-escalation Phase (Ia) enrolled patients with advanced solid tumors to receive intravenous injections of HLX43 at 0.5, 1, 2, 2.5, 3, and 4 mg/kg every three weeks (Q3W). The primary objectives of this part were to assess dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD). The dose-expansion Phase (Ib) assessed the safety and preliminary efficacy (objective response rate [ORR]) of HLX43 in NSCLC patients refractory to standard therapies. Patients were administered HLX43 at doses of 2, 2.5, or 3 mg/kg Q3W to determine the recommended Phase II dose (RP2D).

Results: From November 08, 2023 to January 09, 2025, a total of 114 patients were screened, of whom 85 patients met the eligibility criteria and received HLX43. In Phase Ia, 21 patients with advanced solid tumors were enrolled, while in Phase Ib, 64 NSCLC patients were recruited across three cohorts (2, 2.5, and 3 mg/kg). The median age of the enrolled patients was 60.0 years, with 52 males (61.2%). This study enrolled patients with NSCLC (n=76), thymic squamous cell carcinoma (n=4), cervical cancer (n=1), nasopharyngeal carcinoma (n=1), head and neck squamous cell carcinoma (n=1), uterine carcinosarcoma (n=1), and small cell lung cancer (n=1). Notably, 88.2% (75/85) of patients failed prior checkpoint inhibitor (CPI) therapy. In Phase Ia, one DLT event involving febrile neutropenia was observed in the 4 mg/kg group. Treatment-related adverse events (TRAEs) were reported in 95.2% of patients, mostly Grade 1-2. Grade ≥3 TRAEs occurred in 5 patients (23.8%), all from the 3 and 4 mg/kg cohorts, most frequently decreased neutrophil count (19%), decreased white blood cell count (19.0%) and anemia (14.3%). Among the 76 NSCLC patients (69 efficacy-evaluable), ORR was 31.9% (22/69), with a disease control rate (DCR) of 87.0% (60/69). Subgroup analyses demonstrated promising efficacy of HLX43 in specific populations: the 2 mg/kg and 2.5 mg/kg cohorts in Phase Ib achieved ORRs of 38.1% (8/21) and 33.3% (7/21), respectively; CPI-refractory NSCLC patients (n=61) showed an ORR of 32.8% (20/61); EGFR wild-type non-squamous NSCLC patients (n=19) had an ORR of 47.4 % (9/19); PD-L1-positive NSCLC patients (n=50) exhibited an ORR of 32.0% (16/50) while PD-L1-negative/unknown patients (n=19) achieved an ORR of 31.6% (6/19). In the 2 mg/kg group of Phase Ib, the median progression-free survival was 5.4 months (95% CI: 4.0-not evaluable). Additional data will be revealed with extended follow-up.

Conclusions: HLX43 demonstrated a manageable safety profile and preliminary antitumor activity in patients with advanced NSCLC who were refractory to standard therapies, including those who had progressed after treatment with PD-(L)1 inhibitors. Enrollment in the Phase Ib expansion cohort is ongoing.

Keywords: NSCLC, HLX43, PD-L1 ADC

PT2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.10.04 Efficacy and Safety of TQB2102, a Biparatopic HER2-Targeting ADC, in HER-2 Aberrant NSCLC: A Phase II Study

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Introduction: TQB2102 is a novel biparatopic antibody-drug conjugate (ADC) designed to target two non-overlapping epitopes in ectodomain 2 and 4 of HER2. Conjugated to a topoisomerase I inhibitor payload with a drug-to-antibody-ratio (DAR) of 6, this innovative design enhanced HER2 internalization and improve therapeutic efficacy in preclinical models. Compared to single-target HER2 ADCs, TQB2102 provides better tumor uptake, particularly in heterogeneous non-small-cell lung cancer (NSCLC) with varied HER2 expression profiles.

Methods: This open-label phase II study evaluated TQB2102 in patients with locally advanced or metastatic HER2 aberration NSCLC who had received at least one prior line of therapy. Enrolled patients received TQB2102 as monotherapy at 7.5mg/kg intravenously every 3 weeks. The primary endpoint was objective response rate (ORR) and secondary objectives were disease control rate (DCR), progression-free survival (PFS) and safety.

Results: As of March 31,2025, 59 patients were enrolled in three cohorts: cohort 1 (HER2 mutation, N=37), cohort 2 (HER2 gene amplification or protein overexpression, IHC 2+/3+, N=11) and cohort 3 (co-occurrence of HER2 aberration and EGFR mutation, N=11). Median age was 57 years (range 34-73), with 55.9% male, and 62.7% having an ECOG PS of 1. Among the 51 response-evaluable patients, 32 (62.7%) achieved partial response. The ORR was 61.1% in cohort 1 (22/36), 44.4% in cohort 2 (4/9), and 100% in cohort 3 (6/6). Responses were observed as early as the first tumor assessment in 23 of 32 responders. Notably, one patient in cohort 1 achieved complete response in the target lesion after 4 cycles of treatment. The disease control rate was 97.2%, 88.9%, and 100% in cohort 1, 2 and 3, respectively. In patients with baseline brain metastasis, the ORR was 62.5%. The most common treatment related adverse events (TRAEs) were leukopenia (64.9%), nausea (63.2%), anemia (61.4%), thrombocytopenia (56.1%), neutropenia (54.4%), and decreased appetite (54.4%). Grade ≥3 TRAEs occurred in 66.7% patients, with anemia (17.5%), thrombocytopenia (15.8%), neutropenia (14.0%), and leukopenia (14.0%) being the most frequent. Interstitial lung disease was reported in 2 patients (one grade 2 and one grade 3). Data on progression-free survival (PFS) is not yet mature, we will report the updated PFS data at the conference.

Conclusions: TQB2102 demonstrated robust efficacy, particularly in patients with HER2 mutation and concurrent HER2/EGFR aberration NSCLC. The favorable safety profile supports further investigation of TQB2102 in combination therapy trials and biomarker-driven studies to optimize its clinical application for this challenging patient population.

Keywords: biparatopic HER2-targeting ADC, NSCLC, HER2 Aberrant

PT2.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.11.01 Predictors of Response to PD-(L)1 Blockade in Patients With Oncogene-Driver Negative NSCLC Without History of Tobacco Use

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Introduction: Non-small cell lung cancer (NSCLC) in patients who have never used tobacco is associated with poor response to immune checkpoint inhibitors (ICI). However, most studies have focused on patients with traditional actionable oncogenes (e.g., EGFR, ALK, ROS1, RET), leaving it unclear whether additional biomarkers can aid in treatment stratification for this population.

Methods: Clinicopathologic and outcome data were collected from patients with metastatic, oncogene driver-negative, NSCLC who received ICI across nine academic cancer centers in US and EU.

Targeted exome sequencing was performed to identify genomic correlates of response to ICI. Tumor-infiltrating lymphocytes (TILs) densities were calculated from H&E slides using machine learning.

Results: Among 6,005 patients with metastatic NSCLC analyzed, 741 (12.4%) had never used tobacco and tested negative for actionable oncogenes. Median age was 64 years, 59.8% were women, 88.2% had ECOG PS 0/1, and 83.8% had adenocarcinoma. At a median follow-up of 38.0 months, objective response rate (ORR) was 22.3%, median progression-free survival (mPFS) and overall survival (mOS) were 4.5 and 16.8 months. Patients with PD-L1 TPS ≥1% had significantly higher ORR (32% vs. 17%, p<0.01), and longer mPFS (HR: 0.74, p<0.01) compared to those with PD-L1 <1%. Similarly, patients with very high TMB (≥90th percentile) had higher ORR (52.2% vs 22.9%, p<0.01), longer mPFS (HR 0.48, p<0.01), and mOS (HR 0.40, p<0.01) compared to those with a TMB<90th percentile. Patients with both PD-L1≥1% and TMB ≥90th percentile had the highest ORR (83.3%), longest mPFS (23.0 months, p<0.01), and mOS (not reached, p<0.01) compared to those with either biomarker alone (Figure 1A-C). Treatment outcomes also varied by regimen: patients receiving dual PD-(L)1+CTLA-4 blockade had the longest mPFS (9.4 vs. 6.8 vs. 2.9 months, p<0.01) and mOS (43.3 vs. 18.2 vs.14.8 months, p<0.01) compared to PD-(L)1+chemotherapy and PD-(L)1 monotherapy, respectively. Machine learning-based assessment of TILs showed significantly higher ORR and longer mPFS among patients with high versus low TILs density (Figure 1D-F). Gene mutation enrichment analysis identified mutations in TP53, KMT2D and NF1 among responders to ICI (Figure 1G), while whole transcriptome sequencing identified upregulation in MHCI/II antigen presentation, as well as increased signatures of T-cell activation and proliferation among responders to ICI (Figure 1H).

Conclusions: These results highlight how PD-L1≥1%, TMB≥90th percentile, an immune-enriched tumor microenvironment and dual-ICI regimens are associated with improved outcomes in patients with oncogene driver negative NSCLC without history of tobacco use, aiding personalized ICI use in this understudied population.

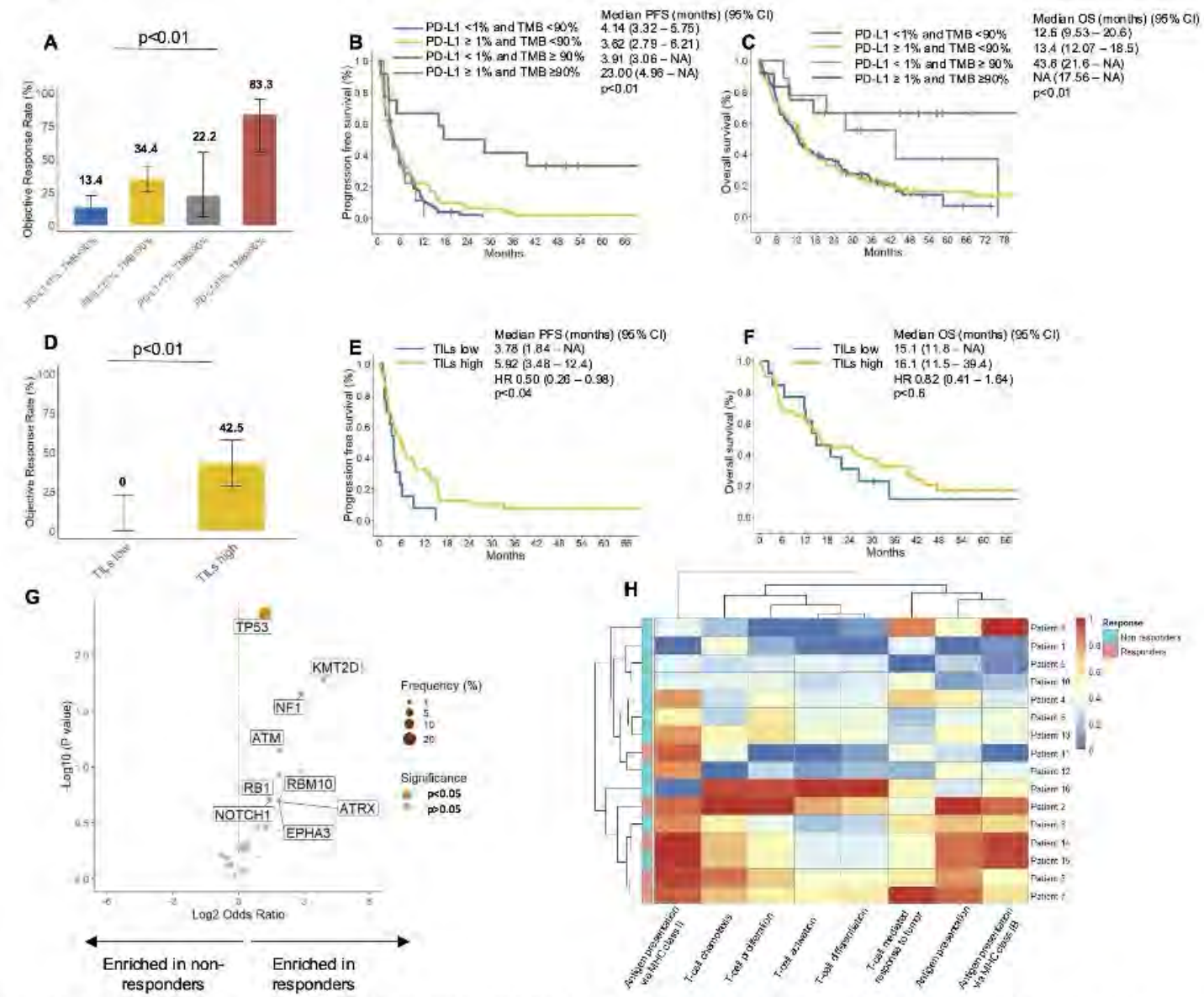

Figure 1. Clinical outcomes stratified by combined PD-L1 and TMB status (A-C) and TILs density (D-F).Genomic (G) and transcriptomic (H) correlates of response.

Keywords: Patients without history of tobacco use, Immunotherapy, Biomarker

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PT2.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.11.02 Rescue by Radiotherapy and Anti-CTLA4/PD-1 After Failure of Anti-PD-1 Therapy in Metastatic NSCLC Patients: the RECLAIM study

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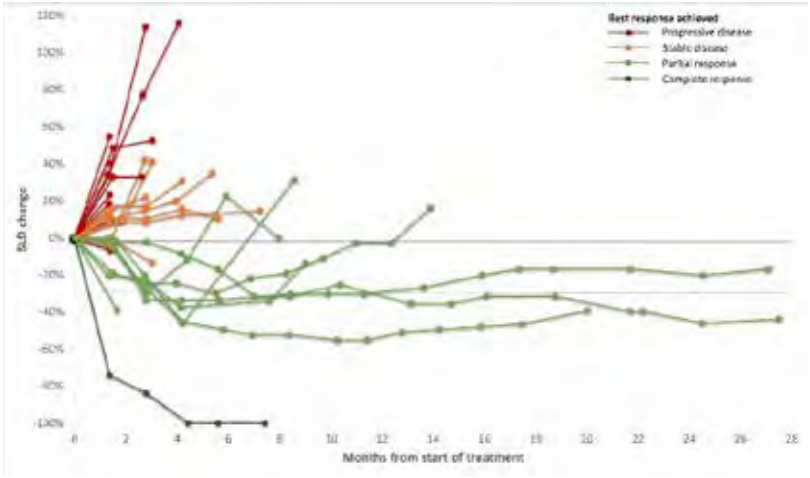
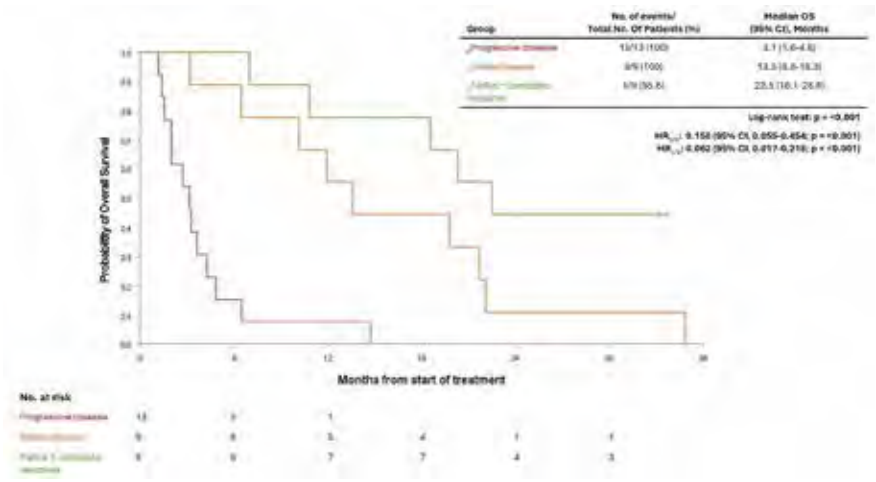
Introduction: Response rates to anti-programmed cell death 1 therapy (anti-PD-1) in metastatic non-small cell lung cancer (mNSCLC) patients with PD-L1 low or negative tumors are generally low. To overcome resistance to anti-PD-1, we combined ipilimumab, nivolumab and medium dose radiotherapy (IPI-NIVO and mRT). Here, we evaluated the safety and efficacy of IPI-NIVO and mRT in mNSCLC patients that progressed on prior anti-PD-1 therapy.

Methods: This single-arm, prospective phase II trial aimed to enroll 30 evaluable patients, with low (1-49%) and negative (<1%) tumor PD-L1 expression. Primary endpoints were safety, disease control rate (DCR) and objective response rate (ORR), measured on non-irradiated tumor lesions. Treatment consisted of IPI 1mg/kg Q6W and NIVO 240mg Q2W for 6 weeks together with mRT, delivered as 3x8Gy to max 4 lesions. Next, IPI 1mg/kg Q6W and NIVO 360mg Q3W was given until disease progression, unacceptable toxicity or 2 years of treatment completion.

Results: In the intention-to-treat population, 31 patients were included. ORR and DCR was achieved in 9/31 (29%) and 18/31 patients (58%). Baseline sum of longest diameters (bSLD) based on RECIST, along with blood inflammatory markers and albumin levels, were predictive of treatment response. Median follow-up was 10.5 months, with significant differences in overall survival (OS) between patients with progressive disease, stable disease and partial/complete response as best achieved response (median OS 3.1 vs 13.5 vs 22.5 months, HR 0.158 and HR 0.062, p<0.001). All patients experienced treatment-related AEs; grade 3 was the highest, observed in 8/31 patients (26%).

Conclusions: Our study showed an ORR in 29% to IPI-NIVO and mRT in mNSCLC patients with low and negative tumor PD-L1 expression, progressing after first-line anti-PD1 therapy. ORR was associated with improved OS. The study treatment was safe and tolerable. bSLD, inflammatory blood markers and albumin levels may serve as predictive marker for treatment response.





Keywords: dual immunotherapy, metastatic NSCLC, radiotherapy

PT2.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.11.03 Phase I Study of Trametinib, Anlotinib, and Tislelizumab in KRAS-Mutant NSCLC: Safety, RP2D, and Preliminary Efficacy

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Introduction: The treatment of KRAS-mutant NSCLC in the later-line setting remains a challenge in clinical practice. Our previous clinical study (NCT04967079) found that the combination of trametinib and anlotinib demonstrated promising clinical efficacy in the later-line treatment of non-G12C KRAS-mutant NSCLC patients. Translational research revealed that anlotinib combined with trametinib could enhance PD-L1 expression and NK cell infiltration. However, the safety and efficacy of the triple therapy with trametinib, anlotinib, and tislelizumab in second-line or later-line treatment for KRAS-mutant NSCLC remain unclear, particularly in patients who have previously received immunotherapy.

Methods: This phase I clinical trial (NCT06456138) enrolled patients with advanced KRAS-mutant NSCLC patients who had previously received at least one standard therapy from June 7, 2024, to December 24, 2024. Patients underwent a trametinib and anlotinib crossover ramp-up trial based on the "3+3" dose-escalation design. Dosage A: 1 mg trametinib plus 6 mg anlotinib; Dosage B: 1 mg trametinib plus 8 mg anlotinib; Dosage C: 2 mg trametinib plus 6 mg anlotinib; Dosage D: 2 mg trametinib plus 8 mg anlotinib. Trametinib and anlotinib were orally administered once daily, with anlotinib given every two weeks followed by a one-week discontinuation cycle. After 2 cycles of trametinib plus anlotinib therapy, the combination of trametinib, anlotinib, and tislelizumab (200 mg, Q3W) was introduced starting from the third cycle. The primary endpoint was to evaluate the safety profile and determine the recommended phase 2 dose (RP2D). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and objective response rate (ORR).

Results: A total of 12 patients with KRAS-mutant NSCLC were enrolled, including 3 with KRAS G12C mutations, 5 with KRAS G12D mutations, 3 with KRAS G12V mutations, and 1 with a KRAS G12R mutation. The majority of patients (10 out of 12) were male, and half had a history of smoking. Eight patients had received first-line standard therapy, while four had undergone third-line treatment. As of the data cutoff date (March 7, 2025), drug-related adverse events (AEs) were observed across different dosage groups. In Group A, reported AEs included rash (Grade 1, Grade 2), diarrhea (Grade 1, Grade 2), hypertension (Grade 1), bleeding (Grade 3), pneumonia (Grade 2), and increased creatine kinase (Grade 2). Group B experienced rash (Grade 1), diarrhea (Grade 1, Grade 2), and hypertension (Grade 1). In Group C, AEs included rash (Grade 1), diarrhea (Grade 1, Grade 2), nausea (Grade 1), oral mucositis (Grade 1), and decreased body weight (Grade 1). Group D reported rash (Grade 1, Grade 2), diarrhea (Grade 1, Grade 2), hypertension (Grade 3), pneumonia (Grade 2), facial swelling (Grade 1), and increased creatine kinase (Grade 1). The median PFS for all 12 patients was 171 days, while the median OS was not reached. The ORR was 33.3%.

Conclusions: These findings suggest that the RP2D for future trial is 2 mg trametinib + 8 mg anlotinib + tislelizumab (200 mg, Q3W). This study provides a potential therapeutic strategy for refractory KRAS-mutant NSCLC patients (especially the patients who have previously received immunotherapy).

Keywords: KRAS-mutant NSCLC, Trametinib plus anlotinib plus tislelizumab, Immunotherapy rechallenge

PT2.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.11.04 Divergent Mechanisms of Hyper-Progressive Disease in Non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors

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Introduction: Hyper-progressive disease (HPD) has emerged as an atypical response pattern to immune checkpoint inhibitors (ICIs), characterized by accelerated tumor progression and profoundly unfavorable clinical outcomes. Although its underlying mechanisms remain unclear, emerging evidence implicates both tumor-intrinsic properties and immune-mediated processes in its development. Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), the two major histological subtypes of non-small cell lung cancer (NSCLC), exhibit fundamentally distinct tumor biology and immune microenvironments. This study aims to delineate the clinical and molecular characteristics of HPD across tumor subtypes to improve patient stratification and optimize the application of ICIs.

Methods: We retrospectively analyzed 630 patients with advanced NSCLC who received ICI monotherapy. Among them, 318 patients who exhibited progressive disease (PD) according to RECIST 1.1 were further classified into HPD and non-HPD based on volumetric assessment. Patients with PD who did not meet the volumetric criteria for HPD were defined as non-HPD. Subsequent analyses were conducted to evaluate clinical and molecular landscapes between these two groups. Transcriptomic profiling of pre-treatment tumor specimens was performed to investigate subtype-specific features of HPD, including gene set enrichment, cytokine signaling inference, and immune cell deconvolution. Systemic immune alterations were assessed using multiparametric flow cytometry on paired peripheral blood samples collected before and during treatment.

Results: HPD occurred in 10.2% of patients (N = 64; LUAD 9.8%, LUSC 11.1%) and was associated with significantly inferior overall survival compared to non-HPD (median OS, 4.6 vs 8.7 months; hazard ratio [HR] = 2.05; 95% CI, 1.55-2.71; P < 0.0001). In LUAD HPD, transcriptomic analysis revealed a marked upregulation of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling (P = 0.01), accompanied by increased M2-like macrophages (P < 0.001) and macrophage/dendritic cell trafficking signatures (P = 0.01). Peripheral immune profiling further demonstrated an expansion of circulating myeloid populations following ICI treatment. Collectively, these findings suggest that HPD in LUAD may be driven by a pronounced shift toward an immunosuppressive phenotype. In contrast, LUSC did not exhibit HPD-specific transcriptional or systemic immune changes. A pervasive immunosuppressive tumor microenvironment (TME) was observed in LUSC non-HPD, characterized by enrichment of M2-like macrophages (P = 0.01), angiogenic signatures (P = 0.002), and epithelial-mesenchymal transition (EMT) pathways (P = 0.003). However, these features were not significantly observed in LUSC HPD, suggesting that its development in this subtype may involve alternative mechanisms, potentially driven by tumor-intrinsic programs. The presence of immunosuppressive traits in LUSC may obscure the distinction of HPD within this subtype, whereas aberrant immune perturbations may serve as key determinants of HPD development in LUAD.

Conclusions: HPD in advanced NSCLC may arise through divergent biological mechanisms shaped by histological subtypes. In LUAD, HPD may appear to be associated with immunosuppressive remodeling, while in LUSC, it is more likely governed by tumor-intrinsic pathways independent of immune modulation. These findings highlight the clinical relevance of histology-specific molecular stratification for identifying patients at heightened risk of HPD and underscore the importance of tailoring immunotherapeutic strategies to each tumor subtype.

Keywords: Hyper-progressive disease, Non-small cell lung cancer, Immune checkpoint inhibitor

PT2.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.11.05 IFI6-High Cancer-Associated Fibroblasts Impede Immunotherapy Response in NSCLC

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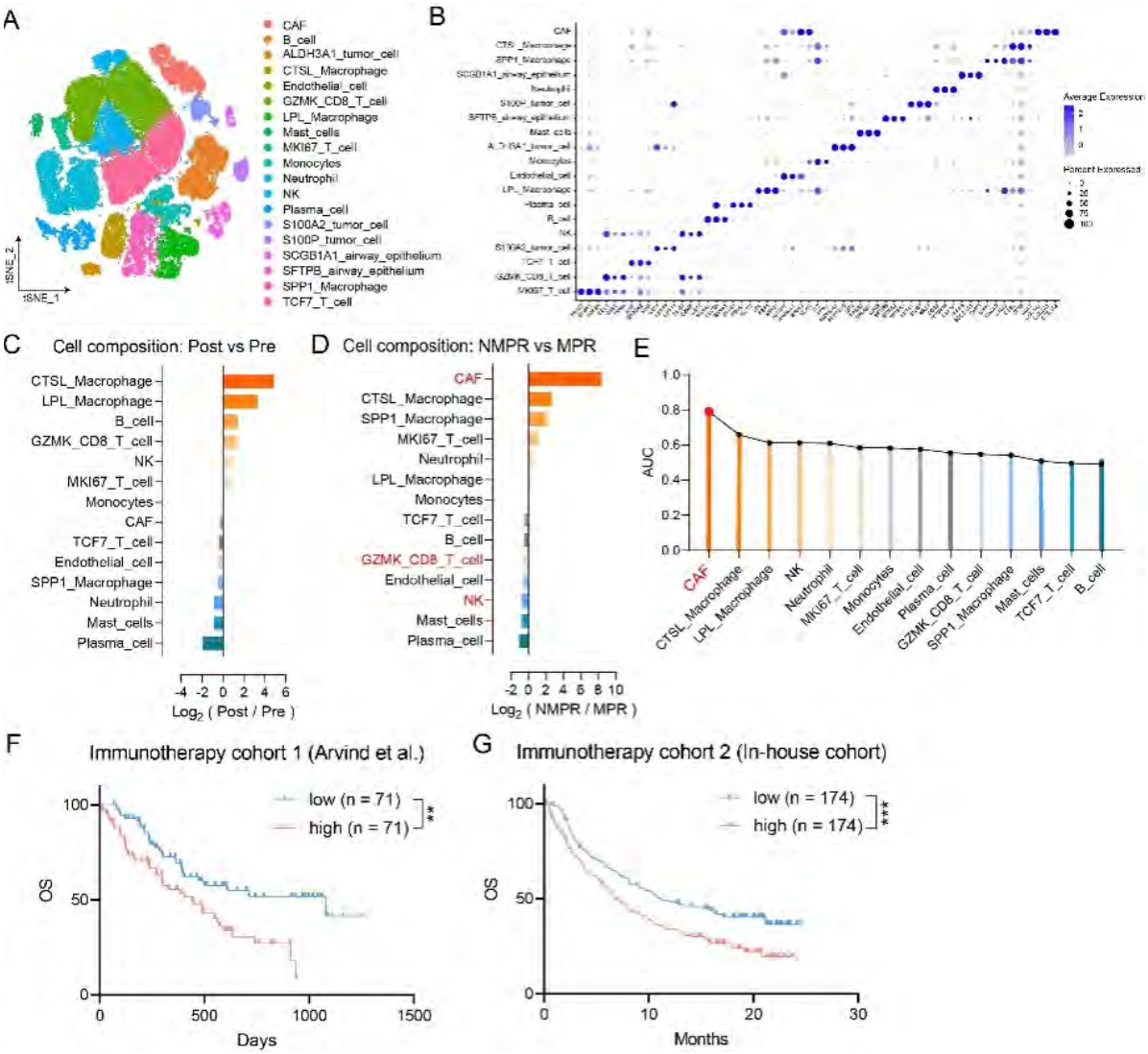
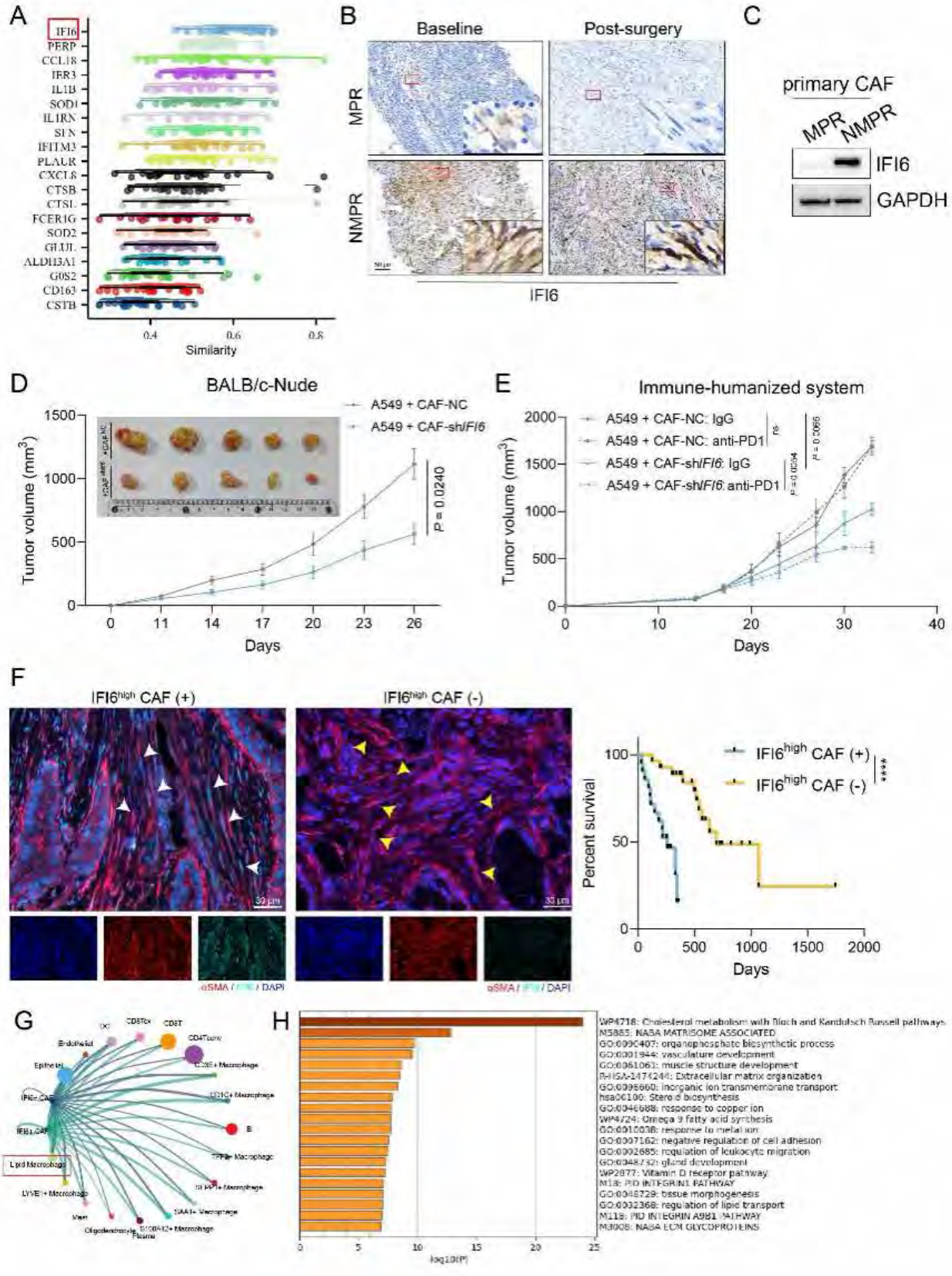
Introduction: Despite groundbreaking advances with immune checkpoint inhibitors (ICIs) in non-small-cell lung cancer (NSCLC), the objective response rate (ORR) to ICI remains suboptimal. Key impediments to ICI response involve tumor microenvironment (TME) immunosuppression requiring further elucidation.

Methods: Paired pre- and post-neoadjuvant chemoimmunotherapy tumor specimens from seven NSCLC patients were subjected to single-cell RNA sequencing (scRNA-seq) to delineate dynamic TME remodeling. The transcriptomic atlas stratified by pathologic response was used to identify the pivotal cell subset and unveil its key molecular signatures, with validation through clinical cohorts and in vitro/in vivo functional assays. CellChat analysis was applied to further decoded the downstream target cell network.

Results: Integrative scRNA-seq analysis revealed non-major pathologic response (NMPR) patients had expanded immunosuppressive CAFs and depleted cytotoxic GZMB+CD8+ T/NK cells versus major pathologic response (MPR) patients. Augur algorithm prioritized CAFs as the top discriminative subset, validated by NMPR_CAF signature predicting successfully in external cohorts. Further screening by Friends algorithm revealed IFI6 as the key hub gene. Confirming in clinical samples of NMPR patients, IFI6 was consistently elevated. Notably, IFI6-knockdown in CAFs (CAFshIFI6) co-injected with LLC1 tumors inhibited tumor growth in NSG mice and diminished ICI resistance in a CDX model, indicating that IFI6-high CAFs have direct interaction with tumor cells and influence ICI efficacy. Clinically, patients with IFI6-high CAFs showed inferior survival post-immunotherapy. Mechanistically, IFI6+ CAFs exhibited crosstalk with lipid-associated macrophages and cholesterol metabolic reprogramming.

Conclusions: High baseline IFI6 expression in CAFs fosters the immunosuppressive TME formation through dual interactions with tumor cells and lipid-associated macrophages, compromising ICI efficacy in NSCLC. Targeting IFI6 synergizes with ICIs may overcome primary resistance.





Keywords: IFI6, Cancer-associated fibroblasts, NSCLC

PT2.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.12.01 Osimertinib Combined With Tegavivint Is Safe and Tolerable as First-Line Therapy in Patients With Metastatic EGFR-Mutated NSCLC

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Introduction: Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKIs) improve clinical outcomes for patients with EGFR-mutated non-small cell lung cancer (NSCLC). However, EGFR TKIs are not curative even when combined with other therapies because of drug-tolerant persister (DTP) cells. Our preclinical studies showed that a subset of EGFR-mutated lung cancer cells enter a persistent state in response to TKIs due to increased transcriptional activity of β-catenin. Treatment of mice bearing EGFR-mutated NSCLC xenografts with the combination of an EGFR TKI and a β-catenin inhibitor caused a greater depth and duration of response than treatment with an EGFR TKI alone. We also observed that patients with EGFR-mutated NSCLC who had the greatest increase in serum levels of the secreted β-catenin transcriptional target PAI-1 following treatment with a TKI had significantly worse progression free survival. These observations provided rationale for a clinical trial that evaluates the combination of an EGFR TKI with an inhibitor of β-catenin transcriptional activity. Tegavivint inhibits the transcriptional activity of β-catenin by disrupting its interaction with its binding partner TBL1 and has been evaluated as a single agent for the treatment of both desmoid tumors and hepatocellular carcinoma.

Methods: NCT04780568 is a single-arm phase Ib clinical trial that investigated the EGFR TKI osimertinib in combination with escalating doses of tegavivint. Patients with metastatic EGFR-mutated NSCLC who had not received prior treatment with an EGFR TKI were eligible. All participants received the FDA-approved dose of osimertinib, and tegavivint was administered using a dose escalation schedule with four dose levels. Dose escalation was determined by Bayesian optimal interval design. The combination of osimertinib and tegavivint was given for four 28-day cycles. Patients then continued maintenance treatment with osimertinib alone. The primary objectives were to assess the safety and tolerability of the combination and to determine the recommended phase 2 dose (RP2D) of tegavivint. Secondary objectives included objective response rate, median duration of response, progression free survival, and overall survival.

Results: Sixteen evaluable patients were treated on study with three patients at each of the first three dose levels, and seven patients at the highest dose level of tegavivint (8 mg/kg), which was determined to be the recommended phase 2 dose. No dose limiting toxicities nor treatment-related serious adverse events occurred. The most common grade 1-3 adverse events included hematologic and GI toxicities, which were likely attributable to osimertinib. Pharmacokinetic analysis showed a dose-dependent increase in the Cmax and AUC of tegavivint, and plasma levels of osimertinib were comparable to those seen historically when administered as a single agent. Clinical outcome data is maturing.

Conclusions: This phase Ib trial demonstrated that the combination of osimertinib and tegavivint is safe and tolerable as first-line therapy in patients with metastatic EGFR-mutated NSCLC. This novel combination has the potential to improve the durability of response through targeting DTP cells and may be better tolerated than current FDA-approved combinations that use chemotherapy or antibody-based therapies. These data provide support for a phase 2 head-to-head study comparing the efficacy of osimertinib versus osimertinib plus tegavivint.

Keywords: EGFR, beta-catenin, drug-tolerant persister cells

PT2.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.12.02 Effect of JIN-A02, a Novel 4Th-Generation EGFR-TKI, on Multiple EGFR Mutations in Comparison With 3Rd-Generation EGFR-TKIs

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Introduction: JIN-A02, a novel fourth-generation tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR) C797S mutation, is currently undergoing phase 1/2 clinical trials in patients with EGFR-mutated non-small cell lung cancer (NSCLC) in Korea, the USA, and Thailand (NCT05394831). NSCLC patients harboring acquired EGFR C797S mutations often exhibit co-occurring mutations, such as exon 19 deletions or T790M, as a result of targeted therapies, leading to tumor tissue heterogeneity. This heterogeneity significantly limits therapeutic options for these patients. To address this challenge, there is an unmet need for the development of fourth-generation EGFR-TKIs capable of targeting multiple EGFR mutations and effectively suppressing heterogeneous tumor tissues. With a view to evaluating the activity of JIN-A02 against common EGFR mutations (including T790M), we conducted an in silico study to estimate its binding affinity compared with third-generation EGFR-TKIs along with an in vitro study to calculate its inhibitory concentration (IC90) in EGFR-mutated cell lines.

Methods: Docking simulation of ATP, JIN-A02, osimertinib and lazertinib were performed using Autodock Vina with the T790M/L858R (pdb: 5EM7) and the T790M/L858R/C797S(pdb: 6LUD) protein structures. Cell-based assays were conducted to determine the IC90 values of JIN-A02 and Osimertinib. EGFR mutant cell lines were cultured and treated with various concentrations of each compound. The cell viability was assessed using an MTT assay, and the concentration required to IC90 of cell growth was calculated.

Results: In the in silico study, the docking score of JIN-A02 for EGFR L858R/T790M dual mutations was -9.043. Given the docking score of ATP for the same mutations (-6.849), JIN-A02 showed better binding affinity. For EGFR L858R/T790M/C797S triple mutation, the docking scores were as follows: JIN-A02 (-9.732), osimertinib (-6.816), lazertinib (-7.846), and ATP (-7.638). In the in vitro study, the IC90 value of JIN-A02 was 229 ng/mL, while osimertinib was >1000 ng/mL in an EGFR ex19del mutant cell line. Similarly, the IC90 value of JIN-A02 was 501 ng/mL, whereas that of osimertinib was >1000 ng/mL in an EGFR L858R mutant cell line.

Conclusions: We demonstrated that JIN-A02 exhibited potent binding affinity to the ATP-binding site of EGFR harboring double and triple mutations, surpassing the binding affinities of third-generation EGFR-TKIs, such as osimertinib and lazertinib. In line with this enhanced binding affinity, the in vitro study showed significantly lower IC90 value, effectively suppressing the proliferation of EGFR-mutated cell lines. These findings suggest that JIN-A02 has the potential to address the unmet therapeutic needs for NSCLC patients with heterogeneous EGFR mutations and, hence, may be a promising option for overcoming tumor tissue heterogeneity.

Keywords: NSCLC, EGFR-TKI, C797S

PT2.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.12.03 Zongertinib in Patients With Previously Treated HER2-Mutant NSCLC and Brain Metastases at Baseline: Beamion LUNG-1

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Introduction: Given the high incidence of brain metastases (BMs) in patients with HER2-mutant NSCLC, it is important to consider the intracranial activity of emerging HER2-targeting therapies; however, patients with active BMs at baseline are often excluded from clinical trials. Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. Phase Ib of Beamion LUNG-1 (NCT04886804) is evaluating zongertinib in patients with HER2-mutant advanced/metastatic NSCLC, including those with BMs at baseline. In an earlier analysis of previously treated patients with HER2-mutant NSCLC, zongertinib demonstrated durable clinical benefit with a manageable safety profile. Here, we report data from previously treated patients with active BMs (Cohort 4) or stable/asymptomatic BMs (Cohort 1) at baseline.

Methods: In Cohort 1, patients were initially randomized to receive zongertinib 120 mg or 240 mg once-daily; the 120 mg dose was selected at an interim analysis. Once selected, all new patients in all cohorts received zongertinib 120 mg. The primary endpoint in Cohort 1 was objective response (RECIST v1.1) by blinded independent central review (BICR). Secondary endpoints included duration of response (DoR) and intracranial objective response (RANO-BM) for patients with baseline central nervous system (CNS) lesions. In Cohort 4, the primary endpoint was intracranial objective response according to RANO-BM by BICR. Secondary endpoints included DoR and progression-free survival according to RANO-BM by BICR (CNS lesions).

Results: As of November 29, 2024, 75 patients had received zongertinib 120 mg in Cohort 1. In the 28 patients with stable/asymptomatic BMs at baseline, the confirmed systemic objective response rate (ORR) was 64% (95% CI: 46-79) and DoR was 14.1 months (95% CI: 4.2-14.1). In 47 patients without BMs, the confirmed systemic ORR was 74% (95% CI: 61-85); DoR was not yet mature. Overall, 27 patients were RANO-BM eligible; the confirmed intracranial ORR was 41% (95% CI: 25-59), including 4 (15%) patients with an intracranial complete response. The intracranial disease control rate was 81% (95% CI: 63-92). Of the 18 RANO-BM eligible patients who had not received brain radiotherapy prior to treatment, 2 had a complete response (CR) and 3 had a partial response (PR). Of the 9 RANO-BM eligible patients who had received brain radiotherapy prior to treatment, 2 patients had a CR and 4 had a PR. Treatment-related adverse events (all/grade ≥3) were reported in 100%/21% of patients with BMs and 96%/15% of patients without BMs. First data from previously treated patients with active BMs (Cohort 4) and updated data for those with stable/asymptomatic BMs (Cohort 1) will be available in May 2025. At the meeting, we plan to present intracranial response by RANO-BM and RECIST v1.1, and PRO data (disease-related symptom and physical functioning scores) for patients with active BMs, and intracranial response by RECIST v1.1 for those with stable/asymptomatic BMs.

Conclusions: Zongertinib demonstrated systemic and intracranial efficacy with a manageable safety profile in patients with advanced/metastatic HER2-mutant NSCLC and BMs at baseline.

Keywords: Zongertinib, Non-small cell lung cancer (NSCLC), Human epidermal growth factor receptor 2 (HER2)

PT2.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.12.04 Osimertinib + Savolitinib in EGFRm Advanced NSCLC With MET Overexp And/Or Amp Post-Progression on Osimertinib: SAVANNAH PROs

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Introduction: In the Phase II SAVANNAH study (NCT03778229), treatment with osimertinib (an oral EGFR-TKI) + savolitinib (an oral, highly selective MET-TKI) showed high, clinically meaningful and durable responses in patients with EGFRm advanced NSCLC with high levels of MET overexpression and/or amplification after progressive disease (PD) on osimertinib. We report patient-reported outcomes (PROs) from SAVANNAH in the primary efficacy population.

Methods: Patients in the primary efficacy population (N=80) had EGFRm advanced NSCLC with MET overexpression (MET IHC3+/≥90% [3+ intensity in ≥90% of tumour cells]) and/or amplification (FISH10+ [≥10 MET gene copies]) after PD on 1L osimertinib, and received osimertinib 80 mg QD + savolitinib 300 mg BID. HRQoL, function and symptoms were measured using EORTC QLQC30/LC13 questionnaires; impact of treatment/disease on health state was measured using EQ-5D-5L; tolerability was assessed using PRO-CTCAE (Table). Data reported from baseline (BL) up to C8D1. DCO: 23 Aug 2024.

Results: EORTC QLQ-C30/-LC13 compliance rates were moderate to high (80% at BL, between 56-70% across visits up to C8D1). GHS showed a consistent, small improvement (3-7 points) across visits; ~30-50% of patients experienced a clinically meaningful improvement from BL; 30-50% remained stable. Approximately ≥70% of patients experienced improved or stable functional and symptom scores over time (EORTC QLQ-C30/-LC13). EORTC QLQ-C30 showed a trend of small improvements (0.4-7 points) across all functional scales, and clinically meaningful improvements in the symptoms of dyspnoea, insomnia and appetite loss; small improvements (3-7 points)/stable scores were observed for fatigue, pain, nausea/vomiting, constipation, diarrhoea and financial difficulties. EORTC QLQ-LC13 showed clinically meaningful improvement in cough and small improvements for dyspnoea, haemoptysis, dysphagia and pain in chest. Symptom improvement rates were high across EORTC QLQ-C30/LC13; EORTC QLQ-LC13: haemoptysis (75%), pain in chest (83%). TTD varied across symptom scores; median TTD ranges were 5.52-13.90 months (EORTC QLQ-C30) and 2.79 months-NR (EORTC QLQ-LC13). EQ-5D-5L showed small improvements in mean VAS scores and index scores (64.8 to 66.2 and 0.68 to 0.72-0.77 at BL [n=64] and C8D1/across visits [n=30], respectively). PRO-CTCAE results showed that osimertinib + savolitinib was generally well-tolerated across visits.

Conclusions: In SAVANNAH, osimertinib + savolitinib treatment led to improved or stable disease/treatment-related symptoms, functions and overall HRQoL, indicating a favourable impact on PROs in patients with EGFRm and MET-overexpressed and/or amplified advanced NSCLC with PD on 1L osimertinib. These data further support osimertinib + savolitinib as a new treatment option in this setting.

PRO instrument	Pre-specified primary scales	Schedule	Analyses
Pre-specified analyses			
EORTC-QLQ-C30	GHS (Global Health Status)/Quality of Life	BL, Q4W	– **Secondary endpoint:** mean change from baseline (clinically meaningful within-patient improvement/worsening [≥10 point changes from BL]) – Symptom improvement rate (% patients with ≤-10 points for ≤2 consecutive visits among those with BL score of ≥10) – TTD (time to deterioration; time to ≥10 point change from BL) – Compliance rates
	Functional scales: physical, role, emotional, cognitive, social		
	Symptom scales: fatigue, appetite loss, pain, dyspnoea, insomnia, constipation, diarrhoea, nausea/vomiting **Other:** financial difficulties		
EORTC-QLQ-LC13	**Symptom scales**: dyspnoea, cough, haemoptysis, dysphagia, pain in chest	BL, QW in C1 and C2 and then Q4W	
Exploratory analyses			
EQ-5D-5L (exploratory endpoint)	**Health dimensions**: mobility, self-care, usual activities, pain/discomfort, anxiety/depression	BL, Q4W	– Index score – VAS (visual analogue scale) score
PRO-CTCAE (exploratory endpoint)	**Treatment-related symptoms** (CTCAE [v4.0]): wheezing, palpitations, rash, itchy skin, hives, aching muscles	BL, QW in C1 and C2 and then Q4W	– Frequency, severity, interference with usual activities

Keywords: Patient-reported outcomes, SAVANNAH, MET overexpression and/or amplification

PT2.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.13.01 A Phase II Trial of Induction Camrelizumab Plus Chemotherapy Followed by Chemoradiotherapy and Consolidation in Limited-Stage SCLC

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Introduction: Limited-stage small cell lung cancer (LS-SCLC) comprises 15-30% of SCLC cases, yet relapses occur frequently following definitive therapy. Although durvalumab consolidation has enhanced outcomes compared to traditional concurrent chemoradiotherapy (CRT), disease progression remains a formidable challenge. Building on findings in locally advanced non-small cell lung cancer, where induction immunotherapy plus chemotherapy improved survival, we conducted a Phase II randomized trial to evaluate whether a similar approach might benefit patients with LS-SCLC. This trial examined the efficacy and safety of induction camrelizumab plus chemotherapy, followed by CRT and camrelizumab consolidation.

Methods: This investigator-initiated, phase II, open-label, randomized controlled trial (ChiCTR2000032275) was conducted at Shanghai Pulmonary Hospital. Patients were randomly assigned (1:1) to either an experimental regimen of induction immunotherapy and chemotherapy (two cycles of camrelizumab plus etoposide-platinum [EP] or etoposide-carboplatin [EC]) followed by CRT, prophylactic cranial irradiation (PCI), and up to 12 months of camrelizumab consolidation (camrelizumab group), or a control regimen of induction chemotherapy (EP or EC) followed by CRT and PCI (cCRT group). The primary endpoint was the 1-year progression-free survival (PFS) rate. Secondary endpoints included overall survival (OS), objective response rate, and safety. Adverse events were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Kaplan-Meier estimations, stratified log-rank tests, and Cox proportional-hazards models were employed to compare survival outcomes.

Results: Between November 2020 and March 2024, 65 patients were screened for eligibility, and 41 were randomly assigned to receive either camrelizumab (n=21) or standard cCRT (n=20). The median follow-up time was 20.9 months (95% CI: 18.6-23.2 months) for the camrelizumab group and 23.2 months (95% CI: 16.3-30.2 months) for the cCRT group. All patients treated with camrelizumab achieved a partial response, compared with 84.2% in the cCRT arm. The 1-year PFS rate was higher in the camrelizumab group than in the cCRT group [59.9% (95% CI: 34.6-85.2%) vs. 39.5% (95% CI: 15.6-63.4%)], and the median PFS was not reached in the camrelizumab arm, whereas it was 11.4 months (95% CI: 9.8-13.0 months) in the cCRT arm (HR 0.42, 95% CI: 0.18-0.96, p=0.047). Similarly, the median OS was not reached in the camrelizumab group, compared with 23.9 months (95% CI: 15.3-32.5) in the cCRT group (HR 0.32, 95% CI: 0.11-0.96, p=0.044). The 1-year OS rate was 100% for camrelizumab and 89.2% for cCRT. Subgroup analysis further indicated that an absolute lymphocyte count (ALC) >2.0 × 10^9/L correlated with significantly longer PFS in the camrelizumab arm. No immune-related deaths were reported; however, one patient experienced grade 3 reactive capillary endothelial proliferation. Notably, induction camrelizumab did not lead to an increased incidence of radiation pneumonitis.

Conclusions: These findings suggest that induction camrelizumab plus chemotherapy followed by CRT and camrelizumab consolidation may improve both PFS and OS in LS-SCLC without exacerbating toxicity. Further research to refine treatment sequencing could provide vital improvements in managing this challenging disease.

Keywords: small cell lung cancer, limited-stage, Induction immunotherapy

PT2.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.13.02 Multi-Cycle Low-Dose Radiotherapy Reshapes Immunochemotherapy for ES-SCLC: The SPUR Phase II Trial

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Introduction: Despite immunotherapy incorporation into first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC), its survival benefits remain modest. Previous studies suggest that low-dose radiotherapy (LDRT) could enhance anti-tumor immune responses and may prolong immunotherapy efficacy. However, the therapeutic potential of single-cycle single-site LDRT remains suboptimal. We initiated a proof-of-concept trial to evaluate the feasibility, safety, and preliminary efficacy of adaptive multi-cycle LDRT combined with serplulimab-based immunochemotherapy in previously untreated ES-SCLC patients.

Methods: The SPUR trial (NCT05765825) is a multicenter, single-arm, phase II study enrolling treatment-naïve ES-SCLC patients. Participants receive four cycles of platinum-etoposide chemotherapy (cisplatin/carboplatin + etoposide) plus serplulimab, along with adaptive multi-cycle LDRT, followed by serplulimab maintenance. The LDRT protocol is as follows: (1) All patients receive LDRT at 15 Gy/5 fractions (15 Gy/5 f) concurrently in the first induction cycle. (2) If primary intrathoracic lesions exhibit <80% reduction or non-response by the end of second cycle, an additional 15 Gy/5 f LDRT is administered at third cycle. (3) For residual extrathoracic metastases, a final course of 15 Gy/5 f LDRT is delivered at cycle four. The primary endpoint is progression-free survival (PFS) per RECIST v1.1. Secondary endpoints include duration of response (DoR), disease control rate (DCR), overall survival (OS), and safety. Additionally, exploratory biomarkers include T-cell receptor (TCR) repertoire profiling and plasma extracellular vesicle proteomics.

Results: Sixty-one patients from 8 centers across China (median age, 60 years) were enrolled. 19 patients (31.1%) had liver metastases, and 10 patients (16.4%) had brain metastases. 13 patients completed all three LDRT cycles. At data cut-off (February 28, 2025), the median follow-up was 12.5 months (range: 0.8 - 21.9). The median PFS was 8.6 months (95% CI: 6.5 - 15.0), with 6-month PFS rate of 63.9% (95% CI: 53.0 - 77.2%) and 12-month PFS rate of 33.3% (95% CI: 21.8 - 50.8%). Patients without liver metastases (median PFS: 11.2 vs. 4.4 months; log-rank P = 0.002) experienced significantly longer PFS than those with liver metastases. The confirmed objective response rate (ORR) was 84.8% (50/59; 95% CI: 73.0 - 92.8%), and DCR was 88.1% (52/59; 95% CI: 77.1 - 95.1%). The median DoR was 8.2 months (95% CI: 4.1 - NR). The OS data was not mature yet. The incidence of any grade treatment-related adverse events (TRAEs) was 88.5% (54/61), and 39.3% (24/61) reported grade ≥ 3 TRAEs. Hematological toxicities were the most common TRAEs. Radiation-related toxicities were manageable, with 6 patients having grade 1/2 radiation pneumonitis; 4 patients reported grade 2 immune-related pneumonia. TCR-α/β-chain sequencing revealed that prolonged PFS was associated with increased TCR repertoire diversity after Cycle 1 but increased clonal TCR repertoires after Cycle 4. The proteomics of plasma extracellular vesicle showed patients with higher baseline expression of adaptive immune response pathway, or increased cytoplasm protein levels after cycle 4, had longer PFS.

Conclusions: This study demonstrated a promising survival benefit and manageable toxicity of first-line serplulimab and chemotherapy combined with multi-cycle LDRT in ES-SCLC. Sixteen patients (26.2%) are still on treatment, long-term follow-up and exploratory analysis results are warranted.

Keywords: Extensive-stage small-cell lung cancer, Immunotherapy combination, Adaptive multi-cycle low-dose radiotherapy

PT2.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.13.03 Spatial Multiomics Profiling Reveals Distinct Tumor Microenvironment and Therapeutic Targets in EGFR-Mutant NSCLC Transformed to SCLC

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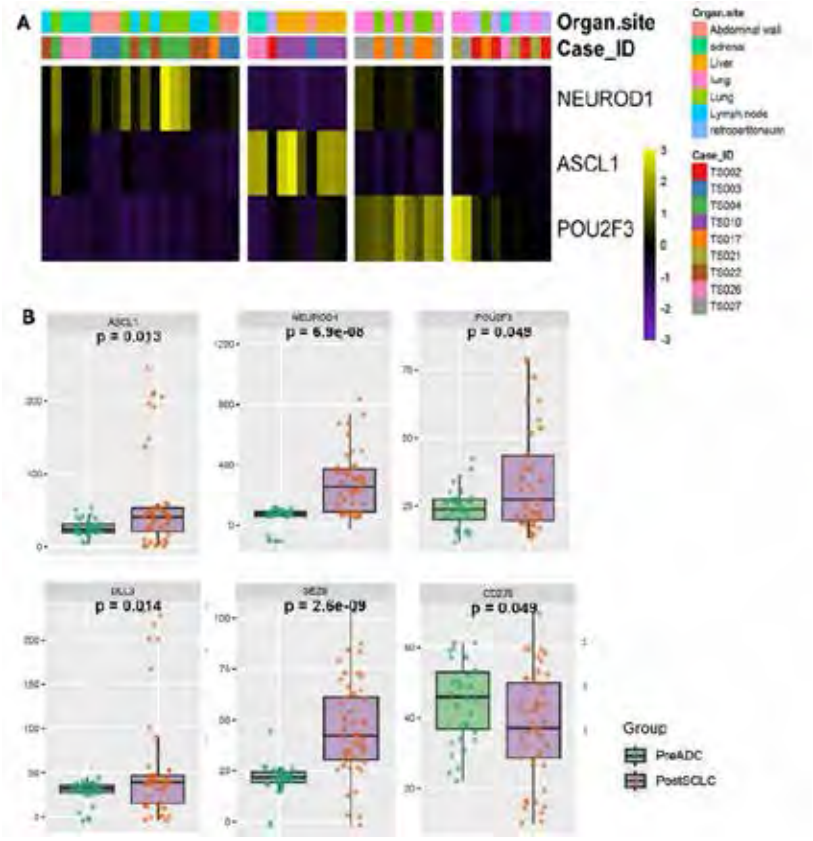
Introduction: 3-10% patients with EGFR-mutant non-small cell lung cancer (NSCLC) undergo histologic transformation to small cell lung cancer (SCLC) under therapeutic pressure. Previous studies identified genomic and transcriptomic characteristics accompanied with this transformation, however spatially resolved profiling of tumor microenvironment (TME) and molecular features of this transformation is lacking. In this study, we investigated spatial transcriptomics and proteomic profiling in pre-transformed EGFR NSCLC (pre-NSCLC) and post-transformed mixed-histology tumors/SCLC (post-mixed/post-SCLC) to shed light on the therapeutic vulnerabilities of this aggressive tumor plasticity.

Methods: Nanostring GeoMx® Digital Spatial Profiling (DSP) was used to analyze Whole Transcriptome Atlas (WTA, >18,000 genes) and 70 protein biomarkers in FFPE samples from patients (N=14) with EGFR NSCLC transformed to SCLC. Three patients have paired pre-NSCLC and post-mixed samples, including one patient with three longitudinal samples. Up to 12 regions of interest (ROIs) per sample were selected by expert pathologists and segmented into Tumor and TME compartments based on the expression of morphology markers (pan-CK, synaptophysin, and CD45). A total of 132 ROIs for WTA and 125 ROIs for protein analyses passed quality control filtering and were included in analyses. In addition, we performed in silico deconvolution of the gene expression data to estimate the abundance of cell populations of the TME.

Results: WTA analyses revealed all four molecular subtypes of SCLC in transformed cases with intra-tumoral heterogeneity. Interestingly, higher expressions of POU2F3 and NEUROD1 are seen across ROIs in the samples (Fig.1A). A subset of the tumor samples expressed higher DLL3, SEZ6 in post-SCLC; while CD276 was expressed across pre-/post-samples (Fig.1B), all are promising cell surface targets with therapeutics available in clinical setting. Gene Ontology (GO) enrichment analyses showed upregulation of neuronal developmental pathways and down regulation of antigen presentation, immune activation and angiogenesis when comparing post-mixed to pre-NSCLC. Lower percentages of macrophages, neutrophils and myeloid dendritic cells are seen in the TME of post-transformed SCLC (p<.0001). Proteomics analyses showed higher levels of immune checkpoints Tim-3, VISTA as well as immune cell markers CD3 and CD45 in pre-NSCLC compared to post-mixed.

Conclusions: These results highlight spatially resolved molecular and immune changes during EGFR-mutant NSCLC transformation to SCLC/mixed histology tumors. In addition, multiple cell-surface targets identified suggests targeted strategies such as antibody drug conjugates may be successful to treat this aggressive disease.



Keywords: SCLC, EGFR NSCLC transformation, spatial profiling

PT2.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.13.04 Real-World Multi-Institution Analysis of Patients With Small Cell Lung Cancer Treated With Tarlatamab

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Introduction: Tarlatamab, a DLL3 bispecific T-cell engager, was approved in relapsed small cell lung cancer (SCLC) based on the phase II registrational trial demonstrating responses in 32-40% of patients. Outcomes for patients receiving tarlatamab who would not have met eligibility criteria for trial inclusion have not been described.

Methods: We identified a cohort of patients with de novo SCLC who received at least one dose of tarlatamab between 5/16/2024 and 3/20/25 at three US academic institutions and analyzed clinical outcomes. Trial-ineligible population was defined as patients with ECOG performance status (PS)≥2, history of ≥grade 2 (G2) pneumonitis, untreated brain metastases, organ dysfunction, oxygen requirement or pleural effusion, history of stroke (past 12 months), or ejection fraction (EF)<50%.

Results: Seventy-five patients were included. Median age was 64 (range 24-82); 55% (n=41) were male and 89% (n=67) were white. Most patients (96%; n=72) were had former or current smoking history with median 40 pack-year exposure, and 61% (n=46) had extensive-stage disease at diagnosis. Tarlatamab was administered after median 9.6 months (range 0.1-45.2 months) with median 1 prior line of therapy after diagnosis of metastatic disease (range 0-6). Overall population: Median time on tarlatamab was 3.1 months, with 48% (n=36/75) continuing therapy at data cut-off. Most common reasons for discontinuation were progression or death (90%; n=35/39), followed by toxicity (10%; n=4/39). Sixty patients were evaluable for response. Best response by clinical assessment was complete or partial response (CR/PR) in 25% (n=15/60), stable disease (SD) or mixed in 25% (n=15/60), and progression in 50% (n=30/60). Seventeen percent (n=10/60) of evaluable patients received treatment beyond progression. Twenty-three percent (n=14/60) of evaluable patients had brain metastasis at progression on tarlatamab. Median overall survival was 8.1 months. Following the first two infusions, sixty percent of patients (n=45/75) experienced cytokine release syndrome (CRS; majority G1), and 32% (n=24/75) had immune effector cell associated neurotoxicity (ICANS; majority G2). Trial-ineligible population: Sixty-one percent of patients (n=46/75) would not have met trial inclusion criteria based on ECOG PS > 2 (20%; n=15/75), untreated brain metastases (24%; n=18/75), history of > G2 pneumonitis (12%; n=9/75), organ dysfunction (11%; n=8/75), pleural effusion or oxygen requirement (25%; n=19/75), EF <50% (16%; n=12/75), or stroke history (4%; n=3/75). Twenty-five patients (33%) met >1 exclusion criteria. In the trial-ineligible population, median time on tarlatamab was 2.4 months, with 46% (n=21/46) remaining on treatment at data cutoff. Tarlatamab was discontinued for progression/death in 88% (n=22/25) and for toxicity in 12% (n=3/25). Thirty-five patients were evaluable for response. Among evaluable patients, 20% (n=7/35) had CR/PR, 20% SD/mixed (n=7/35), and 60% PD (n=21/35). CRS occurred in 59% of patients (majority G2) and ICANS in 39% of patients (majority >G2).

Conclusions: Most patients in this cohort do not meet trial eligibility criteria, highlighting potential opportunity to treat a more broad population. These patients had comparable CRS rates but higher rates of ICANS, lower objective response rate, and more frequent primary progression. Detailed analyses are warranted to understand patient and disease characteristics predictive of toxicity and response to optimize patient selection.

Keywords: small cell lung cancer, tarlatamab, real-world data

PT2.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.14.01 SYSTEMS-2: A Randomised Phase II Study of Radiotherapy Dose Escalation in Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is an aggressive cancer in which pain is very common and analgesics often ineffective. Our SYSTEMS study demonstrated that palliative radiotherapy (20 Gray in 5 fractions) achieved significant pain improvement in one third of patients. We hypothesised that radiotherapy dose escalation would achieve pain relief in more patients and might improve radiological responses and survival.

Methods: SYSTEMS-2 was a randomised multicentre trial comparing hypofractionated, 'dose escalated' radiotherapy (36 Gy, 6 fractions, 2 weeks) with conventional 'control' radiotherapy (20 Gy, 5 fractions, 1 week). It was funded by June Hancock Mesothelioma Research Fund and Beatson Cancer Charity. Participants had a histological and/or multidisciplinary team diagnosis of MPM, Eastern Cooperative Oncology Group Performance Score 0-2, life expectancy >12 weeks and 'worst pain score' >4/10 after analgesia optimisation. Radiotherapy plans compatible with dose escalation were required prior to randomisation. Exclusion criteria included anti-cancer therapy within 4 weeks and previous radiotherapy to overlapping volumes. Primary endpoint was 'worst pain score' by Brief Pain Inventory (BPI) 5 weeks after start of radiotherapy. Secondary endpoints included acute toxicity, quality of life (QoL, weeks 5 and 9), radiological response (modified RECIST, week 9) and overall survival (OS). 112 patients were required to detect a 20% increase in proportion of responders with 90% power and 20% 1-sided statistical significance.

Results: 122 patients were consented between 2016 and 2022 of whom 110 were randomised (54 dose escalated, 56 control) across 17 sites. 'Worst pain' response rates in dose escalated and control groups were 42.6% and 35.7% respectively (intention to treat analysis). The difference of 6.9% was not statistically significant (80% confidential intervals (CI) 6.8-20.6%). Regarding secondary endpoints, toxicities were generally mild with modest increases in incidence of nausea (G1-2), pain (G2-3) and vomiting (G1) during treatment and radiation dermatitis (G1-2) after treatment in dose escalated patients. Pain (G1-2) was reported more frequently in control patients during follow-up. Median OS was 6.6 months (80% CI 4.8-7.5) in the dose escalated arm and 4.8 months (4.2-6.4) in the standard arm. The hazard ratio for death in the dose escalated arm was 0.65 (95% CI 0.44-0.97, p=0.035, Weibull analysis, Figure 1). Six-month OS rates were 51.9% (42.8-60.1) and 41.5% (32.8-50.0) in dose escalated and control arms respectively while 12-month OS rates were 27.4% (19.9-35.4) and 15.9% (9.98-22.3). There were no complete radiological responses (CR) but partial responses (PR) were observed in 18.5% of dose escalated and 10.7% of standard patients, with stable disease (SD) reported in 37.0% and 30.4% respectively. Clinical benefit rates (CR, PR and SD) were 56% and 41% in dose escalated and control arms, absolute difference of 15% (0.6-28.4). No difference in QoL parameters were observed at any timepoints.

Conclusions: SYSTEMS-2 demonstrated that both schedules were well tolerated. There was no improvement in the primary endpoint (worst pain score at 5 weeks) but a reducted risk of death was observed in patients receiving dose escalated radiotherapy and radiological data indicated higher clinical benefit in this group.

Keywords: Mesothelioma, Radiotherapy, Dose escalation

PT2.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.14.02 Human- and AI- Whole Slide Image Assessment of Tumor Immune Microenvironment of Pleural Mesothelioma in Prediction of Patients Outcome

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Introduction: Tumor immune microenvironment (TIM) is critical in cancer progression and therapeutic response. Pleural mesothelioma (PM) shows limited efficacy of immune checkpoint inhibitors underscoring the need for reproducible TIM characterization to identify predictive biomarkers and improve stratification. No universally accepted method exists for a standardized evaluation of the TIM. This study aims to evaluate the concordance between human and AI- whole slide image (WSI) assessment for the quantification of TIM in PM samples, focusing on outcome prediction.

Methods: This preliminary report presents updated findings from the ANEMONE project (a multicenter prospective-retrospective study funded by the European Commission under the TRANSCAN initiative).Immunohistochemistry was performed for pivotal TIM markers. Human-WSI semi-quantitative evaluation was independently conducted by pathologists. AI-based WSI scoring was performed using dedicated software (Visiopharm®).Agreement between AI and human assessment was evaluated through Absolute Standardized Mean Differences (ASMD). Furthermore, Intraclass Correlation Coefficients (ICC) were calculated for continuous variables and Cohen's Kappa (weighted and unweighted) for categorical scores to explore both quantitative and ordinal agreement. Bland-Altman plots were used to visualize systematic bias and variability.A subset of 134 patient (96 males, 38 females; mean age 72years) with complete clinical follow-up was selected, of which 109 epithelioid and 25 sarcomatoid/biphasic mesothelioma. Prognostic significance of marker expression (both AI- and human-derived) was evaluated using Cox proportional hazards models, with hazard ratios (HR), p-values, and Harrell's C-index reported for each marker. Models for histological subtypes (epithelioid vs biphasic/sarcomatoid), were also evaluated and outcome was defined as vital status and time to event.

Results: ASMD analysis confirmed the presence of strong imbalance for CD20 across both score and percent measures (ASMD ≈ 0.66), indicating poor agreement between AI and human evaluation. CD4 and CD68 showed moderate differences (ASMD ≈ 0.19-0.25), while CD3, CD8, and CD163 displayed negligible ASMD values (< 0.1), suggesting high concordance between methods for these markersICC values confirmed excellent concordance for CD57 (ICC = 0.827) and good concordance for CD68 (ICC = 0.659), while CD8, CD3, CD4, CD20, and CD163 showed moderate agreement. Weighted Cohen's Kappa indicated substantial agreement for CD57 and CD68 (0.641 and 0.695), while CD20 had the lowest unweighted Kappa (0.237), reflecting poor categorical agreement. Bland-Altman plots for CD20 revealed a non-linear discordance pattern, with increasing underestimation by AI at intermediate and high expression levels.From a prognostic perspective, CD20 expression assessed by human scoring was significantly associated with improved survival in all cases (HR=0.944; $p < 0.01$) and in epithelioid mesotheliomas (HR = 0.95, p = 0.012). No such association was observed for AI-derived CD20 metrics. In contrast, CD8 expression assessed by AI correlated positively with reduced survival in all cases.

Conclusions: Our preliminary results suggest that AI can provide reliable support for specific markers such as CD8, CD57, and CD68. For some other biomarkers it cannot yet replace human eye, and a more in depth and extensive evaluation is mandatory to calibrate the AI algorithm to obtain reproducible results. Intriguingly CD20, particularly in the epitheloid mesotheliomas, could be a crucial prognostic parameter to assess.

Keywords: mesothelioma, tumor immune microenvironment, human and ai

PT2.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.14.03 Molecular Correlates of Response to Atezolizumab Plus Carboplatin and Paclitaxel in Patients With Thymic Carcinoma

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Introduction: Despite the limited prognosis of advanced or recurrent thymic carcinoma (TC), the development and introduction of novel drugs is often delayed due to its rarity. We previously reported a multicenter, single-arm phase II study of atezolizumab with carboplatin plus paclitaxel in advanced or recurrent TC (Marble study, jRCT2031220144), showing an objective response rate (ORR) of 56%. In post-hoc analyses, PD-L1 expression (SP142) combining TC and IC measurements did not significantly correlate with ORR, but did correlate with longer progression-free survival. However, it is still unclear which patients benefit from this combination therapy. The purpose of this translational research is to characterize genomic and transcriptomic profile of TC and identify predictive response markers from results of Marble study.

Methods: Pretreatment formalin-fixed-paraffine-embedded (FFPE) samples were collected from advanced or recurrent TC patients participated in Marble study. We performed whole exome sequencing (WES) and RNA sequencing (RNA-seq). The analyses of somatic mutation, copy number variation, tumor mutational burden (TMB), and COSMIC mutation signature were conducted using WES data, and analyses of differential gene expression, clustering, and gene enrichment using RNA-seq data.

Results: Out of 48 patients enrolled in Marble study, FFPE samples from 34 patients were available for this biomarker study. 25 patients were responders (best overall response with complete response or partial response) and 9 patients were non-responders (best overall response with stable disease or progressive disease). Mutations in tumor suppressor genes such as CYLD (5/25 versus 0/9), TP53 (7/25 versus 0/9), and SLFN11 (5/25 versus 1/9) were abundant in responders compared with non-responders. Copy number analysis revealed deletions of MTAP, CDKN2A, and CDKN2B genes in 3 responders, but those alterations were not seen in non-responders. Median TMB for responders and non-responders were 10.7 mut/Mb and 12.3 mut/Mb, respectively. RNA-seq was performed to 30 samples which passed quality check, including 22 responders and 8 non-responders. The differential gene expression analysis revealed upregulation of immunoglobulin genes in responders. Gene ontology (GO) analysis to upregulated genes of responders showed enrichment in pathways such as “adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains” and “leukocyte mediated immunity.”

Conclusions: In previously untreated advanced TC, high expression of PD-L1 in IHC, alterations in tumor suppressor genes, and upregulation of immune related pathways may be associated with beneficial response to atezolizumab plus carboplatin and paclitaxel. On the other hand, TMB did not correlate with treatment response.

Keywords: thymic carcinoma, PD-L1 inhibitor, biomarker study

PT2.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.14.04 Efficacy and Safety of Adebrelimab Plus Chemotherapy as Neoadjuvant Treatment for Unresectable Locally Advanced Thymic Carcinoma

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Introduction: While surgery remains the gold standard for early-stage thymic carcinoma, complete resection proves challenging in locally advanced disease. Current multimodal approaches combining chemotherapy, surgery, and radiotherapy have shown limited efficacy in locally advanced cases. Given the unmet clinical need for this rare malignancy, we conducted this study to evaluate the efficacy and safety of adebrelimab combined with nab-paclitaxel and carboplatin as neoadjuvant therapy for unresectable locally advanced thymic carcinoma.

Methods: This study enrolled treatment-naïve patients (pts) with unresectable T3/T4NxM0 thymic carcinoma. Pts received neoadjuvant therapy with adebrelimab (20 mg/kg), nab-paclitaxel (260 mg/m^2), and carboplatin (AUC 4-5) every 3 weeks for ≤3 cycles, followed by surgical resection and adjuvant radiotherapy ± chemotherapy or definitive chemoradiotherapy. The primary endpoint was objective response rate (ORR). Secondary endpoints included surgical resection rate, R0 resection rate, major pathological response (MPR, ≤10% viable tumor cells), progression-free survival (PFS), overall survival (OS), and safety profile. Using a Simon two-stage design, if >2 of 9 initial pts achieved tumor response, enrollment would expand to 24 pts. Treatment efficacy would be considered positive if ≥10 pts achieved objective response.

Results: Between May 2023 and March 2025, 9 pts were enrolled in stage I, all completing planned neoadjuvant therapy. Four pts achieved objective response, while 5 had stable disease resulting in an ORR of 44.4% (4/9) and a DCR of 100% (9/9). Seven pts (77.8%, 7/9) proceeded to surgery, with 7 (100%, 7/7) achieving R0 resection at a median interval of 37 days (range: 30-40) post-neoadjuvant therapy. No treatment-related surgical delays or deaths were observed. Pathological evaluation demonstrated a pathological complete response rate of 14.3% (1/7) and an MPR rate of 42.9% (3/7). At the time of analysis, PFS and OS were not mature. The treatment demonstrated a favorable safety profile without surgical complications. Grade 3-4 adverse events occurred in 7 pts (77.8%), including neutropenia (55.6%, n=5), leukopenia (11.1%, n=1), and rash (11.1%, n=1). The immune-related adverse events (irAEs) associated with adebrelimab were mainly of grade 1-2 (55.6%, 5/9), including rash (22.2%, n=2), infusion reaction (11.1%, n=1), hepatic enzymes increased (11.1%, n=1). The incidence of grade 3 irAE was rash (11.1%, n=1).

Conclusions: In patients with unresectable locally advanced thymic carcinoma, neoadjuvant adebrelimab combined with chemotherapy demonstrated promising efficacy and an acceptable safety profile. The trial is still ongoing to complete accrual in stage II.

Keywords: unresectable locally advanced thymic carcinoma, neoadjuvant treatment, Immunochemotherapy

PT2.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.14.05 Redefining Clinical Outcomes for Peritoneal Mesothelioma (PeM) in the Era of Immunotherapy

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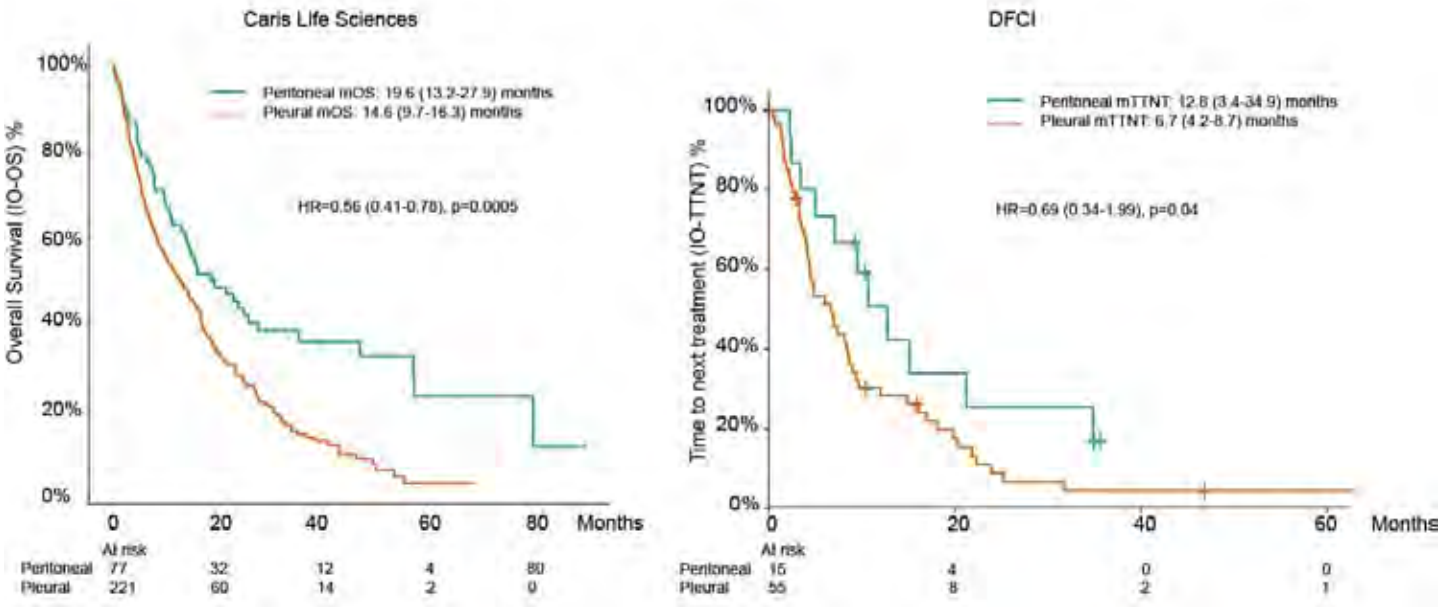
Introduction: Therapeutic strategies for malignant PeM remain poorly defined, often borrowed from protocols developed for pleural mesothelioma (PM). Yet, in the era of immunotherapy, robust data on treatment outcomes specific to PeM are lacking, and direct comparisons to PM are virtually nonexistent—highlighting an urgent need for dedicated research and tailored therapeutic approaches.

Methods: 716 mesothelioma specimens with outcomes were molecularly profiled at Caris Life Sciences. A validation cohort of patients with PeM and PM was curated from Dana-Farber Cancer Institute (DFCI). Treatment groups included patients treated with immune checkpoint inhibitors (IO), primarily nivolumab and ipilimumab. Clinical endpoints included overall survival from the initiation of immunotherapy (IO-OS), and time to next treatment following immunotherapy (IO-TTNT). For the Caris cohort, IO-OS was derived from insurance claims data and calculated from the date treatment initiation (IO) to the date of last clinical contact. For the DFCI cohort, clinical outcomes were obtained through manual chart review and curation. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and p values were calculated using the log-rank test. To characterize the tumor immune microenvironment (TME), immune cell fractions were inferred by deconvoluting bulk RNA expression profiles using quanTIseq (RRID:SCR_022993).

Results: Of 716 patients in the Caris dataset, 298 were treated with IO; 77 (26%) had PeM and 221 (74%) had PM. No significant differences in mutations, tumor mutation burden (>=10), PD-L1 positivity and MMR deficiency were observed between the two group of mesothelioma. PeM specimens however demonstrated significantly higher infiltration of M2 Macrophages (12 vs 8%) and lower infiltration of M1 Macrophages (4 vs 5%, both q<0.05) compared to PM, suggesting a more immunologically active microenvironment potentially influencing response to IO. IO-treated patients with PeM demonstrated significantly longer IO-OS (median 19.6 vs. 13.1 months; HR=0.56) compared to those with PM (both p<0.001, Figure).

Conclusions: Using two independent datasets, our findings highlight PeM as a biologically and clinically distinct disease, characterized by a more immunogenic tumor microenvironment and superior outcomes with IO compared to PM. These data suggest that integration of immunotherapy into the treatment course for patients with PeM may be critical to optimizing survival. Prospective validation is warranted.



Keywords: Mesothelioma, Immunotherapy, Clinical Outcomes

PT2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.15.01 A Randomized Controlled Trial on the Effect of Oncologist's Recommendations on Exercise, Sedentary, and Quality of Life in Patients With NSCLC

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Introduction: Physical activity is associated with better survival in lung cancer, including patients receiving immune-based therapies. Exercise has been demonstrated to be safe and effective in mitigating lung cancer impairments and treatment-related toxicities. Several national and international societies released dedicated guidelines for patients with cancer, strongly recommending engaging in regular exercise. Nevertheless, about 70% of patients with NSCLC are insufficiently active. Promoting physical exercise requires a multidisciplinary team effort, with the oncologist being a crucial player. In this light, the O.R.E. trial aims to explore the effect of the oncologist's recommendation on exercise amount, sedentary behavior, and quality of life (QoL) in patients with NSCLC.

Methods: A single-blind, 3-arm randomized controlled trial design was applied to test the impact of i) oncologist's verbal and written exercise recommendations (EX-G) and ii) oncologist's verbal and written recommendations + dedicated exercise guidebooks (EX-GG) vs. the usual care (CG). The primary endpoint was physical exercise, evaluated using the Godin-Shepard Leisure Time Questionnaire. Secondary endpoints included sedentary habits, assessed with the Sedentary Behavior Questionnaire, and QoL, measured using the EORTC QLQ-C30. Assessments were performed at baseline, after 4 and 8 weeks. Descriptive statistics and mixed-model analysis were used to analyze data.

Results: Overall, 91 patients with NSCLC, stage I-IV (n=31 oncologist's verbal/written recommendation, n=31 oncologist's verbal/written recommendation + guidebook, n=29 control group) were recruited. After adjusting results for disease and socio-demographic characteristics, at 8-weeks, compared to CG, the EX-G reported a significant increase in total (+270.2; 95%CI: 22.2-518.3; p=0.03) and light-intensity (+235.7; 95%CI: 45.6-425.7; p=0.01) physical activity, whereas the EX-GG showed an improvement in total (+250.6; 95%CI: -7.5-508.7; p=0.05) and moderate-intensity (+145.2; 95%CI: -0.8-291.2; p=0.05) activity. No significant changes were observed for sedentary behaviors. Regarding QoL, at 4 weeks, the EX-GG demonstrated an enhancement in cognitive function (+10.1; 95%CI: 1.8-18.3; p=0.01), and EX-G of social function (15.1; 95%CI: 3.0-27.3; p=0.01) than CG. At 8 weeks, EX-GG also reported an improvement in constipation (-14.8; 95%CI: -27.9—1.8; p=0.02) over the CG. No significant differences were observed for other QoL.

Conclusions: An oncologist's recommendation, with or without the combination of a dedicated guidebook, is effective in increasing patients' physical exercise levels and some domains of QoL. Nevertheless, the introduction of a guidebook appears more efficacious in improving the moderate-intensity level. The oncologist, with a few minutes of their time, may positively change lifestyle of patients with NSCLC.

	Control Mean (95% CI)	Exercise Recommendation Mean (95% CI)	Exercise Recommendation plus guidebook Mean (95% CI)	Exercise recommendation vs Control Mean (95% CI)	Exercise recommendation plus guidebook vs Control Mean (95% CI)	Exercise recommendation plus guidebook vs Exercise recommendation Mean (95% CI)
Total (min/week)						
Baseline	108.8 (42.1; 175.5)	223.2 (140.5; 305.9)	252.6 (0.4; 504.7)			
Change from 0 to 4 weeks	+175.2 (+29.0; +321.4)	+138.2 (-119.9; +396.2)	-109.3 (-376.8; +158.2)	112.9 (-107.2; +333.1)	-55.8 (-286.5; +174.9)	-168.7 (-382.9; +45.5)
Change from 0 to 8 weeks	+46.7 (-18.9; +112.3)	+157.1 (-49.4; +363.7)	+45.3 (-323.3; +413.9)	+270.2 (+22.2; +518.3)*	+250.6 (-7.6; +508.7)ǂ	-19.7 (-262.8; +223.4)
Vigorous (min/week)						
Baseline	0.0 (0.0; 0.0)	1.9 (0.0; 5.9)	0 (0.0; 0.0)			
Change from 0 to 4 weeks	0 (0.0; 0.0)	+10.7 (-11.3; +32.7)	+1.0 (-1.1; +3.2)	+11.6 (-5.1; +28.4)	-2.5 (-19.9; +14.9)	-14.2 (-30.5; +2.2)
Change from 0 to 8 weeks	0 (0.0; 0.0)	+8.1 (-8.6; +24.7)	+12.0 (-12.5; +36.5)	+10.8 (-12.5; +34.1)	+18.3 (-5.4; +42.1)	+7.5 (-15.2; +30.3)
Moderate (min/week)						
Baseline	11.7 (0; 26.0)	41.8 (4.0; 79.5)	12.4 (1.5; 23.3)			
Change from 0 to 4 weeks	+12.8 (-18.4; +44.0)	-35.2 (-79.0; +8.6)	+17.1 (-11.0; +45.1)	-15.9 (-47.3; +15.4)*	+5.7 (-26.1; +37.6)	+21.7 (-9.1; +52.5)
Change from 0 to 8 weeks	+23.4 (-6.0; +52.8)	-0.8 (-51.2; +49.7)	+119.0 (-42.5; +280.5)	+4.2(-143.3; +151.7)	+145.2 (-0.8; +291.2)ǂ	+141.0 (-3.3; +285.3)ǂ
Light (min/week)						
Baseline	97.1 (38.4; 155.8)	179.5 (109.6; 249.4)	240.2 (0; 486.6)			
Change from 0 to 4 weeks	+162.4 (+17.5; +307.3)	+162.7 (-82.6; +407.9)	-127.4 (-388.9; +134.1)	+114.7 (-99.7; +329.0)	-59.3 (-285.1; +166.4)	-174.0 (-384.0; +35.9)
Change from 0 to 8 weeks	+57.6 (-0.3; +115.5)	+222.5 (+6.2; +438.8)	-83.5 (-362.4; +195.4)	+235.7 (45.6; +425.7)*	63.0 (-132.4; +258.4)	-172.6 (-359.2; +13.9)

*p<0.05; ǂp=0.05

Keywords: oncologist's reccommendation, physical exercise, quality of life

PT2.15.02 Young Lung Cancer: The Psychosocial Needs Assessment

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Introduction: Young patients (≤50 years) with lung cancer (LC) represent approximately 6-10% of new U.S. LC diagnoses, and little is known about the unique psychosocial needs of this population.

Methods: "Young Lung" is the first and largest single-institution, cross-sectional cohort study designed to characterize the psychosocial needs of young patients with LC and explore differences from older patients. Adult patients with stage I-IV LC were eligible within one year of diagnosis; purposeful sampling was used to enroll equal proportions of patients younger and older than 50 years. The FACT-G questionnaire assessed four quality-of-life subscales (physical, emotional, social, and functional well-being) and FACIT-COST assessed financial distress; higher scores indicated better well-being. Descriptive statistics summarized demographics. Wilcoxon tests examined differences between younger (≤50 years) and older (>50) patients in FACT-G and FACIT-COST scores. Fisher's exact test compared differences by age group in the proportion of patients endorsing individual items.

Results: From 4/2023-12/2024, 199 patients were enrolled, 99 younger and 100 older patients. Among all patients, most (62%) identified as female, White (78%), had adenocarcinoma (61%), and were undergoing treatment (83%). Though the mean total FACT-G score for all patients was 74.5 (SD: 17.7) and was similar between the younger and older cohort (p=0.069), young patients reported worse well-being on the emotional subscale (p=0.002) and were more likely to endorse worse affect across all items on this subscale. Specifically, a higher proportion of young patients endorsed feeling anxious (50% vs 26%; p=0.001) and being worried about dying (49% vs 32%; p=0.03). Trends of higher depression rates were also endorsed by young patients, but not to a statistically significant degree (46% vs 32%; p=0.057). For all patients, the mean COST score was 25.9 (SD: 11.3), with young patients having significantly worse financial toxicity (p=0.015). A higher proportion of young patients were concerned about maintaining employment throughout treatments (42% vs 20%; p=0.002). Young patients were less likely to feel financially in control (62% vs 77%; p=0.03) and more likely to express that their LC has been a financial hardship (49% vs 21%; p<0.001).

Conclusions: Young patients with LC report significantly worse emotional distress and financial toxicity than older patients. Further research will be critical to understand and address the unique needs of this population.

Table 1: FACT-G and FACIT-COST scores among younger (≤50 years) and older (>50) patients with LC.

		Young Patients (n=99)	Older Patients (n=100)	Total	p-value
FACT-Physical well-being (PWB) subscale score *range: 0-28	Mean (SD) Median (Q1, Q3) [Min, Max]	19.04 (6.80) 21.0 (14.0, 25.0) [3.0, 28.0]	20.39 (6.49) 22.0 (17.0, 25.0) [0, 28.0]	19.72 (6.66) 22.0 (16.0, 25.0) [0, 28.0]	0.161
FACT-Social well-being (SWB) subscale score *range: 0-28	Mean (SD) Median (Q1, Q3) [Min, Max]	21.97 (5.21) 24.0 (19.0, 26.0) [8.0, 28.0]	22.65 (4.99) 23.3 (20.5, 26.5) [4.7, 28.0]	22.31 (5.10) 23.7 (20.0, 26.0) [4.7, 28.0]	0.359
FACT-Emotional well-being (EWB) subscale score *range: 0-24	Mean (SD) Median (Q1, Q3) [Min, Max]	15.01 (5.48) 16.0 (11.0, 19.0) [1.0, 24.0]	17.40 (5.01) 18.0 (14.0, 21.0) [2.0, 24.0]	16.21 (5.37) 17.0 (13.0, 20.0) [1.0, 24.0]	0.002
FACT-Functional well-being (FWB) subscale score *range: 0-28	Mean (SD) Median (Q1, Q3) [Min, Max]	15.93 (6.55) 16.0 (11.0, 21.5) [1.2, 28.0]	16.66 (6.75) 16.7 (12.0, 21.0) [0, 28.0]	16.30 (6.64) 16.3 (11.0, 21.0) [0, 28.0]	0.458
FACT-G total score (sum of PWB, SWB, EWB, FWB) *range: 0-108	Mean (SD) Median (Q1, Q3) [Min, Max]	71.96 (17.98) 73.2 (59.7, 85.9) [29.1, 104.0]	76.99 (17.14) 80.0 (66.3, 90.8) [28.0, 106.8]	74.48 (17.70) 76.5 (62.0, 88.0) [28.0, 106.8]	0.069
FACIT-COST: Measure of financial toxicity *range: 0-44	Mean (SD) Median (Q1, Q3) [Min, Max]	23.63 (12.27) 26.0 (15.7, 33.0) [0, 42.9]	28.08 (9.68) 29.0 (22.5, 35.2) [4.0, 44.0]	25.85 (11.25) 27.5 (19.0, 34.0) [0, 44.0]	0.015

Keywords: Young Lung Cancer, Psychosocial Needs, Financial Toxicity

PT2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.15.03 Examining the Role of Frailty Assessments in Older Adult With Lung Cancer to Identify Patient Vulnerabilities and Exploring Patient Outcomes

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Introduction: In oncologic care, frail older adults (OA) are at an increased risk for poor treatment outcomes. The National Compressive Cancer Network recommends pretreatment frailty evaluation using a comprehensive geriatric assessment for OA to optimize treatment plans and improve outcomes. In this study, lung cancer patients were evaluated at the Rush Functional Assessment and Individualized Recommendations (FAIR) Frailty Clinic to identify at-risk patients and gaps in overall care. Patients were referred from a combination of nurse coordinator screening and treating physician referral.

Methods: A retrospective chart review was conducted on 51 patients with lung cancer who were identified to be an at-risk population by their oncologist and referred to the FAIR Clinic between October 2019 and May 2024 for frailty assessment. We collected data on diagnosis, patient demographics, symptoms, functional assessments, post-assessment recommendations, and treatment outcomes. Due to sample size data, descriptive analysis was used.

Results: The average age was 77.2 years old; with 67% female. The racial breakdown was 53% African American, 33% Caucasian, and 12% Hispanic. The most common diagnosis was non-small cell lung cancer 88%, and the most common stages at the time of evaluation were SIII 45.1% and then SIV 23.5%. The average BMI was 26.33, and 78.85% of patients had either a reported or documented weight loss exceeding 10 pounds over the past year. Average scores and ranges for the most notable assessments were: Montreal Cognitive Assessment 17.07 (5-27), Fried Frailty Phenotype (FFP) 2.3 (0-5). Patients had an average of two referrals made per visit, the most common being physical and occupational therapy, social work, and dietitian. After evaluation, Treatment outcomes varied: 11 patients received no further treatment (FFP 3.2, 2 hospitalizations, 3 deaths), 12 received radiation alone (FFP 3.0, 1.5 hospitalizations, 2 deaths), and 27 received systemic therapy with or without radiation/surgery (FFP 2.1, 2.1 hospitalizations, 6 deaths).

Conclusions: Our data demonstrates the majority of the patients referred to the FAIR clinic were pre-frail, cognitively impaired, with significant comorbidity, and ethnically diverse, with a higher population of African American patients compared with the lung cancer patient population at Rush (35%). We identified needs outside of oncologic treatment, including therapy services and social work support. While descriptive, our data suggests patients who did not receive treatment were frailer than those that did. Patients who did receive systemic treatment had a high incidence of treatment-related hospitalizations. Overall, our data highlights the value of frailty clinics in identifying patient vulnerabilities and assisting in individualized treatment plans, though few eligible patients with stage IV lung cancer diagnoses attended the evaluation from a program servicing 700 lung cancer patients annually. Future efforts should focus on closer monitoring of patients receiving systemic treatment and improving access for patients with stage IV cancer, particularly those from lower socioeconomic status.

Keywords: Frailty, Multidisciplinary Care, Functional Status Assessment

PT2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.15.04 Impact of Physical Exercise on Quality of Life in Patients With Advanced Lung Cancer

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Introduction: Recent research has increasingly highlighted the benefits of physical exercise for persons with cancer, particularly in improving quality of life, functional capacity, and overall well-being. Regular PE has been associated with reduced cancer-related fatigue, improved muscle strength, better cardiorespiratory fitness, and enhanced emotional resilience. Additionally, it helps alleviate symptoms such as dyspnea, anxiety, and depression, which are common in people with advanced lung cancer (LC). Despite these benefits, the optimal type, intensity, and frequency of exercise, as well as its role in disease progression and quality of life, remain insufficiently defined in this population. In this abstract, we present the observed changes in quality of life and physical condition in persons with advanced LC enrolled in an ongoing study that comprehensively evaluates the effects of a structured exercise program, assessing its impact on physical and emotional well-being.

Methods: This quasi-experimental, prospective observational study implemented a supervised and structured physical exercise intervention program led by a multidisciplinary team consisting of oncologists, nutritionists, nurses, and professionals in Physical Activity and Sports Sciences. The program consisted of two weekly 60-minute sessions, each including:

- Warm-up (8-12 minutes): Joint mobility and locomotor exercises.
- Main session (40-45 minutes): Targeted strength, mobility, aerobic, and relaxation exercises.
- Cool-down (12-15 minutes): Group discussions, relaxation exercises, and collective reflection.

Quality of life was assessed using the EORTC QLQ-C30 and EORTC QLQ-LC29 questionnaires, along with the Hospital Anxiety and Depression Scale (HADS), administered at baseline and after the 3-month intervention. Physical condition was evaluated using the 5-Repetition Sit-to-Stand Test.

Results: The study enrolled 29 participants between November 2024 and March 2025. Preliminary data from 10 participants (4 men, 6 women; mean age: 68 years; 9 with stage IV non-small cell lung cancer, 1 with stage IIIc small cell lung cancer) revealed significant improvements in the QLQ-C30 functional scales: overall functional score ($p=0.0395$) and emotional functioning ($p=0.0135$). No significant changes were observed in the QLQ-LC29 scale. The HADS indicated a significant reduction in total anxiety scores ($p=0.044$). Additionally, significant improvements were observed in the 5-Repetition Sit-to-Stand Test ($p<0.05$). The adherence rate to the exercise program was 71%.

Conclusions: People with LC benefit from regular, supervised physical exercise, experiencing improvements in quality of life, functional capacity, and reductions in anxiety levels associated with the disease. Routine inclusion of these programs as part of non-pharmacological treatment strategies could contribute to the overall well-being of people with LC.

Footnote: The translation of this abstract was assisted by AI technology (ChatGPT) to maintain linguistic accuracy and clarity.

Keywords: Lung cancer, Exercise, Quality of life

PT2.16 PATIENT ADVOCACY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.16.01 Current Patient, Caregiver and Provider Attitudes Toward Use of AI in Lung Cancer Patient Navigation

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Introduction: Lung cancer care is complex due to disease heterogeneity and the need for personalized treatment strategies. Additionally, current lung cancer resources are fragmented by topic, which makes it challenging for individuals to find the information they need and determine what is relevant to them. These factors make providing tailored, effective support services for each patient challenging, yet access to resources can improve survival. Artificial Intelligence (AI)-based approaches that leverage machine learning and natural language processing offer a promising solution to enhance patient education and navigation. To better understand attitudes toward the use of AI in navigation of patients with lung cancer, GO2 for Lung Cancer (GO2), a lung cancer patient-advocacy organization, implemented a brief survey of both patients and providers in our community.

Methods: As part of a quality improvement initiative, we conducted a cross-sectional survey between January 27 and February 7, 2025, to gather feedback on the feasibility and acceptability of a proposed AI-powered navigation tool for individuals impacted by lung cancer. Participants included healthcare professionals (HCPs) involved in lung cancer navigation and individuals diagnosed with or caring for someone with lung cancer. Survey content was informed by the Consolidated Framework for Implementation Research (CFIR) to ensure alignment with key implementation domains. Two structured electronic surveys were developed: a 13-item survey for HCPs a 10-item survey for patients and caregivers. The HCP survey collected information on clinical background, years of experience, navigation responsibilities, and perspectives on AI integration, including perceived usefulness, confidence in AI-generated information, comfort, and leadership support. The patient and caregiver survey explored familiarity with AI tools, comfort with receiving AI-generated health information, perceived ease of use, willingness to share health history, and desired tool features. Surveys were distributed through GO2 outreach channels to inform the design and future implementation of the navigation tool. Descriptive statistics were used to summarize responses.

Results: Of the 98 responses collected, 42 were from HCPs and 56 were from patients or caregivers. Among HCPs, the most reported backgrounds were pharmacists (42.9%), physicians (26.2%) and nurses (21.4%), with the majority of HCPs (33%) having over 21 years of experience. The survey revealed that over 95% of providers believe AI could improve efficiency and decision-making in patient navigation. Additionally, 90% of providers reported they were likely or very likely to integrate AI-powered patient navigation if a tool was provided. Furthermore, 69% of HCPs believed that patients would respond positively to the use of AI in their care. For patients/caregivers, the survey found that 67% rely on online resources for information. Only 20% expressed discomfort with the use of AI in providing information, while 62.2% were hesitant but open to its use, and 17.8% reported they would have no issues. Patients/caregivers cited simplified medical information (63%), accessing clinical trials (40.9%), and symptom management (38.6) as their top reasons for interest in AI-driven support.

Conclusions: Patients with lung cancer, caregivers, and care providers recognize the potential benefits of AI in care. However, addressing concerns around mistrust and usability will be crucial for widespread adoption.

Keywords: artificial intelligence, navigation, education

PT2.16 PATIENT ADVOCACY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.16.02 Patients Who Reach Clinical Trials and Those Who Do Not,A Structural Analysis of Access Disparities in Japan

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Introduction: Clinical trials are an essential process for scientifically evaluating the efficacy and safety of new treatments and hold significant potential to expand future therapeutic options. To ensure reliability and external validity, it is vital that patients from diverse backgrounds—including differences in age, gender, values, and socioeconomic conditions—can participate equally. However, recent studies in Japan have revealed multiple barriers in patient access to clinical trial information. A 2021 national survey showed that while about half of patients obtained information through websites, information provided by healthcare professionals remained limited. Moreover, the usability of clinical trial search platforms and difficulty understanding technical terminology were reported as significant obstacles. Against this backdrop, the present study aims to visualize the process by which lung cancer patients who express interest in clinical trials actually reach the point of potential participation. We focused on the key turning point of physician referral and analyzed the factors influencing whether or not patients received a trial recommendation, in order to clarify the structural disparities in access.

Methods: From May 20 to June 7, 2024, a web-based survey was conducted targeting lung cancer patients, their families, and bereaved family members who had shown prior interest in clinical trials. Among the 253 total respondents, 148 who had actively considered trial participation were analyzed. We compared 58 patients who were referred to a trial by their physician with 90 who were not. Variables such as type of medical institution (specialized cancer hospital or not), patient behavior (whether they searched or proactively requested trial information), and attitudes toward clinical trials were analyzed using logistic regression.

Results: Patients who expressed interest in trial participation to their physician were significantly more likely to be referred (OR: 4.70, 95% CI: 1.83-12.75). Those receiving care at cancer centers were also more likely to be referred (OR: 4.28, 95% CI: 1.71-11.09). In contrast, patients who searched for trials but did not communicate their interest to their physician had a notably lower likelihood of being referred (OR: 0.04, 95% CI: 0.01-0.12), showing a negative association.

Conclusions: This study highlights that access to clinical trials strongly depends on patients' proactive communication and the type of healthcare institution they attend. Even when patients are interested and seek information, that alone is insufficient—dialogue with physicians plays a crucial role. The current system, where trial implementation is concentrated in certain institutions, may be contributing to regional and institutional disparities. To expand the opportunity for a broader range of patients to participate in clinical trials, it is essential to develop neutral and equitable systems of information provision by healthcare professionals, along with user-friendly environments where patients can easily search, understand, and evaluate options. Furthermore, clinical trial information should not be viewed merely as guidance, but as part of a process that supports patients in making the best possible decisions.

Keywords: clinical trial, diversity, Patient access

PT2.16 PATIENT ADVOCACY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.16.03 Overcoming Lung Cancer Nihilism and Fatalism to Foster Compassion, Empathy, and Support

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Introduction: Lung cancer remains the leading cause of cancer death worldwide. Despite significant advances in lung cancer risk reduction, screening, treatment, and survivorship, deeply entrenched nihilism and fatalism continue to shape public and clinical perceptions, impeding access to optimal care and life-saving interventions. As part of the American Cancer Society National Lung Cancer Roundtable, the Stigma and Nihilism Task Group (S&NTG) recently considered efforts to address the pervasive diagnostic and treatment nihilism that is regrettably common in society and healthcare settings regarding lung cancer and propose evidence-based strategies to shift the narrative toward one of hope, empathy, and progress.

Methods: A multidisciplinary team of experts conducted a comprehensive review of the psychological, social, and systematic factors contributing to lung cancer nihilism and fatalism. The team synthesized existing literature on the psychological and social impact of nihilism/fatalism, communication strategies, and public perceptions. They also identified key opportunities for intervention at individual, clinician, and societal levels.

Results: The findings highlight several actionable strategies to address nihilism and fatalism in lung cancer care.

1. Empathic Communication: Using person-first language and avoiding stigmatizing labels reduces bias and enhances patient engagement.
2. Clinician Education and Screening Promotion: Addressing clinician hesitancy in recommending lung cancer screening is critical to increasing uptake.
3. Public Awareness and Media Representation: Enhancing accurate portrayals of lung cancer in media and public discourse can counter outdated stereotypes and stigma.
4. Addressing Tobacco Stigma Without Blame: Non-judgmental approaches to smoking history can foster trust and improve engagement in cessation and screening efforts.
5. Mental Health and Supportive Care: Given the high rates of distress and suicide among individuals with lung cancer, integrating mental health support is essential.
6. Research Funding and Advocacy: Increased investment in lung cancer research and advocacy efforts is needed to support continued progress in care and policy.

Conclusions: Lung cancer care has undergone transformative advances, yet nihilism and fatalism remain persistent barriers to progress. A concerted effort across healthcare, public health, advocacy, and media is required to realign public perception with the current reality of lung cancer care—one that is increasingly characterized by early detection, effective treatment, and improved survival. The recommendations presented offer a roadmap to fostering a culture of compassion, reducing stigma, and optimizing outcomes for individuals at risk for or diagnosed with lung cancer.

Keywords: Lung cancer, Nihilism, Fatalism

PT2.16 PATIENT ADVOCACY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.16.04 Advancing Lung Cancer Advocacy in Low- and Middle-Income Countries

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Introduction: Lung cancer remains a leading cause of cancer-related deaths worldwide, with an increasing burden in low- and middle-income countries (LMICs). Challenges such as lack of awareness, late diagnosis, and limited access to treatment highlight the urgent need for patient advocacy. The International Association for the Study of Lung Cancer (IASLC) hosted a Patient Advocacy Workshop at the 2025 Pan-Africa Conference on Lung Cancer to identify frameworks to foster multi-sectoral collaboration and best practices for sustainable advocacy strategies in Africa.

Methods: All conference attendees received information about the Workshop. Those who expressed interest received an online Pre-Workshop Survey to assess challenges in lung cancer care in individual countries and patient advocacy experience. The Workshop included formal presentations, panel discussions, and a group discussion during which participants answered 5 key questions on advocacy priorities. The information recorded from panel and group discussions was analysed thematically. An evaluation survey followed the Workshop.

Results: Forty-two conference attendees from 11 countries, 8 of which were on the African continent, participated in the Workshop. Pre-Workshop Survey: 25/42 (60%) responded to the Pre-Workshop Survey, which identified financial cost, limited healthcare infrastructure, and late detection of lung cancer as the three top challenges. Nine had participated in patient advocacy at the hospital level. The findings from this survey were used to guide the discussion agenda for the in-person Workshop in Accra, Ghana. Workshop Discussion: Two case studies were presented: the Move Against Cancer Africa oncology phlebotomy station and the EGFR Resisters. Both projects highlight the power of community engagement and how partnerships between advocates and healthcare institutions lead to long-term changes in cancer care. The discussion created a framework of four key pillars of effective advocacy: connection, community, collaboration, and communication. It also outlined three levels of advocacy progressing from self to community to systemic change. Workshop Group Discussion: We identified 22 themes for the guiding questions answered at the in-person Workshop. The guiding questions included: What does advocacy mean to you? What are your priorities for 2025? What resources are needed to accomplish your priorities? How will collaboration help bring other resources? What are the opportunities for advocacy in your country? Priorities identified were: Investing in resource-sharing platforms, translating and adapting patient and caregiver materials, and developing local pilot programs in collaboration with advocates to enhance cancer advocacy efforts. Additionally, professional organizations should allocate dedicated resources to support advocate development in LMICs, such as scholarships for training and global conferences. Post-Workshop evaluation: 21/42 (50%) responded to the evaluation. 90% of participants were satisfied with the Workshop; 100% stated they would recommend it to others. The top three actions participants felt equipped to take were: advocate for better healthcare policies (81%), share information on early detection (71%), and support lung cancer patients/their families emotionally (62%).

Conclusions: The Workshop highlighted key frameworks for multi-sectoral collaboration, including deploying the four pillars for advocacy. Moving forward, sustained investment, collaboration with patient advocates, and dedicated (digital) professional development opportunities in LMICs will be critical to strengthening advocacy impact.

Keywords: Advocacy in Low- and Middle-Income Countries, Patient advocacy Workshop, Lung cancer in Africa

PT2.16 PATIENT ADVOCACY
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.16.05 Survivorship Needs for Patients With NSCLC Treated With Oral Targeted Therapies

M. Guo[1], C. Burley[2], Y. Wang[2], J. Dobbs[1], C. Eaton[2], S. Olson[2], M.L. Hsu[3], J. Feliciano[1]
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Introduction: Oral targeted therapies (OTT) for treatment of oncogene-driven non-small cell lung cancer have contributed to a growing population of long-term lung cancer survivors (LCS). OTTs provide more patient-specific treatment options compared to standard cytotoxic chemotherapy, easier oral route of treatment administration, and more tolerable side effects due to less off-target effects. However, the survivorship needs of LCS who received OTT, including physical, psychosocial, and care delivery needs, are not well-defined.

Methods: LCS (defined as alive ≥1 year from diagnosis) treated at Johns Hopkins between 2020-2024 were invited to complete a needs assessment survey measuring patients' perspectives on survivorship needs across 4 subscales (physical, social, emotional, medical) rated on a 5-point Likert scale (1=no need, 5=highest need; score 2+ indicating need endorsement). Demographic and clinical information, including lung cancer treatment regimens and intent (palliative vs curative), were collected by chart review and survey response. Patients with >80% survey completion were included for analysis. Wilcoxon rank sum or Kruskal-Wallis tests identified demographic characteristics associated with greater needs among patients who received OTT. As patients on curative-intent therapy were expected to have significantly fewer needs than patients on palliative-intent therapy, a sub-group analysis was conducted to examine differences in needs by OTT-history among patients on palliative-intent therapy only.

Results: 428 patients were invited to complete the needs assessment survey, of which 307 were included for this analysis. Median age was 68, most were female (59.9%), Caucasian (73.9%), and had ECOG performance status 0-1 (91.5%) at time of survey. In terms of treatment history, 36.2% (n=111) had ever received OTT and 60.9% (n=187) were on palliative-intent for most recent line of therapy. More than half of patients who had received OTT endorsed emotional needs of living with uncertainty (80.0%) and fear of recurrence (78.2%). Common physical needs in the ever-OTT cohort were fatigue (82.7%), memory/concentration (64.9%), and hair/skin changes (63.6%). Amongst all ever-OTT patients, age <65 (p=0.002), non-Caucasian race (p=0.024), and non-employed employment status (p=0.022) were identified as factors associated with greater number of social needs. Key comparisons in rates of need endorsement by ever- and never-OTT patients on palliative-intent therapy were identified (Table 1).

Conclusions: Survivorship needs are highly prevalent among LCS patients, regardless of their history of receiving OTT. Certain demographic factors are associated with greater number of social needs amongst ever-OTT patients, suggesting disparities in unmet survivorship needs.

Table 1. Percent of patients on palliative-intent therapy who endorsed needs (Likert scale 2-5)

Need	Ever-OTT (n=102)	Never-OTT (n=95)	P-value
Emotional Needs			
Living with uncertainty	81.2%	74.1%	0.128
Fear of recurrence	77.2%	82.1%	0.697
Physical Needs			
Fatigue	84.1%	80.0%	0.877
Memory/concentration	64.7%	61.9%	0.990
Hair/skin changes	64.3%	46.4%	0.0165
Sleep disturbances	61.8%	73.5%	0.0691
Bowel/bladder dysfunction	59.4%	43.9%	0.0628
Social Needs			
Managing daily activities	45.2%	40.0%	0.375
Returning to work	31.1%	26.3%	0.107
Financial concerns	45.9%	52.5%	0.651

Keywords: Survivorship, Oral targeted therapies, Needs assessment

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PT2.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.17.01 Point-Of-Care Rapid Tissue Diagnosis at Primary Consultation: Optimizing TIME to Treatment in the Neoadjuvant Era

B. Kidane, S. Gowing, L. Tan, G. Qing
University of Manitoba, Winnipeg/MB/CA

Introduction: Tissue diagnosis and molecular testing are necessary to allow for locally advanced or advanced lung cancers. Challenges and delays in achieving this reliably can result in lack of access to the survival advantages of neo-adjuvant therapy or best therapy for unresectable advanced cancers . We assessed the diagnostic yield, sufficiency for molecular testing and resource utilization improvements of a thoracic surgeon-led, point-of-care ultrasound-guided biopsy program in a single-payer publicly-funded healthcare system.

Methods: A prospective cohort study was performed of consecutive patients undergoing ultrasound-guided percutaneous biopsies performed by thoracic surgeons from June 2021 to March 2025 at a tertiary Canadian institution. Diagnostic yield, sufficiency for molecular testing and resource utilization improvements were analyzed.

Results: A total of 211 patients underwent point-of-care ultrasound percutaneous biopsy for locally-advanced or advanced thoracic cancers. Tissue diagnosis was obtained in 89.6% of patients (n = 189). There was sufficient tissue for molecular testing in 95.2% (n=180) of these patients. Due to the rapid point-of-care timing of the biopsy, successful repeat biopsy was able to be done promptly in our clinic (i.e. repeat percutaneous biopsy or EBUS/EUS) without being a source of delayed care. There was 1 post-procedure pneumothorax (adverse event rate 0.5%). This program significantly reduced time-to-treatment by an average of 23 days ($p<0.05$). Reduction was also identified, to a lesser extent, to other patients during the same time period. Root cause analysis showed that this improvement was due to increased access to EBUS, EUS, CT-guided biopsies that were no longer needed by these 189 patients.

Conclusions: Thoracic surgeon-led ultrasound-guided biopsies can be done in an outpatient clinic setting with high diagnostic accuracy, high yield/sufficiency for molecular testing and can reduce time-to-treatment in a clinically-significant way. This benefit at the patient-level appears to also be extended downstream at the system-level by offloading demands on other resources, thereby reducing time-to-treatment for other patients. This appears to be a promising model, especially for low-moderate resource settings.

PT2.17.02 Impact of Timely Treatment Initiation on Outcomes in Non-Small Cell Lung Cancer. A Registry Based Observational Study

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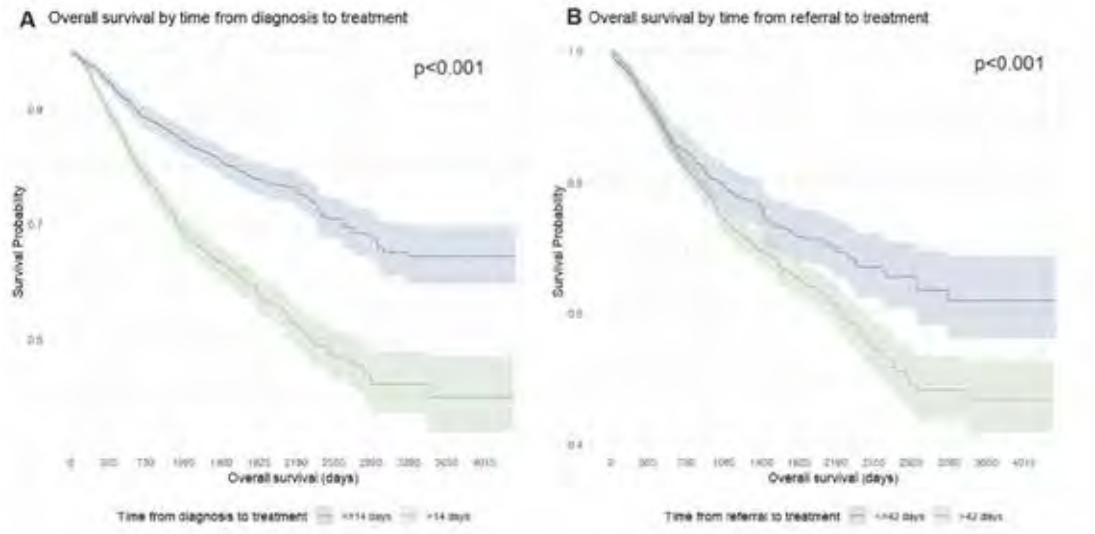
[1]Alfred Health, Melbourne/AU ,[2]Monash University, Melbourne/AU ,[3]Consumer advocate, Melbourne/AU ,[4]University of NSW, Albury/AU ,[5]Grampians Health, Ballarat/AU ,[6]Goulbourn Valley Health, Shepparton/AU ,[7]Bendigo Health, Bendigo/AU ,[8]Cabrini Health, Melbourne/AU ,[9]Epworth Health, Melbourne/AU ,[10]Eastern Health, Melbourne/AU ,[11]Austin Hospital, Melbourne/AU ,[12]Barwon Health, Geelong/AU ,[13]Monash Health, Melbourne/AU ,[14]Northern Health, Melbourne/AU ,[15]Western Health, Melbourne/AU ,[16]Peninsula Health, Melbourne/AU ,[17]Victorian Comprehensive Cancer Centre, Melbourne/AU ,[18]Melbourne Health, Melbourne/AU ,[19]St Vincent's Hospital, Melbourne/AU ,[20]Royal Melbourne Hospital, Melbourne/AU

Introduction: Lung cancer is the leading cause of cancer death in Australia, with evidence of unwarranted variation in clinical care. Timeliness recommendations have been made in international guidelines, although previous studies exploring the effect of timeliness on survival in NSCLC have revealed conflicting results.

Methods: We performed an observational cohort study of all cases of Stage I-II NSCLC in the Victorian Lung Cancer Registry (VLCR), between July 2011 and May 2023. Timeliness intervals were defined by the Australian Optimal Care Pathway for people with lung cancer. A diagnosis-to-treatment interval (DTI) of <14 days and referral-to-treatment interval (RTI) of <42 were defined as timely. The effect of timeliness on overall survival was determined using Cox proportional hazards regression.

Results: We identified 3,016 cases of Stage I-II NSCLC (52% Male). Patients receiving timely treatment (n=1,204, 42%) were younger (median 69 vs 72 years, p <0.001) and never smokers, with fewer comorbidities and better performance status. Patients undergoing surgical resection (n=1,989, 66%) were more likely to receive timely care, whereas those undergoing systemic treatment, radiotherapy, or referred to palliative care were less likely (p<0.001). Median overall survival to census date for timely DTI and RTI were 1,100 days (IQR 585, 1,815) and 1,337 (IQR 713, 2,077) respectively, vs untimely 1,439 (IQR 746, 2,203) and 1,033 (IQR 588, 1,653) p<0.001 Table 1. Both timely DTI and RTI were associated with significantly lower mortality risk (DTI HR 0.57, 95% CI 0.49-0.67, p <0.001, RTI HR 0.75 95% CI 0.63-0.9, p 0.002) Figure 1.

Conclusions: Timely treatment of Stage I-II NSCLC was associated with improved survival, although most cases did not meet recommended timeliness intervals. With lung cancer screening soon to be implemented in Australia, there is a strong impetus to investigate the barriers to timely access to care and help guide future resource allocation.



Time Interval	Median (IQR) (days)	<7 days n (%)	8-14 days n (%)	15-28 days n (%)	29-42 days n (%)	>42 days n (%)	Proportion meeting timely care
RDI	35 (18, 58)	250 (8.3%)	263 (8.7%)	605 (20%)	503 (17%)	1077 (36%)	37%
DTI	23 (0, 45)	1084 (36%)	120 (4.0%)	410 (14%)	482 (16%)	790 (26%)	40%
RTI	64 (43, 93)	34 (1.1%)	56 (1.9%)	193 (6.4%)	348 (12%)	1948 (65%)	35%

n.b. ~10% of cases missing definitive referral date = Meets definition of timely care

Keywords: Management timeliness, Lung cancer registry, nsclc

PT2.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.17.03 Accelerated Biological Aging Is Correlated With the Incidence and Poor Prognosis of Young Lung Cancer

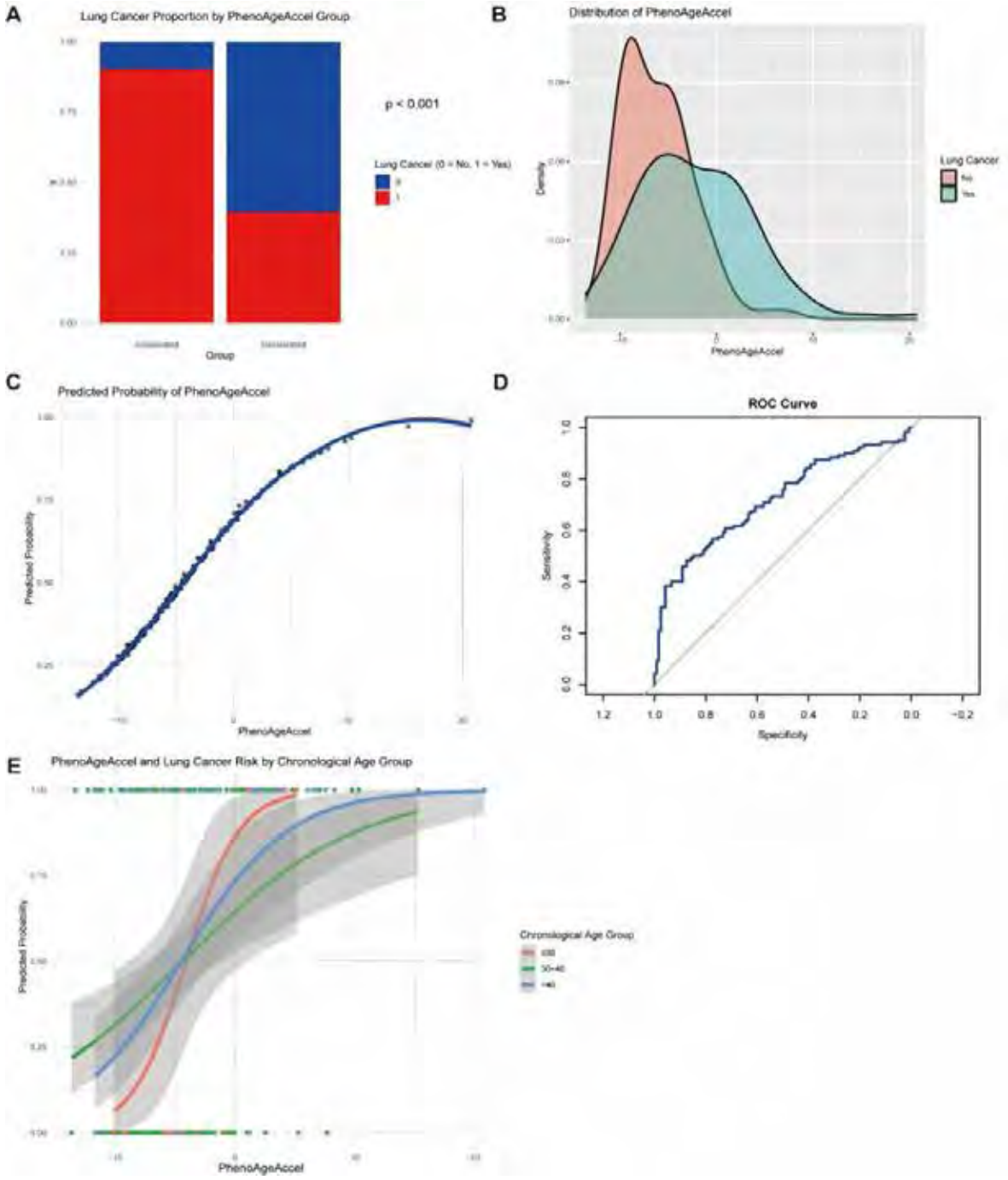
Y. Liao, R. Gao, J. Zhong, J. Wang
Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing/CN

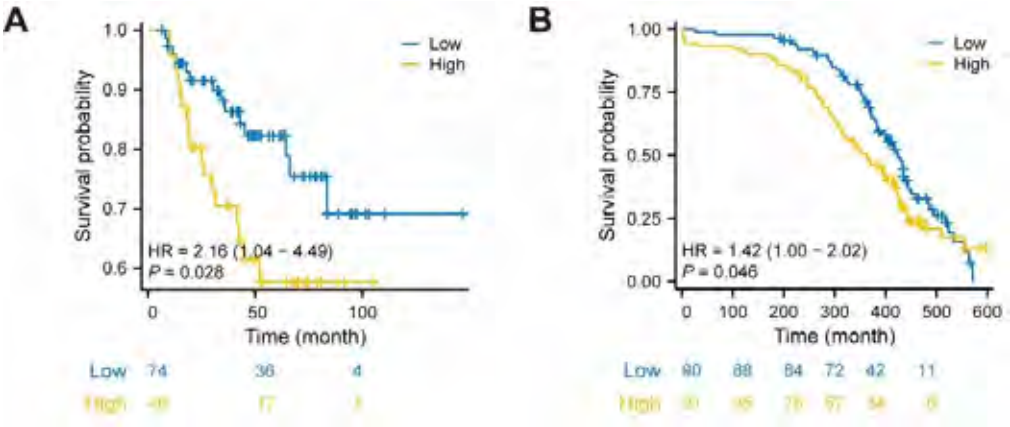
Introduction: While lung cancer is predominantly diagnosed in seniors, the incidence of young lung cancer (≤45 years) is rising. Current screening guidelines primarily target older populations, leaving younger individuals at risk of delayed diagnosis and poor outcomes. Accelerated biological aging, measured by Phenotypic age acceleration (PhenoAgeAccel), has been implicated in cancer susceptibility, yet its role in young lung cancer remains poorly understood.

Methods: A multicenter case-control study in China (120 young lung cancer patients and matched 120 health volunteers) and validation with the UK Biobank were conducted. PhenoAgeAccel was calculated from clinical hematological and biochemical parameters to assess accelerated biological aging. Logistic regression was used to estimate the relationship between PhenoAgeAccel and the lung cancer risk.

Results: Young lung cancer patients exhibited significantly higher PhenoAgeAccel than healthy volunteers ($P < 0.001$), with a dose-dependent increase in cancer risk (OR: 25.8, 95% CI: 8.94-88.9, for high PhenoAgeAccel). Further subgroup analysis based on chronological age indicated a stronger impact of PhenoAgeAccel on cancer risk in earlier adulthood. Senior lung cancer patients exhibited weaker or non-significant associations. Survival analysis demonstrated that higher PhenoAgeAccel was associated with worse overall survival in young lung cancer patients (HR = 2.16, 95% CI: 1.04-4.49). The UK Biobank cohort confirmed these findings.

Conclusions: Accelerated biological aging is strongly associated with higher young lung cancer risk and poorer prognosis. PhenoAgeAccel may serve as a potential cost-effective biomarker for early detection and risk stratification for this specific population.





Keywords: Young lung cancer, Biological aging, Cancer risk

PT2.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
MONDAY, SEPTEMBER 8, 2025 - 14:15 - 15:00

PT2.17.04 First Assessment of IASLC Inclusive Practices and Challenges: Results From the Diversity, Equity, and Inclusion Survey

N. Florez[1,2], Z. Wei[1], L. Kiel[1], R. Kaufman[1], L. Raez[3,4], A. Morabito[1], G.A. Silvestri[5], R. Osarogiagbon[6], D. Jain[7], M. Quist[8], J. Tanizaki[9], S. Nakazawa[1], J. Wang[10], A. Rabea[11], V. Vanderpuye[12], E.M. Urbanska[13], M. Tachihara[14], A-M. Baird[15], Q. Chu[16,17], M. Castro[18], S. Crengle[19], K. Kelly[20], C. Pompili[21]
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Introduction: The International Association for the Study of Lung Cancer (IASLC) is committed to implementing and promoting Diversity, Equity, and Inclusion (DEI) within its organization and iteratively assessing DEI needs and perceptions. Here, we report the first survey-based evaluation of inclusive practices and challenges within the IASLC.

Methods: We administered an online, anonymous survey through QualtricsXM that was shared via the IASLC membership list. Additional outreach took place via social media and direct messaging in WhatsApp™. The survey was available in English, Spanish, Japanese, Italian, French, Portuguese, Korean, and Mandarin. Throughout all outreach efforts, non-IASLC members were also encouraged to participate. Statistical analyses were conducted using R 4.4.0; reported percentages reflect the number of respondents for each question. Pearson's Chi-squared tests or Fisher's exact tests were used to compare responses by subgroups of interest.

Results: A total of 1234 individuals started the survey; 707 (57.3%) partially or entirely completed the survey and were included in this analysis (Table 1). Most reported that the IASLC is always or usually inclusive (always, usually) regarding race/ethnicity (51.5%, 32.5%), gender (58.8%, 29.1%), age (51.4.%, 32.1%), family status (52.1%, 29.7%), socioeconomic status (44.6%, 32.2%), sexual orientation (54.8%, 27.8%), disability status (45.0%, 32.2%), religion (54.5%, 27.3%), profession (47.4%, 32.0%), and language (41.2%, 29.2%). Compared to non-Latin American respondents (n=578), Latin Americans (n=65) were more likely to report non-inclusivity regarding language (43.3% vs 27.5%; p=0.011). Few respondents reported experiencing or witnessing discrimination at IASLC events due to age (experienced, witnessed) (4.4%, 4.7%), disability status (1.6%, 1.8%), gender (6.5%, 6.6%), family status (2.8%, 1.7%), religion (2.0%, 1.8%), sexual orientation (1.8%, 2.5%), language (6.9%, 5.5%), or race/ethnicity (5.7%, 6.4%). Compared to non-Asians (n=479), individuals practicing in East and Southeast Asian countries (n=166) were more likely to report having experienced discrimination due to primary language spoken (13.3% vs 4.4%; p=<0.001). Among all participants, few (12.1%) reported experiencing barriers to accessing IASLC resources, though this was more prominent among members from Latin America (n=65; 23.1% vs 10.8%; p=0.004) and mid-career faculty (n=224; 17.4% vs 10.0%; p=0.007). Conference assistance, increased resources for members, and diverse representation at conferences were common responses regarding how to improve inclusivity. The need to embed DEI principles within the IASLC was reported favorably by respondents, with 39.8% strongly agreeing and 39.0% agreeing.

Conclusions: Survey respondents reported favorable views regarding inclusive practices within the IASLC. Implementing strategies to increase language inclusivity could improve the experience of IASLC members.

Table 1. Respondent Demographics (n=707)

Race and Ethnicity	East Asian 161 (23.7%) White 146 (21.5%) Multi-Racial 83 (12.2%) West European 61 (9.0%) African 30 (4.4%) Asian-American 29 (4.3%) South American 27 (4.8%) Hispanic/Latinx 22 (3.2%) Eastern European 17 (2.5%) Southeast Asian 14 (2.1%) Prefer not to disclose 14 (2.1%) Middle Eastern 9 (1.3%) African American/Black 7 (1.0%) Other 6 (0.9%) Indigenous American/First Nation 2 (0.3%) Central American 1 (0.1%) Caribbean 1 (0.1%)
Role	Physician 506 (73.9%) Scientist 47 (2.2%) Allied Health Professional 17 (2.5%) Student 15 (2.2%)
Language	English 415 (58.7%) Mandarin 101 (14.3%) Japanese 76 (10.7%) Spanish 39 (5.5%) Portuguese 32 (4.5%) French 21 (3.0%) Italian 18 (2.5%) Korean 5 (0.7%)
Gender	Man 355 (55.1%) Women 259 (42.6%) Prefer not to disclose 9 (1.5%) Transgender 3 (0.5%) Non-binary 2 (0.3%)
Age	30-44 270 (39.7%) 45-54 199 (29.3%) 55-64 106 (15.6%) 65+ 57 (8.4%) 18-29 33 (4.9%) Prefer not to disclose 15 (2.2%)
Membership Status	IASLC Member 619 (89.5%) Non-member 73 (10.5%)

Keywords: Inclusion Practices, IASLC, DEI Task Force

PT2.17.05 Benefits of Adjuvant Alectinib in ALK+ Early-Stage Non-Small Cell Lung Cancer, Recurrences Avoided and Savings for the Spanish Health System

J. de Castro[1], R. Bernabé[2], V. Escudero[3], F. Gutiérrez[4], M. Majem[5], R. Gordo[6], I. Arroyo[6], S. Arranz[7], R. Collado[3]
[1]Hospital Universitario La Paz, IdiPAZ, Madrid/ES ,[2]Hospital Universitario Virgen del Rocío, Sevilla/ES ,[3]Hospital Universitario Gregorio Marañón. Instituto de Investigación Sanitaria Gregorio Marañón, Madrid/ES ,[4]Complejo hospitalario Universitario de Canarias, Instituto de Investigación Sanitaria de Canarias (IISC), La Laguna (Tenerife)/ES ,[5]Hospital de la Santa Creu i Sant Pau, Barcelona/ES ,[6]Roche Farma, Madrid/ES ,[7]Hygeia Consulting S.L., Madrid/ES

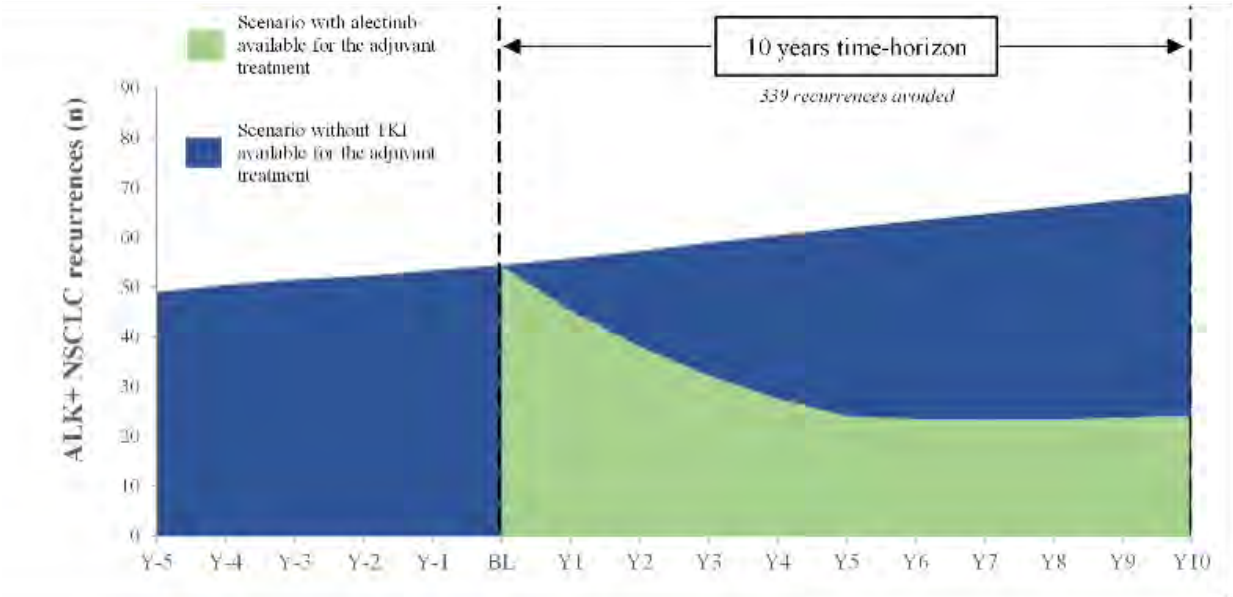
Introduction: More than half of patients with resectable early non-small cell lung cancer (eNSCLC) experience disease recurrence within 5 years. Approximately 3-5% of eNSCLC patients have ALK rearrangements, in whom adjuvant alectinib has shown a significant benefit in disease-free survival (DFS) compared to platinum-based chemotherapy (PbCH). The aim of this analysis was to quantify the potential number of disease recurrences avoided with the introduction of adjuvant alectinib in comparison to the current adjuvant PbCH for ALK+ eNSCLC over the next 10 years in Spain, together with the associated savings in the advanced disease.

Methods: An epidemiological model has been developed to estimate the number of recurrences after adjuvant treatment of early-stage (IB ≥4cm - IIIA [UICC/AJCC 7th edition TNM Classification]) ALK+ NSCLC over the next 10 years (2025-2035) in Spain. Two scenarios were compared, including adjuvant treatment with alectinib versus 4 cycles of adjuvant PbCH. The target population was estimated over the 10-year time horizon based on literature data. Alectinib market introduction was assumed at 85% in the first year, reaching a maximum share of 98% in the fifth year. Recurrence probabilities were obtained from DFS and overall survival data from the ALINA study. The cost of recurrences was obtained from the literature (euros of 2025). The sources used for epidemiological estimation, relapse probabilities and relapse costs were validated by an expert panel.

Results: The target population of patients with ALK+ eNSCLC after complete tumour resection was estimated from 98 individuals in 2025 to 122 in 2035. For the 10-year time horizon, the model projected 680 recurrences in the adjuvant PbCH scenario and 341 relapses in the adjuvant alectinib scenario. The evolution of recurrences in both scenarios is shown in Figure 1. The 339 recurrences potentially avoided with adjuvant alectinib over the next 10 years (estimating that 264 of them would be treated with systemic therapies at progression disease) would result in savings of 46,4 million euros for the Spanish National Healthcare System, an average saving of around €4,6 million/year. Scenario sensitivity analyses provided a range of 42,3 to 49,3 million euros of savings.

Conclusions: The use of adjuvant alectinib in patients with resected ALK+ eNSCLC would substantially reduce the number of recurrences over the next 10 years, resulting in significant cost savings in the management of the advanced disease for the Spanish National Healthcare System.

Figure 1. Evolution of new recurrences over time estimated by the epidemiological model.



Keywords: Early-stage NSCLC, Recurrences, Economic savings

05 | POSTER PRESENTATIONS

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.01 Stage Shift and Then Some - St. Elizabeth Healthcare's Notable Journey, 50,000 Screens Later

M.R. Gieske, D. Alkapalan, I.A. Budhani, E. Fahey, J. Ries
St Elizabeth HealthCare, Edgewood/KY/USA

Introduction: St. Elizabeth Healthcare, a community hospital system in Northern Kentucky and Southeastern Indiana, serving over 400,000 patients, launched its lung cancer screening program (LCSP) in 2013. Over a decade later, the program has not only exceeded benchmarks set by the National Lung Screening Trial but continues to demonstrate increasingly profound stage migration. Our sustained, data-informed, and team-based approach has significantly altered the trajectory of lung cancer detection in our region, resulting in both earlier diagnosis and improved outcomes.

Methods: A weekly multidisciplinary nodule review board evaluates Lung-RADS 4 and suspicious incidental cases to ensure timely, cost-effective, and coordinated diagnostic workup with the least risk to the patient. Three dedicated LCS nurse navigators facilitate patient and provider communication and care coordination for both the LCSP and incidental nodule program. All lung cancer screening diagnoses are entered into a compendium that tracks stage, demographics, and timeliness of care. Performance metrics across 41 screening sites and 210 primary care providers are collated quarterly and shared across our system. Our Population Health Support Services team of twelve RN outreach specialists actively supports patients with follow-up and tracks order completion to improve uptake and enhance adherence.

Results: As of early 2025, more than 50,000 low-dose CT screenings have been completed, yielding over 500 stage I lung cancers. In 2024, 151 lung cancers were diagnosed through screening; 72.2% (n=109) were stage I, and 76.8% (n=116) were early stage (I or II). Notably, since 2022, early-stage lung cancer diagnoses have surpassed late-stage diagnoses across our healthcare system. Between 2015 and Q3 2024, late-stage cancers declined 30.3 percentage points, a rate over 3.5 times faster than national trends. Q4 registry data is pending. A cornerstone chart presented at the 2025 European Lung Cancer Congress underscores this shift (see Figure 1). Additionally, a stage migration analysis from 2015 - 2023 showed that 70.0% of screen-detected lung cancers were found at stage I, compared to 36.3% in the non-screened group. Our uptake compares favorably with the national average of 16.0%, at 51.7% of eligible attributed patients.

Conclusions: Our results demonstrate that a comprehensive, team-based lung cancer screening initiative can progressively reduce late-stage cancer diagnoses and transform care pathways. This work and the advancements in lung cancer diagnostics and treatment are collectively changing the narrative on lung cancer. With maturity and sustained provider engagement, community-based programs can not only replicate clinical trial outcomes but serve as national models of scalable impact.

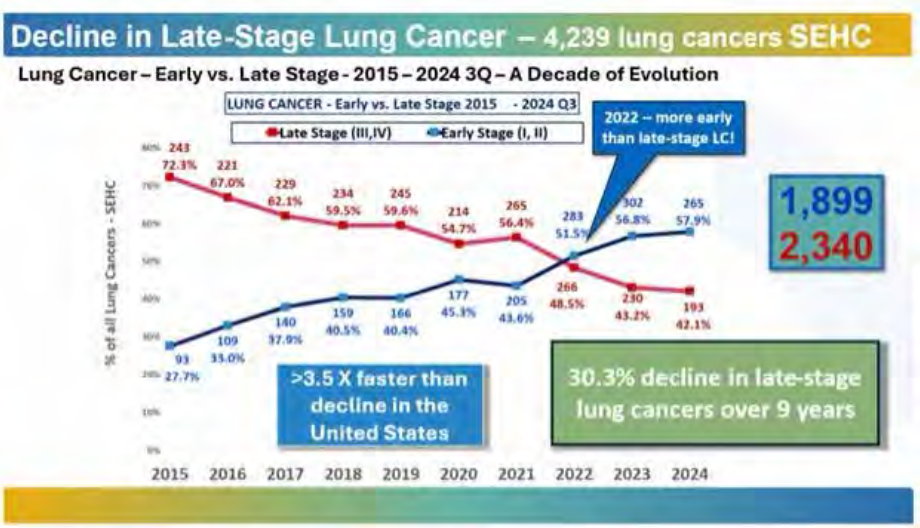


Figure 1. Decline in Late-Stage Lung Cancer at St. Elizabeth Healthcare (2015–3Q 2024). Early-stage lung cancer diagnoses (blue line) surpassed late-stage (red line) in 2022, driven by a decade of consistent LDCT screening programmatic efforts. Total lung cancers over 9 years: 4,239

Keywords: lung cancer screening, stage shift, early-stage lung cancer surpasses late-stage

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.02 Performance of AI Vs. Radiologists in the 4-IN-THE-LUNG-RUN Lung Cancer Screening Trial: Annual Follow-Up Results

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Introduction: Lung cancer screening (LCS) with low-dose computed tomography (LDCT) has demonstrated significant lung cancer-related mortality reduction among high-risk individuals. Artificial intelligence (AI) is widely used as a secondary or concurrent reader in LCS. However, its role as a first reader could reduce radiologists' workload by effectively ruling out negative cases. This study evaluates AI as a first reader in the annual screening round of the European 4-IN-THE-LUNG-RUN (4ITLR) LCS trial, comparing its negative misclassifications (NM) and positive misclassifications (PM) to those of experienced radiologists.

Methods: A total of 2,219 annual LDCT scans from the 4ITLR dataset (acquired between 14 December 2022 and 14 January 2025) were independently assessed by both a radiologist and dedicated AI software. In cases of discrepancy, an expert panel served as the reference standard. A case was classified as NM when the final assessment was indeterminate or positive/referral (defined as a volume-doubling time (VDT) of <600 days or the presence of new nodules >30 mm^3) while either the AI or radiologist had initially classified it as negative. Conversely, a case was classified as PM when the final assessment was negative, but the AI or radiologist had categorized it as indeterminate or positive.

Results: AI accounted for 35 NMs (1.6%) and 492 PMs (22.2%), with a negative predictive value (NPV) of 97.8% (95% CI: 97.1-98.4). Of the 35 NM cases, 33 (94.3%) were indeterminate, and 2 (5.7%) required direct referral. Radiologists accounted for 59 NMs (2.7%) and 15 PMs (0.7%), with an NPV of 97.2% (95% CI: 96.5-97.7). Among these, 56 (94.9%) were indeterminate, and 3 (5.1%) required direct referral. Overall, AI classified 27.8% of cases as indeterminate or referral and 72.2% as negative, compared to radiologists with 5.2% and 94.8%, respectively.

Figure 1 shows an indeterminate NM by the AI at the annual follow-up, where it missed a new nodule. However, the nodule disappeared after three months.

Conclusions: AI demonstrated comparable performance to radiologists in independent CT readings within the annual screening round of a LCS trial. AI exhibited a lower rate of NM cases and a similar NPV, indicating its potential to rule out negative cases as a first reader without increasing the risk of missed or delayed diagnoses. While AI produced a higher number of PMs, limiting radiologist review to AI-flagged indeterminate/positive cases could result in a 73.2% reduction in radiologist workload.

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.03 Comorbidities and Social Factors in Lung Cancer Screening Eligibility: Insights From the Colaus and Lc65 Cohorts in Switzerland

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Introduction: A key challenge in lung cancer screening is the lack of population-level tobacco use data. In the canton Vaud, Switzerland, a pilot project is evaluating lung cancer screening participation and feasibility. This study aimed to provide an accurate description of the resident population eligible for screening.

Methods: We analyzed self-reported, cross-sectional data from two independent sources to assess screening eligibility (age 50-79 years, ≥20 pack-years smoking, ≤15 years since quitting):

- Lausanne cohort 65+ (Lc65+): 2014 data from a random sample of community-dwelling older adults (65-70 years) in Lausanne, the capital of Canton Vaud.
- CoLaus study: 2021 data from a randomly selected cohort of adults aged 35-75 in Lausanne who were recruited in 2000. Participants aged 50-79 were included.

We then compared eligible and non-eligible participants using descriptive statistics.

Results: Among the 1,678 participants in the Lc65+ cohort, 305 (18.2%) met the screening criteria. Eligible participants included more men (47.5% vs. 42.1% in the non-eligible group), while women were less represented (52.5% vs. 57.9%, p=0.15). Their mean age was 68.0 (SD 1.4) vs. 67.9 (SD 1.4) in the non-eligible group (p=0.8). Eligible participants had higher rates of hypercholesterolemia (40.0% vs. 32.6%, p=0.04), coronary heart disease (9.8% vs. 5.5%, p=0.02), and alcohol abuse (12.8% vs. 4.3%, p<0.001). They also reported more frequent fatigue (p=0.04) and exhibited poorer physical performance, with longer completion times for the 20-meter walk test (15.9s vs. 15.2s, p<0.001) and Up & Go test (10.6s vs. 10.2s, p<0.01). Socioeconomic disparities were evident, with eligible participants having lower incomes (CHF 4,383.0 vs. CHF 5,796.3, p<0.001), higher financial insecurity (17.0% vs. 10.6%, p<0.001), and lower educational attainment (p=0.01). They were also less likely to be Swiss-born (78.4% vs. 84.4%, p=0.03) or to hold a driver's license (50.7% vs. 54.8%, p=0.02). In the CoLaus cohort, 770 of 3,839 participants (20.1%) met the screening criteria. Men were more frequently eligible (49.6% vs. 44% in the non-eligible group), while women were less represented (50.4% vs. 56%, p=0.01). Their mean age was 63.4 (SD 8.2) vs. 62.8 (SD 7.6) in the non-eligible group (p=0.09). Eligible participants reported poorer health (p<0.001) and had higher rates of abdominal obesity (39% vs. 25%, p=0.03). Their lipid profiles were less favorable, with lower HDL (1.50 vs. 1.62 mmol/L, p<0.001), higher triglycerides (1.49 vs. 1.28 mmol/L, p<0.001), and slightly elevated LDL (3.12 vs. 3.20 mmol/L, p=0.04). Fatigue (13.5% vs. 10.1%, p=0.001) and self-care difficulties (7.3% vs. 4.8%, p=0.02) were also more frequent among eligible participants.

Conclusions: Participants in the Lausanne cohorts who were eligible for lung cancer screening had more comorbidities, poorer overall health, and were more socioeconomically disadvantaged compared to non-eligible participants. These disparities underscore the importance of developing tailored lung cancer screening programs that address both medical and social barriers to access.

Keywords: Lung cancer screening eligibility, Population-based cohort, Health inequalities

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.04 Effect of Social Determinants of Health on Lung Cancer Screening Uptake in the U.S

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Introduction: Although individual social determinants of health (SDOH) have been linked to lower lung cancer screening (LCS) rates in the U.S., the impact of cumulative SDOH burden across multiple domains remains unclear. To address this, we used item response theory (IRT) to construct a composite SDOH score that reflects multidimensional social disadvantage. We hypothesized that increased negative social drivers of health are associated with lower rates of LCS.

Methods: This cross-sectional study used combined 2022 and 2023 Behavioral Risk Factor Surveillance System (BRFSS) data. Participants who were eligible for LCS based on United States 2021 Preventive Services Task Force guidelines and had data available for SDOH were included. We included 11 SDOH variables encompassing 4 different domains: 1) social (life satisfaction, feel isolated/lonely, social and emotional support, and stress); 2) economic (employment stability, food insecurity, receipt of SNAP, housing insecurity, and utility service insecurity); 3) environmental (transportation) and 4) healthcare affordability. SDOH scores were generated using unidimensional IRT, with a higher score representing increased negative social drivers of health. Logistic regression models were used to examine the association between SDOH and having an up-to-date LCS, defined as a low dose computed tomography (LDCT) scan within the past 12 months. Stratified analyses by age, sex, and race and ethnicity were performed. All analyses were weighted.

Results: A total of 14,583 (weighted N= 6,809,371) individuals were included. 14.3% received LDCT for lung cancer within the past year. Greater social disadvantage, as indicated by higher SDOH scores, was associated with a numerically lower likelihood of being up to date with LCS (OR: 0.92; 95% CI: 0.84-1.01) but was not statistically significant. After adjusting for age, sex, race, education, geographic region and insurance status, the association did not appear to be statistically significant (OR: 0.99; 95% CI: 0.88-1.11). After stratifying by age, sex, and race and ethnicity, no significant associations were found between SDOH scores and LCS uptake (Table).

Conclusions: In contrast to prior studies that assigned equal weight to individual SDOH indicators, our use of IRT to generate a composite SDOH score did not show a significant association with LCS uptake. This discrepancy highlights the importance of how social disadvantage is measured and suggests that weighting and structure of SDOH domains may influence observed associations. Future research should explore the most appropriate ways to quantify cumulative SDOH burden and validate these approaches across diverse populations to better understand their impact on LCS behaviors.

Summary of associations between social determinants of health score and up-to-date lung cancer screening.

	Odds Ratio	95% Confidence Interval
Overall	0.99	0.88-1.11
Age		
50-64	0.96	0.81-1.14
65-79	1.05	0.90-1.21
Sex		
Male	1.09	0.94-1.26
Female	0.90	0.76-1.07
Race/ethnicity		
Non-Hispanic White	0.98	0.89-1.11
Non-Hispanic Black	1.01	0.67-1.51
Hispanic	1.01	0.54-1.89
Other	1.11	0.65-1.89

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.05 Diminishing Eligibility for Lung Cancer Screening According to Standardized Screening Guidelines

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Introduction: In 2021, the United States Preventive Services Task Force (USPSTF) guidelines for lung cancer screening (LCS) expanded the eligibility criteria on age (50-80 years) and smoking history (≥20 pack-years), allowing more racial and ethnic minority individuals and women to be screened. Data are limited on the proportion of individuals diagnosed with lung cancer who could have been screened applying these criteria, especially over time.

Methods: Using linked electronic health record and cancer registry data, we conducted a cross-sectional study of all individuals diagnosed with primary lung cancer from 2014 to 2022 at Kaiser Permanente Northern California, an integrated health care delivery system that serves a socio-demographically diverse population of over 3.6 million U.S. adults. We calculated proportions and 95% confidence intervals of individuals diagnosed with lung cancer who met LCS eligibility in three-year intervals (2014-2016, 2017-2019, 2020-2022), overall and stratified within groups of age, smoking status, race/ethnicity, sex, tumor stage, and neighborhood deprivation index level.

Results: Among 11,736 individuals with lung cancer, the proportion eligible decreased 8.8% overall between 2014-2016 and 2020-2022. In each time interval, the proportion eligible was consistently lower among Asian or Pacific Islander and Hispanic than non-Hispanic white individuals, among women than men, and among individuals living in the least versus most deprived neighborhoods. While the proportion eligible decreased across all groups over time, the absolute decrease was largest among individuals of non-Hispanic Black race (12.4%) and individuals diagnosed with stage I tumors (13.1%).

Conclusions: Our data suggest that the proportion of individuals diagnosed with lung cancer who meet the current USPSTF LCS eligibility criteria at diagnosis is declining over time. This evidence points to a potential growing gap between screening guidelines and the actual population at risk for lung cancer, supporting the continued need to evaluate LCS guidelines and consider other risk factors to ensure effective and equitable early detection of lung cancer.

Diagnosis Year	2014-2016			2017-2019			2020-2022			Absolute Difference from 2014-2016 to 2020-2022 (%)
	N = 4018			N = 4022			N = 3698			
	Total	Eligible		Total	Eligible		Total	Eligible		
		No.	% (95% CI)		No.	% (95% CI)		No.	% (95% CI)	
Overall	4018	1131	28.2 (26.8, 29.5)	4022	913	22.7 (21.4, 24.0)	3698	719	19.4 (18.2, 20.7)	8.8
By Age										
50-80	3152	1131	35.9 (34.2, 37.6)	3106	913	29.4 (27.8, 31.0)	2925	719	24.6 (23.0, 26.1)	11.3
By Smoking status										
Ever Smoked	2748	1131	41.2 (39.3, 43.0)	2702	913	33.8 (32.0, 35.6)	2438	719	29.5 (27.7, 31.3)	11.7
By Race/Ethnicity										
Non-Hispanic White	2573	834	32.4 (30.6, 34.2)	2564	690	26.9 (25.2, 28.6)	2258	543	24.1 (22.3, 25.8)	8.3
Non-Hispanic Black	342	101	29.5 (24.7, 34.4)	359	80	22.3 (18.0, 26.6)	304	52	17.1 (12.9, 21.3)	12.4
Asian or Pacific Islander	657	96	14.6 (11.9, 17.3)	692	71	10.3 (8.0, 12.5)	799	69	8.6 (6.7, 10.6)	6.0
Hispanic	160	22	13.8 (8.4, 19.1)	146	23	15.8 (9.8, 21.7)	156	13	8.3 (4.0, 12.7)	5.5
By Sex										
Male	1902	603	31.7 (29.6, 33.8)	1815	459	25.3 (23.3, 27.3)	1642	391	23.8 (21.8, 25.9)	7.9
Female	2113	528	25.0 (23.1, 26.8)	2207	454	20.6 (18.9, 22.3)	2054	327	15.9 (14.3, 17.5)	9.1
By Stage										
I	839	258	30.8 (27.6, 33.9)	886	219	24.7 (21.9, 27.6)	863	153	17.7 (15.2, 20.3)	13.1
II	295	94	31.9 (26.6, 37.2)	259	68	26.3 (20.9, 31.6)	242	55	22.7 (17.5, 28.0)	9.2
III	678	233	34.4 (30.8, 37.9)	701	194	27.7 (24.4, 31.0)	586	151	25.8 (22.2, 29.3)	8.6
IV	2084	514	24.7 (22.8, 26.5)	1978	399	20.2 (18.4, 21.9)	1864	334	17.9 (16.2, 19.7)	6.8
By Neighborhood Deprivation Index Level										
Quartile 1 (least)	637	132	20.7 (17.6, 23.9)	739	108	14.6 (12.1, 17.2)	771	93	12.1 (9.8, 14.4)	8.6
Quartile 2	1254	332	26.5 (24.0, 28.9)	1223	264	21.6 (19.3, 23.9)	1090	196	18.0 (15.7, 20.3)	8.5
Quartile 3	1131	356	31.5 (28.8, 34.2)	1126	299	26.6 (24.0, 29.1)	1017	241	23.7 (21.1, 26.3)	7.8
Quartile 4 (most)	914	300	32.8 (29.8, 35.9)	865	230	26.6 (23.7, 29.5)	801	187	23.4 (20.4, 26.3)	9.4

Keywords: Screening Eligibility, Temporal trends, Lung Cancer

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.06 AI Performance for Lung Nodule Growth in UK Lung Cancer Screening: Expert Consensus and Histological Validation

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Introduction: To evaluate the performance of a fully automated artificial intelligence (AI) system in assessing lung nodule growth using volume doubling time (VDT) in follow-up low-dose CT lung cancer screening.

Methods: This retrospective sub-study of the UK Lung Cancer Screening (UKLS) trial included 710 participants with 939 LDCT follow-up scans (3-month: n=361; 12-month: n=578), and 9 diagnosed lung cancers. A commercially available AI system (AVIEW LCS software) automatically performed nodule detection, volumetric measurement, nodule matching, and VDT calculation. For comparison, the same procedure was performed by human readers, which included radiologists from the UKLS trial and two EU radiology-trained readers. According to the NELSON-plus protocol, a case was classified as positive if the largest nodule with solid component ≥100mm3 and VDT ≤400 days, otherwise negative. A blinded European consensus read by a panel of three radiologists with 20 years of experience served as the reference standard, while histological lung cancer outcomes were used as the gold standard.

Results: AI had a discrepancy rate based on final CT-scan outcome (positive/negative) of 8.0% (29/361) at 3-month follow-up and 1.4% (8/578) at annual screening. The negative predictive values (NPV) of AI based on histological results were 99.7% (95%-CI: 98.3-99.9%) at 3 months and 100% (95%-CI: 99.4-100.0%) at 12 months. Among the four lung cancers ≥100 mm^3, AI correctly identified all as having VDT ≤400 days on the earliest follow-up CT (3 months). However, one was classified as negative due to AI's measurement below the 100 mm^3 threshold, resulting in the only protocol-defined false negative. In contrast, human readers missed or delayed referrals in up to 3 out of 4 cases. Of five lung cancers <100 mm^3, one showed no growth (adenocarcinoma in situ), one was slow growth (VDT of 689 days), and the other three were correctly identified by AI as VDT ≤400 days.

Conclusions: AI demonstrated robust performance in fully automated VDT assessment during LDCT follow-up lung cancer screening, accurately identifying all actionable lung cancers ≥100mm^3 and achieving high NPV.

Keywords: Lung Cancer Screening, Computed Tomography, Artificial Intelligence

P1.04.07 Projection of the Lung Cancer Screening Eligible Population in Argentina From 2000 to 2050

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Introduction: Cigarette smoking in Argentina has gradually declined over the past decades; however, 22.2% of the adult population continues to smoke, with lung cancer remaining the leading cause of cancer-related mortality. While many high-income countries recommend lung cancer screening (LCS) for high-risk individuals, Argentina's National Ministry of Health has yet to issue a recommendation. Here, we project the annual percentage and number of individuals eligible for LCS in Argentina from 2000 to 2050 to inform policy and clinical decisions.

Methods: We developed an Argentinean version of the Cancer Intervention and Surveillance Modeling Network (CISNET) Smoking History Generator (SHG), a microsimulation model that generates cohort-specific smoking histories by age and gender. Argentina's SHG was parameterized with smoking data from nationally representative surveys, population projections from the United Nations, and mortality data from the Cancer Prevention Study II. Using the simulated population by the Argentinean SHG, we estimated the number of LCS-eligible individuals in the country for the period 2000-2050 under the US Preventive Services Task Force criteria (adults aged 50-80 years who have a 20 pack-year or more smoking history and currently smoke or have quit within the past 15 years).

Results: The Argentinean SHG reproduces the observed smoking prevalence in Argentina. The number of LCS-eligible individuals is projected to rise from 1 million people in 2000 to 1.6 million in 2018, remain stable until 2036, and then decline to 1.3 million by 2050. As the population grows and smoking prevalence continues to decline, the proportion of LCS-eligible individuals aged 50-80 is expected to nearly halve, declining from 15.1% in 2018 (the peak for eligibility) to 7.8% by 2050. Similar trends are observed in both men and women (Figure 1).

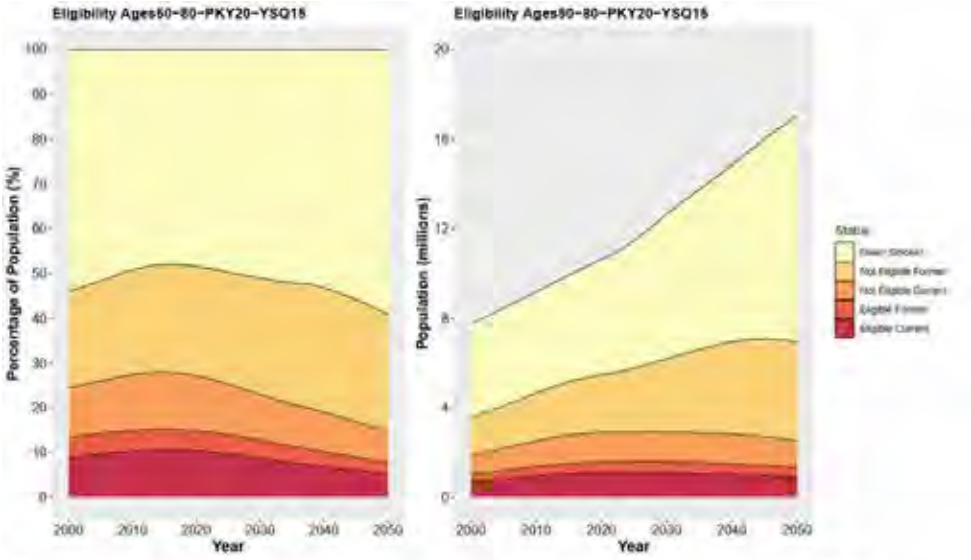

Figure 1. Projected LCS-eligible population from 2000-2050 with age eligibility 50-80. **Left:** Percentage of adults aged 50-80 by eligibility and smoking status (stacked areas). The bottom two areas represent the proportion of LCS-eligible individuals (current and former smokers). **Right:** Projected number of individuals aged 50-80 by eligibility and smoking status (stacked areas). The bottom two areas represent the number of LCS-eligible individuals (current and former smokers).
PKY: pack-years; YSQ: years since quitting; LCS: lung cancer screening.

Conclusions: Although the number of individuals eligible for LCS in Argentina is projected to decline, more than one million people will still qualify by mid-century, underscoring the need for a national LCS program to reduce lung cancer burdens and associated costs. The eligible population for lung cancer screening under current criteria is expected to decline over time, underscoring the urgency of implementing programs in the near future to maximize public health impact.

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Keywords: Lung cancer screening, Argentina, Latin America

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.08 Program Guidelines for Australia'S National Lung Cancer Screening Program: A Robust and Consultative Development Approach

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Introduction: The Australian National Lung Cancer Screening Program (hereafter 'Program') will commence from July 2025. The Program is the first new cancer screening program in Australia in 20 years. The Program aims to improve health outcomes for Australians by detecting lung cancer early and reducing deaths from lung cancer. It represents a significant investment across healthcare sectors, including extensive Aboriginal and Torres Strait Islander (First peoples of Australia) engagement as a mandatory component, reflecting the disproportionate burden of lung cancer among Aboriginal and Torres Strait Islander communities. Cancer Australia commissioned The University of Melbourne, The Australian National University and Lung Foundation Australia, to develop Program Guidelines. This presentation summarises the Guideline content and highlights an agile approach to development.

Methods: The purpose of the Guidelines was to create best practice recommendations to help healthcare providers and participants navigate the Program. A project plan was developed. A desktop review of international guidelines and protocols was undertaken and a robust consultation approach to engage key stakeholders was outlined. Stakeholders included Aboriginal and Torres Strait Islander health professionals and community members, clinicians, consumers, and policy and program advisors. Shared decision-making materials for Aboriginal and Torres Strait Islander communities were developed concurrently. A multidisciplinary working group was formed to provide expert clinical and consumer input throughout development. The project team conducted extensive interviews, focus groups, and workshops with stakeholders to refine content and identify service design issues. Draft content addressed both the breadth and depth of lung cancer screening topics. Draft content was iteratively shared with policymakers. Public consultation commenced in late November 2024 with a final draft being made available for whole of community review. The Guidelines were finalised, endorsed and released in April 2025.

Results: More than 170 stakeholders participated in consultation activities from across all Australian states and territories, geographic areas, and healthcare settings. The Guidelines include specific evidence-based recommendations, practice points, and content summaries to guide implementation. They are tailored to the unique Australian context, addressing issues of equity, cultural safety, smoking cessation, and stigma. The Screening and Assessment pathway covers topics such as promotion and awareness, eligibility, program entry, enrolment and shared decision-making, smoking cessation, delivery of the low-dose CT scan, assessment and reporting, results management, and screening reminders. Low-dose CT scans will be reported using the Program's Nodule Management Protocol. The intersection with the Australian National Cancer Screening Register for results reporting was developed concurrently by clinical experts and policymakers. The Guidelines detail healthcare providers' roles and responsibilities and include links to program-specific resources designed to inform community members and encourage shared decision-making. During public consultation, 96% of respondents agreed that the Guidelines were fit for purpose.

Conclusions: The Program Guidelines will support the delivery of a safe, effective, and high-quality lung cancer screening program for the Australian community. Engaging stakeholders through inclusive approaches is essential to Guideline development. Collaborative efforts will help build awareness and trust in the Program, ensuring its successful and equitable implementation. The robust and thorough development process could be adapted by other jurisdictions.

Keywords: Lung cancer screening, Evidence-based guidelines

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.09 Size Distribution and Short-Term Progression of New Nodules From the 4ITLR Lung Cancer Screening Trial

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Introduction: Lung cancer screening (LCS) with low-dose CT has been shown to reduce mortality in high-risk individuals. Previous studies indicate that new pulmonary nodules detected during follow-up LCS rounds have a higher likelihood of malignancy relative to their size compared to the nodules found in the baseline screening. However, evidence on the optimal management of new nodules in LCS remains limited. This study evaluates new nodules detected during the first annual LCS round in the European 4-IN-THE-LUNG-RUN (4ITLR) trial, and their progression over a three-month period.

Methods: Chest LDCTs from 2,219 annual LCS screening participants of the 4ITLR trial (acquired between 14 December 2022 and 14 January 2025) were included in this study. Each scan was independently evaluated by a radiologist and an AI system. In cases of discrepancy, an expert panel served as the reference standard. New nodules, either solid or part-solid with a solid component of ≥30mm3 that were identified as the reference nodule based on size were selected for analysis. Percentage of participants with new nodules, nodule size category, as well as 3-month progression of new nodules were evaluated.

Results: A total of 90 out of 2,219 participants (4.1%) were identified with a new nodule ≥30mm^3. Of the detected new nodules, 52 (2.3%) were 30-200mm^3, and 38 (1.7%) were ≥200mm^3. Of the cohort with new nodules, 65 of the participants underwent a 3-month repeat CT. Among them, 9 (0.4%) showed growth, 14 (0.6%) remained stable, 6 (0.3%) were in the process of resolving, and 36 (1.6%) had resolved.

Conclusions: In an annual LCS round, 4.1% of participants were found to have new pulmonary nodules, with around half resolving after a 3-month repeat CT. These findings are consistent with previous results from the NELSON trial.

Keywords: Lung cancer screening, New nodules, Computed tomography

P1.04.10 Lung Cancer Screening Completion Rates as Predicted by Social Deprivation

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Introduction: Globally, there is a strong association between lower socioeconomic status (SES) and higher incidence of lung cancer, later stage diagnosis, and poorer overall survival. In the United States (U.S.), lung cancer screening (LCS) via low-dose computed tomography is recommended for those at high risk, but LCS uptake is low (16-20%) overall, and is lower among those with less income. We evaluated social deprivation as a predictor of LCS completion rates among primary care patients seen in a large health system.

Methods: Utilizing electronic health record data from MedStar Health, an integrated delivery network health system in the Mid-Atlantic U.S., we analyzed LCS completion rates in the past 12 months among patients who received a LCS referral (N=829) between September 2022 - August 2023, across 51 primary care clinics. We used the validated 2019 Social Deprivation Index (SDI), with a scale from 1 to 100, with a higher score reflecting more social deprivation and worse SES status. To assess social deprivation as a predictor of LCS completion, SDI was coded as a categorical variable (1-24, 25-49, 50-74, 75-100).

Results: The mean age was 66 (SD=7), 36% were Black or African American, and 65% were currently smoking. About 26% of the sample were in the lowest category of social deprivation, 21% in the 25-49 category, 22% in the 50-74 category, and 31% in the highest category (75-100). Among referred patients, the overall LCS completion rate was 24%. Using a logistic regression model with generalized estimating equations (GEE), SDI predicted LCS completion, controlling for sex, race, smoking status, insurance, and clinic type (hospital- vs. community-based) (Table 1). Compared to patients with the lowest SDI (1-24), patients with the highest SDI (75-100) had significantly lower odds of completed LCS (OR=0.58, 95% CI: 0.36-0.94).

Conclusions: In a large, socioeconomically diverse health system, our findings revealed that higher social deprivation was associated with lower LCS completion among patients referred to screening. One study limitation is the use of a single measure of social deprivation. While a LCS referral is necessary, additional strategies are needed to increase successful completion of LCS among lower socioeconomic groups.

Table 1. Adjusted Results from a Logistic Regression Model with GEE Predicting Lung Cancer Screening Completion Rates among Primary Care Patients with a Smoking History (N=804)

	LCS Completion OR [95% CI]
SDI Categories	
75-100	0.58 [0.36-0.94]*
50-74	0.78 [0.47-1.29]
25-49	0.84 [0.52-1.35]
1-24 (Ref)	
Currently Smoking	
No	1.83 [1.30-2.58]**
Yes (Ref)	
Insurance	
Government/Medicaid/Medicare/Managed Care Organization	0.90 [0.61-1.32]
Self-pay/Other	1.79 [0.71-4.52]
Commercial/Private (Ref)	
Sex	
Female	1.14 [0.81-1.60]
Male (Ref)	
Race	
Black or African American	2.01 [1.40-2.88]**
Other	1.79 [0.97-3.32]
White (Ref)	
Clinic Type	
Hospital Based/Resident Clinic	1.32 [0.91-1.92]
Community Based (Ref)	
**p<0.001, *p<0.05	

Keywords: lung cancer screening, socioeconomic status, social deprivation

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.11 New Nodule Lung Cancer in the UK Lung Cancer Screening Trial: Characteristics and Comparison With NELSON

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Introduction: New nodules detected during lung cancer screening follow-up rounds differ in malignancy risk from baseline nodules. We aimed to characterize new nodules and associated lung cancers in the UK Lung Cancer Screening Trial (UKLS) and compare these findings with results from the NELSON trial.

Methods: We included 875 participants of the multicenter randomized-controlled UKLS trial ("Wald Single-Screen" design, registration number: ISRCTN78513845) that underwent follow-up low-dose CT screening. Non-calcified nodules containing solid components that were registered by the UKLS radiologists as new or smaller than 15 mm3 (study detection limit) at previous screens were defined as new nodules. Nodule volume was generated semiautomatically by software. Lung cancer diagnosis was based on histology, and benignity was based on histology or stable size for at least 2 years. UKLS findings were compared with published results from the NELSON trial.

Results: UKLS radiologists registered 233 new solid nodules in 142 participants who received a follow-up CT. Lung cancer was diagnosed in 5 (4%) of participants with new solid nodules, representing 2% (5/233) of all new solid nodules. Four (80%) lung cancers were diagnosed at stage I. The probability of malignancy was 0% (0/135) in participants with new nodules detected during repeat short-term follow-up (3/6/9 months) and 5% (5/98) in those with nodules detected at annual follow-up (12 months). Lung cancer probability was stratified by nodule volume at first detection: 0% (0/72) for nodules <30 mm^3, 2% (3/129) for nodules between 30-200 mm^3, and 6% (2/32) for nodules ≥200 mm^3. This volume-dependent risk distribution is consistent with the results reported in the NELSON trial.

Conclusions: UKLS results confirm key findings from NELSON, showing that new solid nodules are detected in 4% of screened individuals and that malignancy risk increases with volume. The thresholds of 30-200 mm^3 remain valid for risk stratification of new nodules in lung cancer screening.

Keywords: Lung Cancer Screening, Computed Tomography, New nodule

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.12 Smoking Duration Lung Screening Criteria (Potter Criteria) Captures More Underrepresented Individuals at Risk for Lung Cancer

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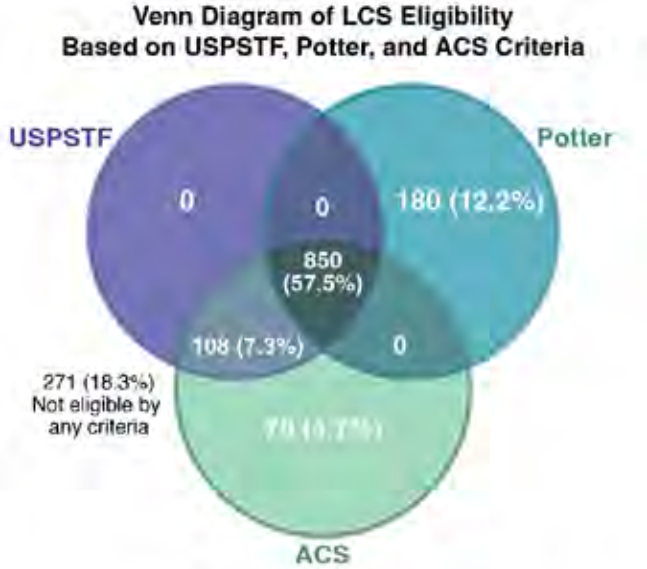
Introduction: Current U.S. Preventative Services Task Force (USPSTF) lung cancer screening (LCS) eligibility criteria exclude many high-risk individuals, especially those from racial and ethnic minority groups. Recently proposed alternatives include the Potter criteria (which replace the 20-pack-year threshold in the USPSTF criteria with a 20-year duration threshold), and American Cancer Society (ACS) criteria (which remove the 15-years-quit requirement). We compared the performance of the USPSTF, Potter, and ACS criteria among individuals diagnosed with lung cancer (LC) at an academic medical center serving a predominantly minority population in Chicago.

Methods: We evaluated LCS eligibility under the USPSTF, Potter, and ACS criteria using data from 1479 individuals with LC diagnosed at The University of Illinois Hospital & Health Sciences System from 2010-2024. Patients without a history of tobacco use were excluded. A multinomial model evaluated race and gender imbalances in eligibility.

Results: Of the 1479 patients, 958 (64.8%) met USPSTF criteria, 1030 (69.6%) met Potter, and 1028 (69.5%) met ACS; 850 (57.5%) individuals met all three criteria (Fig 1). Compared to USPSTF, an additional 180 (12.2%) individuals would have been screen-eligible under Potter and 70 (4.7%) under ACS. Relative to those who met all three criteria, the 180 added under Potter were significantly more likely to be Black (odds' ratio [OR]: 4.77, 95% CI: 2.59-8.79) or Hispanic (OR: 4.77, 95% CI: 2.11-10.8) and the 70 added under ACS were less likely to be Black (OR: 0.47, 95% CI: 0.27-0.81) compared to White patients. Of 108 (7.3%) individuals qualifying for screening under USPSTF but not Potter (due to <20 years tobacco use), most were White, used tobacco with high daily intensity (median: 39 cig/day), and for shorter durations (median: 15 years). 271 (18.3%) individuals met none of the screening criteria, of which 59% were ineligible due to age (<50 or >80). Compared to those meeting all three criteria, those meeting none were more likely to be female or Hispanic.

Conclusions: In this analysis of 1479 patients with LC and tobacco use history, we found that only 64.8% met USPSTF criteria. The Potter criteria identified an additional 12.2% of individuals, most of whom were Black or Hispanic. These data further support that including a tobacco use duration threshold in LCS guidelines can reduce racial and ethnic disparities in screening eligibility and improve equity in opportunities for early lung cancer detection.



Criteria	N (%)	Non-Hispanic Black	Non-Hispanic White	Hispanic	Other/Mixed Race	Unknown
USPSTF & ACS & Potter	850 (57.5)	517	217	58	37	21
USPSTF & ACS	108 (7.3)	51	38	8	6	5
ACS only	70 (4.7)	30	27	6	7	0
Potter only	180 (12.2)	138	12	15	5	10
No criteria met	271(18.3)	142	57	39	20	7

A. Venn diagram showing number of patients eligible for LCS based on one or more of three screening criteria: USPSTF, Potter, or ACS.

B. Table of LCS eligibility based on one or more screening criteria organized by race and ethnicity.

Keywords: Lung cancer screening, Early detection, Potter criteria

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.13 The Impact of Reconstruction Kernel and Hounsfield Unit Threshold on Emphysema Quantification From Lung Cancer Screening Data

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Introduction: Emphysema is a non-reversible disease which currently has no cure. Diagnosing early-stage emphysema using computed tomography (CT) scans remains a challenge. A potential tool is quantitative CT, via the measurement of the lung Low-Attenuation Area percentage (LAA%). However, different parameters could influence this quantification, including the reconstruction kernel and HU threshold. The aim of this study is therefore to investigate the effect of different kernel-HU threshold combinations on the lung LAA% from CT images calculated by AI software.

Methods: 352 lung CT cases were obtained from the Netherlands-China-Big-3 study.The LAA% was calculated for cases by Aview (Coreline Soft, version 42) using different kernels (B30f, D45f and B80f) at different HU thresholds (-940, -950, -960 and -970 HU). Descriptive statistics were calculated for age and sex. Cases were also categorized as emphysema being present (LAA% ≥6%) or not (LAA% <6%). Friedman and Cochran's tests were performed to establish whether there were any significant differences between the LAA% and emphysema characterisation, respectively, across all groups. Individual group comparisons were performed using the Wilcoxon signed rank test and the McNemar test for LAA% and emphysema, respectively, using the Holm multiple testing correction.

Results: The participants have a median age of 62 years (IQR: 8.25), with 51.7% being female. There is a significant difference in LAA% across all kernel-HU thresholds (p<0.001). Kernel D45f produces a higher LAA% than kernels B30f and B80f for all thresholds (Figure 1). Out of 66 group comparisons, 62 are significantly different; all comparisons except for the LAA% for kernel B30f and B80f at the same HU threshold. Furthermore, emphysema categorisation is significantly different when comparing all kernel-HU thresholds together (p<0.001). Among the 12 kernel-HU threshold groups, most patients are categorised as having emphysema for kernel D45f at -940 and -950 HU, while for other groups the majority of patients are categorised as not having emphysema. Out of 66 group comparisons, 54 are significantly different. Kernel B30f and D80f are not significantly different at the same HU threshold. Besides, there is no significant difference between -940-B80f and -970-D45f.

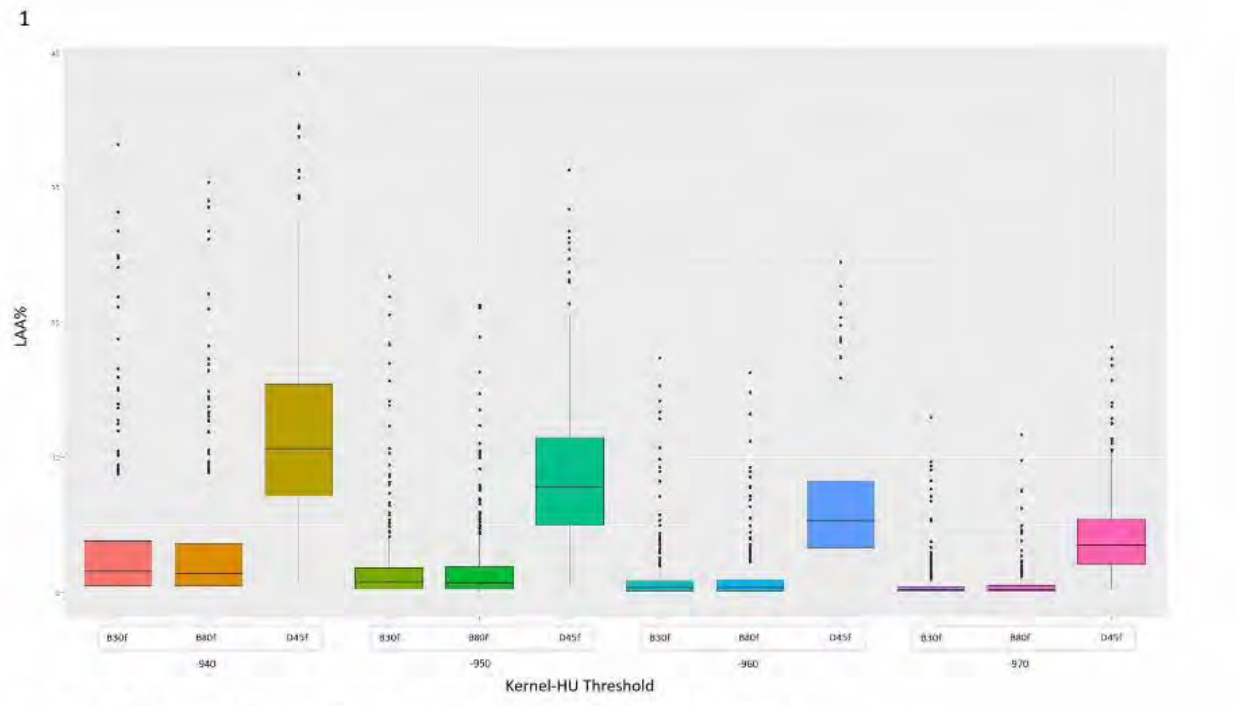

Figure 1: A boxplot of the distribution of LAA% per kernel-HU threshold combination

Conclusions: To conclude, LAA% is influenced by kernel and HU threshold. Notably, the D45f kernel, at higher HU thresholds, categorizes more patients as having emphysemas, which may have implications for diagnosis.

Keywords: Lung cancer screening, Chronic obstructive pulmonary disease, Quantitative computed tomography

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.14 Age, Risk Thresholds and Cost-Effectiveness: Evaluating Lung Cancer Screening Using the PLCOm2012 Model

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Introduction: Lung cancer (LC) is one of the leading causes of cancer related mortality worldwide. However, it has been observed that LC screening using Low dose computed tomography (LDCT) reduces LC mortality. Risk based LC screening which calculates screening eligibility based on individual risk, has shown to improve the sensitivity and specificity when compared with 2013 United States preventive services task force criteria. This study evaluates the effects of PLCOm2012 model with different risk thresholds (0.5-3%) across 6 age groups (55-70, 55-75, 55-80, 50-70, 50-75, 50-80) on screening outcomes- prevented LC deaths, Life years gained (LYG), prevented LC deaths per 1000 screens, LYG per 1000 screens and incremental cost effectiveness ratio (ICER) for efficient strategies in a German population-based setting in a 5-year screening program.

Methods: We used our modular microsimulation model to simulate individual life histories, mapping the development of lung cancer and its progression from first malignant cell to eventual LC death. Smoking behavior related data was obtained from the German Health Update (GEDA) survey (years 2009-2012) and demographic structure (2012) was obtained from the German statistical office. Results for PLCOm2012 risk thresholds (0.5-3%) for all 6 age groups were calculated and compared.

Results: At lower risk thresholds (0.5-1%), prevented LC deaths ranged from 25,588 to 43,421 deaths and LYG ranged from 378,784 to 593,927 years across all age groups. At higher risk thresholds (2.5-3%), prevented LC deaths ranged from 10,221 to 22,351 deaths and LYG ranged from 134,212 to 255,197 years across all age groups. At lower risk thresholds (0.5-1%), prevented LC deaths per 1000 screens ranged from 0.9 to 1.4 deaths and LYG per 1000 screens ranged from 13 to 21 years across all age groups. At higher risk thresholds (2.5-3%), prevented LC deaths per 1000 screens ranged from 2.3 to 2.8 deaths and LYG per 1000 screens 26 to 37 years across all age groups. At lower risk thresholds (0.5-1%), 55-70 years old (yo) age group had higher LYG per 1000 screens and 55-75 yo age group had higher prevented LC deaths per 1000 screens as compared to other age groups. At higher risk thresholds (2.5-3%), both 55-70 yo and 50-70 yo age groups had higher LYG per 1000 screens and higher prevented LC deaths per 1000 screens as compared to other age groups. Risk thresholds (0.6-3%) showed ICER lower than 50,000 euros/LYG (generally assumed ICER threshold for Germany). It ranged from 6,599 to 47,198 euros/LYG. ICER at 0.5% risk threshold was 54,680 euros/LYG.

Conclusions: While higher risk thresholds (2.5-3%) showed higher prevented LC deaths per 1000 screens and LYG per 1000 screens but they also excluded a lot of cases that could have been identified at lower risk thresholds. ICER results suggest that lower risk thresholds might still be cost effective. This study advocates for a tailored, risk-based screening policies to maximize public health benefits while being cost effective.

Keywords: Lung cancer, PLCOm2012 model, Cost-effectiveness

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.15 Lung Cancer Screening in Switzerland: Baseline Results From the Vaud Pilot Project

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Introduction: Lung cancer screening (LCS) with low-dose CT (LDCT) effectively reduces lung cancer mortality. The Vaud LCS pilot project is a four-year project mandated by cantonal health authorities to assess the feasibility of implementing a population-based, organized LCS program. We report insights into the implementation and preliminary clinical results of this pilot project after the baseline LDCT.

Methods: The pilot project enrolled high-risk subjects based on USPSTF 2021 criteria for LCS (adults aged 50-79 years, ?20 pack-year smoking history, cessation ?15 years). Data were collected from November 2023 to December 2024. Recruitment was conducted by mailing 8000 invitations to a random sample of individuals aged 50-79 and through direct inclusion of patients by their physicians across Canton Vaud. During the inclusion visit, participants underwent a guided interview focused on respiratory health, followed by post-bronchodilation spirometry and baseline LDCT. An optional smoking cessation consultation (SCC) was proposed to active smokers. Nodules were evaluated using LungRADS v2022 and NELSON+ classifications. A dedicated multidisciplinary nodule review board (MNRB) integrated clinical and radiological data with the Brock model for risk stratification to refine nodule assessment of indeterminate and positive LDCT results (Lung-RADS/NELSON+ 3 or more; Lung-RADS 0; mediastinal and/or hilar adenopathy) and decide for annual screening in case of downstaging, 3-month follow-up for those assessed indeterminate or further investigations for positive findings.

Results: The mail recruitment achieved a 35% response rate of the estimated eligible population. From the scheduled baseline appointments, we experienced a 3.2% of no-show rate, ultimately including 1,000 participants. 70% were active smokers, of which 54% attending SCC. Baseline LDCT results showed 83.8% negative, 14.6% indeterminate, and 1.6% positive findings. MNRB increased the number of negative LDCT to 87.3%, reducing indeterminate and positive results to 11.2% and 1.5%, respectively. Of the 15 positive cases, 7 were histologically-confirmed lung cancers.

Conclusions: Our baseline preliminary results overall align with published data and participation rates. Incorporating a dedicated MNRB to review indeterminate and positive LCS results may enable a more personalized nodule assessment and management, while driving continuous quality improvement to control false-positive rates. Consolidated results through a comprehensive evaluation of the performance of this pilot program are however required upon completion of the four annual LDCT screening rounds.

Keywords: Lung Cancer Screening, Pilot program, Smoking Cessation

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.16 Real-World Outcomes of Lung Cancer Screening and High-Risk Lung-RADS 4 Nodules at VA Northern California Health Care System

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Introduction: Supported by the Lung Precision Oncology Program, the hybrid lung cancer screening (LCS) program at VANCHCS was expanded in 2021. As of March 1, 2025, 5,283 of 6,509 eligible Veterans (81.2%) have been assessed, with 4,479 (89%) enrolled. Some patients were later excluded due to co-morbidities, new cancer diagnoses, or death. The Lung Imaging Reporting and Data System (Lung-RADS) guides clinical decision-making based on radiographic risk. Lung-RADS 4 (LR4) indicates high-risk nodules requiring prompt follow-up due to elevated malignancy risk. Evaluating follow-up, diagnostic yield, and staging in LR4 nodules offers insight into program effectiveness and patient outcomes.

Objective: To evaluate diagnostic outcomes, pathology-confirmed malignancies, and cancer staging in patients with LR4 nodules in a single-institution LCS program.

Methods: All LCS data were tracked using VA's LCS national dashboard. We analyzed patients with high-risk LR4 data, including demographics, biopsy dates and modalities, pathology results, time from LR4 scan to biopsy, AJCC 8th edition staging, and first specialty consultation.

Results: Since its inception, the program has performed 10,155 low-dose CT (LDCT) scans and is actively tracking 3,946 veterans, maintaining 94.1% adherence to screening guidelines. The program's diagnostic yield for lung cancer was 3.3%. We identified 122 patients diagnosed with cancer in our LCS program. 40 were excluded as they received subsequent care outside the VA. The final analysis included 82 veterans with LR4 findings on LDCT between 2021 and 2024. The mean age at diagnosis was 70.3 years (range 54-79). The median interval from LR4 detection to biopsy was 50.5 days (range 6-342), reflecting wide variability. Final pathology reports are available in 79.3% of cases, with malignancy confirmed in most biopsied nodules. Adenocarcinoma was the most common diagnosis (n=32), followed by squamous cell carcinoma (SCC, n=21), other non-small cell lung cancers (NSCLC, n=14), and small cell lung cancer (n=6). Staging data showed a meaningful spread across early and advanced disease. 39 patients were diagnosed at stage I, 6 at stage II, and 10 at stage IIIA or IIB, supporting the program's role in early detection. However, 5 presented at stage IIIC and 6 at stage IV, emphasizing the need for timely evaluation and care escalation. All patients received prompt specialty referrals to radiation oncology, thoracic surgery, or medical oncology based on disease severity and operability

Conclusions: The LR4 designation reliably identifies high-risk nodules with a high malignancy rate and a predominance of adenocarcinoma and SCC, aligning with national trends. The fact that 67% of cancers were diagnosed at stage I, II, and IIIA or IIIB underscores the effectiveness of LCS in enabling timely, potentially curative interventions. Nonetheless, opportunities remain to improve early detection, particularly by addressing delays in biopsy and inconsistencies in documentation. Standardizing workflows, ensuring structured follow-up, improving patient navigation, and strengthening multidisciplinary coordination are essential next steps. Ongoing tracking of LR4 outcomes and real-time data monitoring will be critical to maintaining high-quality care and maximizing the impact of early lung cancer detection.

Keywords: Early Diagnosis, Lung Cancer Screening, Veterans

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.17 Poor Utilization of Lung Cancer Screening Among Cancer Survivors in the United States

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Introduction: Although lung cancer screening can significantly reduce lung cancer-related mortality, fewer than 20% of eligible patients are screened in the United States each year. Survivors of other cancers who meet lung cancer screening eligibility criteria are at particularly high risk but there are limited national data regarding screening habits among these patients.

Methods: We conducted a cross-sectional analysis of data from the 2022 Behavioral Risk Factor Surveillance System. We included respondents aged 50-80 who reported a 20 pack-year or greater smoking history, a history of prior cancer diagnosis, and smoking within the past 15 years. Respondents with prior lung cancer or ongoing cancer treatment were excluded. Among survivors eligible for lung cancer screening, we assessed sociodemographic and behavioral factors associated with lung cancer screening with low-dose CT within the past year. For survivors meeting United States Preventive Services Task Force criteria for mammography or colonoscopy as well as lung cancer screening, we assessed the comparative utilization of each screening exam. These analyses excluded survivors of breast or colon cancer. Two-tailed p-values <0.05 were statistically significant.

Results: We identified 413,640 cancer survivors who were eligible for lung cancer screening: mean age 66 (IQR 65, 67), 48% women. Overall, 33% of eligible cancer survivors had a screening CT scan. Men were significantly more likely to be screened than women (40% vs. 31%, p=0.007). There were no significant differences in screening based on race, education, income, insurance, or current vs. former smoking status. Of eligible survivors, 17% were United States Veterans who were significantly more likely to undergo lung cancer screening than non-Veterans (50% vs. 29%, p=0.001). 57% of eligible survivors were current smokers; of these, 44% reported a smoking cessation attempt within the past year. Attempted smoking cessation was not associated with lung cancer screening (p=0.27). Of the 185,816 eligible female survivors without prior breast cancer, 71% reported up-to-date mammography. In the same cohort, only 25% of respondents underwent lung cancer screening. Receipt of mammography was not associated with lung cancer screening (p=0.48). Of the 353,177 eligible survivors without prior colon cancer, 84% reported guideline-concordant colon cancer screening. In the same cohort, 31% of patients underwent lung cancer screening. Guideline-concordant colon cancer screening was not associated with lung cancer screening (p=0.48).

Conclusions: Lung cancer screening is poorly utilized among eligible cancer survivors in the United States. By contrast, there is a high prevalence of guideline-concordant breast and colorectal cancer screening in the same patient population. These data reflect a willingness among cancer survivors to undergo further cancer surveillance but suggest gaps in patient and provider education and outreach. Cancer survivors often receive specialized, long-term follow up care in survivorship programs, presenting a unique opportunity for improved population-based screening interventions for this high-risk patient population.

Keywords: lung cancer screening, cancer survivorship

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.18 Diagnosis of Sub-Cm Lung Nodules With Deep Learning Segmentation and Radiomics-Based Machine Learning Classifiers

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Introduction: Lung cancer remains the leading cause of cancer deaths in Canada. Detection, diagnosis, and treatment of early-stage lung cancers via Low-Dose Computed Tomography (LDCT) screening programs have been shown to substantially reduce lung cancer mortality. Developing computer-aided diagnosis (CADx) tools to assist physicians in identifying potential cancerous lung nodules during screening studies are especially desirable for notoriously difficult-to-classify nodules (i.e., sub-cm, <10mm solid component diameter, GGOs) as these cases tend to have relatively small amounts of pixel-based information available to them. Compounded by the large number of small objects often detected during screening programs, the implementation of CADx tools for cost-effective screening prediction is in high demand. We posit that one can train a pipeline consisting of deep learning and machine learning models to segment and classify sub-cm nodules as malignant or benign with radiomic features to greatly speed up nodule assessment speeds and allow for the implementation of early cancer treatment for protocols during baseline scans.

Methods: The discovery dataset for this study draws nodules (N=6944, n=136 cancers) from the Pan Canadian Screening Study (PanCan) which provided LDCT lung volumes. Each nodule was axially segmented using a self-attention UNet, and then three discrete masks that represent the nodule core, core plus edge parenchymal tissues, and the peritumoral region surrounding the nodule were generated. Radiomic features are calculated from each mask and a sequential forward feature selection was applied to identify a highly discriminating radiomic signature. A logistic regression (LR) model was trained from this radiomic signature in a binary classification task of predicting cancer versus benign nodules. In addition, an external validation cohort draws sub-cm nodules (N=2943, n=36 cancers) from the more recent International Lung Screening Trial (ILST) to determine the radiomic signature's generalizability and medical utility.

Results: ROC analysis was performed on the 5-fold cross validated LR model that resulted in an AUC=0.970 [Sen: 0.911, Spec: 0.951]. This radiomics-based CADx model was able to identify 12 cancerous sub-cm nodules at baseline that would have not received interventional treatment as these nodules held a Brock model score <=5%. In addition, the model showed an ability to predict cancerous vs benign nodules up-to 24 months before clinical confirmation of malignancy. Additional analysis will be performed on the external validation cohort in the immediate future.

Conclusions: This study suggests that our pipeline consisting of a deep learning-based segmentation method to machine learning model, trained on a highly discriminating baseline LDCT radiomic signature, can identify sub-cm diameter cancerous nodules up to 24 months before clinical confirmation of malignancy. Pending verification of this model on the external validation cohort, the model shows promise towards potentially facilitating optimal decision-making for the small, sub-cm, difficult nodules that prolifically populate LDCT screening programs.

Keywords: LDCT Screening, Deep Learning, Radiomics

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.19 Evaluating the Impact of Electronic Reminders on Lung Cancer Screening

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Introduction: Adherence to lung cancer screening (LCS) guidelines remains a significant challenge in clinical practice. Our healthcare system implemented a program of electronic reminders for LCS and we assessed its effectiveness in improving LCS rates over a one-year period.

Methods: The electronic reminders program implemented in our electronic medical record system alerts primary care physicians when patients eligible for LCS are overdue for their annual low-dose computed tomography scan. We identified patients included in the electronic reminders program at implementation in 2022 and categorized them as either “Screened within one year” or “Overdue for screening.” The primary outcome was whether patients were screened within one year following implementation. To examine the association of patient demographics and clinical characteristics with the primary outcome, a logistic regression model was utilized, and the findings were visualized using a forest plot.

Results: Among the 8,406 patients eligible for LCS in the electronic reminders program, the mean age was 66.5 years and 5,135 (62%) were male. The 779 (8.9%) patients Screened at rollout were younger (62.1 vs. 67.0 years, SMD -0.50) (Table). Overall, screening rates significantly increased from 8.9% to 15.7% (p<0.001) at one year following implementation (Figure). Among those Screened at rollout, 51% were screened within one year following implementation. Among those Overdue at rollout, 13% were screened at one year following implementation; those who were screened were more likely to have a family history of cancer (OR: 1.97; 95% CI:1.23-3.05, p=0.006), part-time/unemployed status (OR: 1.48; 95% CI:1.23-1.78, p<0.001), and Black race (OR: 1.43; 95% CI:1.08-1.88, p=0.002), while patients who were currently smoking were less likely to undergo screening at one year (OR: 0.82; 95% CI 0.70-0.95, p=0.008).

Conclusions: While electronic reminders can enhance LCS adherence, targeted interventions are necessary to address disparities in screening adherence, particularly among high-risk populations.

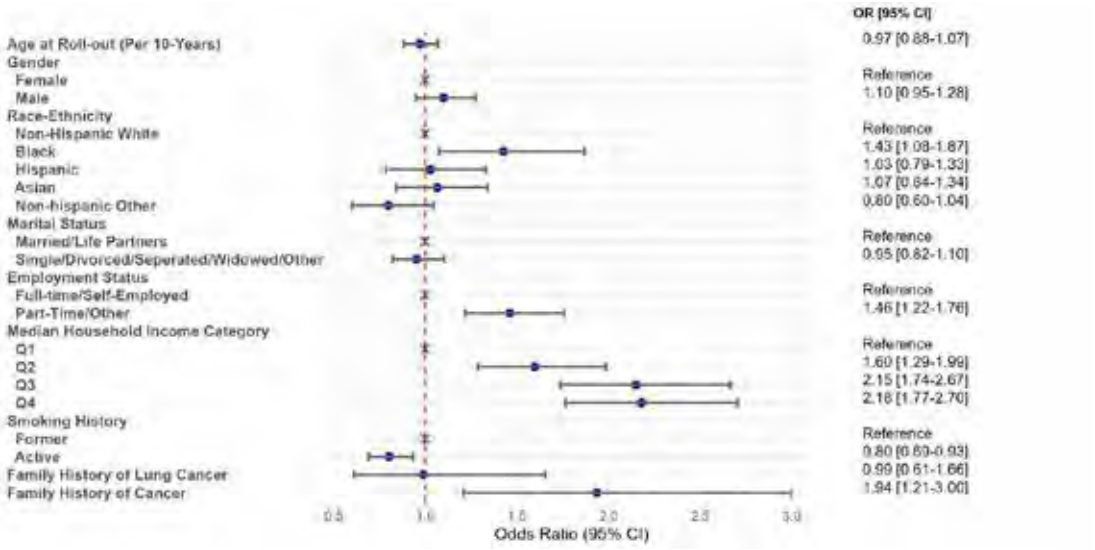

Table: Patient Demographic and Clinical Characteristics by HM Due Status at Roll-out

Characteristic	Overall, N = 8,346	Screened within 1 year N = 779	Overdue for screening N = 7,567	Standardized Mean Difference (SMD)[1]
Age at rollout, mean (SD)	66.5 (8.3)	62.1 (11.38)	67.0 (7.8)	-0.50
Gender, n (%)				0.12
Female	3,209 (38)	260 (33)	2,949 (39)	
Male	5,135 (62)	519 (67)	4,616 (61)	
Unknown	2 (<0.1)	0 (0)	2 (<0.1)	
Race-ethnicity, n (%)				0.16
Non-Hispanic White	2,002 (17)	401 (17)	1,601 (17)	
Black	9,685 (83)	1,897 (83)	7,788 (83)	
Hispanic	678 (8.1)	66 (8.5)	612 (8.1)	
Asian	807 (9.7)	93 (12)	714 (9.4)	
Non-Hispanic other	686 (8.2)	69 (8.9)	617 (8.2)	
Unknown/Decline	457 (5.5)	22 (2.8)	435 (5.7)	
Marital status, n (%)				0.10
Married/life partner	4,481 (54)	426 (55)	4,055 (54)	
Single/divorced/ widowed/other	3,657 (44)	343 (44)	3,314 (44)	
Unknown	208 (2.5)	10 (1.3)	198 (2.6)	
Employment, n (%)				0.21
Full-time/self-employed	2,074 (25)	209 (27)	1,865 (25)	
Part time/not employed/student/disabled/ retired	5,986 (72)	565 (73)	5,421 (72)	
Unknown	286 (3.4)	5 (0.6)	281 (3.7)	
Median household income, n (%)				0.16
Q1	2,068 (25)	162 (21)	1,906 (26)	
Q2	2,043 (25)	176 (23)	1,867 (25)	
Q3	2,044 (25)	188 (25)	1,856 (25)	
Q4	2,028 (25)	234 (31)	1,794 (24)	
Smoking history, n (%)				0.06
Former	5,268 (63)	513 (66)	4,755 (63)	
Current	3,078 (37)	266 (34)	2,812 (37)	
Pack-years, mean (SD)				
Former	38.4 (21.5)	37.8 (20.1)	38.5 (21.7)	0.03
Current	36.5 (18.6)	33.9 (15.1)	36.8 (18.9)	0.17
Family history of lung cancer, n (%)	550 (6.6)	69 (8.9)	481 (6.4)	0.09
Family history of cancer, n (%)	694 (8.3)	87 (11)	607 (8.0)	0.11

[1]SMD: <0.2: no difference 0.2-0.5: small, 0.5-0.8: medium, >0.8: large

Keywords: lung cancer screening, electronic reminders, low dose CT scan

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.20 Barriers to Lung Cancer Screening Among Overdue Patients; a Quality Improvement Initiative

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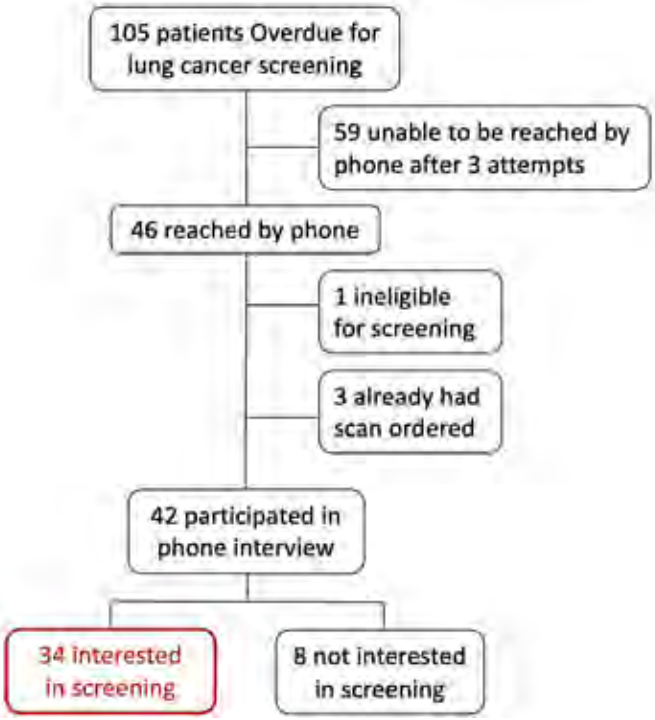
Introduction: Lung cancer is the leading cause of cancer mortality in the US, but screening rates remain low. We explored barriers to lung cancer screening (LCS) in patients overdue for an annual low dose computed tomography (LDCT).

Methods: We identified patients eligible for LCS in primary care clinics within an academic healthcare system, distinguishing those Screened for lung cancer in the past year from those Overdue for screening. Logistic regression was used to investigate predictors of being Overdue for LCS. We conducted phone interviews with Overdue patients and utilized thematic analysis to identify barriers to LCS. IRB exemption was granted for this quality improvement study.

Results: We identified 290 patients eligible for LCS, including 105 Overdue patients (Table). Overdue patients were younger (64 vs. 67 years, p=0.031), more likely to be working (64% vs. 52%, p=0.049), and less likely to have seen their primary care physician within the past year (86% vs. 95%, p=0.01). In multivariable analysis, patients who had not seen their PCP within the past year were more likely to be Overdue (OR 3.41; 95% CI, 1.41-8.57; p=0.007). Of the 105 Overdue patients, 47 patients participated in phone interviews (Figure). Of those, 17 (36%) were not aware of lung cancer screening. When asked about barriers, 19 (40%) cited “other pressing medical/personal issues,” 8 (17%) “didn’t understand LCS or its guidelines,” 4 (8.5%) “felt unheard or PCPs were too busy,” and 7 (15%) had “anxiety about LCS and its findings.” Following the interview, 34 (72%) were interested in LCS.

Conclusions: Most patients overdue for screening were not aware of LCS and less likely to have seen their PCP within the past year. 72% of patients who participated in the phone interviews expressed interest in screening. Targeted education and proactive primary care engagement are key to improving LCS rates.



Characteristic	Screened n=185	Overdue n=105	adjusted OR (95% CI)	P-value
Age (years)	67 (62, 71)	64 (57, 71)	0.98 (0.94, 1.02)	0.352
Sex, n (%)				
Male	126 (68%)	67 (64%)	ref.	
Female	59 (32%)	38 (36%)	1.40 (0.80, 2.44)	0.240
Distance to LCS clinic (kilometers)	13 (7, 23)	13 (8, 22)		
Primary Language (spoken), n (%)				
English	165 (89%)	96 (91%)	ref.	
Not English	20 (11%)	9 (8.6%)	0.87 (0.33, 2.13)	0.758
Marital Status, n (%)				
Married/Life partner	107 (58%)	63 (60%)		
Not married	78 (42%)	42 (40%)		
Employment Status, n (%)				
Working (full-time, part-time, self-employed)	96 (52%)	67 (64%)	ref.	
Retired	89 (48%)	38 (36%)	0.84 (0.43, 1.67)	0.620
Insurance type, n (%)				
Medicare	98 (53%)	44 (42%)	ref.	
Private	55 (30%)	43 (41%)	1.20 (0.62, 2.33)	0.585
Other	32 (17%)	18 (17%)	0.93 (0.43, 21.95)	0.851
Primary race				
White	107 (58%)	52 (50%)	ref.	
AANHPI	44 (24%)	33 (31%)	1.68 (0.90, 3.13)	0.102
Black/African American	6 (3.2%)	5 (4.8%)	2.36 (0.63, 8.58)	0.188
Other	28 (15%)	15 (14%)	1.11 (0.51, 2.36)	0.781
Ethnicity				
Hispanic/Latino	15 (8.1%)	4 (3.8%)		
Non-Hispanic/Non-Latino	169 (91%)	98 (93%)		
Unknown/Declines to state	1 (0.5%)	3 (2.9%)		
Smoking History (Former/Current)				
Former	109 (59%)	67 (64%)	ref.	
Current	76 (41%)	38 (36%)	0.81 (0.48, 1.37)	0.440
Pack Years (IQR; median)	36 (25, 50)	30 (23, 41)	1.00 (0.99,1.00)	0.779
Quit Years for Former Smokers (# of years having quit)	8.0 (6.0, 12.0)	8.0 (3.0, 11.5)		
PCP visit within 1 year of HMDUE status record, n (%)				
Completed	175 (95%)	90 (86%)	ref.	
Not completed	10 (5.4%)	15 (14%)	3.41 (1.41, 8.57)	**0.007**

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.21 Molecular Profiles of Clinical and Radiological Features in Pre-Invasive Lung Adenocarcinoma

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Introduction: Pre-invasive lesions as the initial phrase of lung adenocarcinoma, involve adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), which are critical and curable points for surgery. Diagnosis of early-stage lesions is primarily through imaging, while the biological phenotypes are well reflected in the imaging. However, there is limited research on the relationship between the clinical, radiological features, and molecular profiles of pre-invasive lesions.

Methods: 371 pre-invasive lesions samples with next-generation sequencing (NGS) were for incorporated analysis, investigated the relationship between the mutational landscapes, clinical information and radiological features. Radiological features included marginal spiculation, bubble lucency, cystic airspace, pleural retraction, pleural attachment, lobulation, vessel convergence, vessel crossing and air bronchogram.

Results: The proportion of RET rearrangements (3.23%) was higher than ALK (2.43%) in pre-invasive lesions. Patients with EGFR tended to be older (median 52 vs 48 years, P=0.004), while those with ERBB2 (median 44 vs 51 years, P<0.001) and gene rearrangements (median 40 vs 50 years, P=0.002) were younger. MIA demonstrated a significantly higher of pleural retraction (31.04% vs 13.89%, P=0.032). ERBB2 was significantly enriched in marginal spiculation (46.75% vs 29.25%, P=0.004). Gene rearrangements showed strong association with bubble lucency (86.96% vs 65.52%, P=0.034). RET (33.33% vs 11.70%, P=0.049) and EGFR 19Del (17.74% vs 7.76%, P=0.044) were enriched in cystic airspace. EGFR exhibited positive correlation with pleural retraction (34.27% vs 24.87%, P=0.047), whereas KRAS mutations demonstrated inverse association (9.09% vs 30.66%, P=0.031). The frequency of ALK was higher in pleural attachment (66.67% vs 27.07%, P=0.017), while KRAS again displayed inverse association (9.09% vs 29.23%, P=0.041).

Conclusions: Our study demonstrated the molecular features of pre-invasive lesions in a relatively large data, helping to analyze the biological phenotypes in radiological perspective, and providing a reference for surgical intervention during this curable window.

Keywords: Pre-invasive lesions, Molecular profiles, Radiological features

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.22 The Relationship Between Nodular Pleural Tail Sign and Metastasis or Recurrence of Peripheral Lung Cancer

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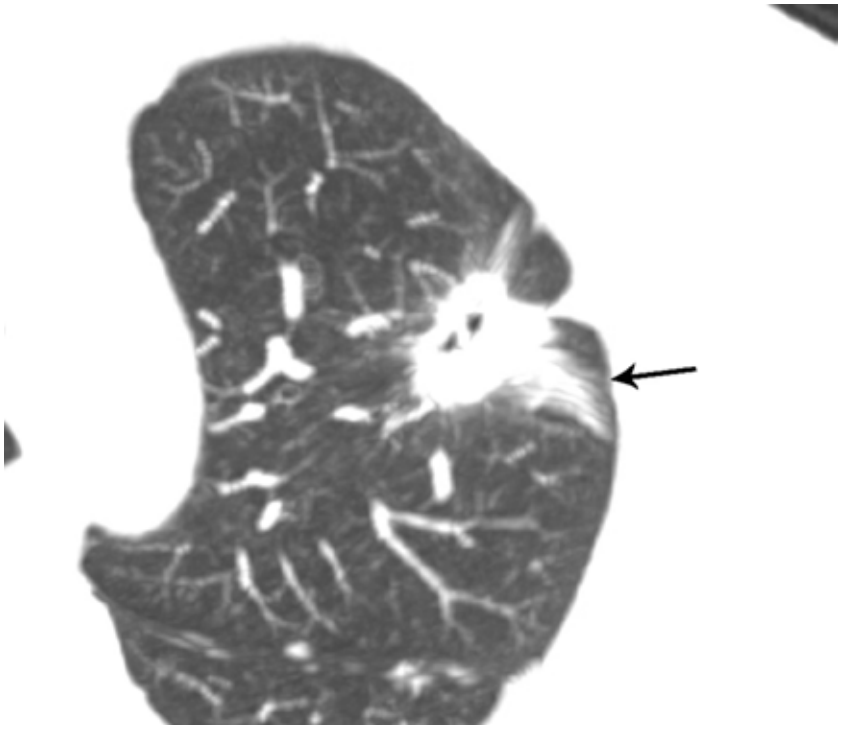
Introduction: This article aimed at exploring the effectof nodular pleural tail sign formed by MIP reconstruction to predict lungcancer invasiveness.

Methods: 55 cases ofperipheral lung cancer with pleural tail sign were collected throughthin-section imaging. The cohort included 35 males and 20 females, with a meanage of 60 years (range: 32-75).Severalreconstruction thicknesses ranged from 0.625 mm to 1.5 mm were available, andthe intervals were equal to each corresponding thickness using a standardreconstruction algorithm, lung window, window width, 1000 HU; window level -700HU. Maximum intensity projection (MIP) slab thickness was five times theoriginal slice thickness resulting in 5-line opacities of interlobar fissure orpleural tail-sign on lung window of unsharpened image, which was known as5-line sign. Nodular tail sign (NTs) and non-nodulartail sign (N-NTs) are challenging to distinguish on conventional thin-sectionCT images, necessitating MIP reconstruction for enhanced visualization. The NTson MIP reconstruction demonstrates two patterns: 1. The lines widened and fusedto form nodule; 2. The density of lines were so weak that the interstitialspaces hardly be observed, most of that accompanying ground glass nodule orsolid nodule. N-NTs refers to the MIP reconstruction image showing a smoothcontour with five lines and clear spaces between the lines.A logistic regression was carried out to assess the effectof sex, age, and NTs vs. N-NTs sign on the likelihood of metastasis orrecurrence.

Results: Among 55 cases (54 with non-small cell lungcancer, 1 with small cell lung cancer), 44 cases showed NTs (Figure),of which30 cases were found metastasis on preoperative imaging and postoperativepathology, in remaining 14 cases, 7 cases were found recurrence and metastasisduring imaging follow-up 2 months to 4 years after surgery. The possibilityof NTs prediction on metastasis and recurrence was statistically significant($p<0.001$) and AUC-ROC is 0.861. Among 11 cases with N-NTs, only 1case was confirmed lymphatic metastasis by both image and pathology, theremaining 10 cases had no recurrence by follow-up 4 to 15 years after surgery. That imply that NTs highly indicate lung cancer metastasisor recurrence. NTs vs. N-NTs ($p<0.001$) was significant.Figure legends: MIP image shows a nodulartail sign (arrow), the patient was found adrenal metastasis 7months aftersurgery.

Conclusions: The nodular tail sign may represent lungcancer invasion into the pulmonary interstitium and is closely linked tometastasis or recurrence.



Keywords: lung cancer, recurrence and metastasis, tomography, x-ray computed

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.23 Real-World Predictive Performance of Lung-RADS in the Evaluation of Part-Solid Nodules

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Introduction: Part-solid nodules (PSNs) are associated with a high malignancy rate and solid component of PSNs are important to predict malignancy. While the Lung-RADS aims to stratify risk and guide clinical management, its predictive value specifically in PSNs remains unclear. This study aims to evaluate the diagnostic accuracy and risk stratification performance of the Lung-RADS categories in PSNs.

Methods: We retrospectively reviewed CT reports of 4,382 participants who underwent lung cancer screening (LCS) between May 2017 and February 2025 at our institution. Among these, PSNs were identified and categorized according to Lung-RADS (2, 3, 4A, 4B, or 4X). The reference standard for malignancy was determined based on histopathologic confirmation or imaging follow-up. We evaluated malignancy rates across Lung-RADS categories and assessed the diagnostic performance of Lung-RADS in predicting malignancy in PSNs.

Results: Of the 79 PSNs identified, 54 nodules in 48 patients were included after excluding cases with indeterminate reference standards. The distribution of Lung-RADS categories was as follows: category 2, 18.5% (10/54); category 3, 46.3% (25/54); category 4A, 13.0% (7/54); and category 4B/4X, 22.2% (12/54). Overall, 24.1% (13/54) of PSNs were malignant. Malignancy rates by category were: 10.0% (1/10) for category 2, 16.0% (4/25) for category 3, 42.9% (3/7) for category 4A, and 41.7% (5/12) for category 4B/4X. When category 3 and above were considered screening positive, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 92.3%, 22.0%, 27.3%, and 90.0%, respectively. When the threshold was set at category 4, the corresponding values were 61.5% for sensitivity, 73.2% for specificity, 42.1% for PPV, and 85.7% for NPV.

Conclusions: In part-solid nodules detected on screening CT, malignancy rates were higher than generally anticipated for lower Lung-RADS categories. The system showed high sensitivity but low specificity with a category 3 threshold, and the distinction between categories 4A and 4B/4X provided limited additional stratification. These findings suggest that Lung-RADS may have limited predictive accuracy for part-solid nodules and underscore the need to improve risk stratification approaches for this subgroup in clinical practice.

Keywords: Lung cancer screening, Lung-RADS, Part solid nodule

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.24 TabPFN Empowered the Ternary Classification of Histological Subtypes in Stage IA LUADs Based on AI Analyzed Histogram Features

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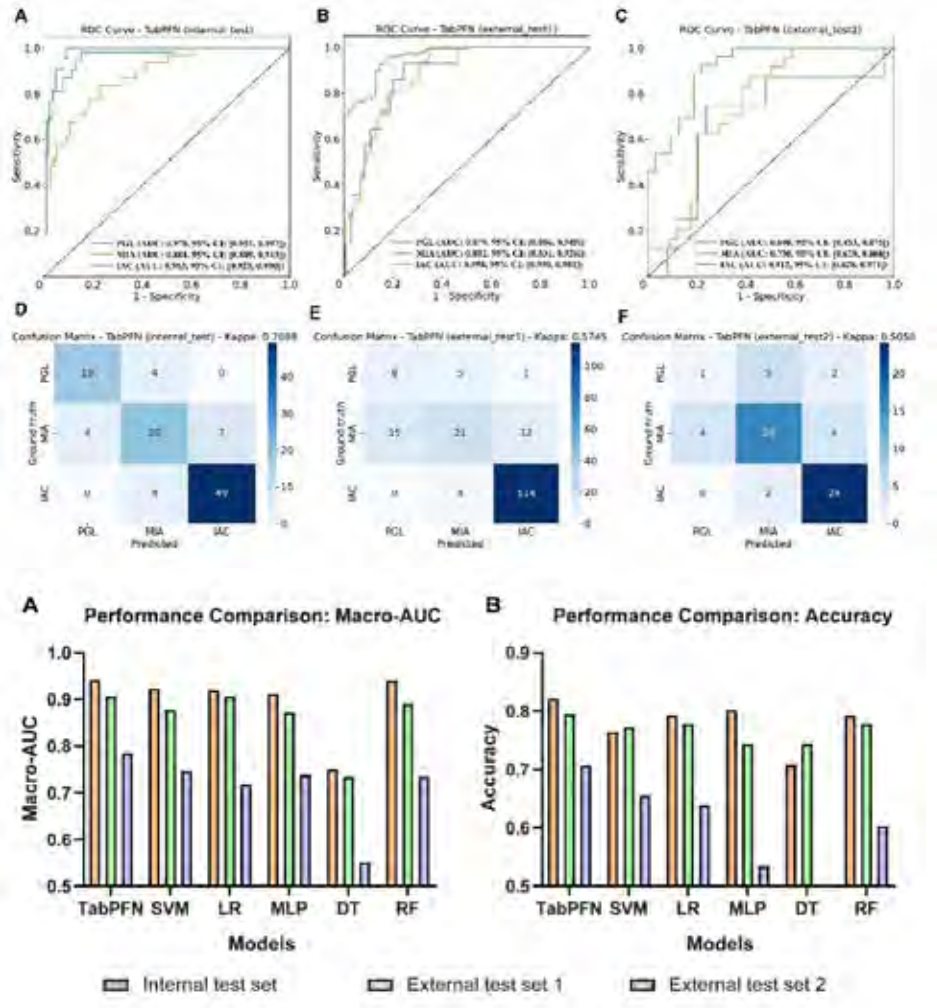
Introduction: Preoperative differentiation of preinvasive, minimally invasive adenocarcinoma, and invasive adenocarcinoma subtypes in stage IA lung adenocarcinoma (LUAD) is critical for surgical decision-making. However, overlapping imaging features and interobserver variability hinder accurate classification. Existing AI models often focus on binary classification or lack multicenter validation. To develop and validate a transformer-based tabular foundation model (TabPFN) for ternary classification of LUAD subtypes using AI-derived histogram features and compare its performance with traditional machine learning (ML) algorithms and intraoperative frozen section analysis.

Methods: This multicenter retrospective study utilized preoperative CT scans from three institutions between September 2014 and October 2023. Data were divided into training, internal validation, and external test sets. Histogram features (n=26) were extracted using a commercial AI system (InferRead CT Lung). TabPFN and five ML algorithms were trained and validated across datasets. Performance was evaluated using accuracy, macro-AUC, sensitivity, specificity, and Cohen's Kappa. Statistical comparisons included DeLong tests for AUC and chi-square tests for categorical variables.

Results: The cohort comprised 584 patients with stage IA LUAD (mean age 57.9±11.0 years; 386 female), divided into training/validation sets (n = 412, center 1) and external test sets (n = 114, centers 2; n =58, center 3). TabPFN achieved macro-AUC of 0.784-0.906 and accuracy of 70.7%-79.4% across external test sets, outperforming all ML algorithms (e.g., XGBoost: 65.2%, AUC 0.721). On external test set 2, TabPFN's accuracy (70.7%) significantly exceeded frozen section analysis (43.1%, p=0.003). Subgroup analysis revealed superior performance for male patients (75.3%, AUC 0.89) and mixed ground-glass nodules (AUC 0.85-0.91).

Conclusions: TabPFN demonstrated robust ternary classification of LUAD subtypes across institutions, with superior performance compared to traditional ML and frozen section analysis. Its computational efficiency (<1 second per case) and sex/nodule-type specificity support its clinical utility for guiding personalized surgical strategies.



Keywords: Deep Learning, Radiomics, LUAD

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.25 Incidental Findings From the Annual Follow-Up in the 4-In-The-Lung-Run Lung Cancer Screening Trial

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Introduction: Lung cancer screening (LCS) with low-dose CT has been shown to reduce lung cancer-related mortality in high-risk individuals. However, LCS often detects incidental findings (IFs) that are not the primary focus of screening. These findings pose challenges for healthcare by increasing costs due to potentially unnecessary diagnostic procedures and causing anxiety among participants. This study examines IFs identified at baseline and during annual follow-ups in the European 4-In-The-Lung-Run (4ITLR) screening trial, with a particular focus on the clinical relevance of IF stability and progression for further work-up.

Methods: Chest LDCT scans from the first annual screening participants (n=2601), acquired between 12 February 2024 and 21 January 2025 from the Dutch 4ITLR centers were included in this study. IFs reported by radiologists were categorized by anatomical location: intrathoracic-intrapulmonary, intrathoracic-extrapulmonary, extrathoracic, and vascular. If IFs were evaluated as potentially clinically significant they were reported to the participant's general practitioner (GP).

Results: Among the 2,601 annual screening participants, 65 (2.5%) had IFs reported by radiologists, with a total of 70 IFs identified, as some participants had multiple findings. IFs were classified into four categories based on location: 23 (0.9%) intrathoracic-intrapulmonary, 14 (0.5%) intrathoracic-extrapulmonary, 18 (0.7%) extrathoracic, and 15 (0.6%) vascular. A total of 25 IFs (1.0%) were reported to GPs, including 9 (0.3%) that were either new or showed progression compared to previous examinations. No acute IFs were reported. Coronary calcifications and pulmonary emphysema were considered comorbidities, while Agatston calcium scores >300 were routinely reported to GPs.

Conclusions: In the annual screening round of the 4ITLR trial, only a limited number of IFs were reported, without any acute consequences over a one year period. Ongoing follow-up studies will help to determine if systematic reporting of IFs in LCS follow-ups will be of clinical benefit to screening participants.

Keywords: Lung cancer screening, Incidental findings, Computed tomography

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.26 The Impact of Brain MRI Surveillance on Survival Outcomes in Initially CNS Metastasis-Free Non-Small Cell Lung Cancer

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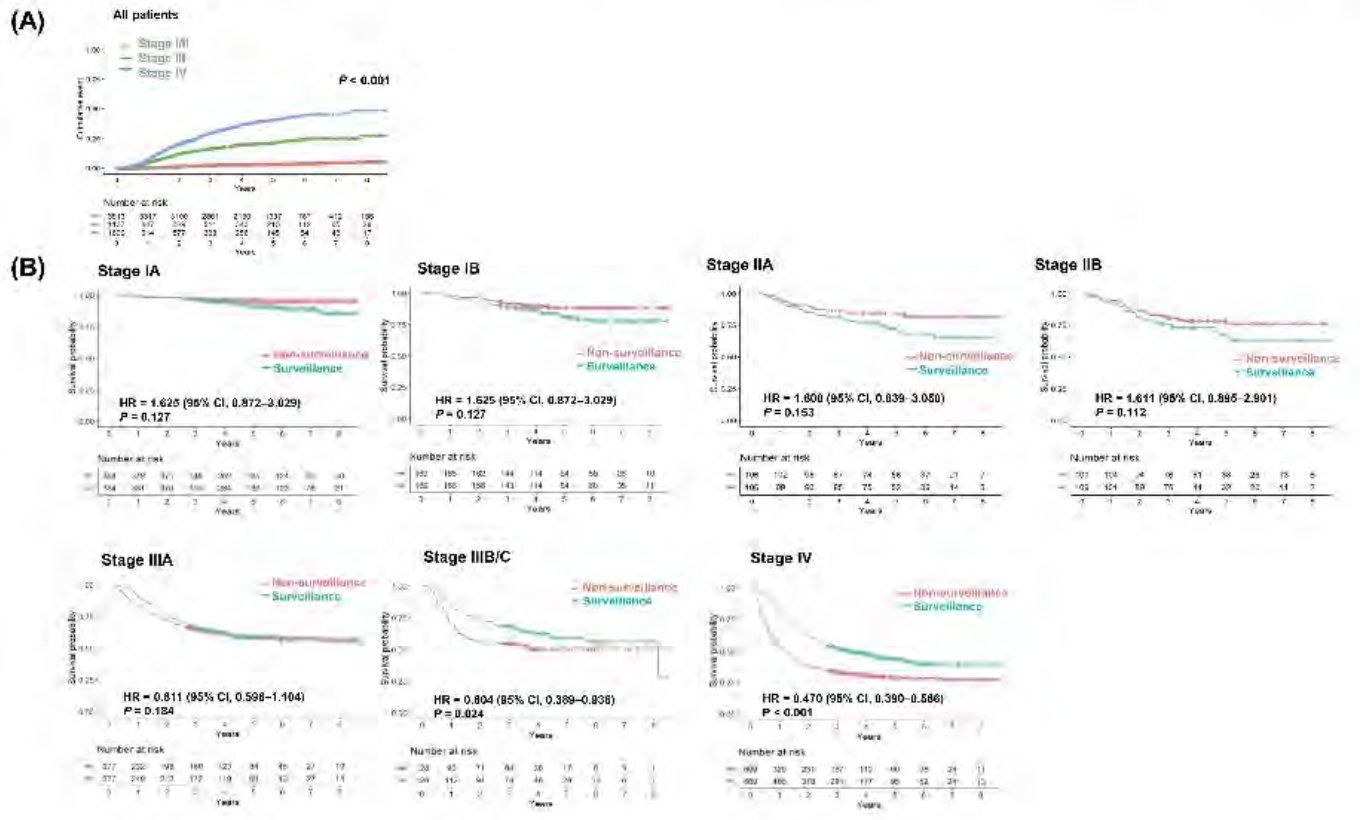
Introduction: Brain metastases are common in patients with non-small cell lung cancer (NSCLC), yet the role of brain MRI surveillance in patients without initial brain metastases remains uncertain. This study aims to evaluate the cumulative incidence of brain metastases and the impact of brain MRI surveillance on survival outcomes in NSCLC patients without brain metastases at initial diagnosis.

Methods: We conducted a retrospective, single-institution cohort study of NSCLC patients diagnosed between September 2014 and December 2019. Patients who underwent staging brain MRI without evidence of brain metastases were categorized into surveillance and non-surveillance groups based on follow-up MRI status. Propensity score matching was used to balance clinical stage, histology, and actionable genetic alterations (AGAs). The primary outcome was the cumulative incidence of brain metastases, while overall survival (OS) was the secondary endpoint.

Results: A total of 6,448 patients met the inclusion criteria, with 2,236 (34.7%) undergoing brain MRI surveillance. The cumulative incidence of brain metastases was higher in patients with advanced-stage disease (0.4% vs. 4.8% vs. 6.9% at 1 year, 1.4% vs. 12.0% vs. 20.1% at 2 years for stages I-II vs. III vs. IV), particularly in patients with adenocarcinoma and specific AGAs (EGFR, ALK, ROS1 alterations). After propensity score matching, brain MRI surveillance was associated with significantly improved OS in stage IIIB/C (HR = 0.604; 95% CI = 0.389-0.936; P = 0.024) and stage IV (HR = 0.470; 95% CI = 0.390-0.566; P < 0.001). Subgroup analysis revealed that the survival benefit was linked to increased utilization of gamma knife radiosurgery and longer durations of tyrosine kinase inhibitor therapy.

Conclusions: Brain MRI surveillance in NSCLC patients without initial brain metastases was associated with improved survival outcomes, particularly in advanced-stage disease. These findings suggest that a risk-adapted approach to brain MRI surveillance may be beneficial, warranting further prospective studies to refine guidelines for brain metastasis monitoring in NSCLC.

Figure 1. (A) Cumulative incidence of newly developed brain metastases in patients by clinical stage (B) Kaplan-Meier survival curves for OS comparing the non-surveillance and surveillance groups after propensity score matching for each clinical stage



Keywords: Non-small cell lung cancer, Brain metastasis, Surveillance

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.27 Radiologic Features Identification of Pathologic Tumor Invasion in Pure Ground-Glass Nodules

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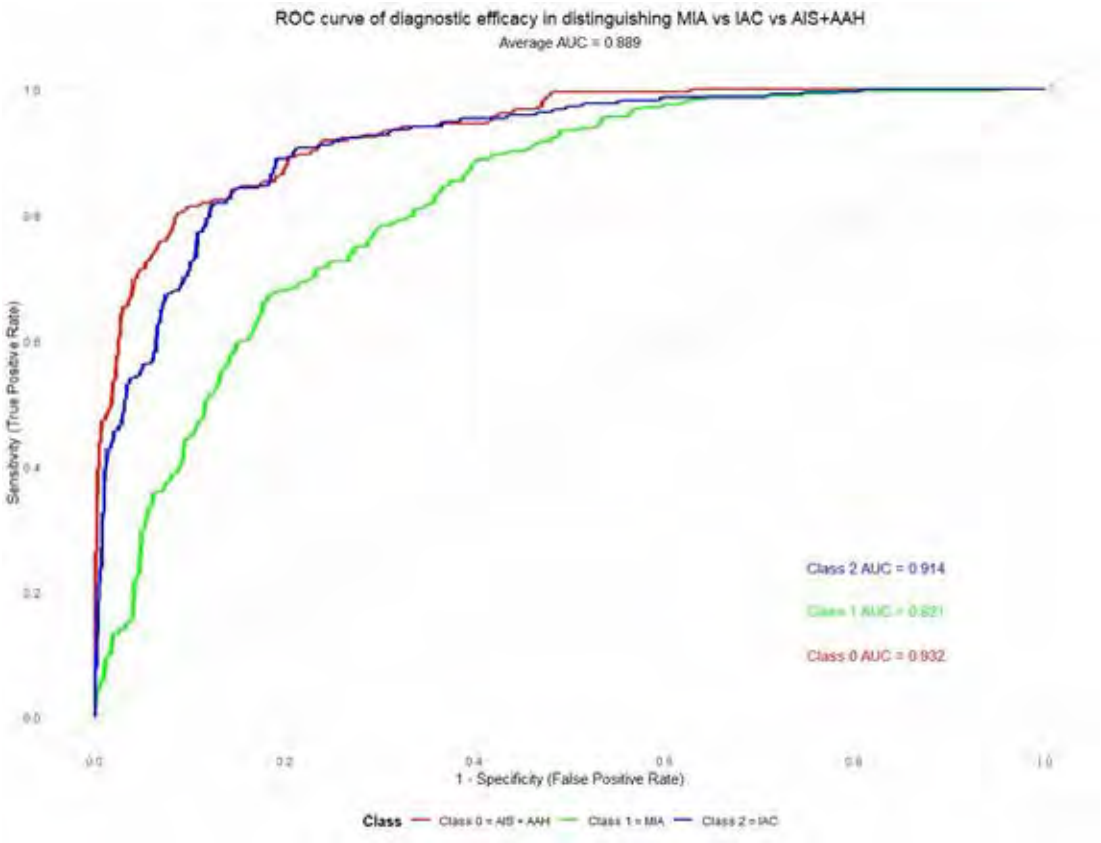
Introduction: Preoperative evaluation of the invasiveness of pure ground-glass nodules (pGGNs) at CT influences clinical decision-making but may be challenging. we aim to explore CT features of pGGNs of all histopathologic subtypes (atypical adenomatous hyperplasia or adenocarcinoma in situ, minimally invasive adenocarcinoma and invasive adenocarcinomas) and determine the radiologic model predicting pathologic invasiveness of pGGNs in a ternary classification.

Methods: A retrospective review was performed of 1683 patients between January 2012 and Jun 2024 who had suspicious pGGNs between 4.0 mm and 30.0 mm on preoperative CT. For each pGGNs, the size, location, margin, shape, nodule CT attenuation, uniformity of density, lobulation sign, reticulation sign, vascular cluster sign, bubble-like lucency sign, air bronchogram sign and pleural indentation sign were evaluated by two radiologists independently who were blinded with clinical information and pathology results. Ternary univariable and multivariable logistic regression and diagnostic accuracy analysis were used.

Results: 1683 patients (1145 [68.0%] female, 538 [32.0%] male) with median age of 53 years (IQR: 45-61 years). Among the 1683 patients, 2125 pGGNs were included. Ternary multivariable logistic analysis demonstrated that the independent radiologic factors for predicting pathologic MIA were age (OR=0.98, 95% CI: 0.97-0.99), nodule size (OR=1.22, 95% CI: 1.14-1.32), number of vessels (OR=3.31, 95% CI: 2.75-3.92), CT attenuation (OR=1.01, 95% CI: 1.00-1.01), uniformity of density (OR=1.77, 95% CI: 1.25-2.54), presence of pleural retraction (OR=2.10, 95% CI: 1.30-3.34), bubble lucency (OR=1.74, 95% CI: 1.02-2.95) and air bronchogram (OR=2.14, 95% CI: 1.16-3.99). Ternary multivariable logistic analysis demonstrated that the independent radiologic factors for predicting pathologic IAC were nodule size (OR=1.69, 95% CI: 1.56-1.84), distance to pleural (OR=1.04, 95% CI: 1.01-1.07), number of vessels (OR=2.77, 95% CI: 1.98-3.73), CT attenuation (OR=1.01, 95% CI: 1.01-1.01), uniformity of density (OR=5.67, 95% CI: 2.99-10.74), presence of lobulation (OR=2.08, 95% CI: 1.25-3.61), pleural retraction (OR=2.93, 95% CI: 1.66-5.00), bubble lucency (OR=2.40, 95% CI: 1.28-4.36) and air bronchogram (OR=2.92, 95% CI: 1.53-5.71). Overall, the diagnostic efficacy using the radiologic model to distinguish IAC vs MIA vs AAH/AIS was 0.89. There were 57 patients had enlarged mediastinal lymph nodes on CT. None of them had N1, N2 and N3 lymph node metastasis.



Conclusions: The independent radiologic factors for predicting pathologic invasiveness adenocarcinoma of pGGNs were nodule size, number of vessels, CT attenuation, presence of pleural retraction and bubble lucency and air bronchogram. Overall, the diagnostic efficacy using the radiologic model to distinguish IAC vs MIA vs AAH and AIS was 0.89.

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.28 Correlation Between Dosimetric Parameters and Radiation-Induced Pulmonary Toxicity in Lung Cancer Radiotherapy

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Introduction: Radiation pneumonitis (RP) and pulmonary fibrosis remain critical concerns in lung cancer radiotherapy, significantly impacting patient outcomes and quality of life. International guidelines, including those by Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) and ASTRO, identify V20% (lung volume receiving ≥20 Gy) and Mean Lung Dose (MLD) as predictors of radiation-induced lung toxicity. This study investigates correlations between these dosimetric parameters and pulmonary toxicity among lung cancer patients treated in a Brazilian cancer center, hypothesizing that elevated V20% and MLD correlate with increased pulmonary toxicities.

Methods: This analysis was conducted on lung cancer patients who underwent definitive or palliative radiotherapy between 2020 and 2025 at a single institution. Dosimetric parameters, including MLD, V20%, Dmax, V35%, V50%, and V60%, were extracted from treatment plans. Pulmonary toxicities were graded using CTCAE v5.0, with a focus on Grade ≥2 RP and pulmonary fibrosis. A multivariate analysis was performed to assess the association between dosimetric variables and toxicity incidence, with $p<0.05$ considered statistically significant.

Results: Among the analyzed patients, 18% developed Grade ≥2 RP, with a significantly higher incidence (28% vs. 12%, p=0.002) in individuals with V20% >30%. The mean V20% was updated to 1.80% (SD ±6.87%) and patients exceeding this threshold demonstrated an increased risk of pulmonary complications. Pulmonary fibrosis was more prevalent in cases where MLD exceeded 4520.92 cGy (p=0.006). Higher values of V35% and V50% also showed a trend toward increased toxicity, reinforcing the importance of limiting high-dose exposure to normal lung tissue. These findings align with international dosimetric constraints, which recommend maintaining V20 ≤35% and MLD ≤20 Gy to minimize RP risk, confirming that V20% and MLD are strong predictive markers for radiation-induced pulmonary toxicity in lung cancer patients receiving radiotherapy. This study reinforce the universal applicability of established dosimetric thresholds and highlight the importance of individualized treatment planning to mitigate toxicity risks while ensuring effective tumor control.

Conclusions: Modern radiation techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), may significantly reduce pulmonary complications. These results emphasize the necessity of refining dosimetric constraints and personalized protocols to enhance radiotherapy safety. Future prospective studies are warranted to further validate these findings and optimize treatment strategies for lung cancer patients.

Keywords: Pulmonary toxicity, Radiotherapy, Dosimetric

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.29 Female Asians Who Never Smoked With Lung Adenocarcinomas (FANSA) Have Unique Survival Outcomes: An ILCCO Analysis

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Introduction: Lung cancer screening programs historically target individuals with a history of tobacco use. However, growing evidence indicates that never-smokers with risk factors, such as a family history of lung cancer or specific demographic profiles, may also benefit from screening. FANSA represent a distinct subgroup often defined by actionable oncogenic drivers, better treatment options at advanced stage, and generally lower comorbidity burden. This study aimed to compare stage-specific overall survival (OS) and cancer-specific survival (CSS) between FANSA patients and other NSCLC patients, and to evaluate the independent impact of FANSA variables; sex, ethnicity, smoking status, and histology on survival outcomes.

Methods: A retrospective pooled analysis of NSCLC patients was performed from 25 International Lung Cancer Consortium (ILCCO) sites across North and South America, Asia and Europe (1990-2020). Multivariable Cox and Fine-and-Gray regression were used to assess survival by stage and identify key drivers of OS and CSS (primary outcomes), with subgroup analyses focusing on stage 1 patients and comorbidity profiles.

Results: Of 36,966 patients, 1,837 were identified as FANSA. FANSA patients had superior OS across all stages compared to ever-smokers and other never-smokers (stage-I hazard ratio (HR) 0.16, 95%CI: 0.12-0.21; stage-II/IIIA HR 0.48, 95%CI: 0.40-0.57; stage-IIIB/IV HR 0.53, 95%CI: 0.48-0.60; all p<0.001). The most pronounced survival benefit was observed in Stage I FANSA patients (5-year OS: 93% for FANSA, 79% other never-smokers, 61% ever-smokers, p<0.001). Interaction analyses revealed that the relationship between OS and sex, ethnicity, smoking status, and histology varied significantly by stage (all p<0.001). In stage I, multivariable Cox analysis revealed that female sex (adjusted (a) HR, 0.74; 95%CI: 0.69-0.78, p<0.001), Asian ethnicity (aHR 0.73; 95%CI: 0.56-0.96, p=0.03), never-smoking (aHR 0.53; 95%CI: 0.47-0.59, p<0.001), and adenocarcinoma histology (aHR 0.72; 95%CI: 0.67-0.77, p<0.001) were each independently associated with improved OS. FANSA patients were younger (median age 60 vs 64 in other never smokers, 66 in ever smokers, p<0.001) and had fewer comorbidities, including respiratory (6% FANSA vs 28% in other patients, p<0.001) and cardiovascular comorbidities (25% FANSA vs 37% other patients p<0.001). In patients with available CSS data, FANSA patients demonstrated improved CSS within five years of diagnosis (p<0.001) with the strongest association in stage I (HR 0.21; 95%CI: 0.15-0.29); though this was also evident in stage II/IIIA (HR 0.60; 95%CI: 0.49-0.73) and stage IIIB/IV (HR 0.77; 95%CI: 0.69-0.87). In stage 1, more favourable CSS was associated with female sex (aHR 0.79; 95%CI 0.67,0.95, p=0.01), never-smoker status (aHR 0.63, 95%CI 0.49,0.82, p=0.002), and adenocarcinoma histology (aHR 0.77; 95%CI: 0.64-0.93, p<0.001), though ethnicity was not significantly associated with CSS (p=0.3).

Conclusions: FANSA patients demonstrate significantly better survival outcomes, particularly with stage I disease. This favorable prognosis may be attributed to younger age at diagnosis and lower comorbidities but it may also reflect unique tumor biology. Given the improved outcomes with early diagnosis, these findings further support the contention that early detection of FANSA in its earliest stages can lead to substantial survival benefits. These findings support the inclusion of select female Asian never-smokers in lung cancer screening programs.

Keywords: FANSA (Female, Asian, Never-Smoker, Adenocarcinoma, Lung Cancer Screening, Survival Outcomes

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.30 Screening of Paraptosis-Related Prognostic Genes in Lung Adenocarcinoma By Bioinformatics Analysis and Experimental Validation

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Introduction: Paraptosis is a key cell death mode for cancer cells to produce anti-tumor effects, but its role in lung adenocarcinoma (LUAD) is not fully understood. This paper attempts to comprehensively study the prognostic value and potential mechanisms of paraptosis-related genes (PRGs) in LUAD.

Methods: Differentially expressed genes (DEGs) were identified from LUAD vs. control samples in the training set, intersected with PRGs to generate candidate genes (CGs). Prognostic genes were then screened from CGs using regression analyses to create a LUAD risk model, validated in the validation set. Clinical characteristics were analyzed to derive independent prognostic factors for a nomogram model. High-/low-risk cohorts from the training set underwent function and immune infiltration analyses. Drugs related to prognostic genes were predicted and docked, and Polymerase chain reaction (PCR) was conducted to validate the prognostic genes.

Results: Based on 27 CGs, 4 prognostic genes (CDKN3, PEBP1, TNFRSF19, PHB) were identified through regression analysis. The prognostic risk model effectively predicted LUAD prognosis and was generalizable. Risk scores showed significant differences in age, T-stage, and N-stage ($P < 0.05$). Risk score, T-stage, and N-stage were independent prognostic factors used to develop a nomogram model, a strong LUAD predictor. High-/low-risk cohorts were enriched in functions like spindle elongation and correlated with differential immune cells. Vorinosta and raloxifene were key drugs binding well to PEBP1. CDKN3 was highly expressed in LUAD, while PEBP1 and TNFRSF19 were lower.

Conclusions: In this study, we focused on PRGs for CDKN3, PEBP1, TNFRSF19, and PHB. CDKN3 and PHB were identified as risk factors for LUAD prognosis, while PEBP1 and TNFRSF19 were not. We explored the tumor microenvironment, revealing the distribution and correlation of differential immune cells influenced by PRGs and riskScore. Besides,we uesd PCR to validate the prognostic genes. However, the specific relationships between some PRGs and immune cells remain unclear and were not fully investigated in our study. Additionally, we developed an independent prognostic model for LUAD and enhanced the functions and pathways of high- and low-risk cohorts. Our drug prediction study provided insights into potential therapeutic directions for LUAD, but further research is needed.

Keywords: Lung adenocarcinoma, Paraptosis, Prognosis

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.31 Implementation of a Lung Cancer Risk Prediction Algorithm: Early Findings From the Lungflag™ Pilot at Geisinger Health System

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Introduction: The Lung Cancer Screening (LCS) program has been implemented at Geisinger since October 2020. Integration of new technologies into clinical workflows holds a promise to improve LCS. LungFlag™ (Medial EarlySign, Hod Hasharon, Israel) is a machine-learning-developed model allowing further risk stratification in the LCS eligible population, predicting individuals who may be at risk for certain respiratory illnesses including lung cancer, enabling targeted recommendation for low-dose computed tomography (LDCT) screening if one was not performed. Geisinger piloted this model from August 2023 to August 2024. Here, we report the early results of the pilot program in a real-world healthcare setting.

Methods: This pilot study integrated LungFlag into routine clinical practice via the hospital's electronic medical record system. LungFlag performs monthly risk evaluations for individuals aged 50-80 eligible for annual lung cancer screening per US Preventive Services Task Force (USPSTF) recommendations. Patients with cancer history and those screened or scheduled for screening in the past year were excluded. Each month, LungFlag flagged 30 individuals with the highest risk scores (LungFlag+). A nurse navigator contacted LungFlag+ individuals with up to three phone calls, notifying them of their status and encouraging them to seek clinical assessments. Individuals who were not flagged (LungFlag-) continue receiving standard care, which includes reminders for LCS during routine visits without additional targeted outreach. This early evaluation focused on screening eligible LungFlag+ and LungFlag- individuals within the initial period from August 2023 to February 2024. Pilot outcomes, including screening compliance and findings from LDCT, are monitored during the follow-up period through August 2024.

Results: During the first six months of the pilot program, 180 individuals from the LCS USPSTF recommended population were flagged as LungFlag+, while 12,893 individuals were not flagged (LungFlag- group). Among the LungFlag+ group, 32 individuals (18%) were excluded after the LCS nurse navigator's chart review due to ineligibility (e.g., non-Geisinger primary care providers (PCPs) and incompatible insurance policies). No chart review was done for LungFlag- group. The 6-month compliance rate for the remaining 148 LungFlag+ individuals was 46% (n=68) for any chest CT and 29% (n=43) for LDCT. Assuming the same exclusion rate for the LungFlag- group, the compliance rates were 15% for any chest CT and 7% for LDCT. Additionally, the time between flagging to chest CT/LDCT was significantly shorter for LungFlag+ individuals, with a median of 26 days compared to 64 days for the LungFlag- group. While clinical impact results are still preliminary, among those who received a LungRADS categorization, the LungFlag+ group was 2.5 times more likely to have "suspicious" findings (LungRADS category 4; 14.3%) compared to the LungFlag- group (5.7%).

Conclusions: Early evaluation of the LungFlag pilot at Geisinger showed that combining AI-developed personalized risk assessment with nurse navigator support led to higher screening compliance rates and reduced waiting times. Based on clinical findings of initial individuals, LungFlag also shows the potential to enhance the efficiency of lung cancer screening programs by identifying more suspicious cases, monitor findings sooner and begin early intervention.

Keywords: Lung Cancer Screening, Machine Learning, Risk Score

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.32 Moving Forward in Early Detection: The ACS/NLCRT Best Practice Guide for Building Lung Cancer Early Detection Programs

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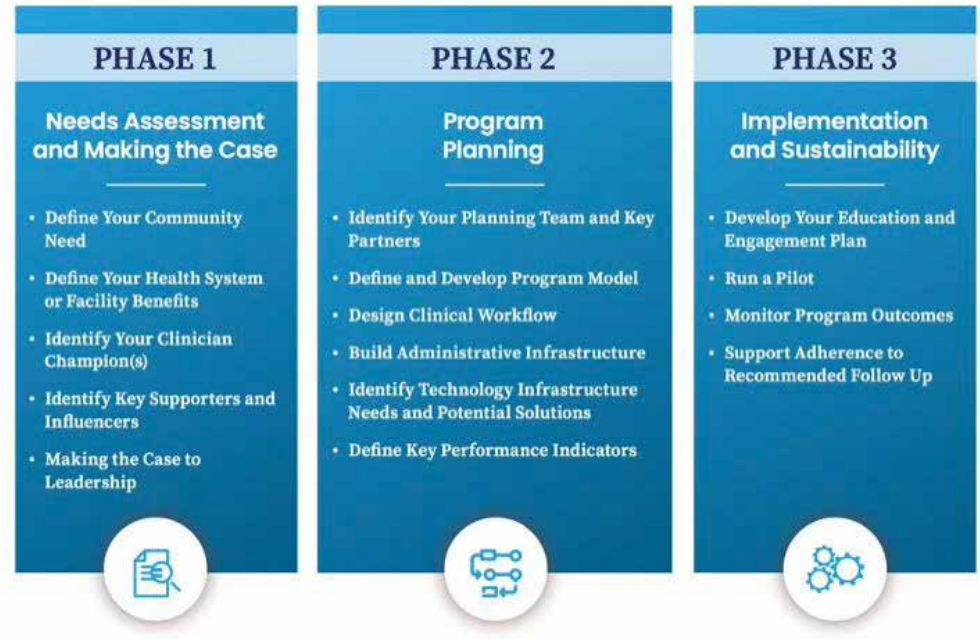
Introduction: Early detection of lung cancer includes both lung cancer screening (LCS) and management of incidental pulmonary nodules (IPNs), and should be a priority to achieve curative-intent treatment, better outcomes, and reduced costs. Yet, most health systems lack a coordinated approach to patient management and tracking for this purpose. LCS and IPN patient populations have different cancer risk, race/ethnicity, and insurance profiles that are important to address in program design. The ACS NLCRT developed the Best Practice Guide for Building Lung Cancer Early Detection Programs to help facilities create, expand, or improve their LCS and IPN programs.

Methods: Members of the ACS NLCRT Steering Committee and leadership of the Early Detection Task Group convened to create the scope and initial outline. Twenty individuals (clinicians, researchers, public health professionals) from 15 organizations (professional societies, advocacy organizations, health systems, industry) then developed the guide, beginning with a series of meetings with iterative feedback to refine the scope and content. Multiple subject matter experts with key informants from the Early Detection and the Provider Engagement Task Groups developed and refined content. This was then reviewed by an advisory committee, including individuals from key partner organizations, AstraZeneca Lung Ambition Alliance and Academy of Oncology Nurse & Patient Navigators, for optimization. Additional cycles of content development, review, and revision were completed prior to product launch in winter 2024.

Results: This guide has a broad audience (navigators, coordinators, providers, program leaders) and can be an essential resource in the work to advance early detection of lung cancer. It outlines 3 phases: 1) Needs Assessment and Making the Case, 2) Program Planning, and 3) Implementation and Sustainability. The guide contains numerous and valuable resources to support the development and optimization of early detection programs, including case studies, forms and data templates, risk calculators, and health equity tools. Links are embedded throughout the guide and compiled in a comprehensive resource section, highlighting many from ACS NLCRT member organizations. The materials are open access and free at the ACS NLCRT website @ https://nlcrt.org/best-practice-guide-early-detection/

Conclusions: The ACS NLCRT Best Practice Guide for Building Lung Cancer Early Detection Programs is a comprehensive, approachable, and flexible guide to building and optimizing LCS and IPN stand-alone or combined programs. This guide focuses on the basic steps to successfully plan and launch new programs and grow and enhance existing programs; it will be updated as major advances, new guidelines, or implementation strategies emerge.



Keywords: Screening, Nodule, Early Detection

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.33 Sybil Pilot for Incidental Pulmonary Nodules

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Introduction: A practical approach to expand early detection of lung cancer is to utilize CT scans already done commonly for non-screening purposes such as cardiac scans. Over 1.6 million patients with incidental pulmonary nodules (IPNs) are identified in the USA annually with an average lung cancer risk of 4-6%, higher than that of the LDCT screening eligible population. IPNs are identified on various scan types completed for other purposes that capture lung windows but usually require repeat low-dose CT scans to assess the nodule. Recently, artificial intelligence (AI) tools to assess medical images, such as Sybil, a deep-learning algorithm to predict 6-year lung cancer risk from a single LDCT scan, have captured attention. Sybil was developed and validated on low-dose lung screening scans. In this pilot, we compared Sybil's scores on a variety of diagnostic 'lung-in-view' and cardiac CT scans with IPNs to dedicated low-dose chest CT on the same individuals.

Methods: A cohort of prospectively and sequentially enrolled patients were included from the IDEAL trial, Vancouver site. All patients completed a dedicated follow-up LDCT chest (T1) which acted as a gold-standard reference for Sybil deep-learning analysis for comparison against their matched baseline (T0) CT scans.

Results: Eighty-five patients with IPNs detected on various CT scan types were identified: 39 (45.9%) cardiac (cardiac with contrast, coronary calcium score, left atrium), 22 (25.9%) high resolution chest without contrast and 20 (23.5%) chest with contrast, 4 (4.7%) neck/spine/shoulder were excluded. Mean time between T0 and T1 scans was 160±91.3 days. There were no statistically significant differences between T0 (4.8%) and T1 (4.4%) risk scores at each time-point over 6-years ($p>0.05$ for all). In a subgroup of patients with a cardiac T0 CT, no significant difference between Sybil scores at any time-point for T0 and T1 were observed ($p>0.79$). Pearson correlation demonstrated strong correlation (0.84) between T0 and T1 year 1 risk scores, decreased to 0.64 at year 6. Bland-Altman analysis showed excellent agreement in this subgroup between T0 and T1 with difference in mean risk of -0.31% for year 1 up to 0.46% at year 6 (Figure 1).

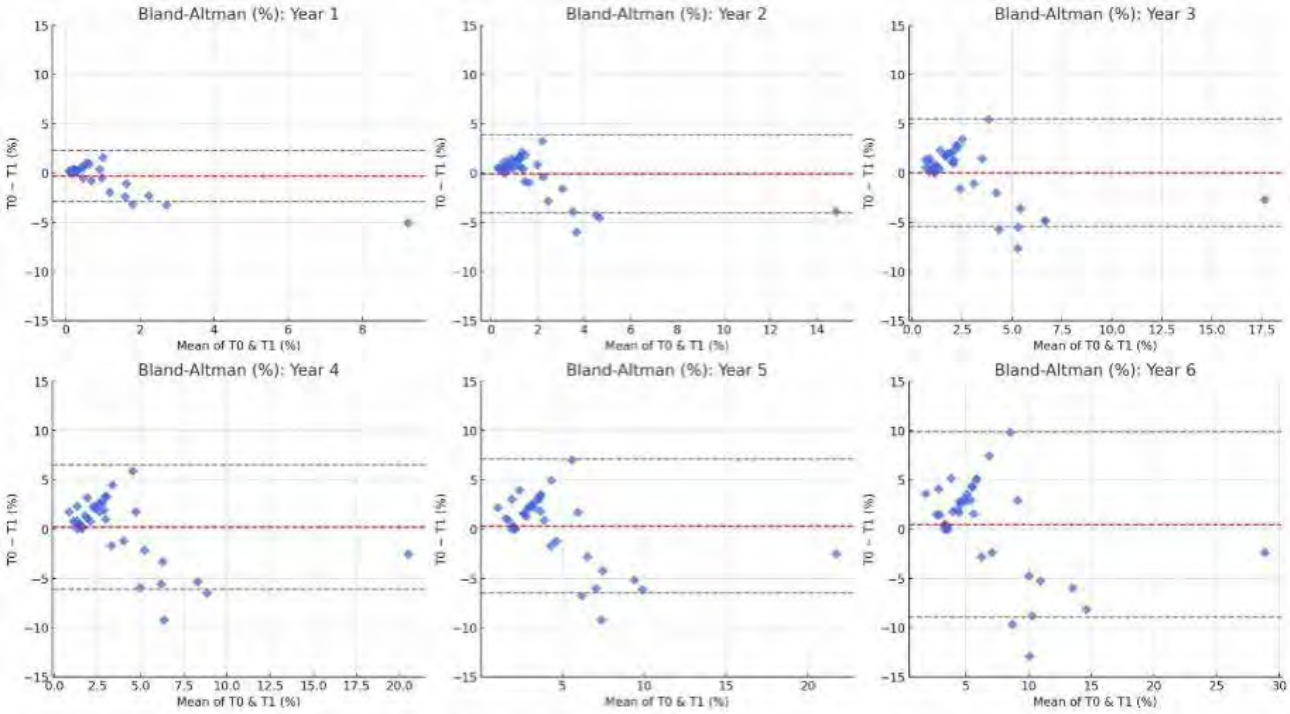

Figure 1: Bland-Altman analysis demonstrating strong agreement between baseline (T0) cardiac CT scans and low-dose CT chest (T1) risk scores for the same patients within an IPN cohort.

Conclusions: In this pilot study, Sybil scores were consistent between dedicated low-dose CT chest and various diagnostic CT scans, including cardiac scans. Further research is required to understand how AI and deep-learning algorithms can utilize pre-existing diagnostic imaging to opportunistically broaden the reach of lung cancer screening.

Keywords: Incidental Pulmonary Nodules, Sybil, AI

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.34 AI Powered Incidental Pulmonary Nodule Program Demonstrates High Lung Cancer Detection Rate: Canadian IDEAL Study

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Introduction: Lung cancer screening has demonstrated a ≥20% mortality reduction in lung cancer through early detection in a high-risk ever smoking population. However, the majority of pulmonary nodules are found incidentally on imaging studies unrelated to screening. Recent studies demonstrate that the majority of patients with incidental pulmonary nodules (IPNs) are not receiving guideline follow-up despite a high incidence of lung cancer in this population. To engage patients with IPNs and broaden the reach of screening and early detection, a systematic approach to identify, track, and manage IPNs for integration into a lung cancer care or screening pathway is required. The purpose of our study is to evaluate a Natural Language Processing (NLP) model that will automatically identify patients with IPNs and create a 'fail-safe' pathway to improve triage and management of IPNs and ultimately increase early detection of lung cancer.

Methods: The Vancouver site of the multi-center IPN Canadian trial - the 'Identifying Early Lung Cancer in a Diverse Population' (IDEAL) study, evaluated a customized, ethics approved, RoBERTa-based transformer model, (SapienNLP) screening tool to screen all "lung-in-view" unstructured CT radiology reports within a large health authority, consisting of 4 major hospitals to identify patients between 50-80 years who have one or more lung nodules ≥ 6 mm. The model scanned the radiology information system every 24-hours for new reports. The list was then screened by a Respirologist to confirm patient's nodules were truly incidental. Patients with a confirmed IPN were invited to be enrolled in the IDEAL study to track and manage their nodules. The participants also underwent lung cancer risk assessment using the PLCOm2012 to determine the proportion of patients who may meet current British Columbia lung cancer screening criteria of >1.51% 6 -year lung cancer risk.

Results: Between November 1, 2023, and March 1, 2025, 66,173 'lung-in-view' radiology reports were analyzed, 17,783 (26 %) of scans identified pulmonary nodules, and 4916 (28%) of these had nodules ≥ 6mm in individuals aged 50-80 years. A total of 596 (12%) nodules were confirmed as true IPNs by a Respirologist. Notably, 215 (36%) of IPNs were identified on cardiac scans. Of the 204 participants enrolled (50% female, 60% non-tobacco users) only 18 (8.8%) were eligible for screening based on PLCOm2012 risk score >1.51%. Lung cancer incidence was 3.9% compared to 1.6% in the screening cohort, with 75% of IPN cancers diagnosed at stage I.

Conclusions: Integration of a natural language model enables efficient identification of patients with IPNs from a large number of lung-in-view CT imaging studies. A significant proportion of these patients were found to have lung cancer but were ineligible for screening. An IPN program provides a complementary method to current lung cancer screening programs, to detect and treat lung cancer early and improve outcomes.

Keywords: Artificial Intelligence, Incidental Pulmonary Nodules, Lung Cancer Screening

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.35 Impact of lung cancer screening eligibility criteria on participants' characteristics and healthcare resources

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Introduction: Selectioncriteria for lung cancer screening (LCS) candidates are essential forimplementing resource-and cost-efficient programs. However, different selectioncriteria may have similar resource requirements but select dissimilarindividuals. This study explores the impact of different inclusioncriteria on eligibility, participants' characteristics and health services inSpain.

Methods: Across-sectional study was conducted using data from 21,007 individuals from the2012 Spanish National Health Survey (ENSE). We analyzed data from the 2012 Survey, the most recent withcomplete data on people who smoke and people with a smoking history. Theproportion of eligible individuals aged 50-80 years was assessed according tofour different LCS criteria. Two criteria were based on the 4 IN-THE-LUNG-RUNtrial; 4ITLR1: ages 60-79, who smoked at least 35 pack-years and currentlysmoke or quit smoking <10 years ago, and 4ITLR2: ages 60-79 who have aPLCOm2012 no race model risk of at least 2.6%. The third criteria was based onthe United Kingdom's Targeted Lung Health Check (TLHC): ages 55-74 with aPLCOm2012 risk of at least 1.51%. Finally, the 2021 United States PreventiveServices Task Force (USPSTF) criteria were evaluated: ages 50-80 who smoked atleast 20 pack-years and currently smoke or quit smoking <15 years ago. Theseestimates were extrapolated to the 2022 Spanish population using data from theNational Institute of Statistics (INE). Eligibility across sex, age groups andsmoking status was evaluated. For the estimation of LCS resource impact, annualand biennial intervals were chosen.

Results: In 2022, among the Spanish population aged 50-80 years(17,651,476individuals), the most restrictive lung cancer screening (LCS) criteria, 4ITLR1, identified 998,760 eligible individuals (5.6% of ages 50-80).The 4ITLR2 criteria included 1,188,790 eligible individuals (6.7% of ages50-80), rising to 1,875,926 (10.6% of ages 50-80) for the TLHC criteria. TheUSPSTF criteria were the broadest, identifying 3,806,525 eligible individuals(21.6% of ages 50-80). Annual screening (with 50% participation) ranged from499,380 participants with the most restrictive criteria (representing an 9.0%increase in national radiological capacity) to 1,903,262 (34.1% increase innational radiological capacity) with the broadest. For biennial screening,these numbers would be halved. All criteria primarily selected men(68.1-82.2% of eligibles). Most criteria favored selecting former smokers(49.4-56.9%). However, eligible women were more often current smokers than menacross all criteria (men: 38.5-46.8%, women: 50.0-64.2%). Former smokers smokedmore cigarettes per day than current smokers (30 vs 20) despite having shortersmoking durations, resulting in higher median pack-years across all criteria(range: 44-66). Overall, pack-year-basedeligibility decreased with age, while risk-based eligibility was stable acrossage groups.

Conclusions: In conclusion, different LCS inclusion criteriadirectly impact required healthcare capacity and yield populations with highly variedcharacteristics. Consequently,balance across these characteristics (age, sex, smoking behavior) should betaken into consideration when choosing the selection criteria.Risk-basedcriteria may provide more balanced eligibility across age-groups.

Keywords: Lung cancer screening, Eligibility criteria, Screening strategies

P1.04.36 LungFlagTM Risk Prediction Validation on Canadian Ever Smokers Pre-Classified as High Risk for Lung Cancer

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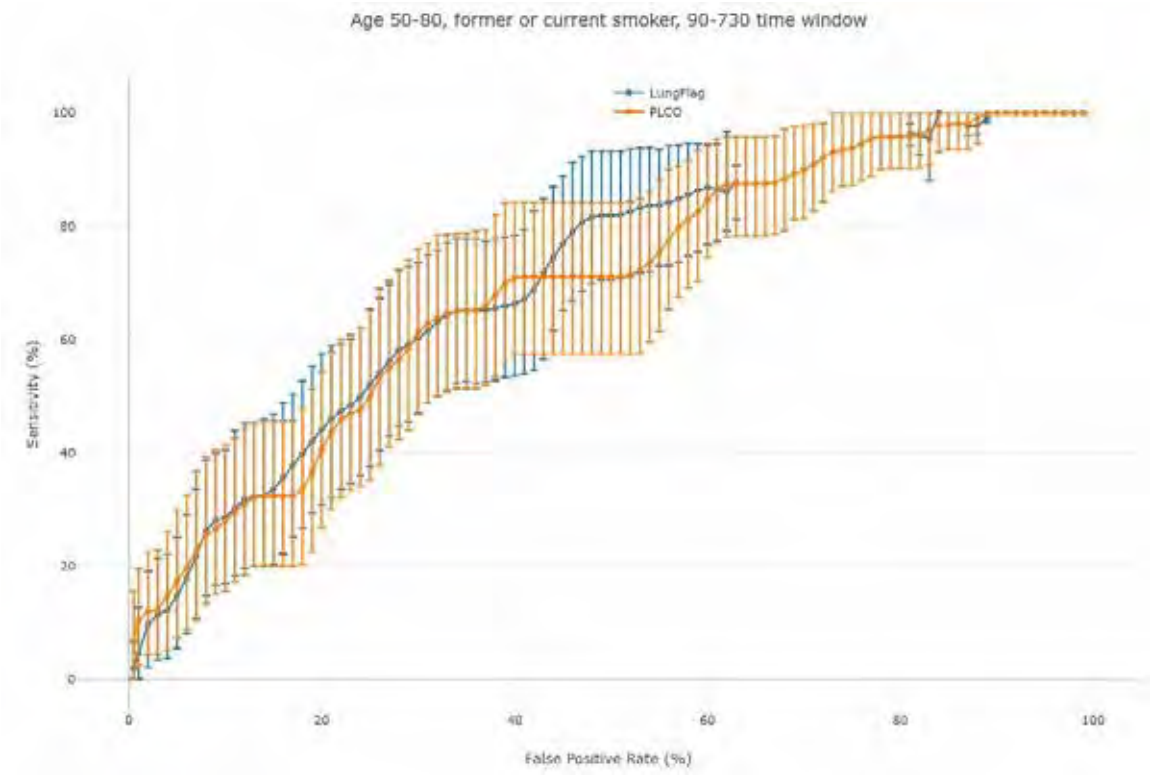
Introduction: The usage of personalized risk scores is increasingly adopted to evaluate specific clinical condition susceptibility. Early detection of Lung Cancer (LC) is clinically important as it translates to more favourable patient outcomes. Thus, development of population health management approaches using risk predictors (i.e. PLCOm2012 and EHR based LungFlag) for identification of individuals who may be in increased probability for having lung cancer is of paramount importance.

Methods: LungFlag (Gould, M.K.et al., 2021. Machine learning for early lung cancer identification using routine clinical and laboratory data. American journal of respiratory and critical care medicine, 204(4), pp.445-453) performance was assessed on a cohort biased towards high risk population, included two independent Canadian data sets (British Columbia) selected in the past for LC screening (1) Lung Screening Population (LSP) - (age: 55-80 years with ≥30 years smoking history who meet either the PLCOm2012 ≥ 1.51% or USPSTF 2013 criteria) and non-eligible population, and (2) the PanCan single-arm longitudinal trial (age: 50-75 years and ≥2% six years lung cancer risk). Sensitivity analysis was performed on combined populations. LungFlag was compared with PLCOm2012 for non-inferiority. LungFlag was not used to select individuals from the ever-smoking populations, disadvantage the algorithm to an already pre-selected population in the USPSTF/PLCOm2012 cohort.

Results: Out of a total population of 3,064 individuals, 2,958 (LSP: eligible - 2,171; non-eligible-703, and PanCan: 84) met the eligibility criteria including 49 LC (mainly due to 2 years prediction time horizon). The average age for cases was 69.0 with 42.9 years smoking duration compared to 64.9 and 36.5 for controls respectively. The proportion of participants with COPD was 35% compared to 14%, cases vs. controls, respectively. The overall AUC (2-years time horizon) on those who had ever smoked between age 50-80 years was comparable between LungFlag and PLCOm2012 (0.707 vs 0.693) (Figure 1), with similar trends on the USPSTF2013 criteria (0.687 vs 0.682) subpopulation.

Conclusions: Despite being conducted among the mostly pre-selected high-risk population, LungFlag consistently demonstrates non-inferior performance compared to the PLCOm2012 or the USPSTF2013 eligibility criteria. The model is applicable to Canadian EHR data. Using a 2-year risk horizon performed comparably well as 6 years horizons. Future studies should focus on prospective evaluation of LungFlag as an independent classifier to identify populations with an elevated risk of lung cancer for screening.



Keywords: Risk prediction, blood Biomarker, lung cancer

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.37 Systematic Enrolment for Lung Cancer Screening Ensures Rapid Stage Shift of Diagnosed Lung Cancers at a Population Level

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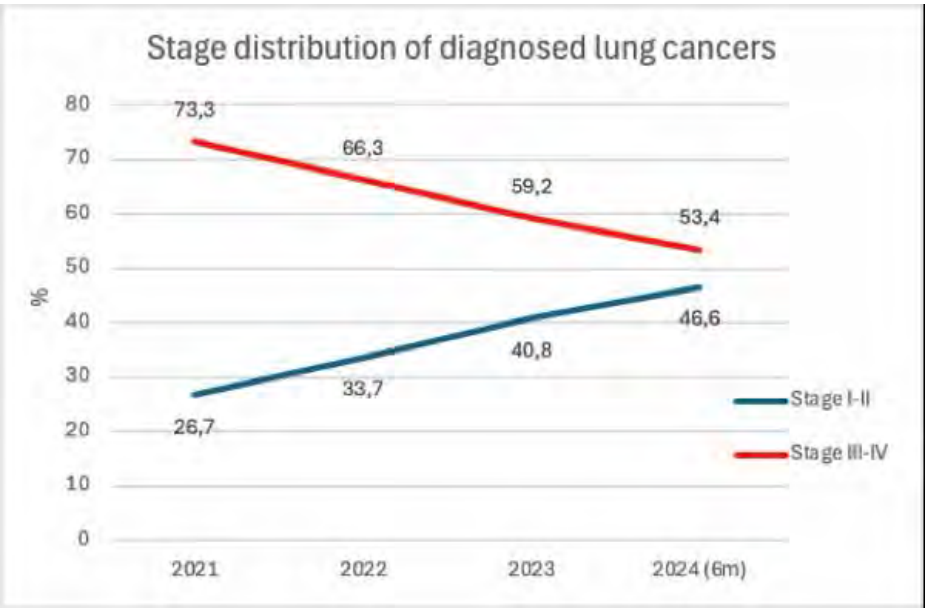
Introduction: Several studies have demonstrated that screening enables lung cancer (LC) detection at earlier stages. However, limited data exists about the effect of screening at population level. The aim of the study was to compare stage distribution and surgical treatment of LC in one region before and after implementation of systematic LC screening (LCS).

Methods: All LC cases, diagnosed in Tartu County in Estonia during 1.01.2021-30.06.2024 were included. In 1.04.2022, a regional LCS pilot study was initiated - individuals aged 55-74 years with elevated LC risk were enrolled by family physicians, who systematically assessed their patients to determine the target group. In the 2nd pilot study year, new individuals were recruited by family physicians, yet reinvitations were done by LCS coordinators. Screening low-dose computed tomographies (LDCT) were performed during 01.05.2022-31.05.2024. Study data was extracted from the pilot study database and hospital case reports.

Results: At the beginning of the pilot study 157758 individuals lived in Tartu County. There were 92 family physicians (74 participated in 1st and 87 in 2nd study year). The target age group in participating family physician practices was 26759 individuals at 1st and 31537 at 2nd year. Altogether during the two years of screening 8210 individuals were referred to LDCT and 7746 (94.3%) attended it - 64 LCs were diagnosed. Respectively, 34 (53%), 9 (14%), 10 (16%) and 11 (17%) in stage I, II, III and IV; 45 LCs (70%) were treated surgically. In Tartu County, in 2021, 75 LCs (17% in stage I and 53% in stage IV) were diagnosed. During the screening years a considerable LC stage shift at diagnosis in whole county was noticed (Figure 1). By the first half of 2024, out of the 58 LCs 36% were in stage I and 40% in stage IV. Also, the proportion of LCs diagnosed due to screening gradually increased to 38% by 2024. After LCS initiation, 181 LCs were detected among individuals, belonging to the family physician practices participating in the screening pilot, and 41 in those not participating. Respectively, LC was detected in stage I in 35% and 17%; in stage IV in 34% and 63%; and surgical treatment was feasible in 44% and 24% of cases.

Conclusions: Population based LCS ensured rapid increase in early-stage detection and surgical treatment of LC. Due to high LCS uptake the results were demonstrated not only in the screened population, but at the county level.



Keywords: screening, lung cancer, enrolment

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.38 The Coincidental Findings of Lung Nodules With AI-Assisted Chest X-Rays in the Tuberculosis Screening Project

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Introduction: Lung cancer screening using chest X-ray with artificial intelligence to analyze abnormalities (AI-assisted chest X-ray) is an alternative screening tool used in many countries. Although chest X-ray is not as effective as low-dose CT scan in lung cancer screening, there are many advantages and interesting points of using AI-assisted chest X-ray, such as the ability to find small lung nodules better than reading the image by the doctor's eyes alone, reducing misdiagnosis, less radiation exposure, lower costs, community screening, being able to integrate the method with existing tuberculosis screening event at the same time, and considering refer for Low-Dose CT scan in cases where chest X-ray with AI detect lung nodules that are likely to be malignant.

Methods: The tuberculosis screening event in Phra Nakhon Si Ayutthaya District was implemented from February to May 2024. When chest X-ray images were obtained from the mobile X-ray vehicle, a two-step analysis process was performed: The first step involved a family physician reading the chest X-ray image results using Inspectra CXR v4 (Perceptra®, Bangkok) software artificial intelligence. If any abnormalities are found or there is a doubt, it will lead to the second step, which is to refer the results to a radiologist for reporting the official results. In the case of a suspected malignant lung nodule, the radiologist will read the results and provide recommendations for a chest CT scan.

Results: A total of 2,597 participants with chronic diseases were screened for tuberculosis, comprising 816 males (31.4%) and 1,781 females (68.6%), with an average age of 62.87 years. After reviewing the results of the 2-step chest X-rays, the lung nodules were detected. (Indeterminate Pulmonary Nodule: IPN) of various sizes and types, totaling 70 (2.70%). The radiologist recommended further examination by chest CT scan for 35 (1.35%). After a 1-year follow-up, 18 (0.69%) underwent chest CT scans as recommended, and 4 participants (0.15%) were found to have lung cancer. Cancer Detection Rate was 1.54:1,000.

Conclusions: Lung cancer screening integrated with tuberculosis screening, utilizing AI-assisted chest X-rays, has the potential to be implemented as a community screening tool. However, the steps taken after the first doctor uses AI to read the results and identify abnormalities in the lung nodules may be adjusted according to the appropriateness of the resources, which differ in each area and level of the healthcare service. In preparing the lung cancer screening system, the screening campaign period, equipment (including mobile X-ray vehicles and artificial intelligence systems), referral systems, service units, and health personnel who will provide further care, both in cases of lung cancer diagnosis and lung nodule follow-up, must be prepared. A campaign should also be launched to raise public awareness of lung cancer and recognize the importance of receiving lung cancer screenings.

Keywords: Lung Cancer Screening, AI-assisted chest X-ray, Lung Nodule

P1.04.39 Markov Model Approach to Optimize Lung Cancer Screening and Early Detection in Patients With Smoking Associated Diseases

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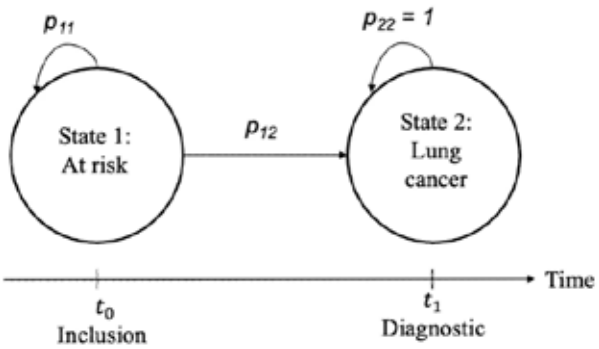
Introduction: We built a theoretical Markov Chain model to predict lung cancer diagnosis after a first round of lung cancer screening (LCS), to test it with real life data and to identify covariates useful for personalized risk stratification.

Methods: We developed a discrete-time Markov Chain model to simulate LCS outcomes after a first LCS round in the PREVALUNG and PREVALUNG ETOILE cohorts (NCT 03976804 and NCT 05649046). The model defined by the matrix Q, represents two states: "At risk" and "Lung Cancer" (Figure 1).

Figure 1: Markov Chain Model



$Q = \begin{bmatrix} p_{11} & p_{12} \\ 0 & 1 \end{bmatrix}$, with p_{ij}, probability of moving from state i to j

We used the msm package in R to build the model. Covariate effects (age, BMI (Body Mass Index), smoking history related covariates) were tested on probabilities pij, but only significant ones—smoking duration and exposure to additional carcinogens (silica, cadmium, arsenic, beryllium, diesel, nickel, coal smoke, soot, asbestos, cannabis)—were included.

Results: Table 1 presents the model-predicted and observed prevalence of each state at each time point.

Table 1: Observed vs Expected prevalences

		t_0	t_1
Observed	**State 1 (n (%))**	565 (100)	549 (97.2)
	State 2 (n (%))	0	16 (2.8)
Expected	**State 1 (n [95% CI] (% [95 % CI]))**	565 (100)	549 [538-555] (97.2 [95.2-98.2])
	State 2 (n [95% CI] (% [95 % CI]))	0	16 [10-27] (2.8 [1.8-4.8])

Smoking duration and additional carcinogen exposure significantly increased the risk of moving from state "At risk" to "Lung Cancer" (impact on p12) (HRsmoking_duration (Hazard Ratio): 2.39 [95% CI: 1.35-4.22], HRcarcinogens: 3.05 [95% CI: 1.14-8.21]). Age and BMI modified significantly this risk when analyzed independently (HRage = 2.02 [95% CI: 1.12-3.64], HRBMI = 0.5 [95% CI: 0.29-0.88]) but were excluded from the model due to its high correlation with smoking duration.

Conclusions: Markov chain modeling is a novel longitudinal and dynamic approach to stratify lung cancer risk. Our model demonstrated the benefits of incorporating risk factors like additional carcinogen exposure, and smoking duration to refine risk-based screening. External validation is needed to assess its role in optimizing screening, decision-making and patient participation before clinical implementation.

Keywords: Lung Cancer Screening, Markov Model, Diagnostic

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.40 Improving Lung Cancer Risk Prediction in Asbestos Exposed Individuals: The AQC Ensemble Model

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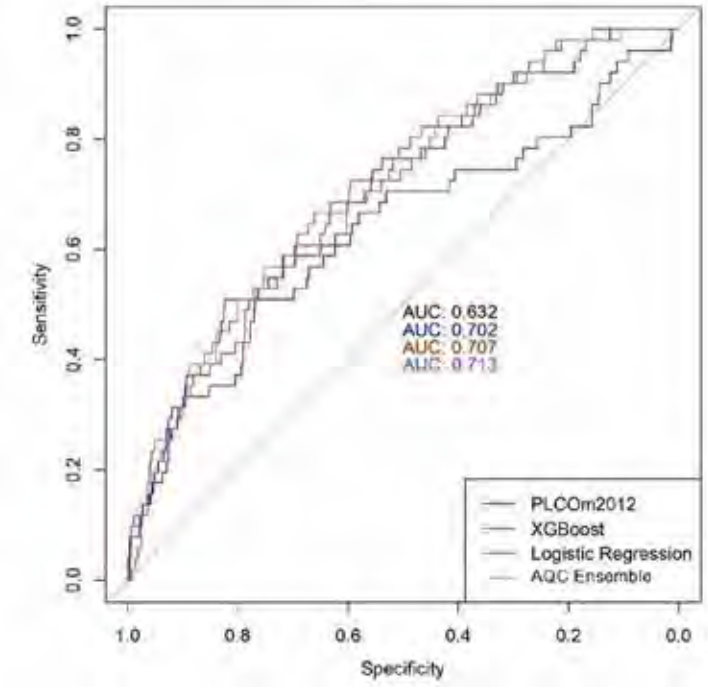
Introduction: Lung Cancer (LC) screening effectiveness is dependent on selecting an appropriate high-risk population. Current risk models underestimate LC risk in asbestos exposed populations, by not accounting for the increased relative excess risk by interaction (RERI) between asbestos and tobacco exposure. The aim of this study was to develop a LC risk model for asbestos exposed populations using a machine learning approach, with external validation.

Methods: Training cohort: 3,258 individuals (162 LCs) from the United States City University of New York (Queen's College) Multisite Cancer Screening Program; External vValidation cohort: Western Australian Asbestos Review Program, 1,357 individuals (51 LCs). Both populations were similar with occupational asbestos exposure, male predominance and comprised mostly of former tobacco users. Variables for risk prediction included: age, sex, smoking duration, smoking intensity, time since quit smoking, education level, self-reported chronic obstructive pulmonary disease, personal history of cancer, family LC history and time since first exposure to asbestos (latency).We developed an ensemble machine learning model (AQC ensemble), combining a parametric logistic regression model and a non-parametric eXtreme Gradient Boosted Tree (XGBoost) model. All models were benchmarked against the PLCOm2012 risk model. AUC-ROC was the primary metric for comparison. The best performing parametric and non-parametric models were combined using Bayesian weighted averaging to generate the final AQC ensemble model's predictions.

Results: Logistic regression demonstrated similar predictive performance in validation (AUC: 0.7067; 95% CI: 0.6369 - 0.7765) over XGBoost (AUC: 0.7021; 95% CI: 0.6284-0.7758). The AQC ensemble model had stronger performance than both comprising models (AUC: 0.7123; 95% CI: 0.6408-0.7838), and the PLCOm2012 model (AUC: 0.6325; 95% CI 0.5432-0.7218). Mean calibration indicated that the AQC ensemble model was well calibrated in the US development cohort, but overestimated risk in validation cohort.Model interpretation using Shapley values indicated that smoking duration was the most impactful variable in the AQC model's predictions, with asbestos exposure latency being the fourth most impactful variable, closely followed by age.

Conclusions: The AQC model is the first LC prediction model to account for the RERI of asbestos and tobacco exposure and performs well in occupationally exposed populations. Given the widespread asbestos exposure in many countries and the resultant interaction of risk with tobacco exposure, the AQC's performance highlights a potential role for cohort specific models in LC screening selection. Further external validation is required.

Figure 1. ROC curves comparing the discriminative performance of the $PLCO_{m2012}$, the best performing Logistic Regression Model, the best performing XGBoost Model and the AQC ensemble model in predicting LC incidence in ARP validation cohort.



Keywords: Lung Cancer Screening, Risk Prediction, Asbestos Exposure

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.41 Survival Differences Following Surveillance Detected Vs. Symptom Detected Recurrence in Patients With Lung Cancer

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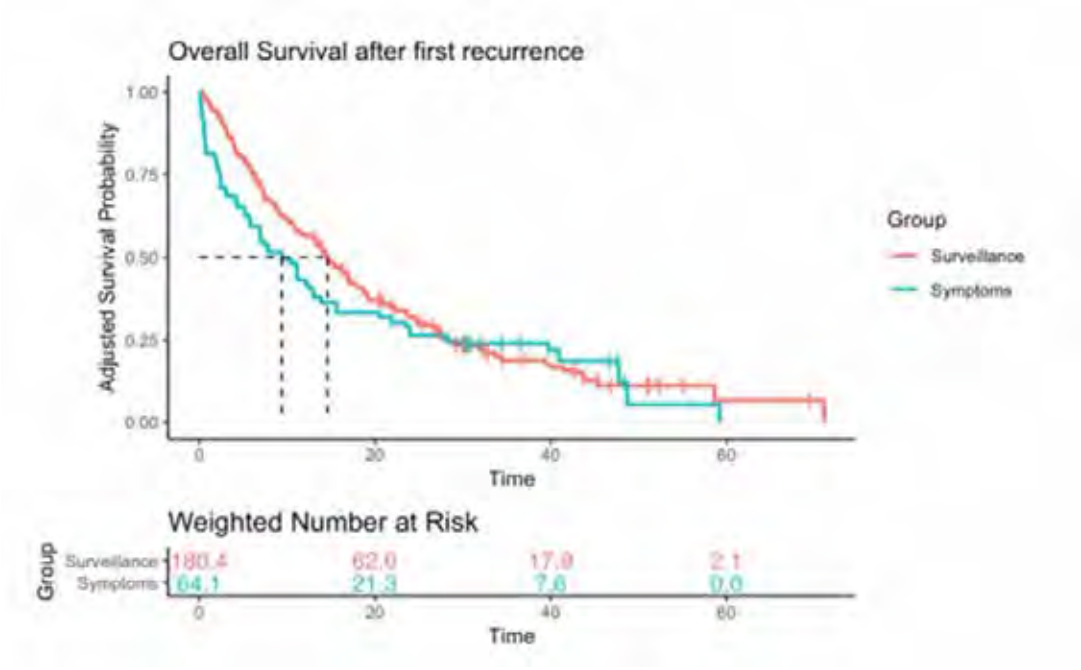
Introduction: Follow-up care for lung cancer patients consists of a one-size-fits-all surveillance method of thoracic CT-scans every six months. This routine follow-up can be a source of anxiety for patients, often lasting several weeks before the scheduled imaging. Moreover, literature shows that many patients who experienced a recurrence already had symptoms in retrospect. Currently, it is unclear if a surveillance method completely based on symptoms would result in different survival outcomes. Therefore, this study examined differences in overall survival (OS) after scheduled versus symptom-based surveillance in patients with lung cancer.

Methods: Data from the SYMPRO-Lung study were used to assess OS differences between surveillance-based versus symptom-based recurrence detection. In the SYMPRO-Lung study, the effect of patient-reported symptom monitoring on health-related quality of life and OS in stage I-IV lung cancer was assessed. The detection method of recurrences during follow-up (scheduled versus symptom) were extracted by the National Cancer Registry and was based on the review of radiology and electronic health record reports. Cox proportional hazards analysis was used to assess differences between scheduled versus symptom-based surveillance on OS, corrected for confounding. Sensitivity analyses were performed to assess OS differences in time to secondary recurrence. In all analyses, we adjusted for age, stage, histology, and treatment.

Results: A total of 444 patients were included of whom 244 (55%) patients developed a recurrence during median follow-up of 46 months. Of these, 181 (74%) recurrences were detected with scheduled follow-up and 63 (26%) were detected after patients contacted the hospital due to symptoms. No statistically significant differences in baseline characteristics were observed between the two groups. Median OS after first recurrence was 14.5 months (IQR: 6.2-28.1) in the surveillance-based group versus 10.4 months (IQR: 2.4-29.4) in the symptom-based group (p= 0.4). After correction for confounding, no significant differences were observed in OS (HR 1.18, 95%CI 0.85-1.63) (Figure 1) neither for time to secondary recurrence (HR 0.63, 95%CI 0.36-1.09).

Conclusions: No differences in OS were observed between patients in whom recurrences were detected via scheduled-based follow-up compared to patients in whom recurrences were detected via symptom-based follow-up. These results might indicate that a symptom-based surveillance strategy using patient-reported symptom monitoring may be as effective (and logistically less intensive) compared to the current one-size-fits-all scheduled surveillance strategy. Nonetheless, more research needs to be performed to validate these findings in larger cohorts.



Keywords: Lung cancer, Surveillance

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.42 Circulating Tumor Cells Combined With Solid Nodular Ratio to Predict High-Risk Pathological Subtypes of Stage Ia Lung Adenocarcinoma

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Introduction: This study aims to analyze the relationship between circulating tumor cells (CTCs) and the clinical, imaging, and pathological characteristics of patients with stage pre-IA and IA lung adenocarcinoma. And to preliminarily explore the significance of CTCs detection in the surgical treatment.

Methods: A retrospective analysis was conducted on 130 cases diagnosed with pre-stage IA or stage IA pulmonary adenocarcinoma and 25 cases with benign pulmonary lesions, all treated by surgical resection from April 2018 to January 2021. All cases were solitary pulmonary nodules. Preoperative peripheral venous blood samples were collected from each patient for CTCs detection. Tumor cells were enriched using magnetic microparticle technology, and in situ fluorescence hybridization (FISH) was employed for identification and quantification. We compared the pathology and imaging features between CTCs-positive and CTCs-negative groups. Patients were categorized based on the degree of pathological infiltration. Univariate and binary logistic regression analyses were conducted, and Receiver Operating Characteristic curves were generated to develop a predictive model for identifying pathological subtypes of stage IA lung adenocarcinoma. Additionally, a three-year postoperative follow-up was performed to assess survival differences between groups, with Kaplan-Meier curves plotted.

Results: 1.Statistically significant differences were found between the CTC-positive and CTC-negative groups regarding patient age, lesion size, fluorodeoxyglucose (FDG) uptake, and the presence of high-risk pathological subtypes. No significant differences were observed in coagulation function or pulmonary tumor markers. Multivariate analysis revealed that with elevated FDG uptake were three times more likely to have CTCs. 2.No significant difference in CTCs positivity rates was noted between the adenocarcinoma in situ (AIS) group and the stage IA lung adenocarcinoma group. However, significant differences in CTCs positivity rates were found between the benign lesions and lung adenocarcinoma, as well as between groups with high-risk pathological subtypes. 3.Significant differences in CTCs positivity rates, smoking history, lesion size, FDG uptake levels, and consolidation/tumor ratio (CTR) were observed between groups with and without high-risk pathological subtypes. Notably, CTCs positivity and a CTR greater than 50% were identified as independent risk factors for high-risk pathological subtypes. The ROC curve analysis demonstrated a predictive AUC of 0.867 (95% CI: 0.783-0.952) for determining the presence of high-risk subtypes. 4.During the follow-up period, there were 2 cases of recurrence after radical surgery (1.54%), with 8 new lesions (6.15%) surgically removed. Patients with high-risk subtype were more likely to develop new lesions within three years post-surgery (p=0.04). No significant difference in three-year survival data was found between patients with preoperative CTC-positive status.

Conclusions: The metabolic activity in lesions of CTCs-positive patients may be higher than that in CTCs-negative lesions. A model combining CTC positivity and lesion solid ratio can accurately predict the presence of high-risk pathological subtypes in stage IA lung adenocarcinoma, offering valuable guidance for surgical approaches. Furthermore, patients with high-risk pathological subtypes may have an increased risk of requiring secondary surgeries within three years, while the predictive value of preoperative CTCs for survival outcomes appears limited.

Keywords: Circulation tumor cells, Stage IA lung adenocarcinoma subtype, Diagnostic model

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.43 Evaluating the Role of Digital Tomosynthesis in Lung Cancer Screening: A Cost-Effective Alternative to Annual LDCT in Resource-Limited Settings

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Introduction: Annual low-dose computed tomography (LDCT) screening has been shown to reduce lung cancer mortality. However, the cost of implementing such programs may be prohibitive in resource-limited settings. Chest digital tomosynthesis (DT), a lower-cost imaging modality with high sensitivity and specificity for pulmonary nodule detection, may offer a viable alternative. Alternating LDCT with DT could maintain early detection rates while reducing overall screening costs.

Methods: In this 5-year prospective study, 634 high-risk individuals (current or former smokers with >30 pack-years), aged 50-70 years, were enrolled between July 2012 and January 2014 at Chulabhorn Hospital, Thailand. All participants underwent baseline LDCT (T0). Those with normal lung findings or stable lesions after two years were followed annually using alternating DT and LDCT. Participants with abnormal findings at any point received LDCT follow-up.

Results: A total of 634 participants underwent initial LDCT screening. Of these, 187 participants with normal baseline findings received DT at year 1 (T1), and 427 participants with stable lung findings after two years received DT at year 3 (T3). All participants received LDCT at years 2 and 4, with additional LDCT as needed based on findings. Lung cancer was diagnosed in 22 participants: 50% at stage I, 18.2% at stage II, 9.1% at stage III, and 22.7% at stage IV. The proportion of stage I lung cancer detected (50%) is comparable to prior randomized controlled trials using annual LDCT, which reported detection rates ranging from 36% to 63%.

Conclusions: A lung cancer screening protocol alternating DT with biennial LDCT demonstrated a similar proportion of stage I diagnoses as annual LDCT programs. In resource-limited settings, DT may be a practical and cost-effective alternative for early lung cancer detection.

Keywords: Lung cancer screening, Low-Dose Computed Tomography (LDCT), Digital tomosynthesis

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.44 Clinical Efficiency of Repeat CT-Guided Transthoracic Needle Biopsy of Peripheral Lung Lesions

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Introduction: Transthoracic CT-guided needle biopsy (CT-TNB) of peripheral pulmonary nodules (PPN) is still method of choice for morphologic diagnosis verification nevertheless false negative and non-diagnostic results are often complicate decision process (the management of this patients). Hereby we present results of repeat biopsies of PPN with real life efficiency and sensitivity of the procedures.

Methods: In period from January 2022 to December 2024 CT-TNB was performed in 504 cases for 478 patients. Following primary non-diagnostic results repeat biopsy was done in 26 (5,16%, 95%CI: 3,54-7,45) patients with suspicion of primary lung cancer and metastatic disease in 32 and 10 cases respectively. All procedures were performed using 18G needles. Median age was 68 (63; 77) years (range 36 - 92 years) with male predominance 26/16. PPN's size distribution to less or more than 20 mm and GGO were as follows: 7, 18 and 1 respectively. Solitary and multiple nodules were presented in 25 and 17 cases respectively. 3 biopsies were performed under the stepwise approach, 8 with the SIRIO navigation system, 15 with CT fluoroscopy control.

Results: Morphologic results were obtained in 20 (76,1%) cases after repeat biopsies (95%CI: 57,95 - 88,97): small cell lung cancer (n=1), Adenocarcinoma (n=7), SCC (n=6), pulmonary fibrosis (n=1), non-differentiated carcinoma (n=1) and metastatic tumors (n=4) were established. Sensitivity, specificity and accuracy for repeat biopsies were 100%, 76,6% and 77,4% respectively. Treatment routing was monitored for 20 patients: Chemotherapy (n=5), CRT (n=2) and Surgery (n=13) were carried out. Follow up was proposed for 6 patients with repeated non-diagnostic results of which in 2 cases lesions were regressed during the first and after 12 month in 3 and 4 cases respectively, one patient was referred to chemo-radiation following strongly suspicion of local tumor recurrence without final confirmation after twice repeat biopsies.

Conclusions: Repeat biopsy of PPN after non-diagnostic results of CT-TTB is informative in more than 50% of cases and is indicated for patients with strongly suspicious of malignant tumor before start of the treatment.

Keywords: Transthoracic CT-guided needle biopsy, peripheral pulmonary nodules, lung cancer

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.45 Multi-Center Validation of a Circulating 9-microRNA Signature for Lung Cancer Early Detection

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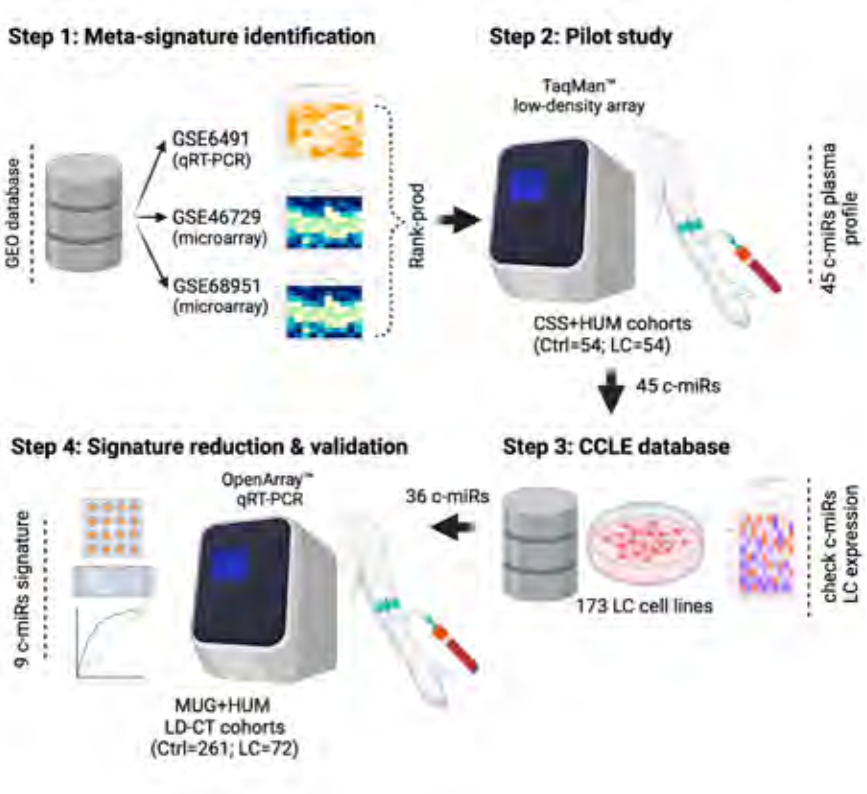
Introduction: Lung cancer remains the leading cause of cancer-related deaths worldwide. Low-dose computed tomography (LD-CT) screening is effective, and combined with effective minimally invasive molecular testing such as circulating microRNAs (c-miRs), it has the potential to further reduce the burden of lung cancer. However, the clinical application of c-miRs requires further validation across diverse patient cohorts from different countries.

Methods: In this study, we present a plasma signature of 9 c-miRs derived from a robust multi-platform workflow with a multi-center design (Figure 1). We first analyzed publicly available c-miR datasets from 150 lung cancer (LC) patients and 136 non-cancer controls (STEP-1), identifying 321 shared c-miRs. Using RankProd meta-analysis, we found 45 differentially expressed c-miRs. We then validated these 45 c-miRs in a case-control cohort of plasma samples form 54 LC patients and 54 non-cancer controls (STEP-2). Next, we cross-checked intracellular expression of c-miRs in 173 LC cell lines to support specificity and assessed their impact on LC risk (STEP-3). We finally analyzed plasma samples from a total of 72 LC and 261 non-cancer controls from two European LD-CT screening cohorts (Medical University of Gdańsk, Gdańsk, Poland; Humanitas Clinical and Research Center, Milan, Italy) to refine a validate the plasma 9 c-miRs signature (STEP-4).

Results: The classification performance of the signature was high in the two screening cohorts, with an AUC of 0.78 (Sens 0.76; Sp 0.67; Accuracy 0.70), and an AUC of 0.75 (Sens 0.82; Sp 0.68; Accuracy 0.71) in the Polish and Italian cohorts, respectively. The diagnostic accuracy of the signature was independent and not influenced by age, gender, smoking (status and intensity), nodule size, and density. Additionally, the signature detected stage I lung cancer, with an AUC of 0.76 (95%CI: 0.68-0.84) and 0.69 (95%CI: 049-0.89) in the Polish and Italian cohorts respectively and a predictive ability of 0.63-73. Finally, the signature discriminated benign from malignant nodules with an AUC of 0.71 (95%CI: 0.58-0.84).

Conclusions: The proposed panel of nine circulating miRNAs serves as a robust and precise diagnostic tool, which could further improve effectiveness of LD-CT screening program. We plan to validate our signature in a cohort of 277 patients at the Fred Hutchinson Cancer Center in the U.S. This extensive validation of our c-miR-based test in screen-detected tumors across multiple, independent cohorts highlights the uniqueness of our study and further supports its clinical utility.



Keywords: microRNA, liquid biopsy, early detection

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.46 Predicting Malignancy in Ground-Glass Opacity Using Multivariate Regression and Deep Learning Models: A Proof-Of-Concept

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Introduction: Background: Ground-glass opacification (GGO) refers to areas of increased lung opacity on computed tomography (CT) scans. Distinguishing malignant from benign lesions using CT remains a significant challenge. This study aims to apply a multivariate statistical regression model and deep learning methods based on pixel features extracted from CT scans to predict malignancy and compare the performance of these two models.

Methods: This retrospective study included 72 patients from Carmel Medical Center who had GGOs. Of these, 46 patients met the criteria for pure GGO, as defined by two independent radiologists. After manually segmenting the GGOs on the CT scans, pixel features were extracted using the MaZda software package, which analyzes six different image texture features. These textural variables were then used as input for the multivariate statistical regression model. Additionally, a deep learning model, developed by our group and hosted on the cloud, was applied using the CT images containing the GGOs.

Results: Among the 46 patients, 35 were diagnosed with malignant lesions and 11 with benign findings. Using the multivariate statistical regression model, we identified 26 variables with significant or near-significant differences through univariate analysis. In subsequent multivariate analysis, two independent variables were identified: S(4,4)AngScMom (p = 0.012) and WavEnLH_s-2 (p = 0.008). The formula based on these two variables yielded a sensitivity of 91% and specificity of 67%. The deep learning model demonstrated a sensitivity of 100% and specificity of 80%.

Conclusions: This proof-of-concept study demonstrates the superior performance of the deep learning model compared to the multivariate statistical regression model, particularly in terms of sensitivity and specificity. However, given the small sample size, these results could potentially improve with larger patient cohorts.

Keywords: Ground-Glass Opacity, multivariate statistical regression model, Deep Learning Model

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.47 Breathomics Meets Deep Learning: A Novel Approach for Early Detection of Lung Cancer

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Introduction: Lung cancer (LC) is one of the most common malignant cancers worldwide representing the leading cause of death. Tobacco smoking is the main aetiological factor in lung carcinogenesis, but long-term exposure to air pollution and genetic susceptibility may play a role. In the last few decades , the diagnosis and therapies of LC have shown great improvement, but its clinical management is still challenging due to diagnosis mainly at advanced stages. Thus, there is an ever-increasing need to develop innovative, easy-to-use, and non-invasive diagnostic methodologies to implement within large-scale screening protocols to enable early detection and improve the management and clinical outcome . Recently, the volatile organic compounds (VOCs) analysis in exhaled breath, known as breathomics, has showed to be promising to identify disease-specific metabolic signatures. In this study, we analysed breath samples to detect and characterize by deep learning the breath fingerprint of patients with lung cancer.

Methods: 195 participants were recruited : 114 patients affected by LC and 81 healthy controls (HC). The method is based on sampling of end-tidal breath directly onto two-bed adsorbent cartridges (Biomonitoring steel tubes, Markes International) by means of automated sampler Mistral (Predict srl). Ambient air samples (AA) were collected at each sampling . Breath samples were thermally desorbed (Unity Ultra-xr Markes) and analysed by Gas Chromatography/Mass Spectrometry (GC Agilent 7890/MS Agilent 5975). Ion channels were acquired across a mass-to-charge (m/z) range from 35 to 250 with unit mass resolution. The instrument operated at a scanning frequency of approximately 3.31 Hz, resulting in around 8805 retention time (RT) points over a period of 44 minutes. Each sample was represented by a matrix dimension of R × 216, where R ≈ 8805. . All experimental temporal scans have been preprocessed using Gaussian smoothing and Savitzky-Golay filtering to increase the signal-to-noise ratio. To reduce the huge amount of experimental data, for each subject, the 216x8805 preprocessed data points have been converted into 2D images in which each pixel is associated with a (m/z, RT) pair and whose color depends on the intensity of the chromatogram signal. Subsequently, these 2D images have been embedded in an Artificial Intelligence workflow to implement a classifier that can distinguish between patients with LC and healthy controls.

Results: A preliminary classification of the images using Decision Tree, Random Forest, and Convolutional Neural Network (CNN) algorithms, performing a 10-fold repeated 5-fold cross-validation, was obtained. The best results have been achieved with CNNs, with both a mean AUC and a balanced accuracy over 0.90 within errors over the 100 iterations of the workflow.

Conclusions: The proposed models demonstrated superior performance compared to conventional expert-driven methodologies, enabling more accurate and efficient classification between healthy individuals and patients with lung cancer, while maintaining high specificity. These findings highlight the potential of this data-driven approach to advance breath-based diagnostic strategies by improving group differentiation, optimizing analytical processes, and facilitating scalable and cost-effective implementation in clinical practice.

Keywords: Volatile organic compounds, Breath analysis, Deep Learning

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.48 Rapid Intra-Operative Detection of Visceral Pleural Invasion in Non-Small Cell Lung Cancer Using Label-Free Multiphoton Microscopy

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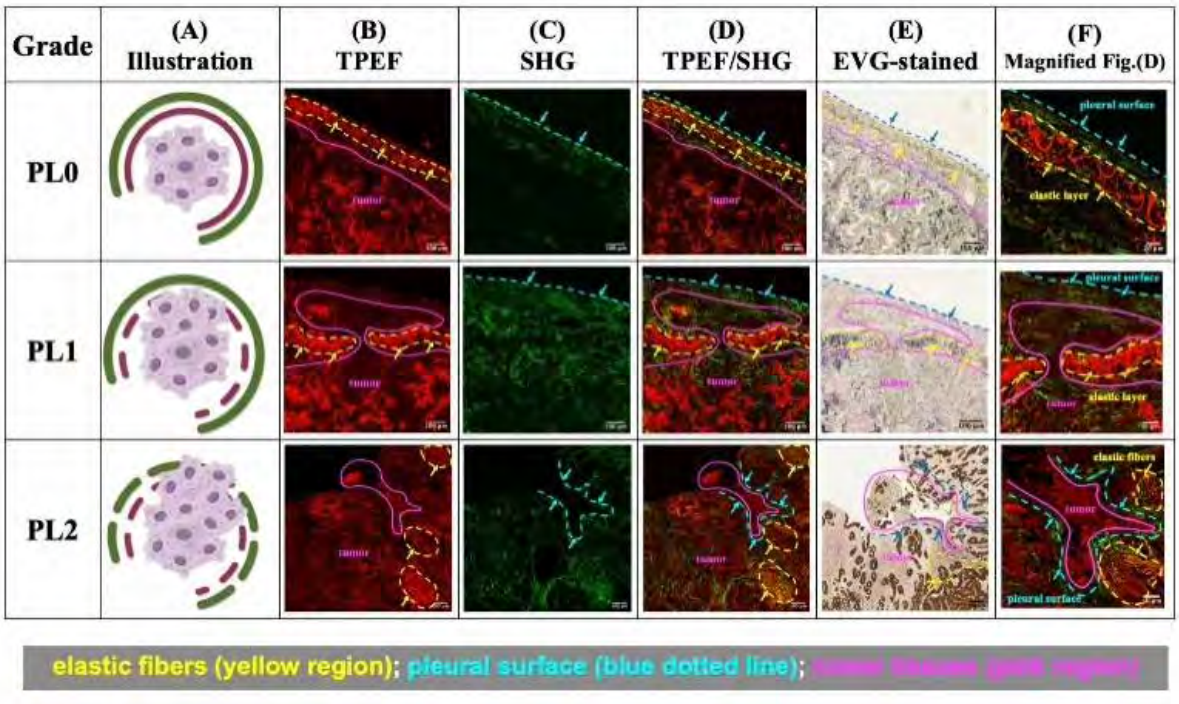
Introduction: Visceral pleural invasion (VPI) constitutes a significant pathological factor in non-small cell lung cancer (NSCLC). The rapid and accurate intraoperative assessment of VPI might be important for determining the appropriate extent of surgical intervention and may contribute to improved disease-free and overall survival rates. However, current intraoperative diagnostic methods for VPI lack reliability. Multiphoton microscopy (MPM) offers promise due to its label-free imaging capabilities and potential for in vivo applications. Therefore, this study aims to investigate the potential of label-free MPM for imaging lung cancer tissues, pleura, and the status of VPI.

Methods: This study analyzed 83 formalin-fixed paraffin-embedded NSCLC specimens, each containing both tumor regions and adjacent pleural tissues. Specimens were stratified by VPI status according to Hammar grading criteria: PL0 (no invasion, n=50), PL1 (elastic layer penetration, n=25), and PL2 (full-thickness pleural infiltration, n=8). Each specimen was sectioned into two serial 10-μm-thick slices: one underwent label-free multiphoton microscopy (MPM) capturing TPEF/SHG signals, while the adjacent slice received Elastica van Gieson (EVG) staining.A board-certified thoracic pathologist first delineated regions of interest (ROIs) containing tumor-pleural interfaces on EVG-stained sections. Two independent pathologists blinded to EVG results evaluated elastic layer integrity and tumor infiltration patterns in MPM datasets, classifying cases into PL0/PL1/PL2 categories. Diagnostic accuracy was calculated by comparing MPM-based assessments with gold-standard EVG-determined VPI status.

Results: Our study systematically validated the diagnostic potential of MPM in visualizing pleural elastic architecture and tumor invasion. The figures present MPM images of lung tissues alongside their corresponding EVG-stained images. MPM-based two-photon excited fluorescence (TPEF) demonstrated high specificity for elastin fibers within pleural tissues. As shown in Figure(B), TPEF signals (color-coded red) exhibited precise correspondence with EVG-stained elastic fibers (yellow regions). The dense, curvilinear architecture of elastic fibers in visceral pleura was clearly delineated by MPM without exogenous labeling.Furthermore, lung cancer cells were identified via intrinsic TPEF signals from NADH and FAD, exhibiting bright cytoplasmic fluorescence and non-fluorescent nuclei (pink regions). In conclusion, MPM effectively visualized the relationships between cancer cells and the visceral pleura elastic layer and parietal pleura, providing equivalent identification capability to EVG staining.

Conclusions: Our findings demonstrate that MPM technology can rapidly and accurately detect VPI in lung cancer. This capability may assist thoracic surgeons in making quick intraoperative decisions regarding the extent of the surgery for patients.



Keywords: Visceral Pleural Invasion, Multiphoton Microscopy, Label-free

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.49 Targeting VEGFR3 Nir Fluorescent Probe for Identification of NSCLC Metastatic Lymph Nodes an Exploratory Study on Surgical Navigation

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Introduction: Lymph node metastasis in non-small cell lung cancer (NSCLC) significantly impacts prognosis, yet current imaging modalities (CT/PET-CT) lack sensitivity for micrometastases. VEGFR3, a key regulator of lymphangiogenesis, is overexpressed in metastatic NSCLC, offering a molecular imaging target. This study developed a VEGFR3-targeted NIR-II fluorescent probe (VEGFR3-ICG) to enhance intraoperative identification of metastatic lymph nodes (LNs), leveraging NIR-II imaging's superior tissue penetration (8mm vs. NIR-I 6mm) and high signal-to-noise ratio.

Methods: VEGFR3-ICG was synthesized by conjugating a VEGFR3-specific peptide (NH2-CGLARGRGC) with indocyanine green (ICG) via solid-phase synthesis. Purity and structure were validated by HPLC and mass spectrometry. Optical properties were assessed via absorption/emission spectra and tissue penetration assays. Cytotoxicity was evaluated in HUVECs and NSCLC cell lines (LLC, A549, H1703) using CCK-8 and acute toxicity tests in mice. VEGFR3 expression was confirmed by Western blot, and probe uptake was analyzed via flow cytometry. Subcutaneous tumor and LN metastasis mouse models were established for in vivo imaging, with tumor/background ratio (TNR) and positive/negative LN ratio (PNR) quantified. NIR-II-guided surgical resection was performed, followed by histopathological validation. Human NSCLC specimens were incubated with the probe for ex vivo imaging correlation.

Results: The VEGFR3-targeted NIR-II probe VEGFR3-ICG demonstrated high specificity and safety in NSCLC applications. With a penetration depth of 8 mm (NIR-II) and spatial resolution of 58-59 μm (FWHM), it achieved superior optical performance compared to conventional NIR-I imaging. At 20 μM, cell viability exceeded 90% in NSCLC cell lines (A549, LLC, H1703), and acute toxicity studies in mice confirmed no significant biochemical or histopathological abnormalities. VEGFR3 expression in NSCLC cells was 3.2-fold higher than in HUVECs ($P<0.01$), driving a 40% increase in probe uptake versus non-targeted ICG ($P<0.05$). In vivo, VEGFR3-ICG exhibited a tumor/background ratio (TNR) of 5.704 in A549 tumors and a positive/negative lymph node ratio (PNR) of 2.224 in metastatic lymph nodes (both $P<0.01$ vs. ICG). Clinical validation using ex vivo human NSCLC specimens revealed strong concordance between TNR/PNR and histopathology ($P<0.01$), confirming its diagnostic accuracy for metastatic LN identification.

Conclusions: VEGFR3-ICG is a novel NIR-II probe with high specificity, safety, and translational potential. It enables precise intraoperative identification of NSCLC metastatic LNs, addressing the limitations of conventional imaging. This technology may revolutionize LN dissection strategies and improve surgical outcomes.

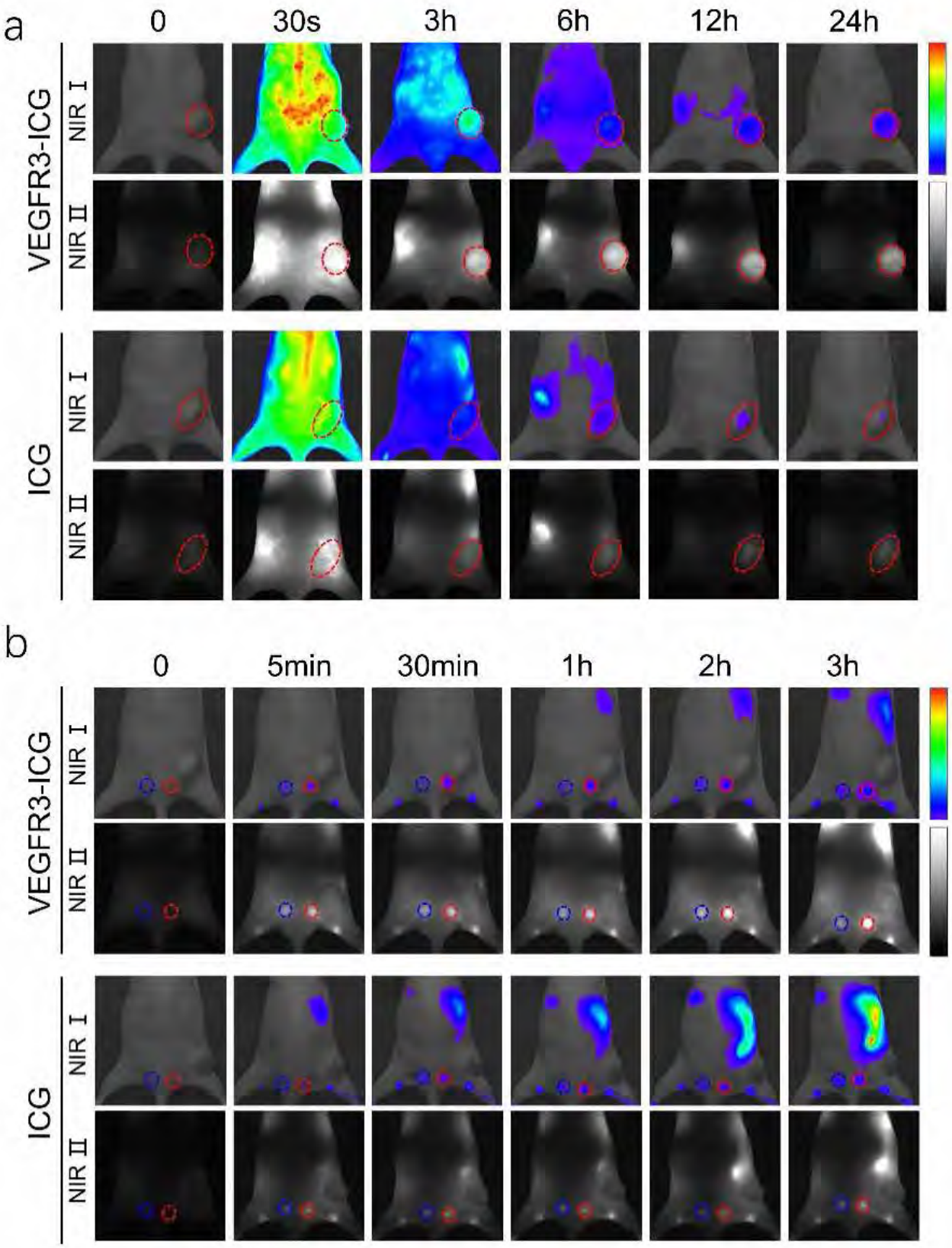

Figure 1. VEGFR3-ICG enables precise identification of Tumor and metastatic lymph nodes. a. NIR I/II imaging of A549 tumor-bearing mice after intravenous injection of ICG and VEGFR3-ICG; b. NIR I/II imaging of A549 lymph node metastasis-bearing mice after bilateral footpad injection of ICG and VEGFR3-ICG;

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.50 Fluorescein-Free Confocal Laser Endomicroscopy for Intraoperative Diagnosis of Pulmonary Nodules: A Comparative Study With Frozen Section

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Introduction: Since low-dose CT (LDCT) screening has increased detection of sub-centimeter pulmonary nodules, 10-20% of indeterminate lesions still require invasive procedures for definitive diagnosis. Current intraoperative frozen section (FS) analysis faces challenges in traumatic biopsy and time delays (30-45 minutes processing). This study aimed to evaluate a novel fluorescein-free confocal laser endomicroscopy (CLE) system for real-time intraoperative diagnosis during minimally invasive thoracic surgery.

Methods: Prospective analysis of consecutive patients undergoing VATS resection for radiologically indeterminate nodules at a tertiary thoracic center. Resected specimens underwent systematic ex vivo CLE imaging with standardized protocol: 1) Anatomical orientation 2) Dual-region scanning (lesion-normal interface) 3) 10-field video capture (>20 seconds recording). Two blinded thoracic pathologists evaluated cellular features using validated criteria. Pathological subtype evaluation was also predicted synchronously. Subsequent intraoperative FS evaluation was performed on the same nodules. According to paraffin section, the diagnostic performance of CLE was compared with preoperative CT and FS.

Results: All procedures were successfully completed without fluorescein, yielding high-quality video data from all 44 nodules (39 malignancies, 4 inflammatory lesions, 1 benign tumor) with no adverse events. CLE demonstrated 93.2% diagnostic accuracy (38/41) malignancies with 97.4% sensitivity and 60% specificity. Compared to preoperative CT, CLE is significantly better than conventional CT (70.5%, $p<0.01$), In 5/44 (11.4%) FS-indeterminate cases, CLE provided definitive diagnoses concordant with final histology. Real-time pathological subtyping was achieved in 28/41 (68.3%) cases.

Conclusions: In this first-in-human study, Fluorescein-free CLE was implemented as a real-time adjunct to FS analysis which provided comparable diagnostic accuracy. The potential advantage of CLE intraoperative diagnosis for patients with early-stage lung cancer lies in the resolution of FS uncertainties and the enabling of immediate histologic subtyping. Further multicenter studies are needed to establish a CLE-guided decision-making procedure for precision thoracic surgery.

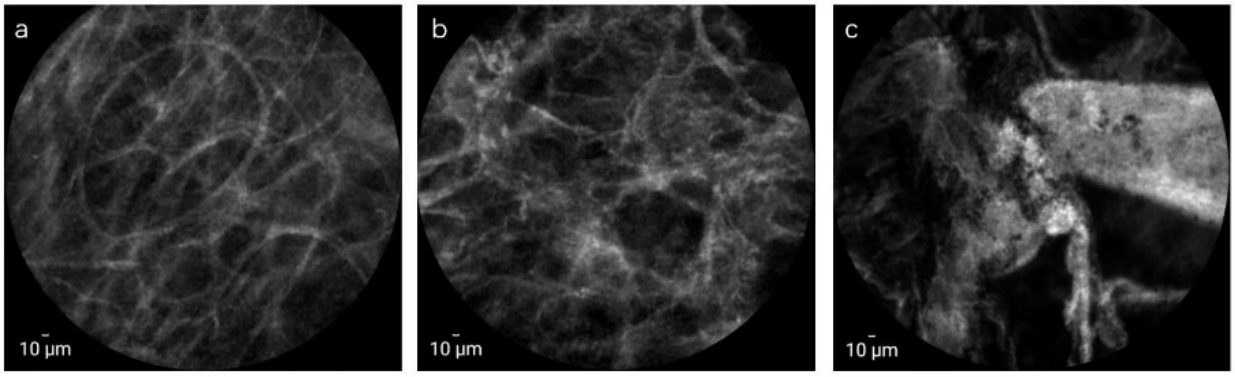

Figure 1: (a) **Normal lung tissue :** Alveolar structure is regular and uniformly sized. The alveolar wall, composed of a single epithelial layer, shows uniform thickness with a smooth surface and no notable tortuosity or thickening.(b) **Malignant nodules :** It exhibit collapsed alveolar structures with thickened, tortuous walls, marked architectural disorganization in surrounding tissue, and aggregated high-signal cell clusters.(c) **Benign nodules :** Alveoli display smooth epithelium and uniformly thin walls without thickening/tortuosity, surrounded by homogeneous tissue with patchy fibrin deposits and no atypia.

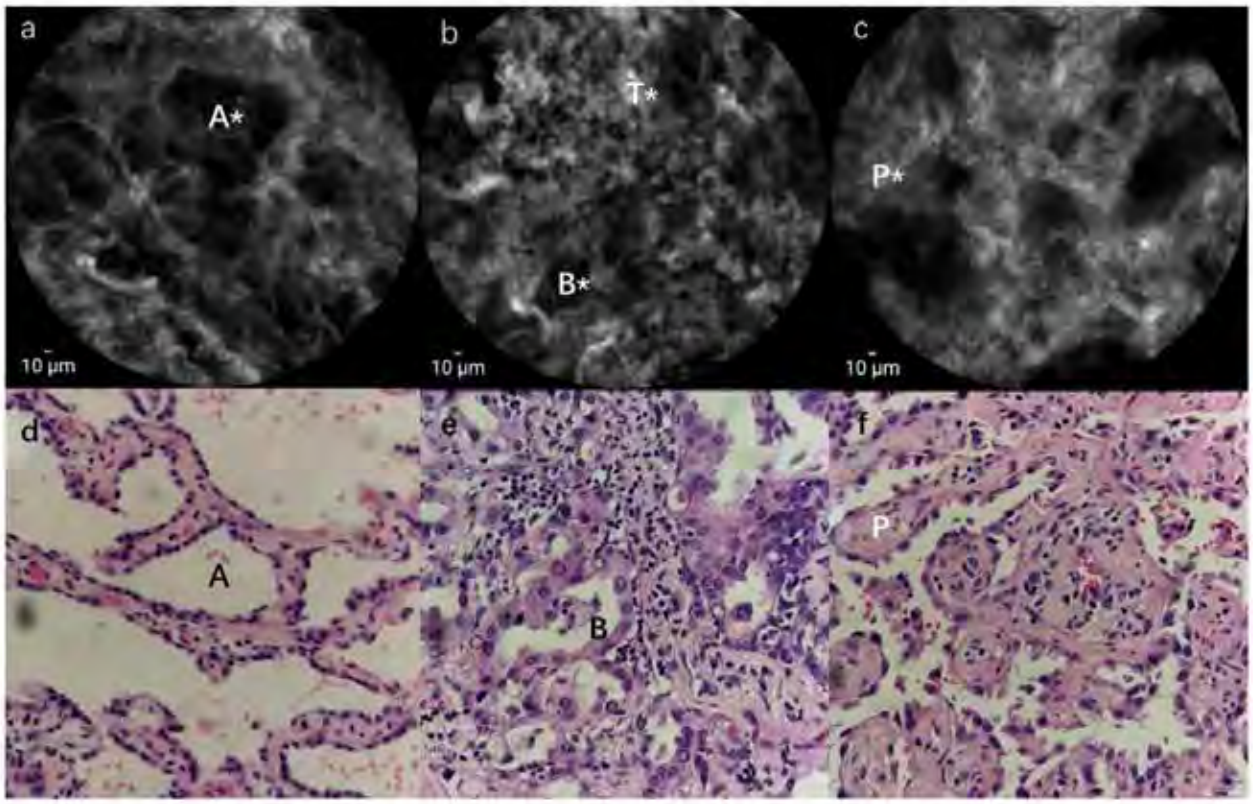

Figure2 : (a、d) **Minimally invasive adenocarcinoma:** CLE and paraffin sections showed collapsed alveoli (A/A*) with mildly thickened walls featuring atypical heterotypic cells and high-signal cell clusters, yet preserved alveolar structure. (b、e) **Acinar-predominant adenocarcinoma:** Tumor infiltrates alveoli, showing high-signal cell clusters (T*) and diagnostic low-signal acinar cavities (B*), that confirm acinar structures(B). (c、f) **Papillary-predominant adenocarcinoma:** CLE shows medium-signal papillary patterns (P/P)* with cell clusters and characteristic peripheral low-signal zones, diagnostic of papillary-predominant adenocarcinoma.

Keywords: Lung cancer, Confocal laser endomicroscopy, Intraoperative diagnosis

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.51 Exploring the Potential of Multimodal Cough Analysis as a Pre-Screening Tool for Non-Small Cell Lung Cancer Detection

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Introduction: Lung cancer screening with low-dose chest CT enhances early detection but comes with high costs and radiation exposure. Moreover, radiological screening for NSCLC primarily targets smokers, leaving non-smokers with limited screening options. Although early diagnosis is crucial, it often occurs at advanced stages. While immunotherapy (IO) holds promise, its long-term benefits are limited to certain patients. Cough, a common symptom of lung cancer, gained attention as a digital biomarker for lung-related diseases during the COVID-19 pandemic. However, its potential remains largely untapped in the NSCLC landscape. The I3LUNG project (NCT05537922) explores AI-based cough analysis as a non-invasive method to distinguish NSCLC patients on IO from healthy individuals. Using machine learning, we aim to develop an accessible, cost-effective pre-screening tool to enhance detection and complement radiological methods.

Methods: Cough recordings were collected from 91 stage IIIB-IV NSCLC patients undergoing IO and 109 healthy individuals, forming a dataset of 200 samples. Preprocessing steps included background noise removal and automatic cough segmentation. An early-fusion multimodal approach was implemented. A total of 39 acoustic features in the temporal and frequency domains were extracted. Then, the set of features was enriched with embeddings extracted from a convolutional neural network (CNN) trained on MFCC-based spectrograms. These embeddings were then reduced in dimensionality using Principal Component Analysis (PCA) while preserving 98% of their variance. The dataset was split into 60% training, 30% validation, and 10% testing. Feature selection was performed using LASSO, and a Support Vector Machine (SVM) classifier was optimized via grid search with a hold-out method. To evaluate performance, three models were compared: a unimodal SVM (acoustic features only), a unimodal CNN classifier (MFCC-based spectrograms only), and an early fusion multimodal model combining acoustic features and CNN-extracted embeddings.

Results: The unimodal SVM model achieved an F1-score of 71%, sensitivity of 73%, and specificity of 69%. The unimodal CNN performed better, with an F1-score of 86%, sensitivity of 100%, and specificity of 75%. The early-fusion multimodal approach, integrating acoustic features and deep learning-based embeddings, outperformed both, reaching an F1-score of 95%, sensitivity of 100%, and specificity of 92%.

Conclusions: Although the analysis was conducted in a limited sample of patients with advanced disease, the multimodal approach yielded the best performance among tested scenarios, highlighting its promise for future research into cough as a biomarker. This method could serve as a non-invasive, accessible, and cost-effective pre-screening tool with the potential to complement existing low-dose CT radiological screening programs. Cough-based technologies can offer economic sustainability and easy access, potentially extending pre-screening efforts to broader populations such as non-smokers or individuals exposed to air pollution who are currently underserved by traditional screening methods. By addressing risk factors beyond smoking, this approach could support the development of more inclusive and economically sustainable screening programs applicable also in rural and low-income countries, toward democracy of cure and reduction of inequalities.

Keywords: Cough analysis, Non-Small Cell Lung Cancer, Early-fusion multimodal model

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.52 A Clinically Applicable and Generalizable Deep Learning Model for Segmenting Anterior Mediastinal Tumors Across Multiple Institutions

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Introduction: Anterior mediastinal tumors, such as thymoma and thymic carcinoma, are rare entities that pose substantial diagnostic challenge due to their low incidence and distinctive radiological features. Accurate pre-treatment diagnosis is essential for effective treatment planning and prognostic assessment. While computed tomography (CT) remains the cornerstone for imaging evaluation, interpretation often demands substantial expertise and experience. Recent advances in artificial intelligence (AI), especially deep learning (DL) algorithms, have shown significant potential for improving the diagnostic accuracy and efficiency of medical image analysis. However, developing deep learning models for rare diseases is inherently challenging due to limited large-scale datasets. Although a few segmentation models for anterior mediastinal tumors have been proposed, no prior studies have validated them across multiple institutions and clinically robust and generalizable models remain lacking.

Methods: This study was a retrospective observational analysis utilizing CT images acquired from multiple institutions. Institutional Review Board approval was obtained from the National Cancer Center of Japan (IRB 2023-229). No-code AI platforms allow model development without the need for specialized programming skills. Using such a platform, we developed a clinician-driven model to segment pre-treatment tumors on multiple institutions CT images. A total of 711 chest CT images were collected between April 1, 2000 and March 31, 2024, from 123 hospitals. Each image was derived from a unique patient with pathologically proven anterior mediastinal tumors (339 males, 372 females). Of these, 485 images were used for training, 62 for internal testing, and 164 for external testing. A 3D U-Net-based segmentation model was trained on the training dataset and evaluated on both internal and external testing datasets. The external testing dataset comprised CT images from institutions not involved in model development or internal validation.

Results: Based on the reference standards provided by board-certified diagnostic radiologists, the trained model achieved average Dice scores of 0.864, precision of 0.906, and recall of 0.858 on the internal testing dataset. On the external testing dataset, it achieved average Dice scores of 0.823, precision of 0.856, and recall of 0.821, demonstrating consistent performance across institutions.

Conclusions: We developed a clinically relevant segmentation model for anterior mediastinal tumors on multiple institutions CT images using a no-code AI platform. Our cohort included an external test set of 164 patients from 123 institutions, highlighting the broad applicability of the model. This study is the first to demonstrate robust and generalizable performance of a segmentation model for anterior mediastinal tumors, addressing the data scarcity challenge for such rare diseases.

Keywords: Anterior Mediastinal Tumors, Deep Learning, Segmentation

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.53 Potential for AI as First Reader in Lung Cancer Screening

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Introduction: To assess the agreement between human and AI readings for low dose CT (LDCT) outcomes according to Lung Reporting And Data System (LungRADS); to test the safety of using AI as first reader in lung cancer screening (LCS).

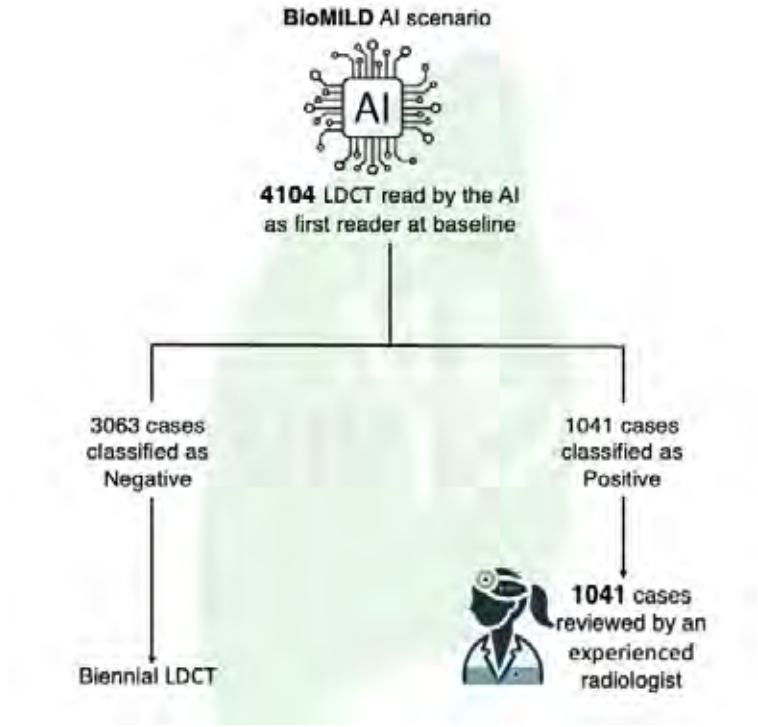
Methods: This retrospective analysis included 4104 volunteers from the BioMILD trial (ClinicalTrials.gov Identifier: NCT02247453). The baseline LDCTs, prospectively read by an experienced radiologist and classified into "negative" (categories 1 and 2 as per LungRADS v1.1) and "positive" (categories 3 and 4), were retrospectively analyzed by an AI software for LungRADS category assignment. The diagnosis of lung cancer (LC) at 2 years from baseline was used as reference standard to test the performance of human and AI readings. Agreement for LungRADS categories between human and AI readings was measured by the k-Cohen Index with Fleiss-Cohen weights (Kw) with 95% Confidence Interval (CI). Performance of human and AI readings was tested for diagnostic accuracy.

Results: The agreement between human and AI readings for negative and positive LDCTs was 83.5% (Kw 0.47; 95%CI: 0.43-0.50) (Table). Among 4104 participants, 68 were diagnosed with LC within 2 years from baseline. For 6 of them, LDCT was classified as negative by AI, but only 1/6 had been classified as positive by human reading (small cell carcinoma, stage IV). Sensitivity and specificity were 91.2% and 75.7% for AI, and 89.7% and 90.0% for human reading. The PPV and NPV were 6.0% and 99.8% for AI, and 13.1% and 99.8% for human reading. The expected reduction in LDCT reading when using AI as first reader is 74.7% (Figure).

Conclusions: Results demonstrated a moderate agreement between AI and human readings and that AI might be safely used as first reader in LCS.AI software was used for LDCT reading (AVIEW, Coreline Soft, Seoul, Korea) and for creating the figure (ChatGPT).

LungRADS Human reading	LungRADS AI reading		
	1-2	3-4	Total
1-2	3011	627	3638
3-4	52	414	466
Total	3063	1041	4104

k-Cohen Index	
Estimate	95% CI
0.47	0.43-0.50



Keywords: Lung cancer screening, Low dose computed tomography, Artificial Intelligence

P1.04 SCREENING AND EARLY DETECTION
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.04.54 Breath-based Lung Cancer Detection: Initial Phase 2 Results for D5-Ethyl-β-D-glucuronide (OWL-EVO1) as a Lung Cancer Probe

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Introduction: Low-dose CT (LDCT) screening for lung cancer has demonstrated mortality benefits but is hampered by low uptake. Breath analysis offers a solution as a non-invasive method for early lung cancer detection. The aim is utility within primary care or a home setting, as an adjunct to CT, to improve compliance with screening. Previous breath-based analyses, focusing on endogenous VOCs, were hindered by high variability and low signal-to-noise ratios. An engineered Exogenous Volatile Organic Compound (EVOC®) probe, with a bespoke analytical approach, has potential to improve both sensitivity and specificity of the breath-biopsy method. We have previously presented in-human safety, tolerability and proof-of-principle data using an IV EVOC® probe, D5-Ethyl-β-D-glucuronide (OWL-EVO1), for targeting extracellular β-glucuronidase for the detection of lung cancer through exhaled D5-ethanol on breath [1]. Here, we present initial findings of a case-control phase 2 study of OWL-EVO1 as an EVOC® probe for the detection of lung cancer, in participants with biopsy-proven lung cancer and co-morbidity/risk factor matched controls.

Methods: The primary endpoint was to report diagnostic accuracy (e.g. sensitivity and specificity) of intravenous (IV) OWL-EVO1 and secondary endpoints included finalising a protocol of optimised testing parameters and further profiling safety and tolerability (through adverse event reporting). Up to ten breath samples from pre-dose to 180min post dose, were collected from 187 patients with lung cancer (all stages), or controls, across seven sites and analysed using gas-chromatography mass-spectrometry.

Results: Breath samples using 2mg/kg doses of OWL-EVO1 (40 cases vs 47 controls) showed no case-control separation at early time points, with modest performance at later timepoints; likely compounded by off-target cleavage. To minimise off-target cleavage, the final optimised protocol included lowering the dose to 0.8mg/kg (50 cases vs 50 controls). Initial optimum performance for stage 1 and 2 lung cancer in this cohort was a 67% sensitivity and 70% specificity for breath samples taken at 130 minutes post-dose. Additionally, in this cohort a reduction in cleaved reporter signal was observed in patients recalled post-lung cancer treatment, at 130 minutes post-dose. There were 29 adverse events; 10 (in 6 participants) were possibly or probably related to OWL-EVO1 and resolved without sequelae. There were no serious adverse events or reactions, or suspected unexpected serious adverse reactions.

Conclusion: This study presents initial diagnostic accuracy data for IV OWL-EVO1 and supports further development of OWL-EVO1 as a probe to diagnose lung cancer using breath. Future work will utilise an inhaled form of OWL-EVO1 allowing for more practical administration in an out-of-hospital setting. The aim is to deliver higher probe concentrations to the tumour site, thereby reducing off-target cleavage to improve sensitivity and test performance.

Reference:

1. P1.13-03 Proof-of-mechanism for a Diagnostic Probe Generating D5-Ethanol as an On-Breath Reporter Molecule for Lung Cancer - Evolution Phase 1 Schee, M.v.d. et al.Journal of Thoracic Oncology, Volume 18, Issue 11, S212 - S213

Keywords: Exogenous Probe, Breath Analysis, Early Detection

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.01 Wearable-Based Evaluation of Tubeless Thoracic Surgery for Early-Stage Lung Cancer

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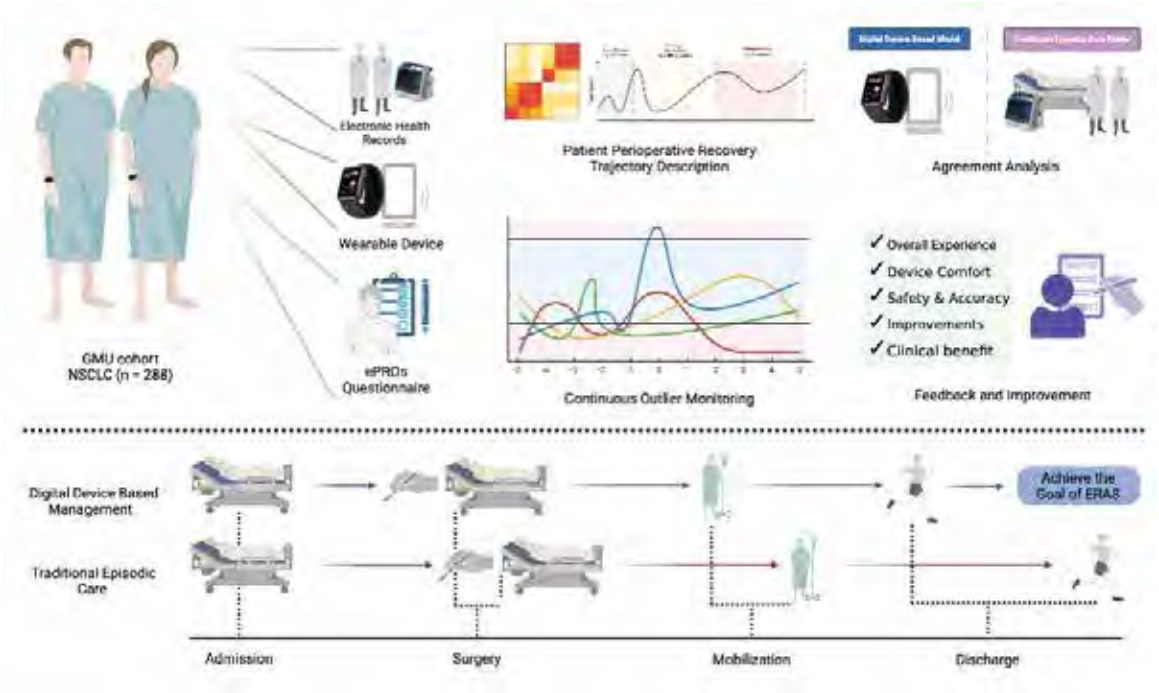
Introduction: Although tubeless thoracic surgery has demonstrated superiority over intubated thoracic surgery, limited research has objectively evaluated its clinical utility. Recent advances in wearable devices and electronic patient-reported outcomes (ePROs) provide more comprehensive, multi-dimensional assessments of surgical outcomes. This prospective, real-world study integrated multimodal digital data to objectively assess the efficacy and clinical utility of tubeless thoracic surgery.

Methods: We prospectively enrolled lung cancer patients underwent thoracic surgery between March 2023 and December 2023. All patients wore wearable devices during hospitalization to record key vital sings. In addition, standardized questionnaires were used to collect ePROs covering nine symptoms. Propensity score matching (PSM) was applied to balance baseline characteristics and multimodal data were compared between tubeless group and intubated group.

Results: 263 patients were included in this study. After PSM, 80 patients were included in each group. Compared with the intubation group, the tubeless group exhibited significantly better postoperative outcomes, including shorter hospital stays (2.78 vs. 3.91 days, $p < 0.001$), reduced chest tube duration (0.93 vs. 2.26 days, $p < 0.001$), and lower chest tube drainage volume (128.90 vs. 313.88 mL, $p < 0.001$). ePROs further indicated significantly less pain, coughing, shortness of breath, and distress in the tubeless group, while wearable device measurements showed improved body temperature, heart rate, blood oxygen saturation, and sleep quality.

Conclusions: Tubeless thoracic surgery significantly improves perioperative outcomes in early-stage lung cancer. Integrating wearable devices and ePROs supports broader adoption and iterative refinement, ultimately enhancing patient recovery and quality of life.



Keywords: Tubeless Thoracic Surgery, Wearable Devices, Electronic Patient-Reported Outcomes

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.02 Septum-Guided Segmentectomy vs Lobectomy for Deeply Located cT1abN0M0 Non-Small Cell Lung Cancer

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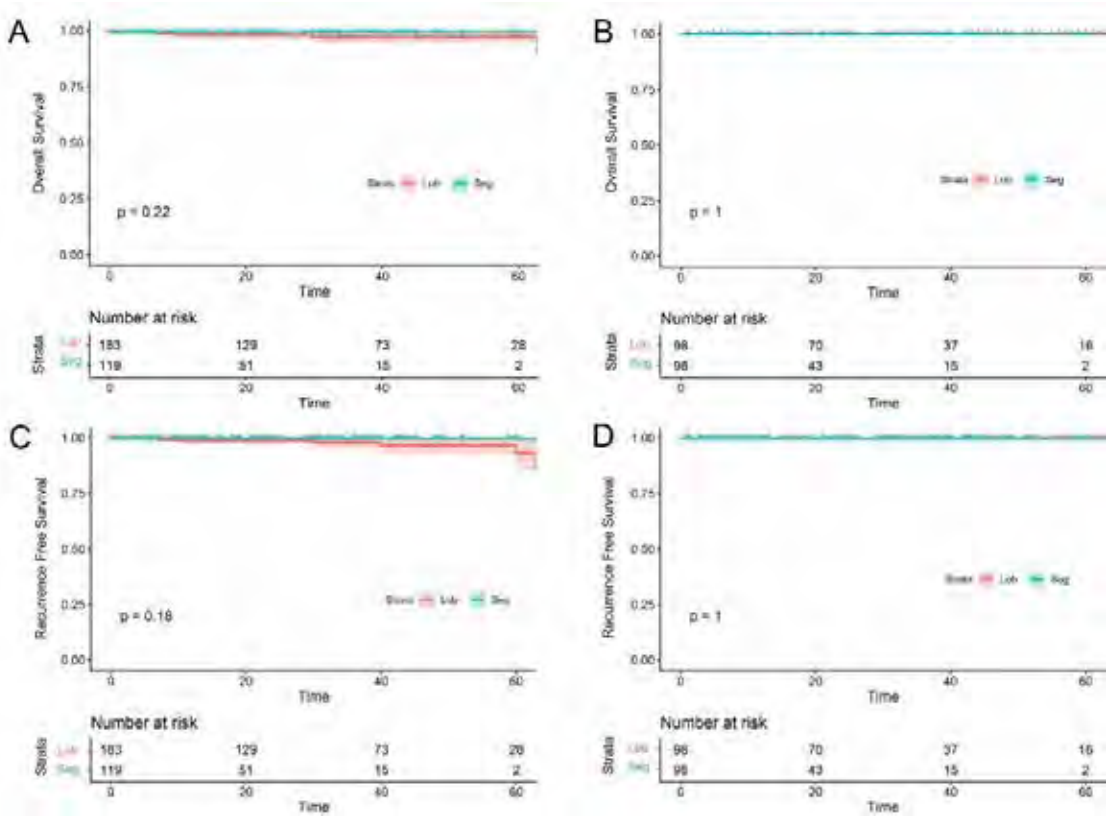
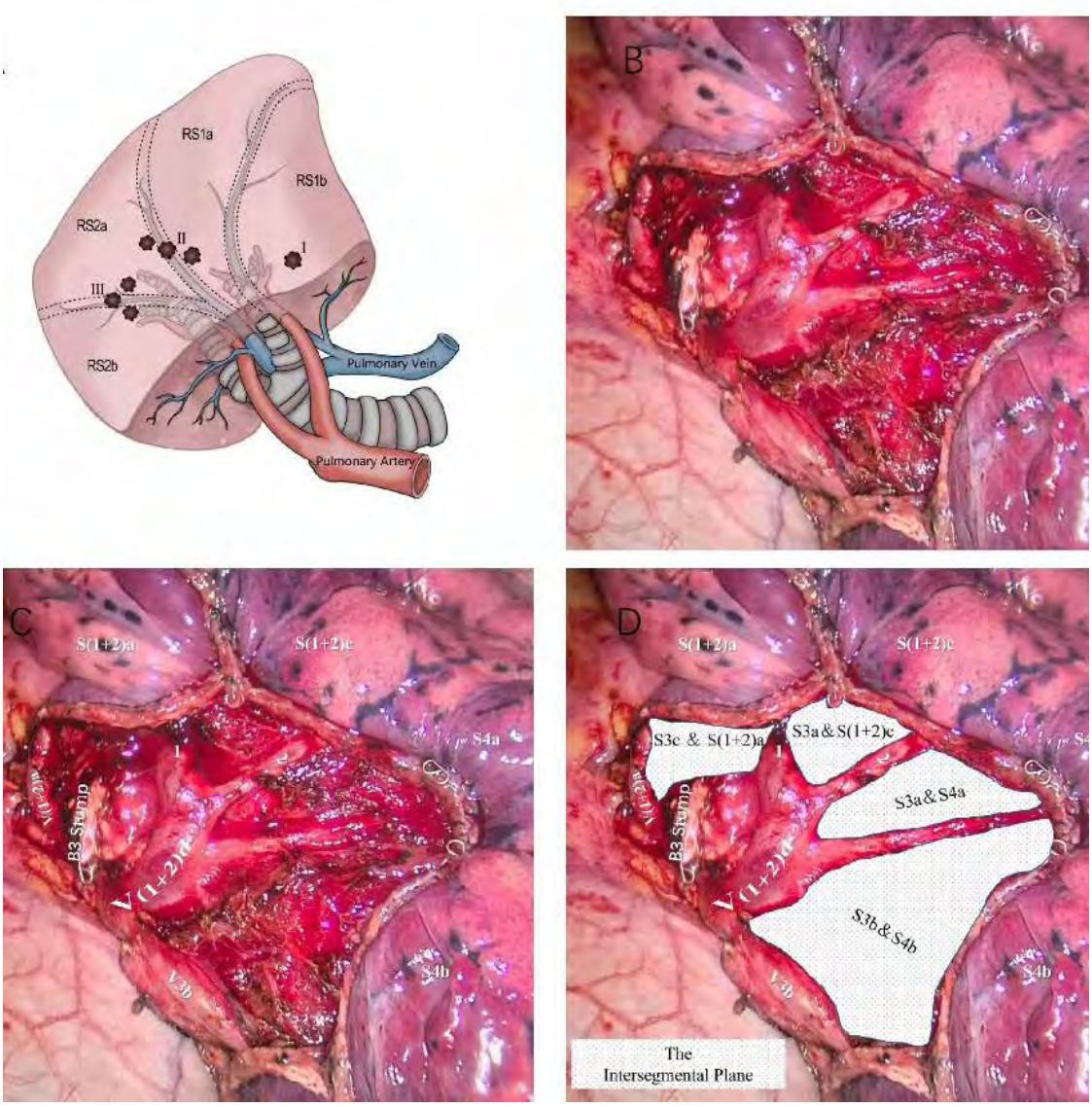
Introduction: While segmentectomy emerges as a lung-preserving alternative to lobectomy for early-stage non-small cell lung cancer (NSCLC), its application to deeply located tumors (inner two-thirds) remains controversial due to conventional margin-dependent paradigms. The septum-guided segmentectomy concept - utilizing intersegmental septa as anatomical barriers - offers a novel approach for these challenging lesions.

Methods: This retrospective study analyzed 407 patients with cT1abN0M0 NSCLC located in the inner two-thirds of the lung parenchyma who underwent either uniportal video-assisted thoracoscopic surgery (VATS) septum-guided segmentectomy or lobectomy between January 2019 and August 2024. After applying inclusion criteria and propensity score matching (PSM), 302 patients (before PSM) and 196 matched patients (after PSM) were included in the analysis. Perioperative data, recurrence-free survival (RFS), and overall survival (OS) were assessed, with a median follow-up of 25.0 months.

Results: There were 6 cases of recurrences or deaths in the lobectomy group before PSM. Remarkably, no cases of recurrence or mortality occurred in the segmentectomy group during the follow-up period. No significant difference was observed in RFS or OS between the segmentectomy and lobectomy groups (p = 0.18 and 0.22 before PSM, p = 1 and 1 after PSM). Although segmentectomy was associated with longer operative times (128.98 vs. 91.88 minutes; p < 0.001), but all patients achieved R0 resection. Rates of perioperative complications, including prolonged air leakage and chylothorax, drainage time, and hospital stay were comparable between the two groups (all p > 0.05).

Conclusions: With uniportal VATS, septum-guided segmentectomy demonstrates equivalent efficacy versus lobectomy for deeply located cT1abN0M0 NSCLC, validating intersegmental septa as reliable oncological boundaries. This anatomical approach eliminates dependence on margin distances and provides reliable evidence for the establishment of new and improved standards for precision resection.





Keywords: Septum-guided segmentectomy, Deeply located lung cancer, Uniportal VATS

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.03 Effectiveness of a Generalizable AI Based Automated Workflow Recognition Model in Multiple Approaches to Lung Resection

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Introduction: The application of artificial intelligence (AI) in surgery is expanding, particularly in surgical video analysis. Automated workflow recognition has potential applications in workflow optimization and surgical education. Developing a more generalizable AI model requires validation across different surgical approaches. While the feasibility of an automated workflow recognition model in totally thoracoscopic surgery has been reported, its accuracy across different approaches remains unclear.

Methods: This study compared the accuracy of an AI-based automated workflow recognition model for lung resection surgery using datasets from both completely video-assisted thoracic surgery (cVATS) and hybrid video-assisted thoracic surgery (hVATS) approaches. A total of 134 patients who underwent lung resection in 2023 were included, excluding multiple resection cases. Surgical workflows were annotated into five phases: Phase 1: Preparation, Phase 2: Resection Preparation, Phase 3: Specimen Removal, Phase 4: Completion of Thoracic Procedures, and Phase Ex: Extra-Thoracic Phase. Surgical videos were extracted at one frame per second, and an AI-based automated workflow recognition model was developed using Swin Transformer. Model accuracy was validated, including an additional analysis using a dataset where the number of hVATS cases or sampled frames was adjusted to match cVATS.

Results: The study included 74 males and 60 females (median age: 70 years, 74 cases of primary lung cancer). There were 102 hVATS and 32 cVATS cases, with 783,034 frames analyzed. The F1 scores for cVATS, hVATS, and the entire dataset were 0.78, 0.84, and 0.83, respectively. The highest positive predictive values for each phase were 0.82, 0.77, 0.82, 0.82, and 0.93 for Phases 1, 2, 3, 4, and Ex, respectively. The best-performing model was the full dataset model validated with cVATS data (F1 score = 0.84). The F1 scores for cVATS and hVATS datasets were 0.78 and 0.84 and remained the same when the dataset was adjusted to match case numbers or frame samples between hVATS and cVATS.

Conclusions: The comparison of approach-specific accuracy in AI-based surgical workflow recognition suggests that limitations in the field of view associated with different surgical approaches may have influenced model performance. Additionally, validation using a dataset with matched hVATS and cVATS cases suggests that case volume significantly impacts model accuracy. Future studies should explore data augmentation and model adaptation to enhance the generalizability of AI-based workflow recognition across different surgical techniques.

AI Disclaimer: This study utilized Swin Transformer, an AI-based image recognition tool, for automated workflow recognition model development and validation.

P1.07.04 MRD Combined With Radiological Tumor Volume as Tool to Identify Resected NSCLC Patients at High Risk of Recurrence

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Introduction: Circulating tumor DNA (ctDNA) is a valuable tool for assessing minimal residual disease (MRD) and predicting recurrence in resected non-small cell lung cancer (NSCLC) patients. As MRD assessment in NSCLC remains biologically challenging, combining ctDNA-detection with other biomarkers could increase prognostic value. This study aimed to correlate MRD status with clinical outcome and integrate ctDNA detection with radiological tumor volume to improve risk stratification.

Methods: Patients with a histological diagnosis of stage I-III resectable NSCLC were prospectively enrolled in the RESIDUAL study from December 2019 to July 2022. Plasma samples were collected before surgery (T0), at landmark (T1, 10-days after surgery) and surveillance timepoints (T2, 20 days, T3, 1 months after surgery and every 3 months for the first year and then at the end of the second year after surgery). A plasma sample was further collected if relapse occurred (TRel). All samples were analyzed using Guardant Reveal, tissue-free, methylation-based assay for the detection and quantification of ctDNA (Guardant Health, USA). Receiver operator characteristics was performed by associating the presence of ctDNA at landmark timepoint with the tumor volume. The cut-off for optimal stratification of tumor volume was calculated based on Youden's J and Cox regression analysis was performed.

Results: Forty-eight patients were enrolled with a median age of 72 years (range 47 to 84); 64.6% were males; most patients were stage I (54.2%), followed by stage II (29.2%) and III (16.6%). Thirty-eight patients (79.2%) were adenocarcinoma (ADK), 9 (18.8%) were squamous cell carcinoma (SCC), while 1 (2.0%) had mixed histology ADK-SCC. Five (10%) patients had a systemic adjuvant treatment post-surgery. Median follow-up was 41.8 months (range 1.2 to 59.8) and 19 (39.6%) patients experienced disease recurrence. Two hundred and seventy plasma samples were collected and analyzed. The overall ctDNA detection rate was 16.7% across all timepoints. Pre-surgical ctDNA-detection was higher in both SCC histology and II-III pathological stage patients, and ctDNA-detection tended to have a worse DFS (ctDNA detected yes vs. no: 34.4 vs. 52.1 months; HR 2.13; 95%CI 0.85-5.33, p>0.05). In the landmark analysis, we found that MRD detection after surgery was associated with a significant worst DFS (ctDNA detected yes vs. no: 6.1 vs. 52.1 months; HR 4.91; 95%CI 1.06-22.75, p=0.024). Serial surveillance sampling yielded a median lead time of 5.3 months compared to radiologic recurrence. Lastly, a volume threshold was calculated with T1 ctDNA status and we found that patients with radiological tumor volume higher than 26'378 mL were at higher risk of relapse rather than patients with a lower volume (volume above the threshold yes vs. no: 5.95 vs. NaN; HR 8.48; 95%CI 3.06-23.49, p < 0.0001).

Conclusions: MRD identification in resected NSCLC is associated with a worse outcome and anticipates radiological relapse months in advance. Moreover, the combination of ctDNA and radiological tumor volume allow to develop a combined tool to better identify patients at high risk of recurrence.

Keywords: Minimal Residual Disease, Early stage resected NSCLC, ctDNA

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.05 Real-World Biomarker Testing and Treatment Initiation in Patients With Resected Early-Stage NSCLC (eNSCLC) in the US and UK

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Introduction: Biomarker testing among patients with eNSCLC is recommended following the approval of immunotherapy and targeted therapies in the neoadjuvant and adjuvant settings. While past studies highlighted the underutilization of biomarker testing in surgically resected eNSCLC, the cause for these gaps remain unclear. This study sought to generate new insights by examining the characteristics associated with biomarker testing in resected eNSCLC, as well as the impact of testing on timeliness of treatment.

Methods: This retrospective study used the electronic health record-derived US and UK Flatiron Health Research Databases and included adult patients with stage IB-IIIA NSCLC who received surgical resection by July 1, 2024. Eligible patients were categorized based on receipt of EGFR/ALK testing in the early setting, with tested patients further stratified by test timing around surgery and neoadjuvant or adjuvant therapy use. Clinical and demographic characteristics were summarized by testing group.

Results: In the US cohort of 13,473 eligible patients, approximately 69% (9,339) received EGFR/ALK testing (Table). More patients in the tested group had Stage IIB or Stage IIIA disease; most characteristics including socioeconomic status were similar across testing groups. Among patients tested, median (IQR) time from initial diagnosis to surgery was 70 (42-127) days for patients tested before surgery versus 22 (1-48) days for patients tested on or after surgery, irrespective of systemic therapy. A higher percentage of patients tested before surgery received neoadjuvant therapy than those tested on or after surgery (30.5% vs 3.6%). Of the 102 eligible patients in the UK cohort, 43 (42%) patients received EGFR/ALK testing, with 15 tested before surgery and 28 tested on or after surgery. Tested patients were more likely to have stage IIB or stage IIIA disease than untested patients (69.8% vs 44.1%). Patients who were tested had a longer time between initial diagnosis and surgery than untested patients (45 vs 33 days).

Conclusions: Despite growing clinical interest, more than 30% of patients with resected eNSCLC did not undergo EGFR/ALK biomarker testing in the US and UK. Testing rates were higher in patients with higher stage of disease, suggesting clinical risk is impacting testing decisions. Biomarker testing in eNSCLC was associated with a modestly longer time to surgery, greatest for testing done before surgery, suggesting planning for biomarker testing is needed to reduce delays in care. Further analyses on the impact of this timing on patient outcomes are needed.

Table. Demographic and Clinical Characteristics of US Patients Stratified by *EGFR/ALK* Early Biomarker Testing

Characteristic	Overall	Has *EGFR/ALK* testing in early setting	No testing in early setting
Patient count	13,473	9,339	4,134
Age at Diagnosis (median, IQR)	70 (64-75)	70 (64-75)	70 (64-76)
Race, n (%)			
Asian	310 (2.3)	244 (2.6)	66 (1.6)
Black or African American	937 (7.0)	627 (6.7)	310 (7.5)
Other Race	1,006 (7.5)	671 (7.2)	335 (8.1)
Unknown/not documented	2,126 (16)	1,545 (17)	581 (14)
White	9,094 (67)	6,252 (67)	2,842 (69)
Ethnicity, n (%)			
Hispanic or Latino	474 (3.5)	355 (3.8)	119 (2.9)
Not Hispanic or Latino	9,598 (71)	6,560 (70)	3,038 (73)
Unknown/not documented	3,401 (25)	2,424 (26)	977 (24)
Group Stage, n (%)			
Stage IB	4,463 (33)	2,711 (29)	1,752 (42)
Stage II	214 (1.6)	131 (1.4)	83 (2.0)
Stage IIA	1,265 (9.4)	873 (9.3)	392 (9.5)
Stage IIB	3,811 (28)	2,776 (30)	1,035 (25)
Stage IIIA	3,720 (28)	2,848 (30)	872 (21)
Socioeconomic Status (SES), n (%)			
1 - Lowest SES	2,166 (16)	1,464 (16)	702 (17)
2	2,553 (19)	1,738 (19)	815 (20)
3	2,869 (21)	1,959 (21)	910 (22)
4	2,789 (21)	1,988 (21)	801 (19)
5 - Highest SES	2,222 (16)	1,576 (17)	646 (16)
Unknown/not documented	874 (6.5)	614 (6.6)	260 (6.3)
Earliest systemic treatment, n (%)			
Adjuvant	6,614 (49)	5,231 (56)	1,383 (33)
Neoadjuvant	1,355 (10)	1,034 (11)	321 (7.8)
No adjuvant or neoadjuvant treatment	5,504 (41)	3,074 (33)	2,430 (59)
Early *EGFR/ALK* testing result, n (%)			
Not positive	7,687 (82)	7,687 (82)	N/A
Positive	1,652 (18)	1,652 (18)	N/A
Time from initial diagnosis to surgery (median, IQR)	33 (2-63)	35 (2-66)	27 (1-57)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IQR, interquartile range.

Keywords: Biomarker testing, EGFR/ALK Alterations, Real-world Data

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.06 Impact of Mediastinal Lymph Node Dissection/Sampling on Survival in Frozen Section-Upgraded Invasive Lung Adenocarcinoma

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Introduction: Mediastinal lymph node dissection or sampling (MLND/S) is a vital part of diagnosis and treatment for invasive lung adenocarcinoma. Surgeons frequently rely on frozen section to determine the necessity of MLND/S. Limited studies have evaluated the prognostic significance of MLND/S in patients with invasive adenocarcinoma initially misclassified as adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) by frozen section.

Methods: A retrospective cohort of 635 patients with invasive adenocarcinoma misclassified as AIS/MIA by frozen section was analyzed. These patients with invasive adenocarcinoma include 32 AIS and 603 MIA by frozen section, all of them underwent lobectomy or sublobar resection. Prognostic outcomes, including 5-year overall survival (OS) and recurrence-free survival (RFS), were compared between patients who underwent MLND/S (n=417) and those who did not (n=218). All patients underwent either lobectomy or sublobar resection.

Results: From a preoperative imaging perspective, the chest CT findings of these patients predominantly exhibited imaging characteristics of early-stage lung cancer, with over 80% of nodules measuring less than 3 cm in diameter and more than 50% demonstrating a CTR (consolidation-to-tumor ratio) of less than 0.5. Only one patient died of community-acquired pneumonia in MLND/S group and one patient died of lung cancer metastasis in the non-MLND group. The 5-year OS and RFS rates were 99.7%%/100% in the MLND/S group and 99.5%/99.5% in the non-MLND group, with no statistically significant differences observed (p>0.05). Notably, no positive N1 or N2 lymph nodes were identified in either cohort.

Conclusions: For patients with invasive adenocarcinoma misclassified as AIS/MIA by frozen section, MLND/S does not confer survival benefits, regardless of surgical approach (lobectomy or sublobar resection). These findings suggest that omitting MLND/S in this subset of patients is oncologically safe and may reduce unnecessary surgical trauma.

Keywords: frozen section, upgrade, Mediastinal Lymph Node

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.07 The Presence of STAS Leads to Poor Prognosis After Sublobar Resection in Stage I NSCLC: Results From an Individual Patient Data Metanalysis

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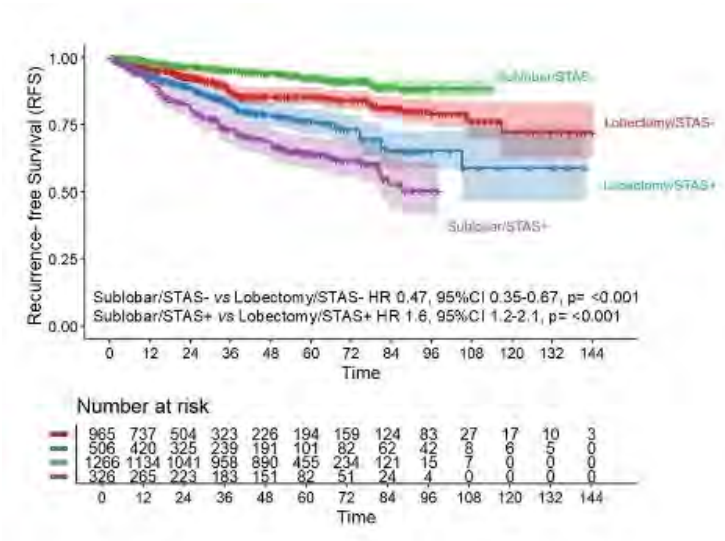
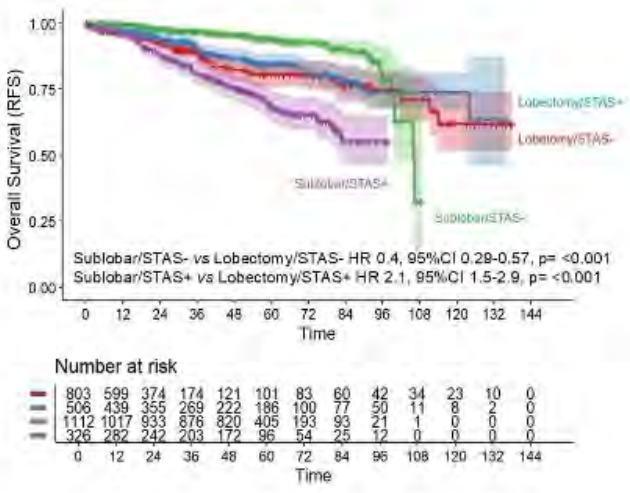
Introduction: Recently, tumour spread through air spaces (STAS) was identified as an independent factor influencing both survival and recurrence rates across various types of lung cancer. To date, the choice of surgical procedure for early-stage NSCLC with STAS remain unclear. This study aimed to analyzed the prognostic impact of STAS on sublobar resections compared to lobectomy for stage I NSCLC.

Methods: An individual patient data (IPD) meta-analysis was conducted, including patients from the studies that analyzed patients with stage I NSCLC treated with sublobar or lobar resections who presented or did not STAS. IPD was reconstructed from Kaplan-Meier curves of the included studies using the IPDfromKM method. The primary outcomes of this study were overall survival (OS) and recurrence free survival (RFS).

Results: The literature search identified 175 records; 6 reports were included in the study. A total of 3063 patients were included, of which, 1471 (48.0%) were treated with lobectomy and 832 (27.2%) presented STAS. Adenocarcinoma was the most common histology (93.7%) while an history of smoking was found in 52% of the included patients. The RFS analysis showed that in the STAS+ group, patients treated with sublobar resections had a significantly shorter RFS compared to lobectomy (HR 1.6 95%CI 1.2-2.1; p= <0.001) while in the STAS- group, patients treated with sublobar resections had a significantly improved RFS compared to lobectomy (HR 0.47 95%CI 0.35-0.67; p= <0.001, Fig. 1a). Data for OS were available for 2748 patients (43.2% lobectomy). In the STAS+ group, patients treated with sublobar resections showed a significantly shorter OS compared to those treated with lobectomy (HR 2.1 95%CI 1.5-2.9; p= <0.001, Fig. 1b). The OS in the STAS- group was significantly improved in the sublobar resections compared to lobectomy (HR 0.4 95%CI 0.29-0.57; p= <0.001).

Conclusions: Our metanalysis showed that patients with stage I NSCLC who presented STAS on pathological examination treated with sublobar resections had a significantly worse RFS and OS compared to lobectomy. Further studies are needed to find predictors of STAS in order to guide the extent of resection.





Keywords: segmentectomy, early stage NSCLC, STAS

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.08 Comparing Outcomes of Different Surgical Methods for Small-Sized NSCLC With VPI- A Population-Based Study

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Introduction: Sublobar resection (SR) has been increasingly validated as an effective alternative to traditional lobectomy for small (≤3 cm), peripheral non-small cell lung cancer (NSCLC). However, its efficacy in treating small NSCLC tumors with visceral pleural invasion (VPI) remains uncertain. This nationwide population-based study aims to compare the prognostic outcomes of patients with small (≤3 cm), stage IB NSCLC exhibiting VPI who underwent different extents of pulmonary resection (SR versus lobectomy).

Methods: This study utilized data from the Taiwan Cancer Registry Database (TCRD) from 2011 to 2017. We included patients diagnosed with pathological stage IB non-small cell lung cancer (NSCLC) defined as pT1a-c N0M0 with visceral pleural invasion (VPI) and tumor size ≤ 3 cm. The primary endpoint was overall survival (OS). Propensity score matching (PSM) was employed to balance baseline characteristics between patients undergoing lobectomy versus sublobar resection. Survival outcomes were compared between the matched groups. Subgroup analyses were performed based on the extent of pleural invasion (PL1 and PL2). Cox proportional hazards regression models were used to identify independent predictors of OS in this cohort.

Results: A total of 1330 patients with stage IB NSCLC (≤ 3 cm with VPI) were included, comprising 153 who underwent sublobar resection (SR) and 1177 who underwent lobectomy. The overall cohort had a mean age of 62.6 ± 10.1 years; 60.9% were female, and 75.7% were non-smokers. After propensity score matching (creating 118 matched pairs), Kaplan-Meier analysis revealed no significant difference in overall survival (OS) between the SR and lobectomy groups (log-rank p=0.37). Subgroup analyses confirmed comparable OS between SR and lobectomy, irrespective of PL1 (p=0.55) or PL2 (p=0.46) invasion status. Multivariable Cox regression analysis identified age > 75 years, smoking history, and poor tumor differentiation as independent predictors of worse OS.

Conclusions: In this nationwide study, sublobar resection demonstrated comparable overall survival to lobectomy for patients with small (≤3 cm), stage IB NSCLC exhibiting VPI, including both PL1 and PL2 subgroups. These findings suggest that sublobar resection represents a viable and effective surgical option for carefully selected patients within this specific cohort. Further validation from prospective studies is warranted.

Keywords: Sublobar resection, Visceral pleural invasion, Non-small cell lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.09 Real-World Efficacy of an AI-Driven 3D Reconstruction System on Pulmonary Surgery

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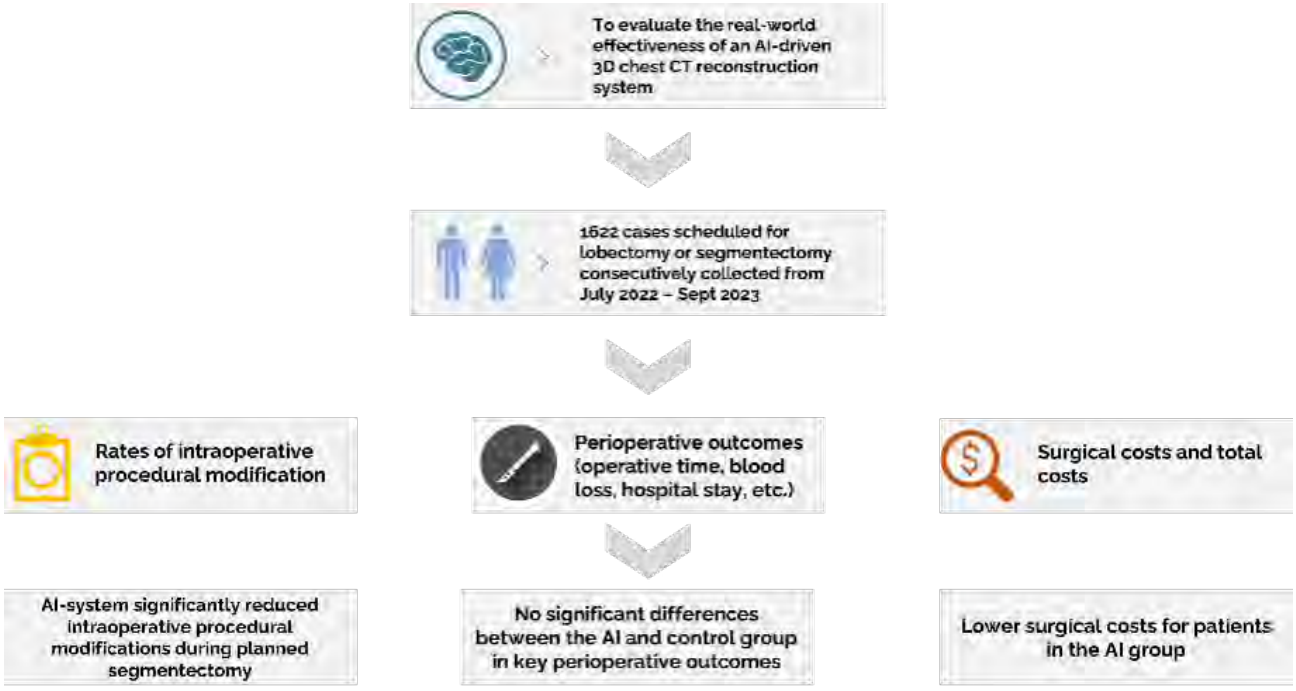
Introduction: Three-dimensional (3D) chest CT reconstruction significantly enhances thoracic surgical planning with superior spatial visualization over standard imaging. While our previous multi-reader multi-case study established the benefits of 3D CT, its real-world clinical effectiveness requires further evaluation.

Methods: We retrospectively evaluated an AI-driven 3D reconstruction system implemented in routine practice at our center (July 2022 - Sept 2023). Consecutive patients initially scheduled for lobectomy or segmentectomy were included. Surgeons utilized the AI system based on clinical judgment before surgery. Patients receiving AI-assisted planning (AI group) were compared to those undergoing standard planning (control group) within the same period. We assessed rates of intraoperative procedural modification, standard perioperative outcomes (operative time, blood loss, drainage, length of stay, complications including transfusions, reoperations, chest tube reinsertion), and surgical costs.

Results: This study included 1622 consecutive patients initially scheduled for pulmonary resection, comprising 1038 lobectomies and 584 segmentectomies. The AI-driven 3D reconstruction system was utilized preoperatively at the surgeon's discretion in 17.9% (186/1038) of lobectomy cases and substantially more often, in 58.6% (342/584), of planned segmentectomy cases. For patients initially scheduled for lobectomy, the overall rate of intraoperative conversion to any alternative procedure did not differ significantly between the AI group (3.8%, 7/186) and the control group (3.2%, 27/852; P=0.85). However, the conversion to segmentectomy was significantly more frequent following AI-assisted planning compared to controls (3.8% vs 0.9%; P<0.01). Among patients scheduled for segmentectomy, the use of the AI system resulted in a significant reduction in overall intraoperative procedural modifications (6.1% [21/342] in AI group vs 20.7% [50/242] in control group; P<0.001). This decrease was primarily driven by the complete elimination of conversions to less precise wedge resections in the AI group, compared to a 16.5% conversion rate in the control group (0% vs 16.5%; P<0.001). In cases where the initially planned surgery was performed without modification, most perioperative outcomes showed no significant differences between the two groups. Analysis of costs revealed significantly lower surgical costs for patients in the AI group (RMB: 10505.70[9395.39, 11684.58] vs. 10729.75 [9201.05, 12406.25], P<0.001).

Conclusions: In routine clinical practice, this AI-driven 3D reconstruction system significantly reduced intraoperative procedural modifications during planned segmentectomies, notably eliminating conversions to wedge resection (P<0.001), and was associated with lower overall surgical costs. These findings suggest the system enhances surgical precision and planning, particularly for complex resections, supporting its clinical utility despite minor time implications. Further validation in diverse settings is warranted.



Keywords: lung surgery, 3D reconstruction, artificial intelligence

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.10 Prognostic Impact of Resection Margin Distance in Patients With Completely Resected Stage INSCLC After Lobectomy

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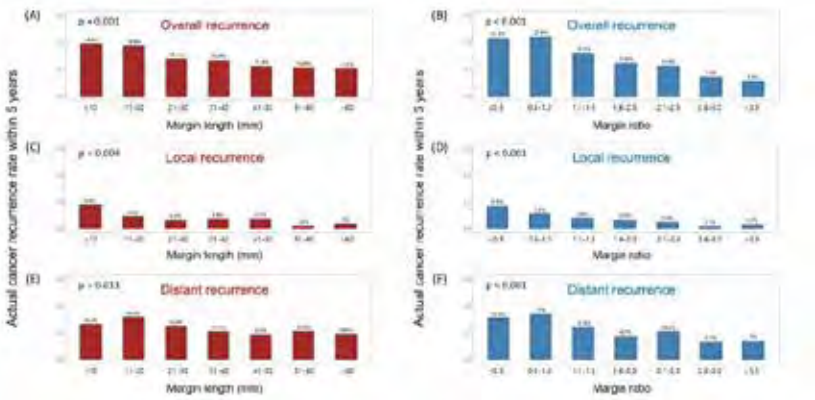
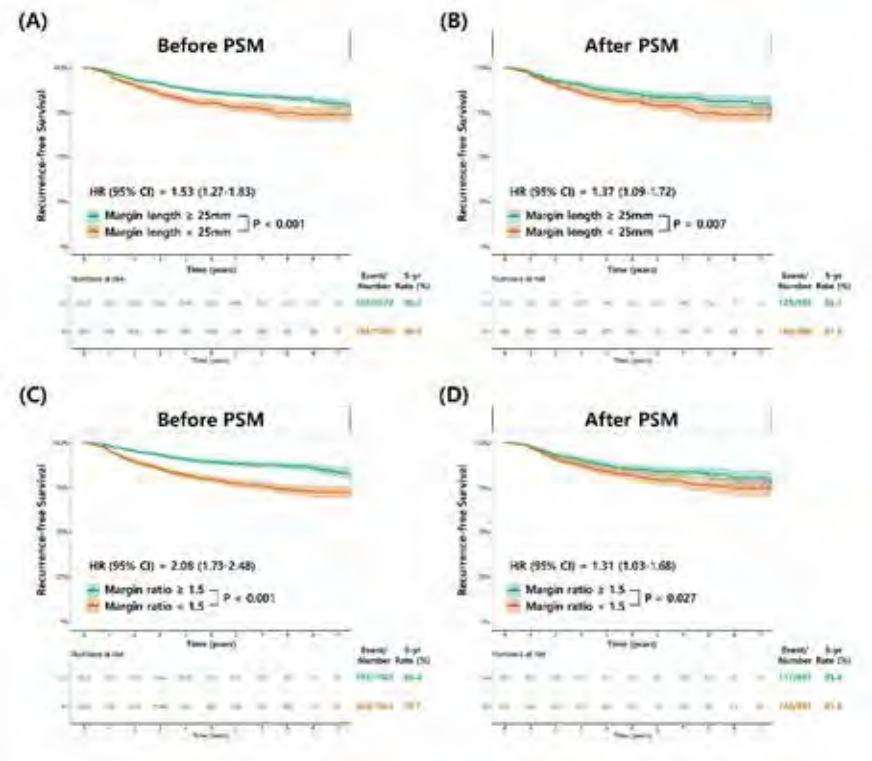
Introduction: Unlike sublobar resection, the prognostic impact of margin distance has not been fully evaluated in patients who underwent lobectomy for stage I non- small cell lung cancer (NSCLC). We investigated the prognostic value of the resection margin distance and determine the cutoff value in these patients.

Methods: Between 2011 and 2021, data of patients with completely resected stage I NSCLC after lobectomy were analyzed. The margin distance and ratio were defined as the distance from the primary tumor to the bronchial resection margin and the margin distance divided tumor size. The optimal cutoff value was selected using a maximally selected log-rank statistic.

Results: A total of 3,727 patients were included as the final cohort, of whom 211 (5.7%), 1202 (32.3%), 1175 (31.5%), and 1139 (30.6%) patients were in stages IA1, IA2, IA3, and IB, respectively. The most optimal cutoffs for the margin distance and the margin ratio for cancer recurrence within 5 years were 25mm and 1.5, respectively. In the multivariable analysis, the margin distance (<25mm vs. ≥25mm; hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.11-1.61; p = 0.002) and the margin ratio (<1.5 vs. ≥1.5; HR, 1.40; 95% CI, 1.14 to 1.71; p <0.001) were significant factors for recurrence-free survival in patients after lobectomy for stage I NSCLC.

Conclusions: The margin distance has a significant prognostic impact in patients who underwent lobectomy for stage I NSCLC. Cutoff values of margin distance ≥25mm and margin ratio ≥1.5 could help clinicians enact proper treatment strategies and surveillance for these patients.





Keywords: margin distance, recurrence, early stage lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.11 AI-Based 3D Reconstruction in Lung Surgery

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Introduction: Segmentectomy is currently accepted as treatment of choice for <2cm non-small cell lung cancer (NSCLC) leading to comparable disease-free and overall survival as lobectomy, while preserving more lung tissue. However, anatomical variations in vascular and bronchial structures pose challenges. Furthermore, accurately localizing tumors within a lung segment based solely on a CT scan can be challenging. AI-based 3D reconstruction can potentially help recognize these variations and aid in surgical planning, it is not yet routinely implemented.

Methods: We analysed the perioperative data of patients who underwent a lung segmentectomy after 3D lung reconstruction between October 2023 and December 2024 (Group A) and compared them with patients who underwent lung segmentectomy without 3D reconstruction between 2021 and 2023 (Group B). The 3D reconstruction was performed using an AI-based program by "Infervision". Collected data included operative time, blood loss, R0 resection rate, complications (according to Clavien-Dindo classification), hospital stay and conversion rate to open surgery.

Results: Group A included 37 patients with a median age of 67.42 years. Anatomical variations were observed in 26% of arteries and 13% of bronchi. In 17.3% the planned resection was adjusted after 3D reconstruction to achieve the complete resection.

Perioperative data for Group A: median hospital stay of 6 (d), conversion rate of 0%, complication rate of 24.3% (Grade III - 10.8%).

Group B included 46 patients with a median age of 66.00 years. Perioperative data for Group B: median hospital stay of 9 (d), conversion rate of 4.35% and complication rate of 23.9% (Grade III - 15.2%)

Conclusions: 3D reconstruction allows better surgical planning through preoperative identification of anatomical variations and tumor position. It leads to lower complication rates and reduced hospital stay. Further studies are needed to confirm its long-term benefits.

Table 1. Patient Characteristics Table 2. Comparison Group A and B

Table 1.

Parameter	10/2023 -12/2024
VATS – Segmentectomy with 3D	37 cases 69 segments resected
ICG-application	10
Simple segmentectomy (one intersegmental area)	11 (29%)
Complex segmentectomy (multiple intersegmental areas)	26 (71%)
Variations of the segmental artenes	18 (26 %)
Variations of the segmental bronchi	9 (13 %)
Adjustment of the extent of resection	in 12 cases (17,3 %)
Median ages	67,42 [36,8 – 83,3]
Histopathological result	NSCLC [25] • Adenocarcinoma x 19 • Squamous cell carcinoma x 4 Metastasis 6 Benign findings [6] • Hamartoma x 3, organizing pneumonia x 3

Table 2.

Parameter	Median with 3D	Median without 3D	p-value	Odds Ratio
Safety margin (cm)	1.2 [Range: 0.2-3.4]	1.7 [0.1-2.6]	0.813	-
Surgery duration (minutes)	141.5 [70-305]	143.0 [76-303]	0.769	-
Blood loss (ml)	50 [20-300]	50 [20-490]	-	-
Hospital stay (d)	9 [4-36]	5 [4-18]	0.00004	-
Conversion rate (%)	2/46 (4.35%)	0/37 (0%)	0.500	-
Postoperative complications	11/46 (23.9%)	9/37 (24.3%)	1.000	0.98
Grade 3 complications	7/46 (15.2%)	4/37 (10.8%)	0.747	1.48

Keywords: NSCLC, Segment rescection, Artificial intelligence

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.12 Independent Risk Factors for Occult Lymph Node Metastasis in cIA Left Upper Lobe Lung Adenocarcinoma: A Nomogram-Based Prediction Model

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Introduction: The management of left upper lobe lung adenocarcinoma presents various surgical challenges, particularly in cases of occult lymph node metastasis (OLNM). Inadequate lymph node dissection in patients with clinical stage IA (cIA) disease may compromise oncological outcomes. This study aimed to identify independent risk factors and develop a predictive nomogram for OLNM in cIA left upper lobe lung adenocarcinoma.

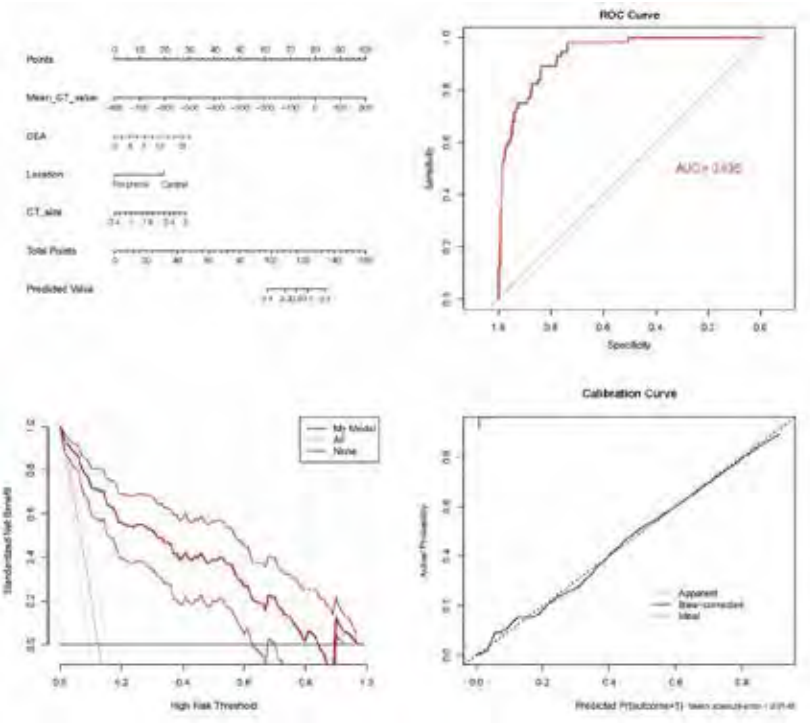
Methods: We conducted a retrospective analysis of 452 consecutive patients with clinical stage IA (cIA) left upper lobe lung adenocarcinoma between January 2018 and May 2022.Univariate and multivariate logistic regression analyses were performed to identify preoperative risk factors for OLNM. A nomogram was subsequently developed and validated using receiver operating characteristic (ROC) curve analysis, calibration plots, and decision curve analysis (DCA).

Results: OLNM was identified in 56 cases (12.39%). Multivariate analysis identified four independent predictors: elevated carcinoembryonic antigen (CEA) levels, mean computed tomography (CT) attenuation values, location of tumor, and CT tumor size. The nomogram demonstrated excellent predictive accuracy with an area under the ROC curve of 0.935. Calibration plots showed optimal agreement between predicted and observed outcomes, while DCA confirmed the clinical utility of the model.Three continuous variables were used to predict occult lymph node metastasis, including CEA, CT size and mean CT value. With regard to the cut-off value obtained by the ROC curve, the cut-off value of CEA was 2.45ng/ml (AUC = 0.68). The cut-off value of the CT size was 2.05cm (AUC = 0.72) and the cut-off value of the mean CT value was -19.80 (AUC = 0.87).

Conclusions: This study presents a validated nomogram incorporating CEA levels, mean CT values, location of tumor, and tumor size for predicting OLNM in cIA left upper lobe lung adenocarcinoma. This tool may assist thoracic surgeons in preoperative planning and decision-making regarding the extent of lymph node dissection.

Patient Clinicopathological Characteristics

Variables	Total (n = 452)	pN (n=396)	pN+(n=56)	*p*-value
Gender				0.680
female	267 (59.1)	232 (58.6)	35 (62.5)	
male	185 (40.9)	164 (41.4)	21 (37.5)	
BM	64 (14.2)	56 (14.1)	8 (14.3)	1.000
COPD	6 (1.3)	4 (1.0)	2 (3.6)	0.345
AS	35 (7.7)	31 (7.8)	4 (7.1)	1.000
high-grade	184 (40.7)	130 (32.8)	54 (96.4)	<0.001
STAS	80 (17.7)	55 (13.9)	25 (44.6)	<0.001
LVI	31 (6.9)	10 (2.5)	21 (37.5)	<0.001
pleural	98 (21.7)	66 (16.7)	32 (57.1)	<0.001
CTR				<0.001
<50%	184 (40.7)	183 (46.2)	1 (1.8)	
≥50%	268 (59.3)	213 (53.8)	55 (98.2)	
Location				<0.001
ventral	395 (87.4)	363 (91.7)	32 (57.1)	
peripheral	57 (12.6)	33 (8.3)	24 (42.9)	
Adjacent pleura	266 (58.8)	222 (56.1)	44 (78.6)	0.002
Spiculated sign	250 (55.3)	206 (52.1)	44 (78.6)	<0.001
Lobulation sign	217 (48.0)	177 (44.7)	40 (71.4)	<0.001
Irregular	408 (90.3)	364 (91.9)	44 (78.6)	0.004
Pleural Indentation Sign	228 (50.4)	190 (48.1)	38 (67.9)	0.008
Vacuole Sign	157 (34.7)	142 (35.9)	15 (26.8)	0.236
Vascular penetration	427 (94.5)	373 (94.2)	54 (96.4)	0.709
Age	62.00 [55.00, 68.00]	62.00 [54.75, 68.00]	62.50 [56.50, 68.25]	0.580
BMI	24.22 [22.23, 26.54]	24.19 [22.31, 26.43]	24.86 [21.98, 26.93]	0.577
CEA	2.24 [1.41, 3.42]	2.08 [1.35, 3.32]	3.28 [2.41, 7.05]	<0.001
Cyfra21-1	2.40 [1.81, 3.10]	2.40 [1.81, 3.06]	2.60 [1.85, 3.27]	0.508
CT size	1.60 [1.30, 2.00]	1.50 [1.20, 2.00]	2.10 [1.60, 2.50]	<0.001
Mean CT value	-186.32 [-417.32, 20.13]	-220.34 [-451.02, -28.28]	32.58 [21.31, 44.33]	<0.001
Duration of tube placement (day)	3.00 [3.00, 5.00]	3.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.400
Intraoperative bleeding(ml)	30.00 [20.00, 50.00]	30.00 [20.00, 50.00]	25.00 [20.00, 50.00]	0.852
Conversion to open	7 (1.5)	6 (1.5)	1 (1.8)	1.000
Complication				
none	419 (92.7)	364 (91.9)	55 (98.2)	0.347
arrhythmia	16 (3.5)	16 (4.0)	0 (0.0)	
pneumothorax	13 (2.9)	12 (3.0)	1 (1.8)	
hemorrhage	4 (0.9)	4 (1.0)	0 (0.0)	
Surgical Procedures				
wedge resection	61 (13.5)	59 (14.9)	2 (3.6)	<0.001
segmentectomy	142 (31.4)	135 (34.1)	7 (12.5)	
lobectomy	249 (55.1)	202 (51.0)	47 (83.9)	



Keywords: Lung Adenocarcinoma, Left Upper Lobe, Occult Lymph Node Metastasis

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.13 Impact of TP53 Co-Mutation in Resected Early-Stage EGFR-Mutated Lung Adenocarcinoma

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Introduction: Epidermal growth factor receptor (EGFR) mutations are known as the most common oncogenic driver mutations in lung cancer. With advances in next-generation sequencing techniques, the analysis of co-existing mutations in EGFR-mutated lung adenocarcinoma has progressed significantly. In advanced stage, TP53 co-mutation is associated with poor responses to EGFR tyrosine kinase inhibitors (TKIs). However, the impact of TP53 co-mutations in resected early-stage EGFR-mutated lung adenocarcinoma remains unclear. We aimed to evaluate the impact of TP53 co-mutation on clinicopathological features, prognosis, and recurrence patterns in resected early-stage EGFR-mutated lung adenocarcinoma.

Methods: Four-hundred patients with pathological I-III lung adenocarcinoma who underwent complete resection from January 2014 to September 2018 and examination of genomic alterations using whole-exome sequencing at our institution were screened. Among them, 121 had common EGFR mutations (exon 19 deletions or L858R). We divided these patients into two groups according to co-mutation status of TP53 alteration: TP53 co-mutation group and TP53 wild group. We then compared clinicopathological features, prognostic outcomes, recurrence patterns, and the efficacy of EGFR-TKI treatment post-recurrence between these groups.

Results: TP53 co-mutations were identified in 22 cases (18.2%). The TP53 co-mutation group had significantly more lymphovascular invasion (p = 0.037) and a higher tumor mutation burden (p = 0.007) compared with the TP53 wild group. The TP53 co-mutation group exhibited poorer recurrence-free and overall survival rates [hazard ratio (HR) 2.32, 95% confidence interval (CI) 1.12-4.85, p = 0.025; HR 2.54, 95% CI 1.01-6.36, p = 0.047, respectively] than TP53 wild group. Among the entire cohort of 121 patients, 33 experienced recurrences. Of these, nine patients were in the TP53 co-mutation group, and 24 were TP53 wild group. In the analysis of the initial recurrence sites, there were no significant differences between the two groups. After recurrence, six patients in the TP53 co-mutation group received EGFR-TKIs as first-line treatment (two were treated with first- or second-generation TKIs and four were osimertinib), and 13 patients in the TP53 wild group (eight were first- or second-generation TKIs and five were osimertinib). Progression-free survival in those treated with first-line EGFR-TKIs did not differ significantly between the groups.

Conclusions: The TP53 co-mutation in completely resected early-stage lung adenocarcinoma harboring common EGFR mutation was associated with poor pathological characteristics, and may be associated with poor recurrence-free survival and overall survival. The efficacy of TKI treatment after recurrence needs to be further investigated by collecting more cases.

Keywords: EGFR, TP53, Co-mutation

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.14 Exploring the Effect of Surgical Resection on Quality of Life in Older Adults for Stage IA Non-Small Cell Lung Cancer

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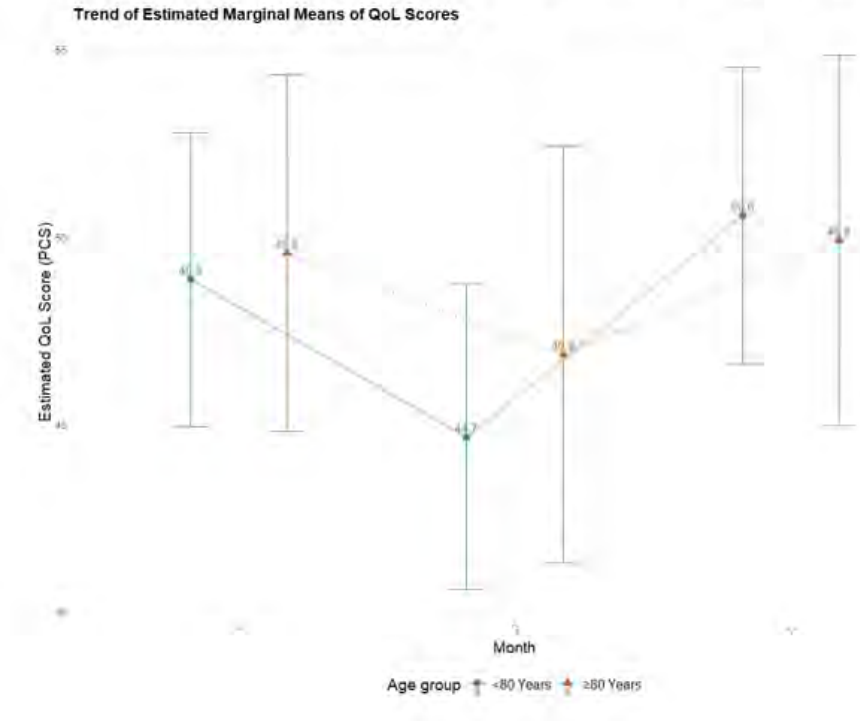
Introduction: With the tremendous strides made in expanding and improving lung cancer screening programs, an increasing number of older individuals are diagnosed with early-stage lung cancer, where surgical resection is curative. Despite this, a balance must be achieved between the need to treat for physicians versus the need to maintain a good quality of life (QoL) for patients, especially for the oldest. We explored the effect of surgical resection on QoL for patients <80 (non-octogenarians) and those ≥80 (octogenarians).

Methods: The study used a prospective cohort of Stage IA non-small cell lung cancer patients enrolled in the Initiative for Early Lung Cancer Research on Treatment (IELCART) study since 2016 who underwent surgery. QoL was measured before surgery, and at 1-, 6- and 12-months post-surgery using SF-12 [physical (PCS) and mental health (MCS)]. Sociodemographic and clinical factors, nodule and surgery characteristics were compared between octogenarians and non-octogenarians. We applied a piecewise linear mixed-effects model to track QoL shifts, with an inflection point at 2 months post-surgery to capture the recovery phase. After adjusting for sociodemographic and clinical variables, including sex, smoking status and pack-years, maximum nodule size on CT, nodule consistency, histology, surgery extent, and type of surgery, the model was used to estimate the baseline, 2-month, and 12-month marginal means of QoL scores.

Results: 818 patients were included, with 104 (12.7%) octogenarians and 714 (87.3%) non-octogenarians. The estimated baseline PCS score was 49.57 for octogenarians and 48.86 for non-octogenarians. At 2 months post-surgery, PCS scores dropped to 46.86 for octogenarians and 44.66 for non-octogenarians. By 12 months post-surgery, both groups showed improvement, with scores of 49.90 for octogenarians and 50.57 for non-octogenarians. The estimated baseline MCS scores were 49.89 for octogenarians and 49.28 for non-octogenarians. At 2 months, scores changed to 47.73 for octogenarians and 49.26 for non-octogenarians, with both improving by 12 months to 50.25 and 50.66, respectively. Pairwise comparisons showed no statistically significant differences between age groups at any time point for either PCS or MCS scores (all p-values >0.90). The comparison did not show any clinically significant (2-3 points) differences between age groups either.

Conclusions: Physical and mental health QoL measures returned to baseline for both non-octogenarians and octogenarians 12 months post-surgery. With the appropriate pre-surgical tests and evaluation, octogenarians can fully be cured of early-stage lung cancer without diminishing their QoL. Longer-term QoL needs to be studied to fully understand the effect of surgery on health outcomes.

Figure 1: Estimated Marginal Means of SF-12 Physical Component Summary (PCS) Scores Comparing Quality of Life in Octogenarians and Non-Octogenarians Undergoing Surgery for Stage IA Lung Cancer at Baseline, 2 Months, and 12 Months Postoperatively



Keywords: quality of life, octogenarians, lung cancer surgery

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.15 Oncologic Outcomes of Sublobar Versus Lobar Resection for Clinical Stage IA Pure Solid Non-Small Cell Lung Cancer

D.W. Yoon[1], S. Shin[2], Y.J. Jeon[3], J. Lee[3], S.Y. Park[3], J.H. Cho[3], Y.S. Choi[3], H.K. Kim[3], H.Y. Lee[3]
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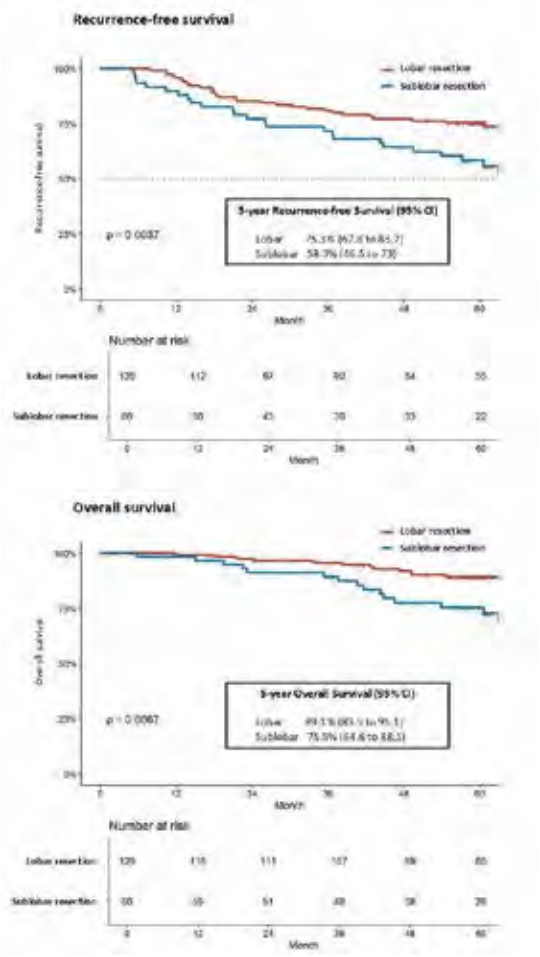
Introduction: The impact of sublobar resection (SL) on the prognosis of small (<3 cm) non-small cell lung cancer (NSCLC) remains uncertain, especially when manifesting as a pure solid nodule on computed tomography. This study aims to evaluate oncologic outcomes in patients with clinical stage IA pure solid NSCLC undergoing SL compared to lobar resection (L).

Methods: Patients with clinical stage IA pure solid NSCLC who underwent curative-intent SL (n=60) or L (n=303) between August 2018 and October 2020 were retrospectively analyzed. After 1:2 propensity score matching based on age, ASA classification, and clinical T category, 60 SL and 120 L patients were included in the final analysis. Recurrence-free survival (RFS), overall survival (OS), and recurrence patterns were analyzed.

Results: After matching, no significant differences were observed between the SL and L groups in terms of age, sex, ASA classification, pulmonary function, clinical T category, peripheral tumor location (outer two-thirds), or pathologic stage. The SL group was associated with significantly fewer dissected lymph nodes than the L group (median, 8 vs. 20; p < 0.01), and pathologic lymph node metastasis (pN+) was less frequent in the SL group (6.7% vs. 13.0%; p = 0.20), although this difference was not statistically significant. Furthermore, significantly fewer patients in the SL group received adjuvant treatment (3.4% vs. 16.0%; p < 0.01). The SL group also showed significantly lower 5-year RFS (58.3% vs. 75.3%; p < 0.01) and OS (75.5% vs. 89.1%; p = 0.01) compared with the L group. Overall recurrence rates were 30.0% in the SL group and 20.8% in the L group (p = 0.20). The incidence of isolated locoregional recurrence (5.0% vs. 0.8%; p = 0.11) and systemic recurrence with concurrent locoregional involvement (8.3% vs. 2.5%; p = 0.12) were higher in the SL group, although the differences were not statistically significant. Systemic recurrence alone was comparable between groups (16.7% vs. 17.5%; p = 1.00).

Conclusions: In real-world practice for patients with clinical stage IA pure-solid NSCLC, the SL group showed significantly worse 5-year survival outcomes compared to the L group. This may be partly explained by the lower number of dissected lymph nodes in the SL group, which could have led to under-staging and, consequently, missed opportunities for appropriate adjuvant therapy. These findings indicate that further research is needed to define appropriate indications for SL in pure-solid NSCLC.



Keywords: sublobar resection, pure-solid NSCLC

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.16 The Association Between Sarcopenia and Postoperative Outcomes and Survival in Lung Cancer Patients Who Underwent Curative Resections

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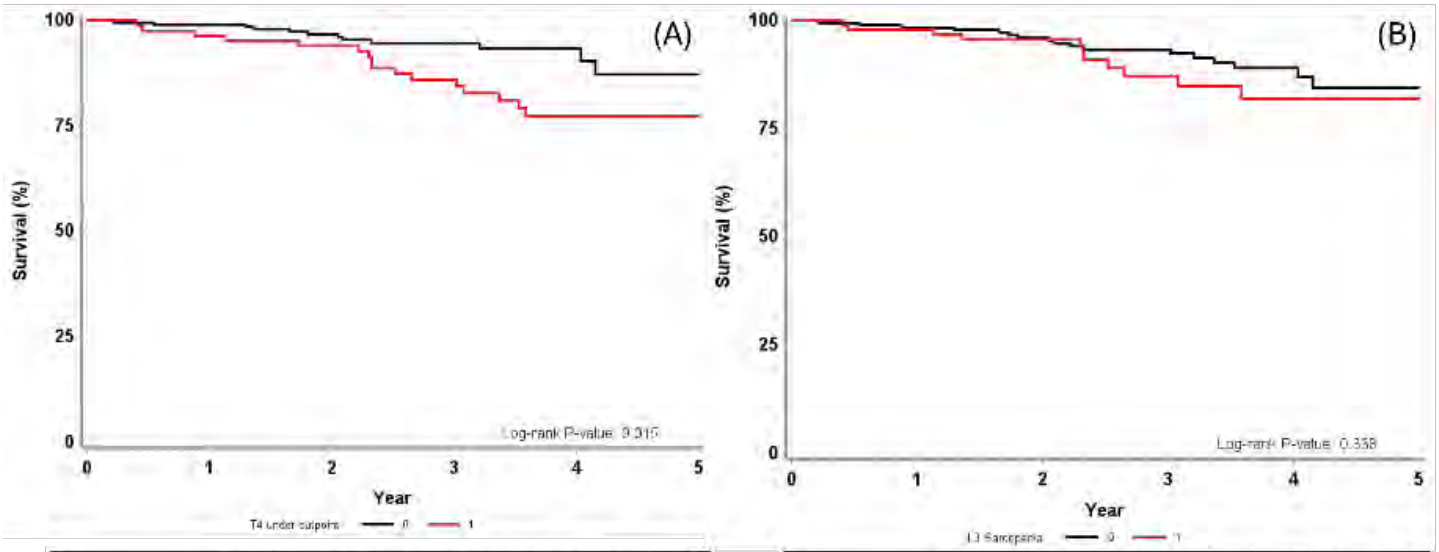
Introduction: Sarcopenia, defined as loss of skeletal muscle by the psoas muscle index at the third lumbar (L3) vertebral body, has been associated with post-operative morbidity and mortality. This study evaluated sarcopenia at the fourth thoracic (T4) vertebral body and its association with respiratory postoperative complications (RPOC) and 5-year survival following lung cancer resection (LCR).

Methods: Retrospective cohort study of individuals who underwent LCR from 11/2011-12/2021. Sarcopenia was assessed at L3 using positron emission tomography (PET) scans and at T4 using computerized tomography (CT). Optimal sex-specific T4 cutpoints were identified using Youden's index; traditional L3 cutpoints were employed. Primary outcome was RPOC; secondary outcomes were any postoperative complication (APOC) and 5-year overall survival for Stage 1 LC. Univariate and multivariable logistic regressions were performed using a backward selection method, starting with anatomic resection, age, and waist-hip ratio, and retaining only variables with a p-value of less than 0.05. For survival analysis, Kaplan-Meier curves and Cox regression models were performed.

Results: Among 431 individuals, the prevalence of sarcopenia was 33% by L3 and 64% by T4. On univariate, T4 sarcopenia was significantly associated with an increased odds of RPOC (OR=1.83, 95%CI[1.06-3.13], p=0.027). In multivariable, T4 was associated with RPOC (OR=1.61, 95%CI[1.02-2.98], p = 0.090); DLCO<60 was statistically significant in the final model. DLCO 40to<60 (OR=2.59, 95%CI 1.33-5.07, p = 0.005) and DLCO<40 (OR=2.34, 95%CI[1.33-4.72], p=0.018). L3 was statistically associated with APOC in both univariate analysis and the multivariable final model (OR=1.94, 95%CI[1.24-3.04], p=0.004). Anatomic resections (OR=2.13, 95%CI[1.28-3.54] p=0.004); Age>70 (OR=1.59, 95%CI[1.04-2.43], p=0.033), DLCO<70(OR=1.79, 95%CI[0.37-2.70], p=0.006) increased the likelihood of APOC. Sarcopenia at T4 and DLCO<60 was associated with worse five-year survival.

Conclusions: T4 sarcopenia is associated with increased RPOC and worse five-year survival. Further analysis with larger sample sizes is necessary to evaluate these associations thoroughly.



	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
T4 over cut point						
Number at risk	225	193	147	87	33	6
Survival	100%	99.1%	96.8%	94.6%	93.4%	87.3%
Standard error	0	0.006	0.013	0.018	0.022	0.046
T4 undercut point						
Number at risk	85	80	75	56	26	3
Survival	100%	96.4%	94.0%	86.1%	77.4%	77.4%
Standard error	0	0.020	0.026	0.039	0.051	0.051

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
No L3 sarcopenia						
Number at risk	208	184	150	102	42	5
Survival	100%	98.5%	96.1%	93.4%	89.1%	84.6%
Standard error	0	0.009	0.014	0.019	0.028	0.041
L3 sarcopenia						
Number at risk	102	89	72	41	17	4
Survival	100%	98.0%	95.7%	87.3%	82.1%	82.1%
Standard error	0	0.014	0.021	0.041	0.053	0.053

Table 1. Study cohort characteristics by respiratory complications

		Total (n=431)	No respiratory complication (n=348)	Respiratory complication (n=83)	p-value
		N (%)	N (%)	N (%)	
Male gender		156 (36)	121 (35)	35 (42)	0.210
White race		404 (94)	326 (94)	78 (94)	0.920
Hypertension		284 (66)	231 (66)	53 (64)	0.660
Coronary Artery Disease		93 (22)	76 (22)	17 (20)	0.790
Diabetes		76 (18)	62 (18)	14 (17)	0.840
Obese		166 (39)	143 (41)	23 (28)	0.024
Waist-hip ratio					0.330
	Low risk	68 (16)	56 (16)	12 (14)	
	Moderate risk	61 (14)	45 (13)	16 (19)	
	High risk	302 (70)	247 (71)	55 (66)	
BMI					0.038
	Under 18.5	10 (2.3)	9 (2.6)	1 (1.2)	
	18.5 to < 25	129 (30)	93 (27)	36 (43)	
	25 to < 30	141 (33)	116 (33)	25 (30)	
	30 to <35	89 (21)	74 (21)	15 (18)	
	35 to < 40	35 (8.1)	33 (9.5)	2 (2.4)	
	40+	27 (6.3)	23 (6.6)	4 (4.8)	
		Median (IQR)	Median (IQR)	Median (IQR)	
Age		68 (62, 73)	67 (61, 73)	70 (63, 74)	0.090
WHR		0.997 (0.932, 1.069)	0.995 (0.931, 1.058)	1.000 (0.938, 1.121)	0.230
Last Creatinine Level		0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)	0.180
Last Hemoglobin Level		13.7 (12.7, 14.6)	13.6 (12.7, 14.6)	13.9 (12.8, 14.7)	0.820
FEV1 Predicted		83.0 (69.0, 96.0)	84.0 (70.0, 96.5)	81.0 (67.0, 95.0)	0.360
Pack-Years Of Cigarette Use		38.0 (15.0, 50.0)	36.0 (15.0, 50.0)	40.0 (20.0, 50.0)	0.540
		N (%)	N (%)	N (%)	
DLCO predicted					0.006
	<40	71 (17)	52 (15)	19 (23)	
	40 to <60	82 (19)	58 (17)	24 (29)	
	60 to <75	107 (25)	88 (26)	19 (23)	
	75 to 140	166 (39)	145 (42)	21 (25)	
ECOG Score					0.990
	0	276 (65)	225 (65)	53 (64)	
	1	137 (32)	110 (32)	27 (33)	
	2	16 (3.7)	13 (3.7)	3 (3.6)	
Stage					0.330
	Stage IA1, Stage IA2, Stage IA3, Stage IB	311 (72)	257(74)	61 (73)	
	Stage IIA, Stage IIB, Stage IIIA, Stage IIIB, Stage IV, Stage IVA	120 (28)	91(26)	22 (27)	
VATS approach		356 (83)	288 (83)	68 (82)	0.86
Adjuvant Chemotherapy		79 (19)	65 (19)	14 (17)	0.68
Adjuvant Radiotherapy		16 (3.8)	14 (4.1)	2 (2.4)	0.22
		Median (IQR)	Median (IQR)	Median (IQR)	
Length of Stay Surgery to Discharge		4.0 (3.0, 7.0)	4.0 (3.0, 5.0)	8.0 (6.0, 11.0)	<0.000 1
		N (%)	N (%)	N (%)	
Sarcopenia_Pre_T4 cut off point. 48.5 for women, 68.9 for men		277 (64)	215 (62)	62 (75)	0.027
Sarcopenia L3 criteria Literature 39 for women, 55 for men		143 (33)	112 (32)	31 (37)	0.37

Keywords: Lung Cancer Resections, Sarcopenia, Survival

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.17 A Neglected Dimension in Lung Cancer Surgery: Sleep Disorders Before and After Anatomical Resection

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Introduction: Sleep disorders are frequently underdiagnosed in lung cancer patients undergoing surgery, despite their potential detrimental effects on surgical outcomes. Moreover, anxiety and complications are traditionally associated with impaired sleep quality. This study aims to investigate the preoperative prevalence of sleep disturbances in this population, evaluate postoperative sleep changes, and identify contributing factors.

Methods: From January to August 2024, consecutive patients with lung cancer scheduled for upfront minimally-invasive anatomical lung resection at a tertiary university referral center have been prospectively enrolled. Sleep was assessed preoperatively, 45 days and six months after surgery through polysomnography using the Apnoea-Hypopnea-Index (AHI), Epworth-Sleepiness Scale (ESS), International Physical Activity Questionnaire (IPAQ), and Short Form-36 (SF-36) tests. Descriptive statistics were reported as mean±standard deviation or frequency (%). Statistical analysis was performed using SPSS version 23.0, including Chi-square, Mann-Whitney and logistic regression tests.

Results: To date, 32 patients have been enrolled; demographics and baseline pulmonary function results are shown in Table1. 68.8% (22/32) of patients underwent lobectomy, 31.2% (10/32) received segmentectomy; 59.4% of procedures were performed by VATS, 40.6% by RATS. Histologic subtypes included adenocarcinoma (62.5%), squamous cell carcinoma (31.2%), and large cell carcinoma (6.3%). According to 9th TNM edition the tumor was staged I in 65.6%, II in 28.1%, IIIa in 6.3%. The average baseline-AHI was 10.13±9.10 events/h, with an ESS-score of 5.2±3.8. Notably, 46.9% (15/32) of patients had an AHI>5 events/h, suggesting previously undiagnosed sleep apnoea. Hypertension (p-value=0.036), cardiovascular disease (p-value=0.028), and ASA-status (p-value<0.001) were positively associated with preoperative undiagnosed sleep disorders. Early postoperative data revealed that 37.5% (12/32) of patients experienced significant sleep deterioration, persisting at 6 months, while 62.5% (20/32) maintained stable sleep parameters. Sleep deterioration was significantly associated with lobectomy (p-value=0.041), stage II-IIIa disease (p-value=0.045), smoking history (p-value=0.002), hypertension (p-value=0.026) as well as other cardiovascular diseases (p-value=0.039). Interestingly, non-adenocarcinoma histology showed a trend towards increased sleep deterioration, though without reaching statistical significancy (p-value=0.053).

Conclusions: Routine preoperative sleep evaluation can uncover undiagnosed sleep disorders in lung cancer patients, potentially enhancing clinical preparation to surgery. Furthermore, a significant proportion of patients may experience new or worsening postoperative sleep disturbances, possibly related to the extent of resection, disease stage, smoking history, and cardiovascular comorbidities, warranting close perioperative monitoring. Further research is ongoing to assess whether targeted interventions on sleep quality can improve postoperative outcomes. In the era of tailored multimodal strategies, sleep health should no longer be excluded from the multidisciplinary assessment of lung cancer patients.

Demographics	N = 32
Females, n (%)	14 (43.8)
Age in years, mean (SD)	67.0 (11.0)
BMI, mean (SD)	25.7 (6.2)
Smoke exposition, n (%)	19 (59.4)
Packs-years, mean (SD)	29.3 (17.4)
Acute coronary syndrome, n (%)	2 (6.3)
Hypertension, n (%)	14 (43.8)
Atrial fibrillation, n (%)	2 (6.3)
Any cardiovascular pathology, n (%)	16 (50.0)
COPD, n (%)	5 (15.6)
Sleep-interfering drugs, n (%)	9 (28.1)
Mallampati, n (%)	
Score I	8 (25.0)
Score II	17 (53.1)
Score III	7 (21.9)
ASA score, n (%)	
ASA I	1 (3.1)
ASA II	19 (59.4)
ASA III	12 (37.5)
ppFEV1, mean (SD)	98.29 (17.52)
ppFVC, mean (SD)	105.14 (15.14)
FEV1/FVC, mean (SD)	0.73 (0.09)
ppDLCO, mean (SD)	77.70 (21.03)

Abbreviations: SD: Standard Deviation; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; ASA: American Society of Anesthesiologists; ppFEV1: percent predicted Forced Expiratory Volume in the 1st second; ppFVC: percent predicted Forced Vital Capacity; ppDLCO: percent predicted Carbon monoxide Lung Diffusion Capacity.

Keywords: Sleep Disorders, Non-Small Cell Lung Cancer, Surgery

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.18 Peri-Operative Immune Cell Profiling in Lung Cancer Resection: A Longitudinal Study

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Introduction: Resection surgery for non-small cell lung cancer (NSCLC) is known to trigger systemic inflammation and immunosuppression. CD45RA and CCR7 are markers used to identify naïve, central memory, effector memory and terminal differentiated T cells. Progressive differentiation occurs with down-modulation of CD45RA followed by re-expression in terminal differentiation, alongside the loss of CCR7. This results in T cell senescence, a dysfunctional cellular pathway, acting as T regulatory (Treg) cells and leading to tumour immunity evasion. CD127 is down modulated on Treg cells and signalling through its ligand IL7 is impaired in malignancy. CD25+CD127- markers are used to describe a subtype of Treg cells. Tregs and T cell senescence have been shown to negatively impact overall survival in NSCLC, and a poor prognostic indicator for those undergoing immunotherapy treatment. γδ T cells display potent anti-tumour properties in NSCLC, with trials ongoing for therapeutic use. Vδ1 and Vδ2 are the two main subtypes. We present a longitudinal study examining T cell populations in the peri-operative blood of patients with resectable NSCLC.

Methods: Pre-operative (baseline), and postoperative 2-4 days (1FU) and 6-9 weeks (2FU) post-surgery peripheral blood mononuclear cells (PBMCs) in 18 patients via MultiColour flow cytometry were analysed, using BD LSRFortessa. 56% were female, 67% over 65, 66% adenocarcinoma histology, with Stage 1A to 3A. Median time to follow up is 7 months. FlowJo v10.0 software was utilised to quantify the expression of CD3+, CD4+, CD8+, Vδ1 and Vδ2 T cells, biomarkers CD45RA, CCR7, CD25, CD127 also reviewed. Student's T test and ANOVA were performed on parametric data and Wilson Signed Rank and Friedman's test on non-parametric data via STATABE v18.0 software.

Results: CD45RA positivity, significantly reduced across all timepoints for CD4+ (p= 0.0006) and CD8+ (p= 0.0302) T cells. CD45RA+CCR7+ (naïve T cells) significantly reduced between baseline and 2nd follow up (p=0.0112, p=0.0055). Terminally differentiated T cells (CD45RA+CCR7-) increased across timepoints, however this was not statistically significant (p=0.1787) CD4+CD25+CD127- (denoted CD4+ Treg Cells) significantly increased throughout the three timepoints (p=0.0242). On review of the γδ T cells population, Vδ2 cells increased significantly between baseline and 2nd follow up (p=0.0208). This study shows a reduction of naïve T cells and a move toward terminal differentiation, 6-9 weeks after lung cancer surgery, however this was not statistically significant (p=0.1787). CD4+ Tregs increased significantly (p= 0.0242) between timepoints. These cell populations drive immunosuppression and are poor prognostic indicators for patients undergoing adjuvant treatment. Anti-tumour immune cells, Vδ2, γδ T cells, showed statistically significant increase (p=0.0208) between baseline and 2nd follow up, with 1.65% frequency. Memory and effector T cells as well as correlation with clinicopathological characteristics will be presented. Cohort is currently under expansion to 45 patients, if numbers change to significant when data set increased, this will be presentation.

Conclusions: There is a complex interplay between pro-tumour and anti-tumour immunity post resection for NSCLC. Monitoring for T cell senescence and the increase of Treg cells and γδ T cells can give keen insights into survival as well as prognostic indicators for immunotherapy.

Keywords: Immunology profiling, lung cancer resection surgery, Senescent T Cells

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.19 Prospective Cohort Study on Stage 1A Non-Small Cell Lung Cancer in Older Adults (>80 Years): Prevalence, Surgical Treatment, and Complications

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Introduction: With rising life expectancy, more older adults are diagnosed with lung cancer, yet those aged ≥80 years are often excluded from screening programs and trials due to concerns about comorbidities and surgical risks. Data are limited. This study examines the prevalence, clinical presentation, surgery, and postoperative complications in patients aged ≥80 years undergoing surgery for early-stage lung cancer.

Methods: We analyzed data from the Initiative for Early Lung Cancer Research for Treatment (IELCART), a prospective multi-institutional cohort study initiated in 2016. Patients included in this analysis underwent surgical resection for lung cancers measuring ≤30 mm. We compared patients aged ≥80 years to younger ones using descriptive statistics to assess clinical presentation, surgery, and postoperative outcomes.

Results: Among 864 patients who underwent surgery for lung tumors ≤30 mm, 112 (13%) were aged ≥80 years. The median age in this group was 82 years (IQR 81-85) compared to 69 years (IQR 63-74) in patients <80 (p<0.001). Fewer older patients were female (51% vs. 62%, p=0.03). Self-reported race differed significantly between age groups. Patients aged ≥80 were less frequently African American (8.9% vs. 15%) and Asian (6.3% vs. 12%), and more frequently White (79% vs. 60%) or categorized as Other (5.4% vs. 13%) (p=0.001).

Older patients had fewer current smokers (3% vs. 13%) and more former smokers (72% vs. 59%), while never-smoker rates were similar (25% vs. 28%, p=0.002). Comorbidities were generally comparable, including hypertension (57% vs. 51%, p=0.3) and diabetes (15% vs. 20%, p=0.2), but COPD was significantly less common in the older group (9.8% vs. 22%, p=0.002).

Radiologic features were similar between patients aged ≥80 and <80, including nodule consistency (solid: 78% vs. 83%; part-solid: 22% vs. 17%, p=0.3), size (16 mm vs. 15 mm, p=0.3), and location (p>0.9). Older patients underwent fewer lobectomies (21% vs. 33%) and more wedge resections (71% vs. 57%) and segmentectomies (8% vs. 6.9%) (p=0.008). Resected tumors were larger in the older group (18 mm vs. 16 mm, p=0.015). Histology differed (p=0.002), with more adenocarcinomas (88% vs. 75%) and fewer squamous carcinomas (8% vs. 10%) in older patients. Angiolymphatic invasion was more frequent (41% vs. 29%, p=0.008), while vascular invasion (3.6% vs. 3.6%, p > 0.9) and margin status (15 mm vs. 15 mm, p=0.6) were similar.

Postoperative hospital stay was similar (median 3 days, p=0.10), but complications were more frequent in older patients (40% vs. 22%, p<0.001), particularly cardiovascular (11% vs. 5.9%, p = 0.051). Pulmonary (8.9% vs. 5.9%, p=0.2) and infectious (1.8% vs. 0.8%, p=0.3) complications were comparable. ICU admissions (2.7% vs. 0.8%, p=0.1) and 30-day readmissions (7.1% vs. 3.3%, p=0.06) were slightly higher but not statistically significant.

Conclusions: Among 864 patients with resected lung cancer ≤30 mm, 13% were aged ≥80 years. They had similar comorbidities and tumor characteristics but underwent fewer lobectomies and more sublobar resections. In older patients, adenocarcinomas with angiolymphatic invasion were more frequent. Despite more complications, hospital stay and short-term recovery remained comparable to patient<80. Further research is needed to refine screening and treatment for this understudied group.

Keywords: Elderly, Early-stage lung cancer, Complications

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.20 Feasibility of Limited Resection in Invasive Mucinous Adenocarcinoma of the Lung

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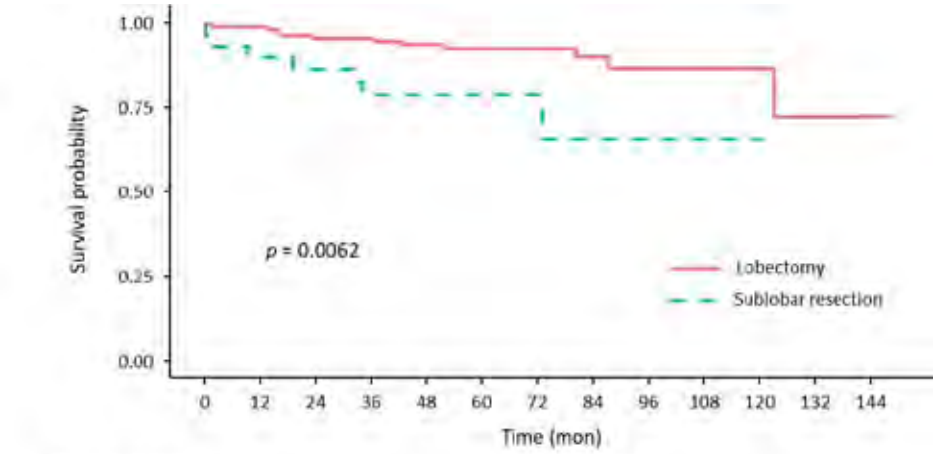
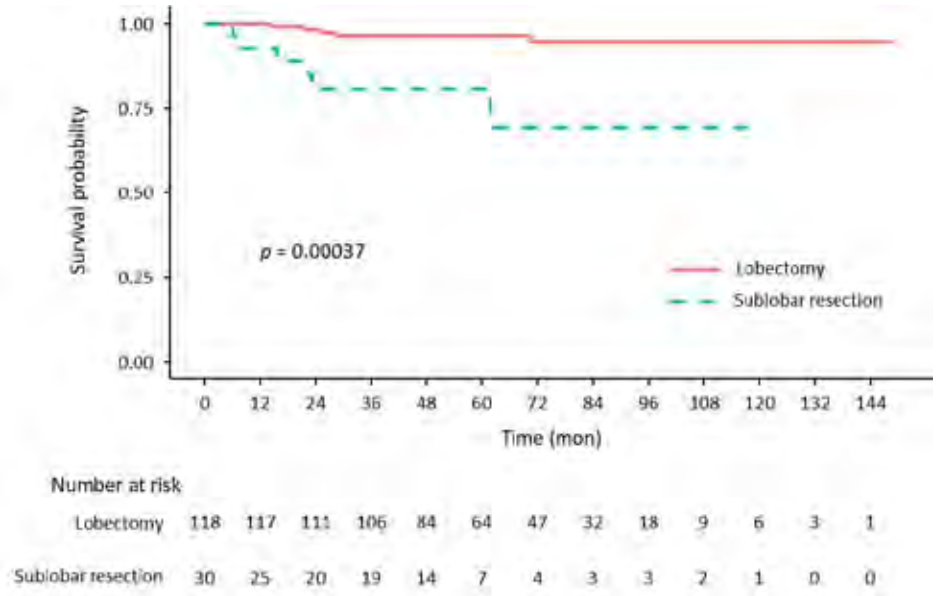
Introduction: Pulmonary Invasive mucinous adenocarcinoma (IMA) is a relatively rare subtype of invasive lung adenocarcinoma. However, the effects of sublobar resection of early-stage IMA remain unclear. This study aimed to evaluate the clinical and oncological outcomes of sublobar resection compared with lobectomy in patients with stage I IMA.

Methods: We retrospectively reviewed patients who underwent surgical resection for stage I lung cancer between 2011 and 2021. Among 2,333 patients, 148 were pathologically diagnosed with IMA. Patients were categorized into two groups based on the surgical procedure: lobectomy and sublobar resection. Clinical characteristics, surgical outcomes, and oncologic outcomes, including overall survival (OS) and relapse-free survival (RFS), were analyzed.

Results: Of the 148 patients with IMA, 118 underwent lobectomy and 30 underwent sublobar resection. During the follow-up period, 11 patients experienced recurrence, 6 in the sublobar group and 5 in the lobectomy group. The sublobar resection group demonstrated significantly worse OS (49.1 vs. 61.0 months, p = 0.009, figure 1) and RFS (45.8 vs. 60.8 months, p = 0.002, figure 2). Notably, all patients in the sublobar group had stage IA disease (100% vs. 74.6% in the lobectomy group, p = 0.005). Other clinical characteristics were comparable between the groups.

Conclusions: Despite being limited to early-stage disease, sublobar resection in IMA was associated with inferior oncologic outcomes compared to lobectomy. These findings suggest that limited resection should be approached with caution in patients with early-stage IMA.





Keywords: Invasive mucinous adenocarcinoma, Sublobar resection, stage I lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.21 Lobectomy Versus Multi-Segmentectomy for Left Upper Lobe Lung Cancer: A Propensity Score-Matched Analysis

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Introduction: Lobectomy has been the gold standard of surgical treatment for resectable lung cancer. However, recent advancements in imaging and surgical techniques have allowed for the expansion of indications for segmentectomy, particularly for small, peripheral tumors. The left upper lobe is divided into two anatomical units: the upper division (segments 1+2 and segment 3) and lingula (segments 4 and 5), similar to the right upper and middle lobes. Therefore, we hypothesized that multi-segmentectomy, such as trisegmentectomy and lingulectomy, may offer oncologic outcomes comparable to lobectomy for left upper lobe lung cancer. In this study, we compared the oncologic outcomes and survival rates of lobectomy versus multi-segmentectomy in patients with tumors located in the left upper lobe.

Methods: In this retrospective study, we included patients who underwent either lobectomy or multi-segmentectomy resection for left upper lobe lung cancer at two institutions between January 2012 and December 2017. Propensity score matching (PSM) was used to balance baseline characteristics and facilitate fair comparison between the two groups; 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) and patterns of local and distant recurrence were assessed. Additionally, a subgroup analysis was performed for patients with relatively advanced disease, defined as tumor diameter > 2 cm and the consolidation-to-tumor ratio (CTR) > 0.5.

Results: A total of 191 and 57 patients underwent lobectomy and multi-segmentectomy, respectively. Before PSM, there was no significant difference in OS between the two groups. s, although RFS was better in the multi-segmentectomy group. After matching, 53 patients were included in each group, and significant preoperative disparities, such as tumor size and CTR, were effectively neutralized. Post PSM, both OS and RFS remained comparable between the two groups, indicating similar long-term outcomes. Rates of local and distant recurrence were also not significantly different between the two groups. In the subgroup of patients with tumor diameter > 2 cm and CTR > 0.5, no significant differences in OS and RFS were observed.

Conclusions: Our findings suggest that multi-segmentectomy is a lung-sparing alternative to lobectomy for patients with left upper lobe lung cancer, with comparable 5-year OS and RFS. Subgroup analysis comparing the prognosis of relatively advanced cases suggests that multi-segmentectomy for left upper lobe lung cancer may be indicated for more advanced cases. It may also be especially beneficial for patients in whom lung preservation is important due to age or general condition. Further prospective studies are warranted to validate these findings and clarify the patient populations that benefit most from these lung-sparing surgical procedures in left upper lobe lung cancer.

Keywords: Lung cancer, Segmentectomy, Propensity score matching

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.22 LANTERN1: AI Model for Postoperative Complications Prediction for NSCLC Lung Resection: Prospective Multicentric Study and Extern Validation

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Introduction: Artificial intelligence(AI) may combine omics datasets to create predictive models. LANTERN-project comprises prospective multicenter observational clinical trial involving five European centers. This study aims to develop AI-based predictive model of post-operative complications after lung resection for NSCLC.

Methods: In LANTERN-project Consortium, data from 212 lung cancer patients were retrospectively collected from 5/2023 to 3/2024. Among these, 170 underwent curative surgery for Stage I-III NSCLC and were analyzed, taking into account 59 preoperative clinical features and 52 spirometric variables, to predict post-operative complications. Prediction models were developed on the basis of different feature selection algorithms (MIM, MRMR, Lasso logistic regression) and machine-learning models (logistic regression, elastic-net logistic regression, random forest). Performance was assessed based on 3-fold cross validation using the area under the curve (AUC)metric for clinical parameters only, spirometry parameters only, and their combination. External dataset of 232patients surgical series from a large-volume cancer center was adopted following TRIPOD level2b methodology (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis). The external cohort was homogenous to ours concerning p-stage, kind of surgery and number of complications.

Results: Clinical characteristics are reported in table1. Majority of patients had Stage I disease(135; 79.4%) and underwent lobectomy (98; (57.8%). 29 patients(17.1%) experienced post-operative complications. AI-based models showed Charlson comorbidity index (pathologic score) (AUC=0.70, 95% CI[0.60-0.80])(Figure 1A) and pre-opFEV1 (AUC=0.77, CI[0.65-0.89])(Figure 1B) were the most relevant variables. Combining them, improved overall prediction was obtained (AUC=0.82, CI[0.72-0.92])(Figure 1C).Testing the models on the extern dataset, pathologic score alone was not confirmed to be a predictive factor (AUC=0.49 CI[0.41-0.57]). Pre-opFEV1 (AUC=0.28 CI[0.21-0.34]) and combination of Pathologic score and pre-opFEV1 (AUC=0.68 CI[0.61-0.75]) were confirmed to predict post-op outcome (figure 2). Analysis to predict the cardiovascular complications only (cardiac ischemia, pulmonary embolism, and atrial fibrillation) and the respiratory complications only (pleural effusion, air leakage, subcutaneous emphysema, and pneumonia) was performed. Only pre-opFEV1 was validated (AUC= 0.24 CI[0.13-0.36] and 0.31 CI[0.23-0.39], respectively) for both kind of complications, as well as the combined model (pathological score and pre-opFEV1) (AUC=0.70 CI[0.57-0.83] and 0.66 CI[0.57-0.74]) even though the validation performance was reduced if compared to the FEV1 alone.

Conclusions: Combining collected preoperative data, the identified factors predicted post-operative complications, in particular, FEV1 and (to a lesser extent) the pathologic score. The external validation confirmed that FEV1 only can accurately predict post-operative complications. This parameter could improve the process of counselling and the perioperative management of lung resection candidates.

		N. of patients
Age at surgery ± SD		67.6 ± 10.5
ECOG	0	105 (61.8%)
	1	62 (36.5%)
	2	3 (1.7%)
Smoker	Yes	47 (27.6%)
	No	32 (18.8%)
	Former	91 (53.6%)
COPD	Yes	52 (30.6%)
	No	118 (69.4%)
Heart disease	Yes	109 (64.1%)
	No	61 (35.9%)
Age score	0	2 (1.2%)
	1	8 (4.7%)
	2	22 (12.9%)
	3	61(35.9%)
	4	77 (45.3%)
Pathologic score	=5	118 (69.4%)
	>5	52 (30.6%)
cStage VIII edition	I	135 (79.4%)
	II	18 (10.6%)
	III	15 (8.8%)
	IV	2 (1.2%)
Surgery	Lobectomy	98 (57.8%)
	Bilobectomy	3 (1.7%)
	Segmentectomy	22 (12.9%)
	Pneumonectomy	3 (1.7%)
	Wedge resection	44 (25.9%)
Mean operating time ± SD		138.9 ±50.4
Histology	Adenocarcinoma	128 (75.3%)
	Squamous cell carcinoma	25 (14.7%)
	Other	17 (10%)
Complications	Yes	29 (17.1%)
	No	141 (82.9%)
Cliven Dindo grade	I	7 (24.1%)
	II	10 (34.5%)
	IIIa	7 (24.1%)
	IIIb	5 (17.3%)

Table 1. Clinical-pathological features

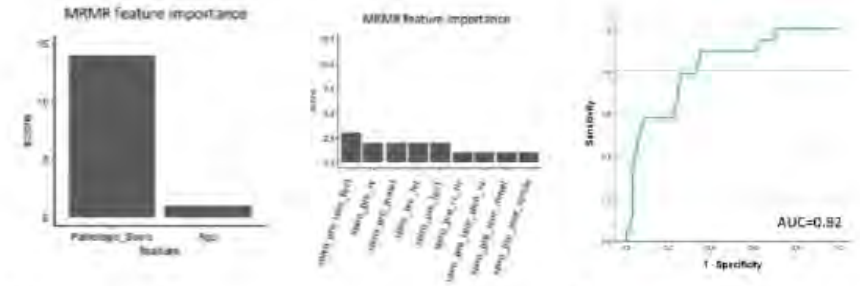

Figure 1. A. Charlson age comorbidity index (pathologic score) (AUC=0.70, 95% CI=[0.60-0.80]) **B.** FEV1 (AUC=0.77, CI [0.65-0.89]) **C.** ROC curve of the final model combining pathologic score with FEV1

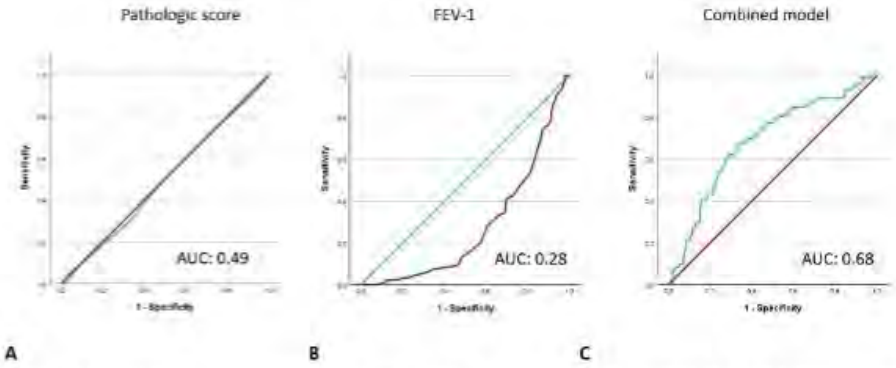

Figure 2. A. Charlson age comorbidity index (pathologic score) (AUC=0.49, 95% CI=[0.41-0.57]) **B.** FEV1 (AUC=0.28, 95% CI=[0.21-0.34]) **C.** Curve of the final model combining pathologic score with FEV1 (AUC= 0.68, 95% CI=[0.61-0.75])

Keywords: Artificial Intelligence, NSCLC, Surgery

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.23 Impact of Pulmonary Resection on Early Postoperative Cardiac Function

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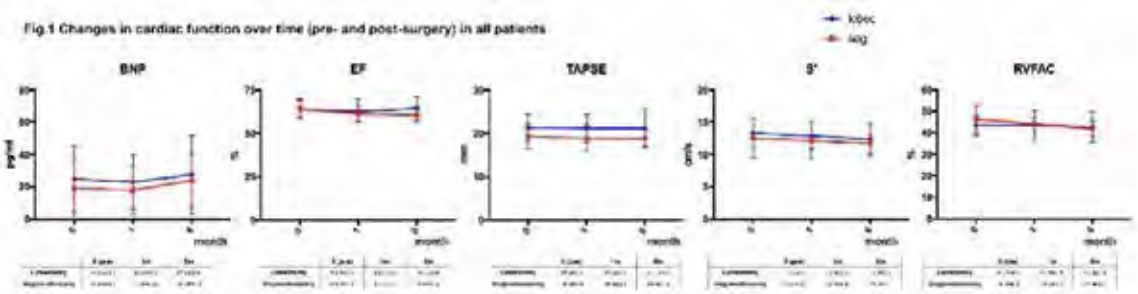
Introduction: The JCOG0802 trial demonstrated that segmentectomy yielded better prognostic outcomes than lobectomy, previously considered the standard surgical approach. One possible reason for this is the lower incidence of non-lung cancer-related deaths in the segmentectomy group. While comparisons of postoperative cardiac function between pneumonectomy and lobectomy have been reported, similar analyses between lobectomy and segmentectomy remain limited.To evaluate whether there are changes in cardiac function before and after surgery depending on the type of pulmonary resection, focusing on cardiac function as a contributing factor to non-cancer-related mortality.

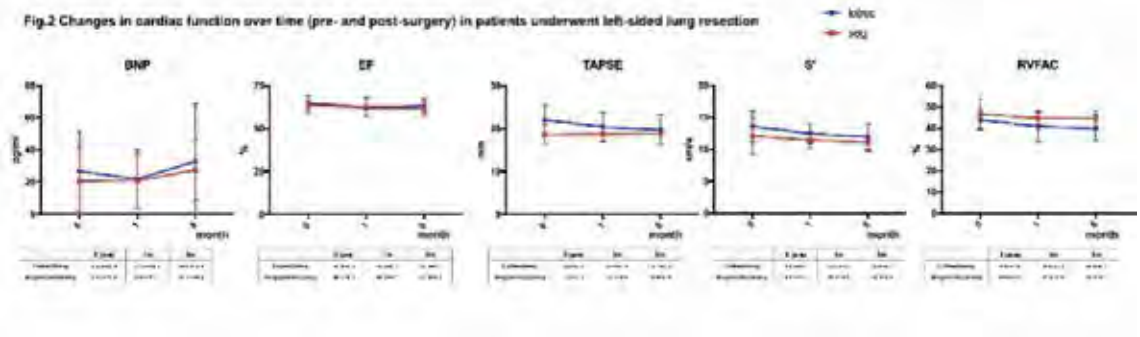
Methods: We retrospectively analyzed 55 patients who underwent pulmonary resection (segmentectomy or more extensive procedures) for primary lung cancer at our institution between January 2023 and March 2024. All patients underwent echocardiography before surgery and at 1 and 6 months postoperatively. Patients with pre-existing cardiac disease and pre-/post-operative chemotherapy were excluded. Left ventricular function was assessed using plasma brain natriuretic peptide (BNP) levels and echocardiographic left ventricular ejection fraction (EF). Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (S'), and right ventricular fractional area change (RVFAC).

Results: Among the 53 cases, 43 underwent lobectomy (L group) and 10 underwent segmentectomy (S group). The male-to-female ratio was 24:19 in the L group and 7:3 in the S group. The median ages were 73 years (range: 64-82) and 74 years (range: 68-81) for the L and S groups, respectively. Surgical approaches included video-assisted thoracoscopic surgery (VATS), robot-assisted surgery, and thoracotomy, with distributions of 19:21:3 in the L group and 8:2:0 in the S group. Changes in each parameter before and after surgery are shown in Figure 1. No significant differences were observed between the two groups in changes in either left or right ventricular function. Since right middle lobectomy cases (with relatively smaller resected volumes) were included in the L group for right-sided surgeries, a subgroup analysis was conducted limited to patients who underwent left-sided pulmonary resection. These results are shown in Figure 2, which also demonstrated no significant differences between the groups in either left or right heart function.

Conclusions: There was no clear decline in early postoperative cardiac function—including right ventricular function—between lobectomy and segmentectomy. As this study focused only on early postoperative changes, further investigation with a larger cohort and longer-term follow-up is warranted.

Note: This abstract was translated into English with the assistance of ChatGPT, an AI language model.





Keywords: Cardiac function, Lung resection

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.24 Radicality of Lymphadenectomy in NSCLC Resection: Impact on Survival. Results From the Spanish Video-Assisted Thoracic Surgery Group (GEVATS)

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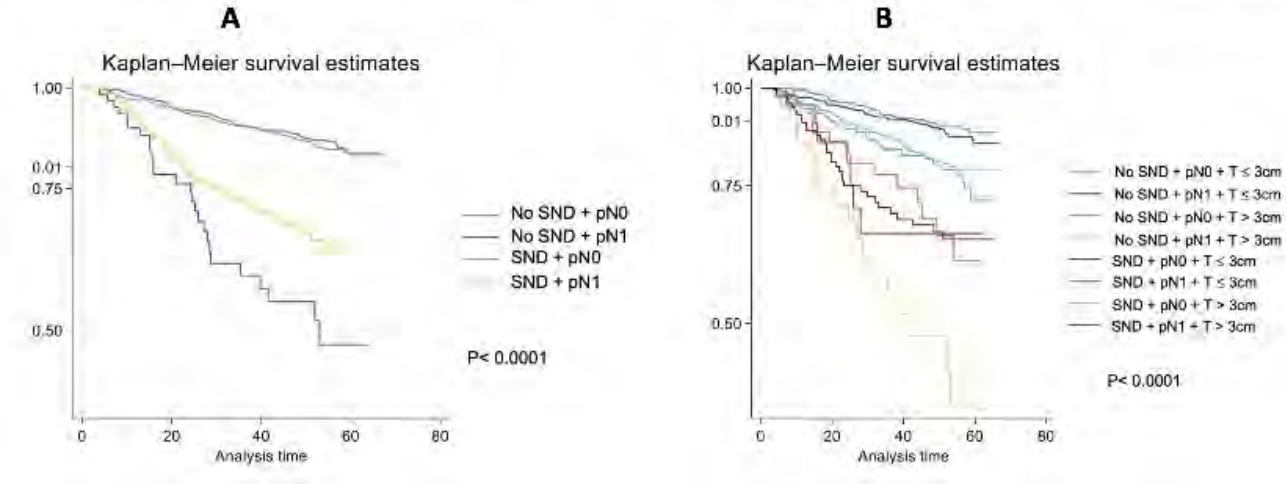
Introduction: The type and the extent of lymph node (LN) dissection in resected non-small cell lung cancer (NSCLC) have been widely evaluated, although the impact on survival remains unclear. While some studies have not observed any difference in survival according to lymphadenectomy practice, others have observed survival benefit according to type of lymphadenectomy, number of resected LN and number of LN stations explored. The objective of this study is to analyse survival differences according to the intraoperative nodal assessment performed (systematic nodal dissection [SND] or no SND) in patients with resected lung cancer from the Spanish Video-Assisted Thoracic Surgery Group (GEVATS).

Methods: Prospective multicentre cohort study of anatomic pulmonary resections (n=3533) performed from December, 2016 to March, 2018. Follow-up was completed in September 2022. For the purpose of this study, SND implied the removal or sampling of a minimum of 6 lymph nodes, at least 3 of them from the mediastinum and always including the subcarinal station. Main surgical, clinical and oncological variables were compared according to the use of SND. Corresponding tests for homogeneity were performed. The Kaplan-Meier method and multivariate Cox regression analysis were used to analyse the overall (OS) and cancer specific survival (CSS) depending on whether SND was performed or not, and then subanalysed by pathologic (p) N category.

Results: After exclusions, 1548 patients were eligible for this study. Kaplan-Meier curves showed no differences in OS (p=0.538) and CSS (p=0.108) in patients undergoing SND or no SND, but there were differences when analysing by pN category (Figure 1A) and also when subanalysing by tumour size (p<0.0001) (Figure 1B). Cox regression analysis revealed no significant difference in lung CSS between SND or no SND in the general cohort (HR 0.98; 95%CI: 0.75-1.28; p=0.883) and in the pN1 cohort (HR 0.68; 95%CI: 0.42-1.11; p=0.123). However, in patients with pN1 and tumour size >3cm, the HR for SND was predictor of better CSS survival (HR 0.49; 95%CI: 0.27-0.88; p=0.017).

Conclusions: SND was not associated with a better overall and cancer specific survival in the GEVATS cohort. However, in the subgroup of patients with pN1 and > 3 cm tumours, the HR for SND group show a significant improvement in survival. Therefore, SND should be performed routinely specially in this subgroup of patients.

Figure 1A. Kaplan Meier curves for cancer specific survival according to SND practice and pN category.
Figure 1B. Kaplan Meier curves for cancer specific survival according to SND practice, pN category and tumour size ≤ or > 3cm.



Keywords: intraoperative nodal assessment, NSCLC, survival

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.25 Trajectories of Synchronous Subsolid Nodules in Patients With Resected Subsolid Lung Adenocarcinoma: A Multicenter Cohort Study

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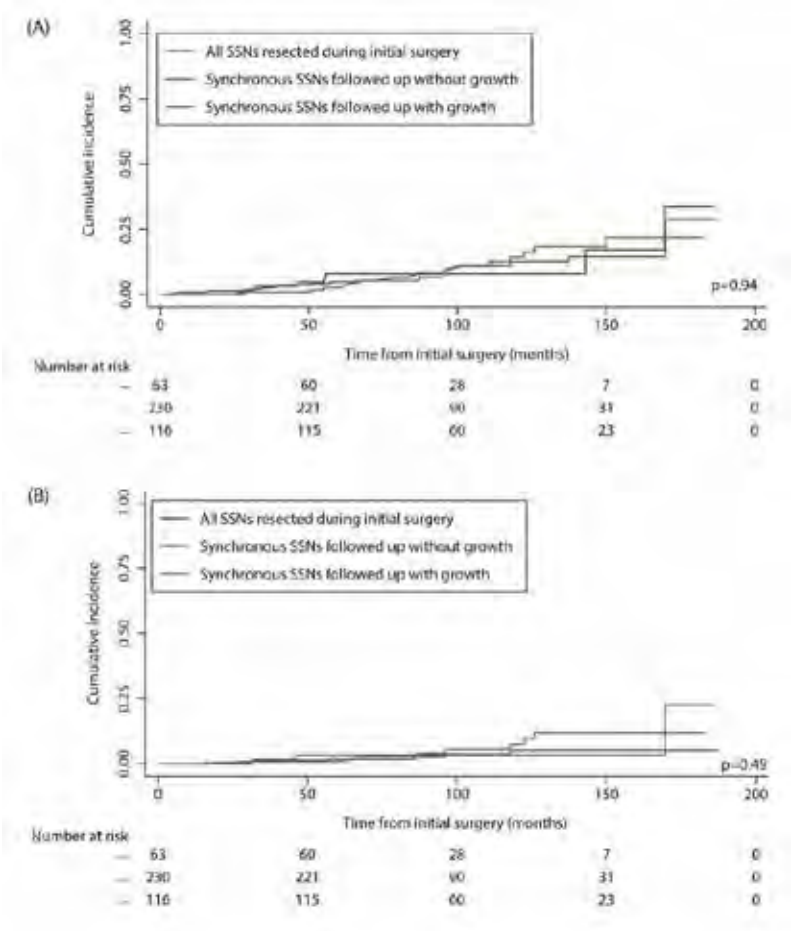
Introduction: Multifocal subsolid nodules (SSNs) are increasingly detected through widespread lung cancer screening and advanced thoracic imaging, representing a spectrum of (pre-)invasive lung adenocarcinomas (LUADs). When synchronous SSNs coexist with surgically confirmed LUAD, their clinical trajectories remain poorly understood, leading to uncertainty in management strategies. Therefore, we aimed to evaluate the trajectories and clinical impact of multi-synchronous SSNs in patients with surgically resected subsolid LUAD and identify features associated with their progression.

Methods: We analyzed the clinical course of synchronous SSNs in individuals who underwent surgical resection for subsolid LUAD between January 2009 and December 2019 at four referral centers in South Korea. Longitudinal outcomes, including growth patterns and subsequent lung cancer diagnosis, were evaluated using comprehensive nodule-level assessments. Multivariable Cox regression models were used to identify risk factors associated with SSN trajectories and patient-level mortality outcomes.

Results: Overall, 409 LUAD patients with 1,791 synchronous SSNs were included, of which 1,002 SSNs were followed up over a mean duration of 80.6 months after the initial surgery. Among the 1,002 SSNs, 16.9% exhibited growth, and 7.9% were subsequently diagnosed as lung cancer—all of which were stage 0-I adenocarcinomas. Factors associated with SSN growth and lung cancer diagnosis included part-solid type, larger nodule size, presence of bubble lucency, and pleural retraction. Notably, the number of synchronous SSNs was not associated with an increased risk of growth. At the individual patient level, neither the absolute number nor the mere growth of synchronous SSNs significantly impacted lung cancer-related mortality or overall survival.

Conclusions: Synchronous SSNs in patients with subsolid LUAD exhibited a considerable growth rate with varying trajectories and clinical impact. Identified risk factors were primarily related to the characteristics of each SSN. Our findings highlight the need for nodule-based, individualized management strategies, along with a more clinically relevant growth threshold to guide balanced intervention decisions.



Keywords: Lung adenocarcinoma, subsolid nodule, multifocal lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.26 Applicability of Artificial Intelligence Based Tumor Segmentation in Planning for Sublobar Resection in Lung Cancer: A Meta-Analysis

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Introduction: Patient-specific precise tumor demarcation is critical for successful sublobar resection in lung cancer treatment, particularly for early stage Non Small Cell Lung Carcinomas (NSCLC). Artificial Intelligence (AI) methods, such as deep learning-based segmentation, are emerging as promising tools to assist in tumor delineation for treatment planning. This meta-analysis evaluates the effectiveness of AI-based algorithms in pulmonary nodule segmentation and their possible impact on sublobar resection planning.

Methods: A meta-analysis was performed on studies evaluating AI-based segmentation of pulmonary tumors, using Dice Similarity Coefficients (DSC) as the primary performance metric. PubMed, EMBASE and Google Scholar databases were thoroughly searched for the studies examining performance of various AI-based models in pulmonary tumor segmentation. A total of sixteen studies were included in the analysis and pooled DSC scores were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with funnel plots and Egger's test.

Results: The meta-analysis included 16 studies with a total of 17,389 images. The pooled effect size for AI performance in lung nodule segmentation, as measured by the Dice Similarity Coefficient (DSC), was 1.25 (95% CI: 1.00, 1.50). This suggests a strong overall effect of AI in segmenting lung nodules, with consistent performance across studies. High heterogeneity (I^2 = 98%) was observed among the studies. No significant publication bias was detected in Egger's test.

Conclusions: AI-driven segmentation of pulmonary tumours demonstrates high accuracy. The result predicts the promising role of AI in patient-specific surgical planning, particularly in improving precision for tumor localization and resection margin determination in early stage NSCLC. However, further studies are needed to evaluate the direct impact of AI-based localization on surgical precision and postoperative recovery.

Keywords: Artificial Intelligence, Tumor Segmentation, Sublobar Resection

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.27 A Newly Developed 3D Simulation System for the Preoperative Planning for Central-Located Lung Cancer

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Introduction: Surgical resection of centrally located lung cancer remains challenging due to the tumor's proximity to hilar structures, complicating the identification of optimal resection and anastomosis sites. Conventional CT imaging often fails to provide sufficient spatial detail for precise preoperative planning. This study evaluates the clinical efficacy of Bioxel, a novel 3D simulation system, in improving preoperative planning for centrally located lung cancer surgeries.

Methods: A cohort of 100 patients with centrally located lung cancer underwent chest CT scans. The study comprised two phases. In Part I, Surgeon A (experienced in >300 similar surgeries) utilized Bioxel for preoperative planning in 50 cases, while traditional CT-based planning was employed for another 50 cases. In Part II, Surgeon B performed preoperative planning for 100 patients using CT alone, followed by re-evaluation with Bioxel. Key outcomes included accuracy of tumor invasion assessment, surgical duration, intraoperative blood loss, and positive margin rates.

Results: Bioxel significantly improved the accuracy of tumor invasion assessment from 78% (CT alone) to 89% (Bioxel), with a combined accuracy of 94% when both methods were integrated. Surgical duration decreased from 216.2 ± 1.9 minutes (CT) to 196.8 ± 6.9 minutes (Bioxel; p = 0.008), while intraoperative blood loss was reduced from 301.2 ± 53.7 mL to 158.2 ± 39.8 mL (p = 0.011). Positive surgical margin rates declined from 8% to 2% (p = 0.049).

Conclusions: Bioxel enhances surgical precision and safety for centrally located lung cancer by providing detailed 3D reconstructions and reducing reliance on invasive procedures such as bronchoscopy. These findings underscore its potential to optimize surgical outcomes and streamline clinical workflows.

Keywords: Central-located lung cancer, 3D surgical simulation, preoperative planning

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.28 Segmentectomy vs Lobectomy for Clinical Stage IA1-2 NSCLC and Upstaging Due to Pathologic Visceral Pleura Infiltration

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Introduction: Segmentectomy has become the standard of care in selected patients with stage IA1 and IA2 NSCLC. Lobectomy remains the treatment of choice for stage IB NSCLC. However, it is unclear how patients with clinical stage IA1-2 NSCLC should be managed if upstaging occurs due to visceral pleura infiltration on final pathology (stage IB). We aimed to compare the outcomes of patients who underwent lobectomy or segmentectomy for clinical stages IA1-2 NSCLC and had visceral pleura infiltration on final pathology.

Methods: We retrospectively analyzed all patients with clinical stage IA1-2 NSCLC and postoperative upstaging due to visceral pleura infiltration who underwent surgery at our center between 2013 and 2024. Disease-free (DFS) and overall (OS) survivals were calculated from the date of surgery until recurrence or death, respectively. Univariate analysis was performed to study the impact of clinical variables on DFS and OS.

Results: We identified 46 patients in clinical stage IA1-2 NSCLC who underwent lobectomy (n=18) or segmentectomy (n=28) and had upstaging to stage IB due to visceral pleura infiltration on final pathology report. There was no difference in patient demographics or clinical characteristics between the groups. Most of the resections (89%) were performed by VATS. None of the patients from the segmentectomy group had completion lobectomy due to visceral pleura infiltration on final pathology report. One death occurred within the first 90-days following surgery due to pneumonia in the lobectomy group. Median tumor size was 1.7 cm (range 1-2cm). Number of removed lymph nodes was significantly lower in the segmentectomy group (15.5 vs. 22.5 p=0.031). Resection margin was significantly smaller in the segmentectomy group (median 2.15cm vs. 3.4cm p=0.028). Five-year DFS (62% vs. 83%, p=0.393) and OS (49% vs. 63%, p=0.213) were not statistically significantly between the segmentectomy and lobectomy groups. Patients with a margin to tumor ratio MTR≥ 1 had significantly better DFS (87% vs. 39%, p=0.019) than those with a MTR <1. In patients with less comorbidities (Charlson Deyo comorbidity score < 5), lobectomy offered significantly better survival (100% vs. 44%, p=0.031).

Conclusions: Five-year OS and DFS were not different in our cohort of patients with stage IA1-2 NSCLC who underwent lobectomy or segmentectomy and had upstaging due to visceral pleura infiltration. Therefore, upstaging may not necessitate completion lobectomy. Further studies are still required to confirm our findings.

Keywords: Segmentectomy, Lobectomy, Visceral pleura infiltration

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.29 Prediction of Postoperative Pulmonary Function and Blood Flow Redistribution Using SPECT/CT in Patients Undergoing Lobectomy

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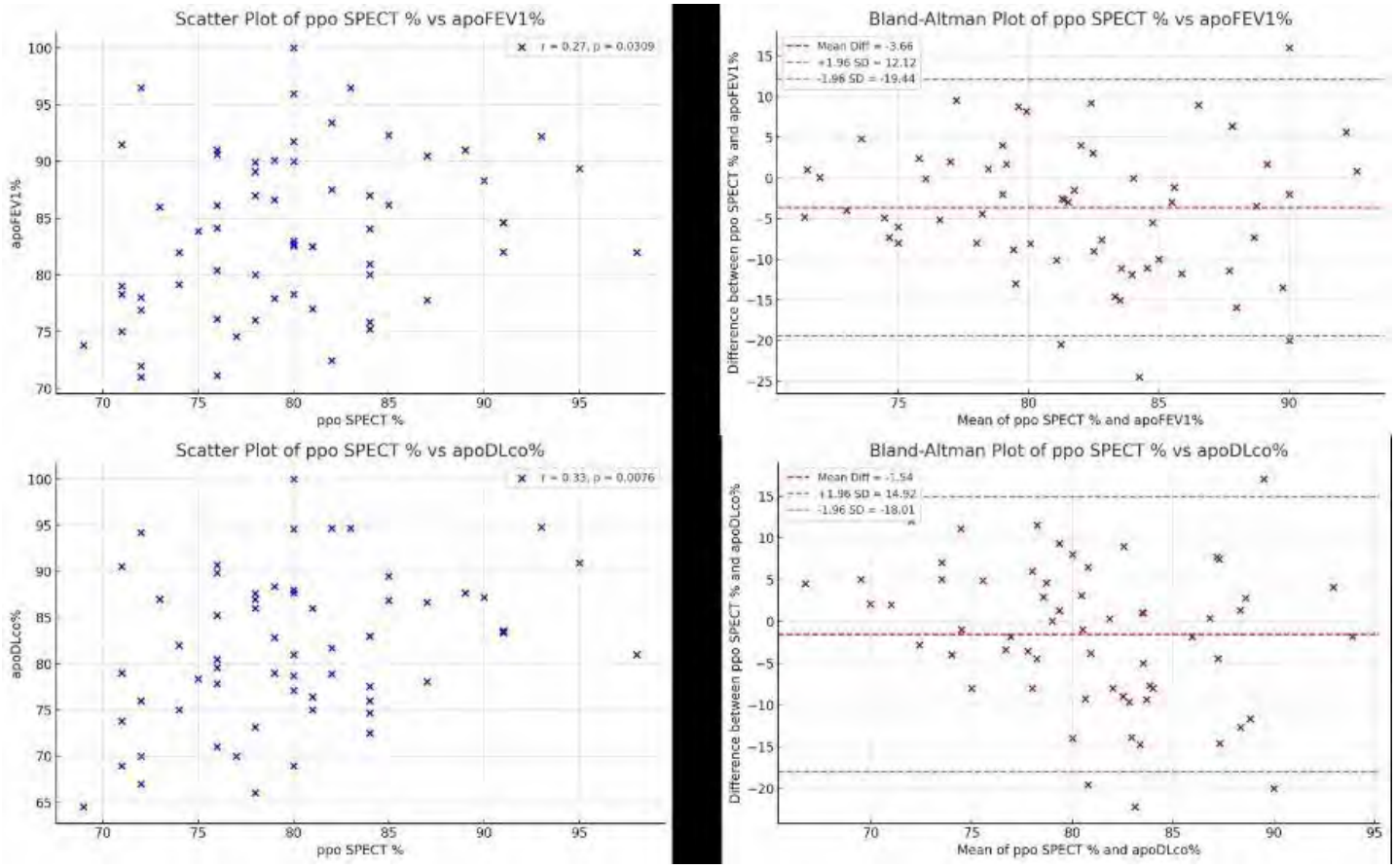
Introduction: Lobectomy remains the standard surgical treatment for patients with non-small cell lung cancer (NSCLC). Accurate preoperative assessment of pulmonary reserve is essential for predicting postoperative outcomes and minimizing complications. Conventional methods for estimating predicted postoperative (ppo) pulmonary function have known limitations. Furthermore, to date, little is known about postoperative pulmonary blood flow redistribution following lobectomy. This study aimed to evaluate the utility of perfusion SPECT/CT in predicting postoperative pulmonary function and to characterize changes in pulmonary perfusion patterns during early period after pulmonary lobectomy.

Methods: A retrospective study was conducted on 63 patients who underwent lobectomy for NSCLC at a single institution between September 2023 and April 2024. Predicted postoperative FEV1 and DLCO values were calculated using the preoperative perfusion fraction from SPECT/CT imaging. These values were then compared with actual postoperative pulmonary function test results to evaluate prediction accuracy. Additionally, for assessing blood flow redistribution, the target lobe's contribution to total perfusion (as measured preoperatively) was subtracted, and the remaining perfusion was assumed to redistribute evenly among residual lobes (expected values). These were compared with actual postoperative perfusion measurements obtained via follow-up SPECT/CT.

Results: The mean predicted postoperative FEV1 using SPECT/CT (ppoFEV1%) was 80.1 ± 6.5%, compared to an actual postoperative FEV1% (apoFEV1%) of 83.7 ± 6.9%. Similarly, the mean predicted postoperative DLCO (ppoDLCO%) was 81.6 ± 8.0%. A weak but statistically significant positive correlation was found between apoFEV1% and ppoFEV1% (r = 0.27, p = 0.03), while a moderate positive correlation was observed between apoDLCO% and ppoDLCO% (r = 0.33, p = 0.007) (Fig.1). Regarding perfusion redistribution, overall right-sided pulmonary flow increased by 2.4% postoperatively. However, subgroup analysis revealed that in right-sided lobectomies, right lung perfusion decreased by 17%, whereas in left-sided lobectomies, right lung perfusion increased by 21.8%, indicating asymmetric compensatory flow.

Conclusions: Perfusion SPECT/CT may serve as a valuable tool for predicting postoperative lung function, particularly DLCO, following lobectomy. Additionally, it provides novel insights into the physiological redistribution of pulmonary blood flow, which appears to vary depending on the laterality of the resected lobe. These findings support the integration of SPECT/CT into preoperative functional assessment to optimize surgical planning and improve patient outcomes.



Keywords: SPECT/CT, Lobectomy, Pulmonary function prediction

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.30 Beyond the Lung: Distinct Recurrence Patterns of Mucinous and Non-Mucinous Lung Adenocarcinoma After Surgery

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Introduction: Recent findings suggest that invasive mucinous adenocarcinoma (IMA) predominantly exhibits lung-limited behavior, resulting in favorable clinical outcomes following surgical resection. However, comparative research examining recurrence patterns between IMA and invasive non-mucinous adenocarcinoma (INMA) remains scarce due to the rarity of IMA. This study aimed to investigate differences in recurrence patterns between IMA and INMA following surgical resection in lung cancer patients without nodal or systemic metastasis.

Methods: We retrospectively analyzed 4919 patients who underwent curative surgery for adenocarcinoma between 2011 and 2021. Propensity score matching yielded 722 INMA and 368 IMA patients, balancing clinical characteristics. Recurrence patterns were categorized as intrapulmonary (IPR) and extrapulmonary recurrence (EPR). Freedom from recurrence (FFR) and cumulative incidence of recurrence (CIR) analyses were performed to evaluate differences.

Results: A total of 4919 patients were included. After matching, patients with IMA exhibited significantly higher FFR (p=0.03) compared to INMA patients. The overall recurrence rate was lower in the IMA group (8.4% vs. 13.0%, p=0.036). While intrapulmonary recurrence rates were comparable between groups (p=0.54), extrapulmonary recurrence was significantly lower in the IMA group (p=0.017). Multivariate analysis identified IMA histology as an independent factor associated with a lower risk of extrapulmonary recurrence (HR=0.45, 95% CI: 0.22-0.89, p=0.023). Visceral pleural invasion was a significant predictor for extrapulmonary recurrence (HR=3.25, 95% CI: 1.54-6.87, p=0.002).

Conclusions: IMA patients demonstrate better recurrence-free survival and a lower risk of extrapulmonary recurrence compared to INMA following surgical resection. Effective control of intrapulmonary recurrence in IMA patients could potentially enhance long-term survival outcomes.

Figure 1.
Comparison of freedom from recurrence between invasive non-mucinous and mucinous adenocarcinoma patients following surgery before and after matching
A. Freedom from recurrences of overall cohort
B. Freedom from recurrences of matched cohort

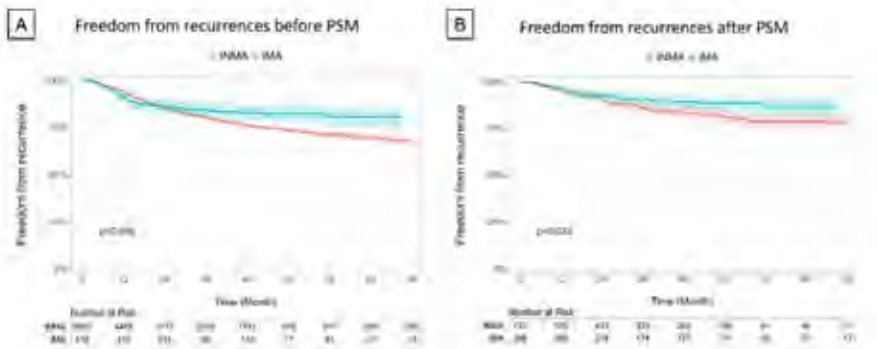
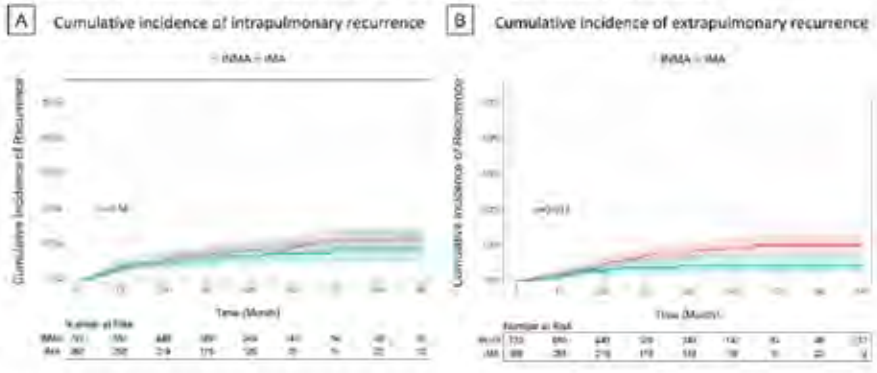


Figure 2.
Cumulative incidence of recurrence curves in INMA and IMA patients according to recurrence location after matching
A. Cumulative incidence of recurrence curves of intrapulmonary recurrence
B. Cumulative incidence of recurrence curves of extrapulmonary recurrence



Keywords: Invasive mucinous adenocarcinoma, Lung surgery, Recurrence pattern

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.31 Adjuvant Immunotherapy for Clinically Node-Negative Non-Small Cell Lung Cancer

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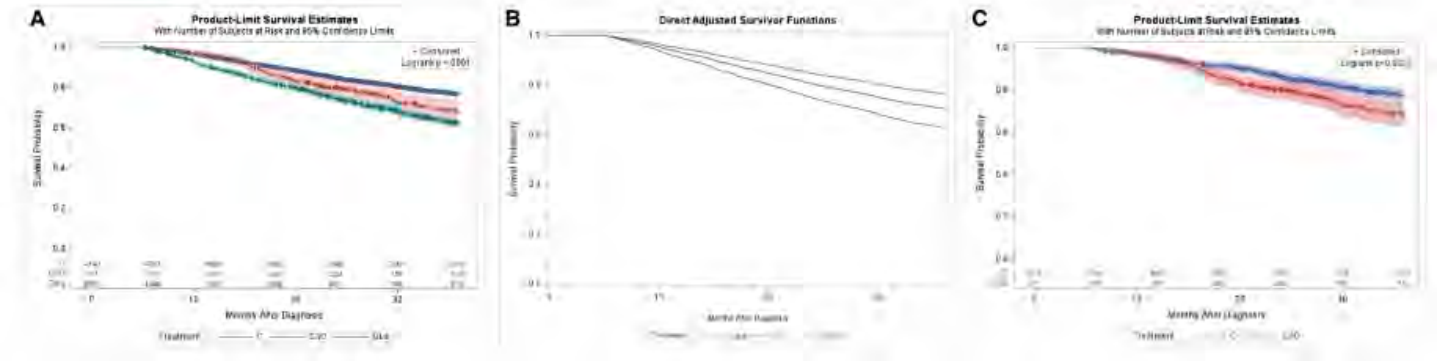
Introduction: Localized non-small cell lung cancer (NSCLC) is generally treated with upfront surgical resection with curative intent, but many patients harbor clinically occult nodal disease discovered on pathologic evaluation ("nodal upstaging"), a common indication for adjuvant therapy. Here we describe real-world survival trends in the National Cancer Database (NCDB) for localized NSCLC with nodal upstaging who receive different adjuvant modalities, with a focus on immunotherapy.

Methods: Adult patients with clinical T1 or T2, clinical N0, clinical M0, adenocarcinoma or squamous carcinoma of the lung diagnosed between 2017 and 2021 and treated with upfront definitive surgery were included. Patients were grouped based on adjuvant regimen as follows: none/observation, chemotherapy, and chemoimmunotherapy. Kaplan-Meier curves for 3-year overall survival were landmarked at 20 weeks. Propensity-matching for survival curves and Cox proportional hazards models were adjusted for year of diagnosis, age, sex, race, ethnicity, insurance status, facility type, region, Charlson-Deyo score, histologic subtype, clinical and pathologic T and N stages, and R0 resection.

Results: The proportion of nodal upstaging was 11.9%. A total of 6896 patients were eligible for inclusion: 1396 (19.8%) received no adjuvant therapy, 4740 (68.7%) received chemotherapy, and 377 (5.5%) received chemoimmunotherapy. Chemotherapy patients had higher 3-year overall survival (76.8%) than patients receiving chemoimmunotherapy (67.8%) or no adjuvant therapy (62.5%, p<0.0001, Figure 1A). In a Cox model, chemotherapy had lower mortality risk than chemoimmunotherapy (HR 0.56, 95% CI 0.50-0.63, p<0.0001) and observation (HR 0.76, 95% CI 0.61-0.94, p=0.01, Figure 1B). Propensity-matched analysis of 3-year overall survival demonstrated a similar trend: 72.2% chemotherapy vs 67.8% chemoimmunotherapy (p=0.002, Figure 1C).

Conclusions: In this real-world population, adjuvant chemoimmunotherapy did not outperform adjuvant chemotherapy in 3-year overall survival, after propensity matching for patient and tumor characteristics. These results serve as a complement to recently published and ongoing clinical trials of adjuvant chemoimmunotherapeutic approaches for resected NSCLC, suggesting that non-targeted use of adjuvant immunotherapeutic agents may not provide a survival benefit, and highlighting the need for careful patient selection.

Figure 1: A) unadjusted Kaplan-Meier 3-year overall survival curves landmarked at 20 weeks comparing: observation (Obs), adjuvant chemotherapy (C), and adjuvant chemoimmunotherapy (C/IO); B) Cox proportional hazards model directed adjusted curve of 3-group comparison; C) propensity-matched Kaplan-Meier 3-year overall survival curves landmarked at 20 weeks comparing adjuvant chemotherapy (C) and adjuvant chemoimmunotherapy (C/IO).



Keywords: non-small cell lung cancer, surgery, immunotherapy

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.32 Prognostic Value of Consolidation-To-Tumor Ratio in Stage IA Solid Predominant Non-Mucinous Adenocarcinoma

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Introduction: The optimal consolidation-to-tumor ratio (CTR) cutoff for prognostic stratification in radiologically solid-predominant adenocarcinoma (CTR > 0.5) remains unclear. This study aimed to evaluate the prognostic significance of CTR in clinical- stage IA non-mucinous lung adenocarcinoma with CTR > 0.5.

Methods: We retrospectively analyzed patients who underwent curative resection for clinical stage IA non-mucinous adenocarcinoma with CTR > 0.5 between 2011 and 2021. Optimal cutoffs for overall survival (OS) and freedom from recurrence (FFR) were determined using maximized log-rank statistics. Patients were stratified according to the derived CTR cutoff values, and OS and FFR were compared among the CTR groups before and after propensity score matching (PSM).

Results: Among 2,789 patients included, the optimal CTR cutoffs for OS and FFR were 0.84 and 0.85, respectively. Based on the 0.85 cutoff, patients were categorized into three groups: 0.5 < CTR ≤ 0.85 (n = 672), 0.85 < CTR < 1 (n = 229), and CTR = 1 (n = 1,888). OS and FFR were significantly worse in the 0.85 < CTR < 1 group compared to the 0.5 < CTR ≤ 0.85 group ($p < 0.05$) but not significantly different from the CTR = 1 group ($p > 0.05$). These trends persisted after PSM. The 0.85 < CTR < 1 group exhibited a higher proportion of pathological risk factors (high-grade patterns, lymphovascular invasion, and nodal metastasis) than the 0.5 < CTR ≤ 0.85 group (all $p < 0.05$) and was comparable to the CTR = 1 group, except for lymphovascular invasion ($p = 0.045$). Dichotomization into 0.5 < CTR ≤ 0.85 and 0.85 < CTR ≤ 1 revealed significantly worse OS and FFR in the 0.85 < CTR ≤ 1 group across PSM cohorts for both lobectomy and sublobar resection.

Conclusions: A CTR cutoff of 0.85 effectively distinguishes survival outcomes in patients with clinical stage IA adenocarcinoma and CTR > 0.5 and may inform risk stratification and postoperative surveillance.

Keywords: Consolidation-to-tumor ratio, Lung adenocarcinoma, Clinical stage IA

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.33 Sublobar Resection Versus Lobectomy in Peripheral NSCLC After Neoadjuvant Chemoimmunotherapy: A Retrospective Study

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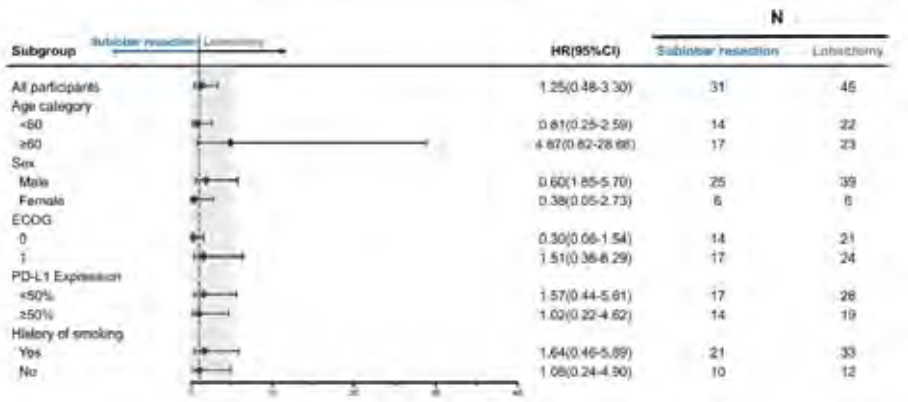
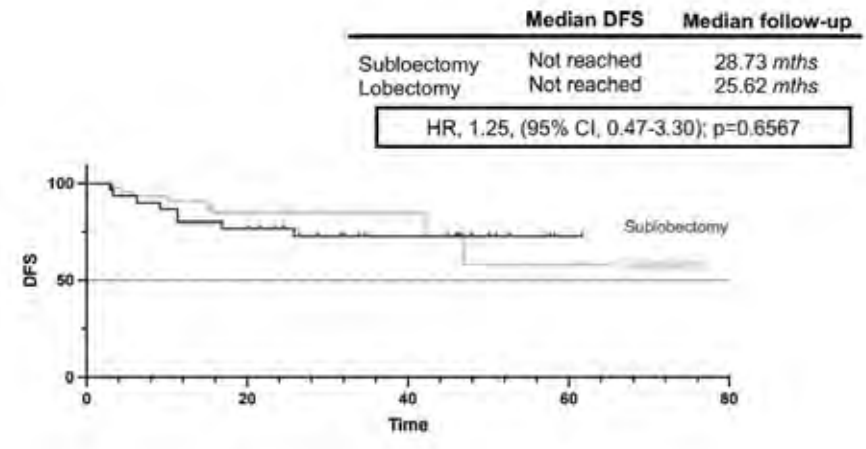
Introduction: The optimal surgical extent (sublobar resection vs. lobectomy) for peripheral non-small cell lung cancer (NSCLC) achieving partial response (PR) or complete response (CR) after neoadjuvant chemoimmunotherapy remains unclear. This study aimed to compare survival outcomes between these approaches.

Methods: Patients with stage IB-IIIA (IASLC 9th edition) peripheral NSCLC who received neoadjuvant chemoimmunotherapy (paclitaxel/nab-paclitaxel/pemetrexed plus carboplatin/cisplatin and nivolumab) at Guangdong Provincial People's Hospital (2018-2024) and underwent surgery after MDT evaluation were retrospectively analyzed. The neoadjuvant treatment lasted for 2-3 cycles depending on the patient's response and tolerance. Imaging-confirmed primary lesions with PR/CR were categorized into lobectomy or sublobar resection groups based on surgical approach. Sublobar resection (including wedge resection and segmentectomy) was selected based on tumor location, size, and patient's cardiopulmonary function. All patients underwent systematic lymphadenectomy (≥ 6 stations). Primary endpoint: DFS; secondary endpoints: OS, recurrence, and complications.

Results: Among 76 patients (sublobar:31; lobectomy:45), baseline characteristics are balanced. At a median follow-up of 28 months, median DFS is unreached in either group (HR=1.25, 95%CI: 0.47-3.30; p = 0.657). Subgroup analyses (Age, Sex, ECOG, PD-L1 expression, Smoking) reveal no DFS differences (p > 0.05). Local recurrence rates (9.68% vs. 8.89%) and distant metastasis rates (12.90% vs. 13.33%) show no significant differences (p > 0.9999).

Conclusions: For peripheral NSCLC patients achieving PR/CR after neoadjuvant chemoimmunotherapy, sublobar resection with lymphadenectomy demonstrated comparable DFS to lobectomy, while preserving more lung function, accelerating postoperative recovery. However, this study is limited by its small sample size and short follow-up duration, necessitating validation through prospective trials with extended follow-up.





Keywords: Immunotherapy, Neoadjuvant therapy, Surgical extent

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.34 Toxicity Profile for Connective Tissue Disease Patients Treated With Lung Stereotactic Body Radiation Therapy

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Introduction: Connective tissue diseases (CTDs) have historically been considered as presenting contraindications to radiotherapy (RT), in particular lung RT, due to concern for increased rates of severe toxicity. Lung stereotactic body radiation therapy (SBRT) used for inoperable early-stage lung cancer or oligometastases is associated with very low rates of high-grade toxicity. The present study seeks to provide updated information on the toxicity profile of lung SBRT in CTD patients.

Methods: A single institution IRB-approved prospective lung SBRT registry was surveyed for all pts with a connective tissue disease treated for primary cancer, oligometastasis, or salvage from 2006 - 2024. Tumors were characterized as peripheral or central per RTOG criteria. Treatment-related toxicity was graded per CTCAE version 3.0. Medical management of CTDs was recorded at time of cancer consultation.

Results: A total of 118 CTD pts undergoing 144 courses of lung SBRT was available for analysis. Median age was 72 years (65 - 79, IQR) and 82 pts (69%) female. Median KPS was 80 (60 - 90, IQR). Median follow-up was 19 months (9 - 51, IQR). Median tumor size was 1.9 cm (1.5 - 3.2, IQR). Patient characteristics were 55 (47%) with rheumatoid arthritis (RA), 17 (14%) with systemic lupus, 28 (24%) with interstitial/idiopathic lung disease, 6 (5%) with scleroderma, and 42 (36%) with other CTDs. Twenty-six (22%) patients had multiple CTDs. At SBRT, 58 (49%) patients were on active medical treatment. Considering treatment characteristics, median SBRT BED10 was 120 Gy (100 - 149, IQR, with the most common dose schedule being 50Gy/5fx. Twenty-eight tumors (24%) were central, of which 22 (19%) were considered ultracentral.[Overall, 29 (26%) treatments resulted in grade 2 or higher toxicity, with 6 (5%) grade 3 and 1 grade 5 (0.1%). Lung toxicities included 13 (11%) chest wall pain, 11 (9%) pneumonitis, 2 (2%) cough, 1 (1%) pleural effusion, and 1 (1%) hemoptysis. Grade 3 pneumonitis rate was 11% for pts with interstitial/idiopathic lung disease, 2% for RA, and 0% for lupus and scleroderma. The case of grade 5 pneumonitis was associated with interstitial lung disease. No patient with a central tumor had ≥ grade 2 toxicity. Three (14%) of the patients with ultracentral tumors had grade 2 chest wall toxicity, 2 (9%) had grade 2 pneumonitis, 1 (4.5%) had esophagitis and another had hemoptysis. Median time to first pulmonary function test was 2 months (1 - 4, IQR), with a median FEV1% change of -6 (1 - (-35), IQR) and a median DLCO change of -6 (0 - (-30), IQR).

Conclusions: Lung SBRT for CTD patients was not associated with increased rates of high--grade toxicity compared to historical results. Pts with interstitial/idiopathic lung disease were at increased risk for grade 3 or higher pneumonitis.

Keywords: inoperable early stage lung cancer, SBRT, conncective tissue disease

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.35 Stereotactic Body Radiation Therapy for Medically Inoperable Stage I/II EGFRm NSCLC: Global, Multicenter, Retrospective Study

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Introduction: Stereotactic body radiation therapy (SBRT) is the standard of care (SoC) for patients with medically inoperable stage I/II non-small cell lung cancer (NSCLC). However, patients remain at risk for regional and distant recurrence. The PACIFIC-4 trial (NCT03833154) is examining the efficacy and safety of the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) osimertinib following SBRT in a single-arm cohort of patients with medically inoperable stage I/II NSCLC harbouring a sensitising EGFR mutation; the primary endpoint is 4-year progression-free survival (PFS). Here, we report the final results from a global, retrospective, real-world study in patients with medically inoperable stage I/II EGFRm NSCLC who received SBRT as SoC.

Methods: Data were extracted from medical records of adult patients with medically inoperable, stage I/II EGFRm (Ex19del/L858R) NSCLC diagnosed between Jan 2016 and Dec 2019, who received SBRT as SoC. The primary endpoint was real-world PFS (rwPFS). Secondary endpoints included: patient characteristics, mutation testing, treatment patterns, real-world overall survival (rwOS) and real-world time to next treatment or death (rwTTNTD). Data cut-off was 31 Dec 2022.

Results: Eighty-two patients were enrolled across six countries: South Korea (43%), Japan (30%), USA (18%), UK (5%), Austria (2%) and France (1%). Median age was 80 years; 63% of patients were female; 43% were former or current smokers; 44% had Ex19del and 56% had L858R (1% had both mutation types); 72% of patients had an ECOG PS of 0-1. Median follow-up time from the index date was 43.3 months (interquartile range [IQR] 30.8-54.9). Median SBRT dose was 56 Gray (IQR 48-60) in a median (IQR) of 4 (4-4) fractions. Thirty-one patients (38%) progressed following SBRT, of which 25/31 (81%) received a first subsequent treatment: 3 (12%) received SBRT; 21 (84%) received EGFR-TKIs alone (14 gefitinib, 5 osimertinib, 2 afatinib); and 1 (4%) received an EGFR-TKI (gefitinib) + SBRT. Among all 82 patients, the median rwPFS was 47.1 months (95% CI 38.7, 57.8; number of events = 42), rwTTNTD was 49.8 months (40.7, not evaluable [NE]) and rwOS was 62.9 months (50.8, NE); at 4-years, landmark rwPFS rate was 48% (95% CI 35, 60), rwTTNTD rate was 51% (37, 62) and rwOS rate was 68% (55, 78). The factors significantly associated with 4-year rwPFS were older age (≥80 years vs <80 years old) with hazard ratio (HR) of 2.61 (95% CI 1.14, 5.97), p=0.0237, and high Charlson Comorbidity Index score with HR of 1.41 (95% CI: 1.10, 1.81), p=0.0061. In patients who received subsequent treatment following disease progression on SBRT, the median rwPFS2 and rwTTNTD2 were 10.9 months (95% CI 3.1, 14.7) and 12.9 months (95% CI 3.5, 24.6) versus 23.2 months (95% CI 9.7, NE) and 30.0 months (95% CI 11.6, NE) for patients that received first/second-generation EGFR-TKIs (n=17) versus third-generation EGFR-TKIs (n=5), respectively.

Conclusions: In this real-world analysis of patients with medically inoperable, stage I/II EGFRm NSCLC who underwent SBRT as SoC, the 4-year rwPFS rate of 48% suggests an unmet need in this patient population for more effective long-term treatments.

Keywords: Non-small cell lung cancer, Epidermal growth factor mutation, Stereotactic body radiation therapy

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.36 A Three-Gene Signature Predicting Local Recurrence in Stage I-III NSCLC Patients Treated With Radiation Therapy

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Introduction: Treatment decisions for non-small cell lung cancer (NSCLC) are largely driven by surgical candidacy and patient preference, with limited molecular biomarkers to guide modality choice. Identifying genomic predictors of recurrence could refine treatment strategies. Prior studies suggest certain mutations influence radiosensitivity, but their clinical significance remains unclear. This study aimed to identify genomic predictors of recurrence in patients treated with radiation therapy (RT) or surgery.

Methods: We analyzed data from the de-identified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database, which includes patients from ~280 US cancer clinics, including clinical stage I-III NSCLC patients treated with RT or surgery. Univariable logistic regression was performed to identify genomic mutations associated with recurrence risk in each cohort. Statistical significance was defined as $p<0.05$. Analyses were conducted using R and Python 3.7 with libraries including scipy.stats, statsmodels, and sklearn. We developed a three-gene signature based on significant univariate Cox results and genes known to influence radiosensitivity, including RB1, BRCA1, and ATM. We conducted a multivariate Cox regression analysis including the three-gene signature and adjusting for birth sex, race, clinical group stage, tumor type, ECOG performance status, and radiation therapy type.

Results: A total of 2,693 patients (mean age 69.9) were analyzed, including 630 who underwent surgery (mean age 69.2) and 2,063 treated with RT (mean age 70.1). Several mutations were associated with decreased recurrence risk in the RT cohort, including ATM (hazard ratio [HR]: 0.66, 95% confidence interval [CI]: 0.50-0.88, p=0.005), BRCA1 (HR: 0.67, 95% CI: 0.46-0.99, p=0.044), and RB1 (HR: 0.68, 95% CI: 0.49-0.94, p=0.019). Presence of a mutation in any of RB1, BRCA1, or ATM was also associated with decreased risk of local recurrence on univariable analysis (HR: 0.63, 95% CI: 0.51-0.78, $p<0.001$) and multivariable analysis (HR: 0.68, 95% CI: 0.54-0.85, p=0.001). Several mutations were associated with increased recurrence risk in the RT cohort including NFE2L2 (HR: 1.94, 95% CI: 1.54-2.45, $p<0.001$), TP53 (HR: 1.49, 95% CI: 1.21-1.83, $p<0.001$), PIK3CA (HR: 1.42, 95% CI: 1.12-1.79, p=0.004), and KEAP1(HR: 1.24, 95% CI: 1.00-1.53, p=0.047). No mutations were significantly associated with decreased recurrence risk in the surgery cohort.

Conclusions: Our findings suggest that ATM, BRCA1, and RB1 mutations are associated with improved outcomes in NSCLC patients treated with RT but not surgery. These associations were not observed in the surgery cohort, highlighting their potential role in RT response rather than general prognosis. In contrast, mutations in NFE2L2, TP53, PIK3CA, and KEAP1 were linked to increased recurrence risk in RT-treated patients, suggesting radioresistance. Clinically, patients with radiosensitizing mutations may benefit from RT and potentially lower radiation doses, while those with radioresistance mutations may require closer surveillance, dose escalation, or consideration of alternative therapy. These findings support the integration of molecular biomarkers into treatment decision-making for early-stage NSCLC. Further studies are needed to validate these results and explore targeted therapeutic approaches.

Keywords: NSCLC, Radiosensitivity, Genomic Signature

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.37 Using Tissue and Blood to Find Oncogenic Drivers Upfront in Patients With Lung Cancer Evaluated for Neoadjuvant Therapy-LEADER

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Introduction: Oncogenic driver testing at diagnosis is critical to identify patients with lung adenocarcinomas most likely to respond to neoadjuvant chemoimmunotherapy (cancers negative for EGFR mutations and ALK fusions) vs. those most likely to respond to targeted therapy (positive for actionable oncogenic drivers).

Methods: The Lung Cancer Mutation Consortium, with the support of the Lung Cancer Research Foundation, designed the LCMC4 LEADER (NCT04712877) neoadjuvant screening trial to determine the frequency of actionable oncogenic drivers (primary objective), using both tissue and blood, from 1000 patients under evaluation for neoadjuvant therapy (operable, resectable, clinical stage IA2-III). Results were provided to treating physicians to assist in planning care.

Results: Twenty-three US sites have enrolled 341 patients to date, with evaluable data in 241 patients with lung adenocarcinomas. In this group, women comprised 57%; former smokers 59%; never smokers 28%; current smokers 14%, with clinical stages as follows: IA2, 23%; IA3, 20%; IB, 11%; IIA/B, 21%; IIIA, 22%; IIIB, 4%. We identified an actionable oncogenic driver using any test performed in a CLIA setting (tissue and/or blood) in 47% of patients (95% CI 41 to 53%). Drivers detected were KRAS G12C in 18% of patients, EGFR exon 19 deletion or L858R in 16%, ALK fusion in 3%, HER2 mutation in 3%, MET exon 14 splice site variants in 2%, EGFR exon 20 insertion in 2%, RET fusion in 2%, ROS1 fusion in 2%, NTRK fusion in 2%, BRAF V600E in 1 %, HER2 amplification in 1%, and 0% MET amplification. Both blood and tissue specimens were evaluated in 114 patients. Among drivers detected in tissue, only 17% were found in paired blood. All 12 drivers found in blood were found in tissue.

Conclusions: We identified an actionable oncogenic driver in half of patients (47% overall, 19% EGFR exon 19 del and L858R or ALK) with lung adenocarcinomas under evaluation for neoadjuvant therapy and surgery. For patients with paired blood and tissue testing, all drivers detected in ctDNA were also found in tissue; across all oncogenic drivers detected in tissue, only 17% tested positive in the paired ctDNA sample. Based on our findings, a positive driver finding in blood-based ctDNA testing is reliable to recommend a targeted therapy. A negative "liquid biopsy," however, is insufficient to support the recommendation of neoadjuvant chemoimmunotherapy and instead should trigger tissue-based testing. Neoadjuvant strategies for lung adenocarcinomas with oncogenic drivers must be individualized, with patients encouraged to enroll in clinical trials. Supported by Foundation Medicine, Inc., AstraZeneca, Genentech, Lilly/Loxo, Merck, BMS/Mirati, Novartis, Pfizer, Regeneron, Sanofi.

Keywords: Neoadjuvant, Targeted Therapy, Chemoimmunotherapy

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.38 Neoadjuvant Iruplinalkib in Resectable ALK/ROS1 Fusion-Positive NSCLC: Updated Results of the Exploratory Neo-INFINITY Study

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Introduction: Previous trials showed perioperative alectinib and lorlatinib were effective for resectable ALK-positive NSCLC. In Stage 1 of the phase II, single-arm, multicenter Neo-INFINITY study, perioperative iruplinalkib demonstrated encouraging efficacy. Here, updated results in ALK-positive cohort were reported.

Methods: This trial was conducted in China, enrolling adults with pathologically confirmed resectable ALK/ROS1-positive NSCLC at stage IB-IIIA or IIIB (T3N2M0 only) according to AJCC Cancer Staging Manual 8th Edition. Treatments consisted of neoadjuvant oral iruplinalkib at 180 mg/day (with a 7-day lead-in at 60 mg/day) for eight weeks, then surgery and adjuvant iruplinalkib at the same dose and lead-in. The total treatment period was no more than two years. The primary outcome was major pathologic response (MPR). The trial adopted Simon's optimal two-stage design, with a threshold of two or more MPR among eight patients in Stage 1 required to proceed to Stage 2, where additional 18 patients would be recruited.

Results: Eleven ALK-positive patients were enrolled from February 2023 to March 2025. Patients had a median age of 60 years (range 42-78), and four (36%) were male. Adenocarcinoma was diagnosed in nine patients (82%), and seven (64%) had IIIA disease. One patient was still on neoadjuvant therapy, and 10 patients completed neoadjuvant therapy and underwent surgery as planned. Five (50%) of 10 achieved MPR, and three (30%) achieved pathologic complete response. Median residual viable tumor percentage reached 18% (range 0-75%). Nine (90%) patients demonstrated an objective response. Four (40%) showed radiologic downstaging, and R0 resection was successful in all cases. Two were waiting for adjuvant therapy initiation. In eight patients on postoperative iruplinalkib treatment, median interval from surgery to adjuvant iruplinalkib initiation and duration of adjuvant iruplinalkib exposure were 29.5 d (range 13-50 d) and 7.0 months (range 1.7-17.5 months), respectively. Two (18%) of 11 patients had grade≥3 iruplinalkib-related adverse events (AE), including alanine aminotransferase increased (two [18%]) and aspartate aminotransferase increased (one [9%]). No serious AE or dose discontinuation was related to iruplinalkib, while three (27%) patients required a dose interruption, and another (9%) had a dose reduction due to iruplinalkib-related AE.

Conclusions: These updated results suggest neoadjuvant iruplinalkib is effective for resectable ALK-positive NSCLC, demonstrating favorable safety profiles. The trial has progressed to Stage 2. Further data will provide insights into long-term outcomes.

Table. Efficacy endpoints

Endpoints	*ALK*-positive patients (n =10)
Major pathologic response	5 (50%)
Pathologic complete response	3 (30%)
Median residual viable tumor percentage	18% (0–75%)
Objective response	9 (90%)
Radiologic downstaging	4 (40%)
R0 resection	10 (100%)

Note: Data are presented as n (%) or median (range).

Keywords: Iruplinalkib, Non-small cell lung cancer, ALK/ROS1 fusion

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.39 Pooled Efficacy and Safety Profile of Neoadjuvant Therapies in Operable EGFR-Mutant Non-Small Cell Lung Cancer: A Meta-Analysis

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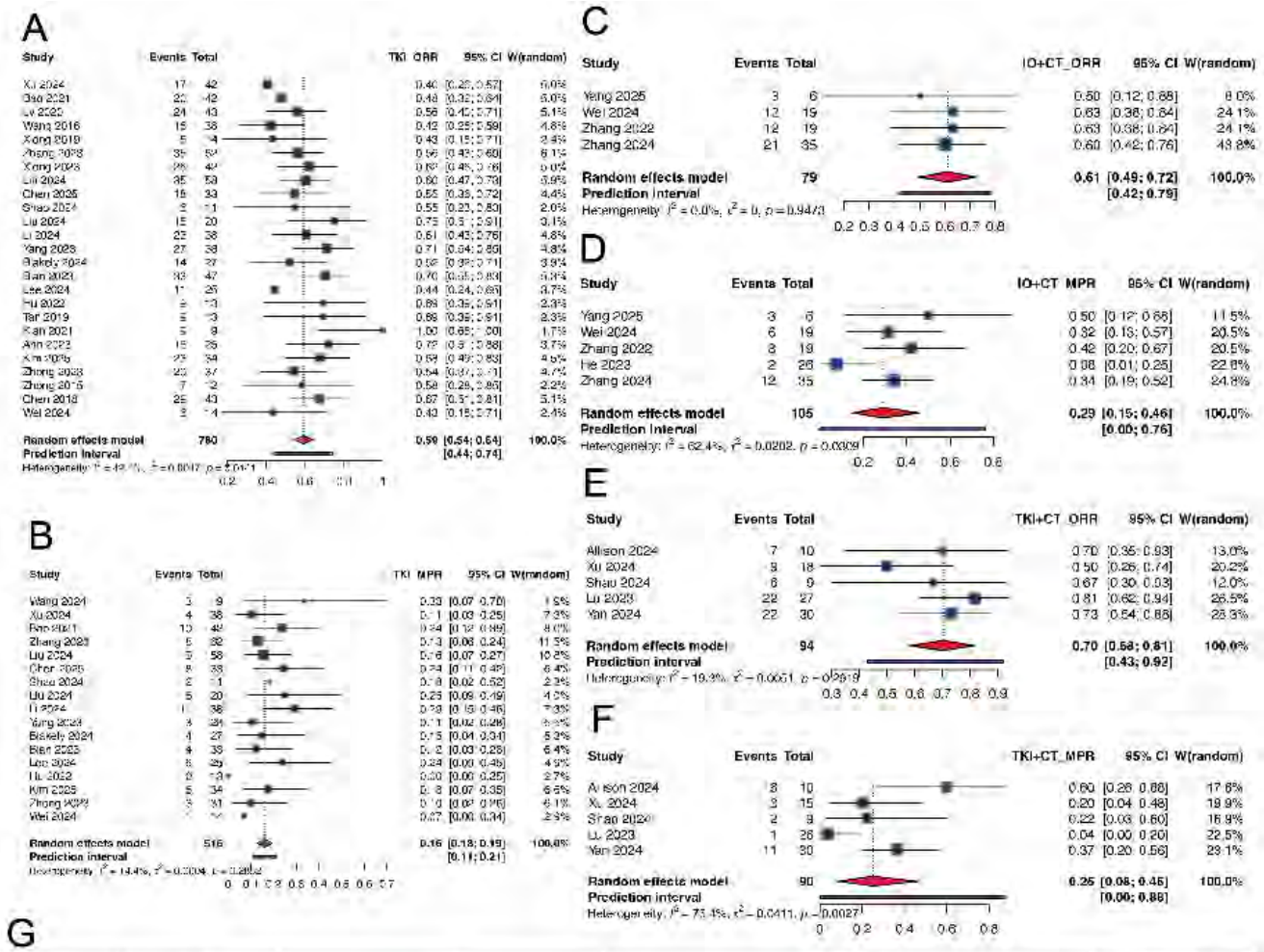
Introduction: The therapeutic efficacy of neoadjuvant therapies for operable EGFR-mutated non-small cell lung cancer (NSCLC) remains debated.

Methods: We searched PubMed, Web of Science, Embase, and conference proceedings through March 20, 2025. Primary outcomes include objective response rate (ORR) and major pathological response (MPR). The protocol is registered with PROSPERO, CRD420251023318.

Results: We included 3 RCTs, 3 RWSs, 13 single-arm trials and 14 retrospective studies involving 1107 patients and four neoadjuvant strategies (chemotherapy [CT], tyrosine-kinase inhibitors [TKI], immune checkpoint inhibitor plus chemotherapy [IO+CT], TKI plus chemotherapy [TKI+CT]). Pooled ORR was significantly higher in TKI (59% [95% CI 0.54-0.64]) and IO+CT (61% [95% CI 0.49-0.72]) compared to CT (37% [95% CI 0.29-0.46]), with TKI+CT demonstrating superior efficacy (70% [95% CI 0.58-0.81]). All regimens achieved near-complete disease control rates (DCR). Pathological outcomes revealed TKI+CT significantly outperformed TKI monotherapy in MPR (25% vs 16%; 95% CIs 0.08-0.46 vs 0.13-0.19), while IO+CT showed marginally higher MPR (29% [95% CI 0.15-0.46]). Similar trends emerged in pathological complete response (PCR) rates. Safety profiles showed comparable adverse event (AE) frequencies between TKI and IO+CT groups. Grade ≥3 AEs occurred in 17% (95% CI 0.09-0.27) of IO+CT and 17% (95% CI 0.06-0.32) of TKI+CT recipients. Mutation subtype analysis revealed differential responses: exon 19 deletions (19del) exhibited superior ORR to TKI vs L858R mutations (65% vs 50%), whereas L858R demonstrated better response to IO+CT across MPR, PCR, and ORR endpoints (ORR: 67% vs 54%). Third-generation TKIs demonstrate superior efficacy compared to overall TKIs (ORR: 67% vs. 59%). Survival analysis limited to TKI monotherapy showed median OS 55.84 months (95% CI 41.16-70.51) and DFS 24.66 months (95% CI 13.48-35.84), with insufficient data for other regimens.

Conclusions: TKI+CT and IO+CT emerge as preferred neoadjuvant strategies, demonstrating complementary efficacy profiles: TKI+CT shows superior radiographic response while IO+CT achieves enhanced pathological regression, aligning with respective mechanisms of tumor growth inhibition versus immune-mediated cytotoxicity. Mutation-specific responses suggest 19del subtypes may derive greater benefit from targeted neoadjuvant therapy, whereas L858R mutations appear more responsive to immunochemotherapy. These findings underscore the potential for precision neoadjuvant approaches based on EGFR mutation subtypes to optimize outcomes in operable NSCLC.



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	CT	TKI	IO+CT	TKI+CT
ORR	37%[0.29;0.46]	59%[0.54;0.64] 19del: 65% L858R: 50% 3rd TKI: 67%[0.57,0.75]	61%[0.49;0.72] 19del: 54% L858R: 67% Other: 65%	70%[0.58;0.81]
DCR	96%[0.86;1.00]	99%[0.98;1.00]	96%[0.90;1.00]	97%[0.90;1.00]
MPR	/	16%[0.13;0.19] 3rd TKI: 18%[0.11,0.25]	29%[0.15;0.46] 19del:31% L858R:39% Other: 23%	25%[0.08,0.46]
PCR	/	1%[0.00;0.03]	9%[0.04,0.16] 19del:11% L858R:21% Other:0%	5%[0.00;0.17]
AEs	/	75%[0.56;0.90]	76%[0.34;1.00]	/
Grade >=3 AEs	31%[0.21;0.42]	5%[0.02;0.09]	17%[0.09,0.27]	17%[0.06,0.32]
R0 resection	65%[0.4;0.76]	94%[0.90;0.98]	/	97%[0.91;0.98]
down-staging	/	55%[0.35;0.74]	/	77%[0.62;0.90]
VATS	/	72%[0.53;0.89]	/	80%[0.65;0.92]
OS	36.9[25.6;48.1]	55.84[41.16;70.51]	/	83.81
PFS	11.4[7.1;15.7]	16.62[6.54;26.70]	/	/
DFS	/	24.66[13.48;35.84]	EFS: 21.1 months	/

Keywords: EGFR, neoadjuvant therapy, non-small cell lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.40 Detection of ctDNA Prior to Neoadjuvant Osimertinib Treatment Correlates With Decreased EFS in EGFR-Mutated NSCLC

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Introduction: Neoadjuvant osimertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) is being investigated in multiple clinical trials. In a multi-institution phase II trial of neoadjuvant osimertinib (NCT03433469), 27 patients (pts) with surgically resectable stage I-IIIA (AJCC V7) EGFR-mutant (exon 19 del or L858R) NSCLC were enrolled and achieved a major pathological response (MPR) rate of 15% (J Clin Oncol. 2024 Sep 10;42(26):3105-3114). MPR was not predictive of event free survival (EFS) in this trial. In the metastatic setting, detection of circulating tumor DNA (ctDNA) prior to initiating osimertinib and after initial treatment correlate with worse clinical outcomes. This study investigated whether detection of ctDNA prior to neoadjuvant osimertinib or after 1 cycle of therapy was predictive of EFS in patients enrolled in NCT03433469.

Methods: Plasma was collected prior to initiating neoadjuvant osimertinib (C1D1) and after 1 cycle of osimertinib treatment (C1D28) in patients enrolled in NCT03433469. Plasma samples were analyzed using the Guardant Infinity platform, which detects ctDNA through both genomic alterations and DNA methylation. Kaplan-Meier estimates of median EFS were compared between patients with detectable ctDNA at C1D1 and C1D28 vs. those without detectable ctDNA at these timepoints by the log-rank test. Cox proportional hazards regression was performed to adjust for age, sex, tumor stage, race, EGFR mutation subtype, and time on osimertinib prior to surgery.

Results: 23 of 27 patients had both C1D1 and C1D28 plasma available for analysis. Median follow-up time for EFS was 36.3 months. Patient characteristics are presented in Table 1. 9 of 23 patients (39%) had ctDNA detectable at C1D1. 5 of 23 patients had ctDNA detectable at C1D28. Median EFS was significantly reduced for patients with detectable ctDNA on C1D1 vs. those without (8.5 vs. 45.6 months, HR: 3.78, 95% CI: 1.09 - 13.13, p = 0.036) as well as those with detectable ctDNA on C1D28 vs. those without (18.7 vs. 45.6 months, HR: 5.90, 95% CI 1.09 - 32.01, p = 0.038). Cox regression analysis demonstrated that detectable ctDNA on C1D1 correlated with decreased EFS when controlling for other variables (HR: 10.57, 95% CI 0.98 - 107.6, p = 0.039).

Conclusions: Detection of ctDNA prior to neoadjuvant osimertinib treatment is associated with decreased EFS in patients with EGFR p.L858R or exon 19 deletion mutated NSCLC independent of patient age, mutation subtype, race, or tumor stage. Analysis of ctDNA may be considered prior to initiating neoadjuvant osimertinib therapy.

Table 1. Patient Characteristics	
Characteristic	N (%)
No. of patients	27 (100)
No. with C1D1 and C1D28 plasma for ctDNA analysis	23 (85)
Detectable ctDNA C1D1	9 (39)
Detectable ctDNA C1D28	5 (22)
Sex, N (%)	
Female	18 (78)
Male	5 (22)
Race or ethnicity, N (%)	
Asian	10 (43)
Non-Asian	13 (57)
Age (years), median (range)	70 (39-82)
Median # days on neoadjuvant osimertinib (range)	55 (30-68)
Overall Clinical Stage (AJCC V7), N (%)	
IA-IIB	16 (70)
IIIA	7 (30)
EGFR mutation, N (%)	
Exon 19 deletion	9 (39)
Exon 21 p.L858R	14 (61)

Keywords: circulating tumor DNA, Neoadjuvant, EGFR

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.41 Exhaled Breath Analysis in Patients With Resectable NSCLC Treated With Neoadjuvant Immune Checkpoint Inhibitors

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Introduction: In patients with resectable NSCLC, immune checkpoint inhibition (ICI) became a cornerstone in the curative multimodality treatment. The multicentric, non-comparative phase II study NEOpredict-Lung (NCT04205552) confirmed the primary endpoint of feasibility of neoadjuvant dual PD-1 and LAG-3 inhibition. In this abstract we present data on exhaled breath analysis (EBA).

Methods: Patients with NSCLC (stages IB-IIIA) eligible for surgery were randomized (30 per arm) to receive two preoperative doses (q14d) of nivolumab (240 mg, arm A), or nivolumab plus relatlimab (240/80 mg, arm B or 240/240mg, arm C). Patients treated at the Belgian site could consent to participate in the EBA. The measurement took place at 2 time points: before start of ICI and pre-operatively. Exhaled breath was analyzed real-time using a cloud-based electronic nose: SpiroNose (Breathomix, Leiden, The Netherlands). A model to discriminate healthy individuals from cancer patients was built using linear discriminant analysis (LDA) and validated using leave-one-out cross-validation. A student's T-test identified sensors that differ significantly in patients achieving major pathological response (MPR; <10% residual viable tumor).

Results: In total, 17 patients underwent EBA and 33 measurements were collected. The NEOPREDICT-EBA cohort was compared to a reference healthy (HEALTHref; n=50) and lung cancer (CANref; n=30) cohort. Controls were matched for age, sex, BMI, smoking status, and histology. The NEOPREDICT-EBA cohort was considered a representative cohort: no significant differences were noted with CANref, and a significant distinct breathprint was noted from HEALTHref (Fig.1, LDA AUC=0.969). Of the 17 EBA-patients treated with neoadjuvant ICI, 2 had a major pathological response (MPR). In patients achieving MPR, 2 sensors (S6 and SBH4) differed significantly from patients not achieving MPR (p<0.001) (Fig.2).

Conclusions: Pre-operative exhaled breath analysis can potentially identify patients achieving MPR after neoadjuvant ICI. Further expansion of the data set is planned with neoadjuvant chemotherapy+ICI treated early-stage NSCLC patients.

Figure 1: t-SNE (t-distributed stochastic neighbour embedding) plot comparing healthy controls, lung cancer controls and the NEOPREDICT-exhaled breath analysis cohort.

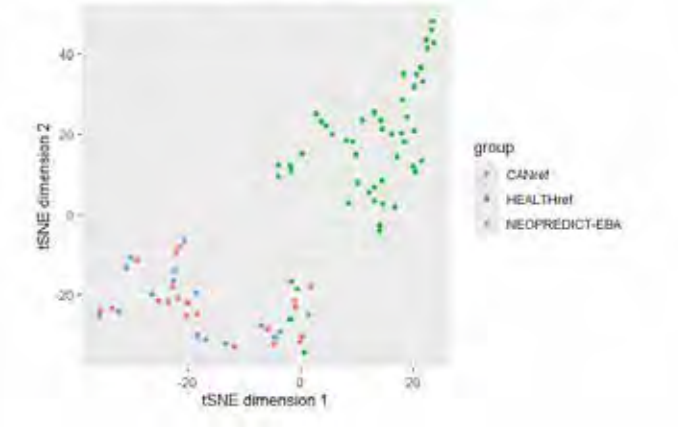
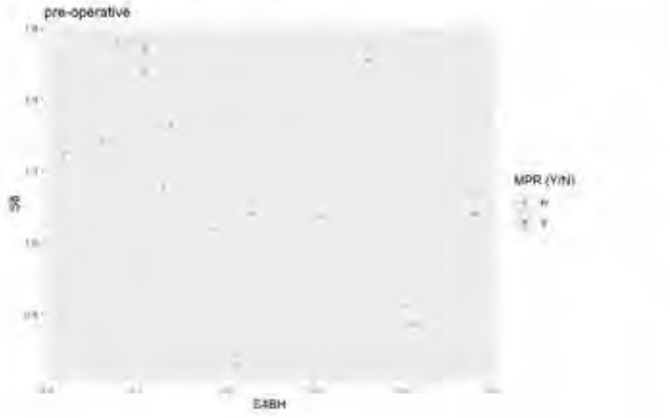


Figure 2: Comparison of patients achieving major pathological response (MPR; <10% residual vital tumor) to non-MPR patients. A statistically significant difference was noted in sensors S6 and SB4H (both p <0.001).



Keywords: neoadjuvant, immune checkpoint inhibitor, exhaled breath analysis

P1.07.42 Multi-Temporal Imaging and CT-To PET Translation Based Predictive Model on Neoadjuvant Immunotherapy for Non-Small Cell Lung Cancer Patients

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Introduction: The efficacy of neoadjuvant immunotherapy (NIT) for non-small cell lung cancer (NSCLC) is challenged by the spatiotemporal heterogeneity (TSH) of tumors, complicating reliable patient selection. Radiomics-based biomarker prediction models, including those leveraging PET and CT radiomics, hold promise in addressing this challenge. Delta radiomics, which captures dynamic changes in imaging features over time, offers a more nuanced representation of TSH. This study aims to develop a multimodal predictive model incorporating delta radiomics to assess the efficacy of NIT in NSCLC patients.

Methods: We retrospectively analyzed 149 NSCLC patients (stage IA-IIIB) from Guangdong Provincial People's Hospital who underwent pre-NIT and pre-surgical chest CT and PET/CT scans with pathological confirmation. The dataset was divided into training and validation cohorts in a 7:3 ratio. Our previous work introduced a generative adversarial network (GAN)-based image-to-image translation model capable of CT-to-PET translation (CPT), facilitating the generation of metabolic features. We leveraged this model to extract multi-timepoint delta radiomics features and integrated CT, PET, and metabolic data into a multimodal collaborative learning framework to predict NIT response.

Results: In preliminary analyses, we evaluated the performance and stability of nine predictive models, identifying XGBoost as the most stable and effective. Among single-modality delta radiomics features, ΔCT exhibited the highest predictive performance (AUC: 0.804, 95% CI: 0.730-0.869), outperforming both ΔPET (AUC: 0.723, 95% CI: 0.637-0.797) and ΔMeta (metabolic) features (AUC: 0.731, 95% CI: 0.644-0.810). When combining baseline and delta features, the integration of baseline metabolic and ΔMeta features yielded an AUC of 0.796 (95% CI: 0.720-0.862), comparable to baseline CT and ΔCT features (AUC: 0.783, 95% CI: 0.704-0.859) and superior to baseline PET and ΔPET features (AUC: 0.752, 95% CI: 0.671-0.827). The highest predictive performance was achieved by integrating ΔCT and ΔPET (AUC: 0.855, 95% CI: 0.791-0.913), surpassing the model incorporating ΔCT, ΔPET, and ΔMeta features (AUC: 0.788, 95% CI: 0.708-0.861).

Conclusions: Our delta-radiomics-based multimodal model offers a cost-effective, non-invasive, and reproducible strategy for predicting NIT efficacy in NSCLC, enabling more precise patient stratification and treatment optimization.

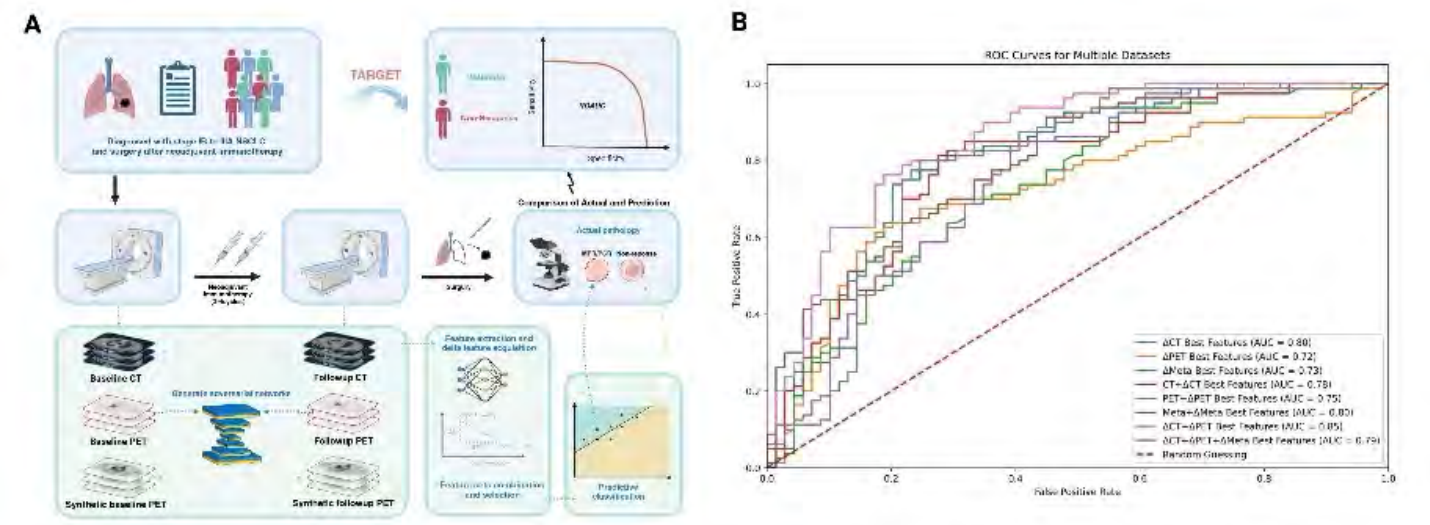

Figure 1. A. The framework and process of study. **B.**ROC curves of the integrated models based on the combination of delta CT, delta PET, and delta metabolic radiomics.

Keywords: Delta radiomics, Neoadjuvant immunotherapy, Generative adversarial network

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.43 Clinico-Genomic Correlates of Pathologic Response to Neoadjuvant Chemo-Immunotherapy in Patients With Early-Stage NSCLC

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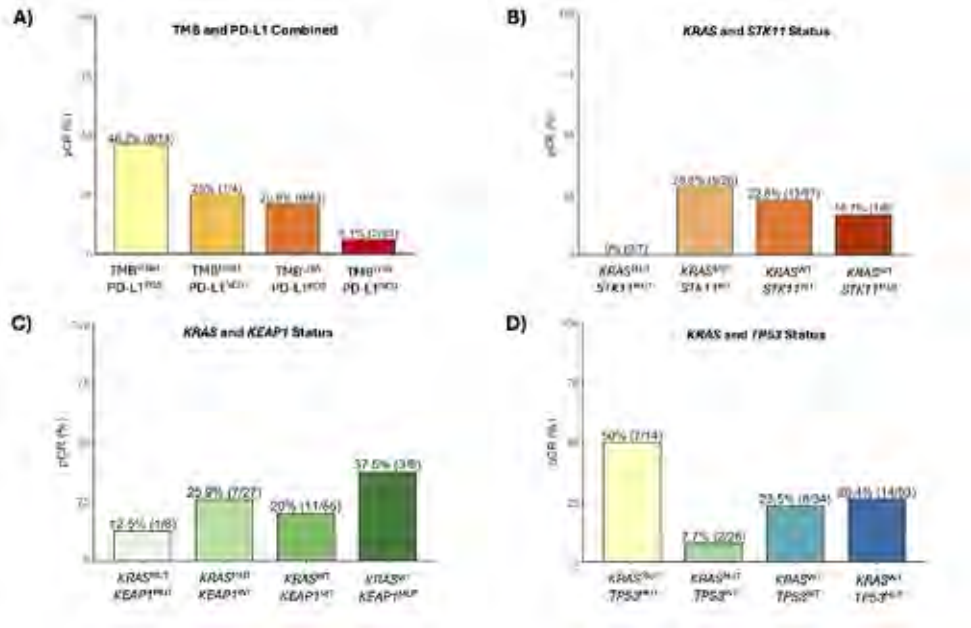
Introduction: While neoadjuvant chemotherapy combined with PD-(L)1 blockade improves clinical outcomes in patients with early-stage non-small cell lung cancer (NSCLC), most patients do not achieve a pathologic complete response (pCR) and develop disease recurrence. This study aims to identify clinically available biomarkers of response or resistance to neoadjuvant chemoimmunotherapy (CT-ICI).

Methods: This multicenter, retrospective study analyzed clinicopathologic and genomic data from patients with stage IB-IIIC NSCLC treated with neoadjuvant CT-ICI, ± adjuvant immunotherapy, across six academic centers in the US and EU. Tumor mutational burden (TMB), assessed using OncoPanel and MSK-IMPACT platforms, was normalized using the ordered quantile normalization transformation.

Results: A total of 221 patients who received neoadjuvant CT-ICI were included. Median age was 67 years, 50.7% were female, and 90.5% had a history of smoking with a median tobacco exposure of 30 pack-years. Most patients had stage IIB-IIIA disease (78.3%). Patients who achieved a pCR (N=58), had significantly longer median event-free survival compared to those without pCR (not reached vs. 20.5 months, p=0.001). There was no difference in pCR rates between patients with non-squamous (N=151) vs. squamous (N=70) histology (odds ratio [OR] 1.2, p=0.62). Baseline PD-L1 tumor proportion score (TPS) ≥50% (N=69) was associated with the highest pCR rate, compared with 1-49% (OR 2.9, p=0.004) and <1% (OR 5.2, p<0.001). Paired PD-L1 TPS pre- and post-CT-ICI was available for 27 cases and, among them, PD-L1 expression increased in 40.7% and decreased in 37.0%. Higher TMB (≥90th percentile) was associated with greater likelihood of pCR (OR 4.42, p=0.008). Concurrent PD-L1 and TMB were available in 93 patients. The highest pCR rate was observed in the High-TMB/PD-L1-positive group (46.2%, N=6/13), and the lowest in the Low-TMB/PD-L1-negative group (6.1%, N=2/33) (Figure 1A). Genomic data were available for 98 patients who had targeted exome sequencing. pCR was lowest in patients with co-occurring KRAS/STK11 (0%, N=0/7) and KRAS/KEAP1 (12.5%, N=1/8) mutations (Figure 1B-C). Among 127 patients with TP53 mutational status available, the KRAS/TP53 co-mutant subgroup had the highest pCR rate (50%, N=7/14) (Figure 1D).

Conclusions: Patients with high PD-L1, elevated TMB, or KRAS/TP53 co-mutations were more likely to achieve a pCR after to neoadjuvant CT-ICI, while those with KRAS/STK11 or KRAS/KEAP1 mutations showed limited benefit. These findings support the integration of molecular and immunologic biomarkers into treatment algorithms to optimize patient selection and enhance therapeutic efficacy, underscoring also the need for novel strategies to overcome resistance in biomarker-defined subgroups.

Figure 1. pCR rates according to PD-L1 and genomic features.



Keywords: Neoadjuvant, Chemo-immunotherapy, Biomarker

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.44 Multicenter Assessment of Clinical-Radiomic Predictors for Pathologic Response in NSCLC Patients Receiving Neoadjuvant Chemoimmunotherapy

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Introduction: This study aimed to identify clinical factors and develop a predictive model for pathologic complete response (pCR) and major pathologic response (MPR) in non-small cell lung cancer (NSCLC) patients receiving neoadjuvant chemotherapy combined with immune checkpoint inhibitors (ICIs).

Methods: Cases meeting inclusion criteria were divided into high- and low-risk groups according to 75 clinical indicators based on 10-fold LASSO selection. Logistic regression was employed to analyze both pCR and MPR. The accuracy of the nomograms was assessed using the time-dependent area under the curve (AUC).

Results: A total of 883 patients from four multiple centers were included in the study, with 526 assigned to the training set and 357 to the testing set. The AUC was determined for the prediction of pCR (training: 0.92; testing: 0.87) and MPR (training: 0.94; testing: 0.85). Significant associations were observed between the preoperative tumor maximum diameter, preoperative tumor maximum standardized uptake value (SUVmax), changes in tumor SUVmax, percentage of tumor reduction, baseline total CYFRA21-1 and pathological response ($P < 0.001$).

Conclusions: The combined application of clinical indicators including non-invasive tumor imaging and hematology can help clinicians to obtain a higher ability to predict NSCLC patient's pathological remission, and the effect is better than that of clinical factors alone. These findings could help guide personalized treatment strategies in this patient population.

Keywords: lung adenocarcinoma, neoadjuvant immunotheraoy combined with chemothera, pathological response

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.45 Transforming Outcomes With Neoadjuvant Chemo-Immunotherapy in Operable Non-Small Cell Lung Cancer (NSCLC): A Propensity-Matched Analysis

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Introduction: Neoadjuvant chemo-immunotherapy has emerged as a transformative approach for early-stage NSCLC, offering survival and surgical benefits over traditional adjuvant strategies. This study evaluates the comparative impact of neoadjuvant versus adjuvant immunotherapy on long-term survival in operable NSCLC using real-world data from the TriNetX database

Methods: We conducted a retrospective cohort study of patients with operable NSCLC treated with neoadjuvant chemo-immunotherapy or adjuvant immunotherapy. Propensity score matching addressed baseline differences, ensuring comparability across groups. Key characteristics before matching included significant imbalances in male sex (42.5% vs. 48.7%, p=0.006), White race (55.8% vs. 61.1%, p=0.019), history of cerebrovascular disease (26.4% vs. 20.9%, p=0.004), and liver disease such as cirrhosis (35.2% vs. 25.1%, p<0.001). Matching yielded balanced cohorts (all p>0.05) for analysis. Key outcomes included 5-year and 10-year mortality rates. Absolute risk reduction (ARR), number needed to treat (NNT), and adjusted odds ratios (aOR) were calculated.

Results: In the cohort study, Neoadjuvant chemo-immunotherapy demonstrated significant survival benefits compared to adjuvant immunotherapy in operable NSCLC. Significant survival benefits were observed in females (RR: 0.53, 95% CI: 0.31-0.90, p = 0.0167) and White patients treated with neoadjuvant therapy compared to adjuvant treatment (RR: 0.56, 95% CI: 0.39-0.77, p = 0.0004) Hispanic patients showed no differences in outcomes between the two approaches. Notably, no significant differences in the frequency of immunotherapy-related adverse events were documented in any specific subgroup. Furthermore, one additional life was saved for every 17 patients treated with neoadjuvant chemo-immunotherapy over 5- and 10-year periods. Adjusted analyses revealed substantial mortality reductions (5-year aOR: 0.59, 95% CI: 0.42-0.83; 10-year aOR: 0.59, 95% CI: 0.42-0.83), providing a strong reassurance of its effectiveness and clinical utility.Conclusion: Our study underscores the transformative benefits of neoadjuvant chemo-immunotherapy in early-stage NSCLC, with significant reductions in 5- and 10-year mortality rates and significant advantages in key subgroups. However, women and racial minorities were underrepresented in the cohort, limiting the generalizability of our findings. Neoadjuvant chemo-immunotherapy offers a compelling strategy for improving outcomes in operable NSCLC with survival benefits compared to an adjuvant therapy approach.

Conclusions: Our study underscores the transformative benefits of neoadjuvant chemo-immunotherapy in early-stage NSCLC, with significant reductions in 5- and 10-year mortality rates and significant advantages in key subgroups. However, women and racial minorities were underrepresented in the cohort, limiting the generalizability of our findings. Neoadjuvant chemo-immunotherapy offers a compelling strategy for improving outcomes in operable NSCLC with survival benefits compared to an adjuvant therapy approach.

Outcome	Chemo-Immunotherapy Neoadjuvant Immunotherapy (%)	Adjuvant Immunotherapy (%)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)
5-Year Mortality	9.8	15.6	5.8%	17
10-Year Mortality	10	16	6.0%	17

Keywords: Non-Small Cell Lung Cancer, Neoadjuvant chemo-immunotherapy, Disparities

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.46 Adjuvant Systemic Therapy for Resected Stage IB-IIA NSCLC (AJCC 8Th Edition): A Real-World Cohort Study From SEER Database

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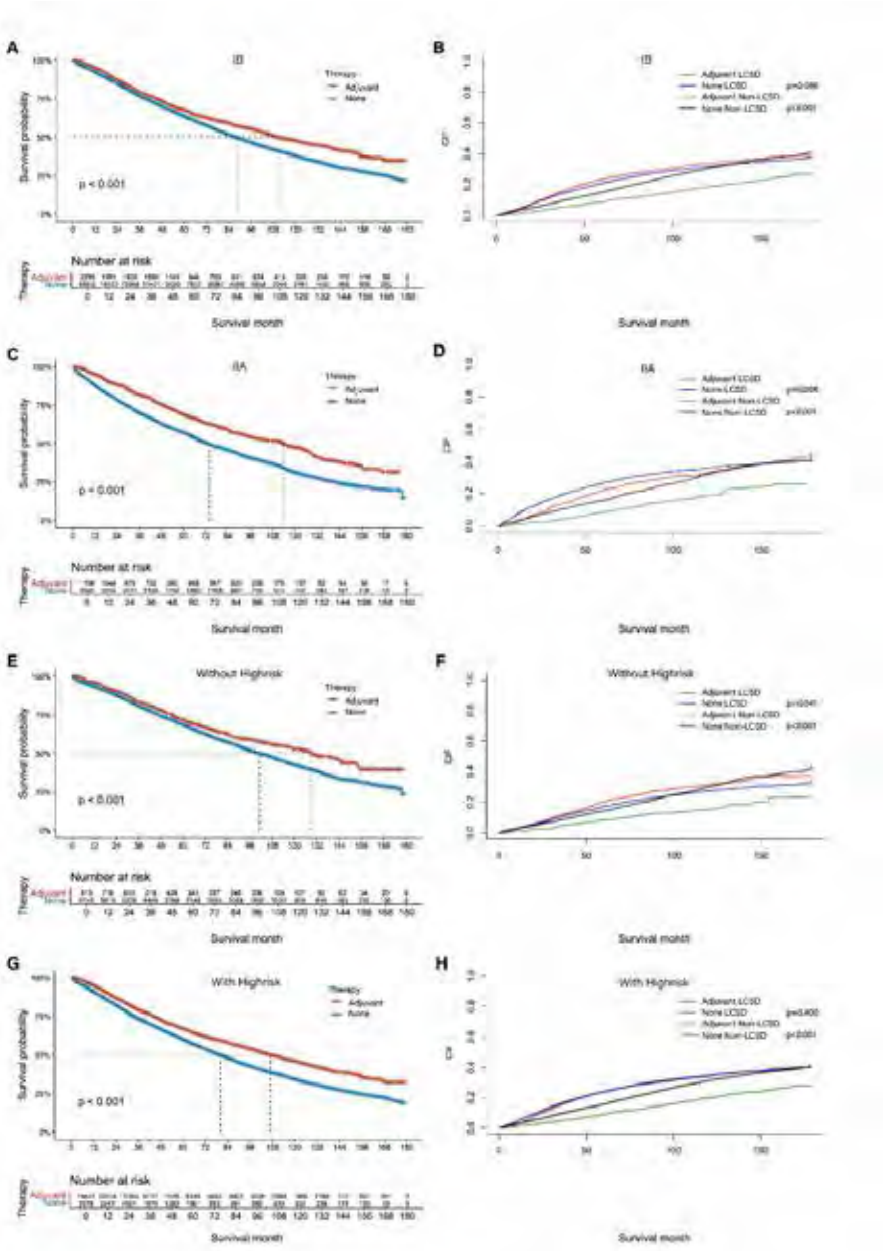
Peking University People's Hospital, Beijing/CN

Introduction: Although adjuvant chemotherapy is recommended for complete resected stage IB-IIA NSCLC with high-risk features, the role of adjuvant therapy in this particular population remains controversial.

Methods: Surgical resected NSCLC patients diagnosed as pathological stage IB-IIA according to AJCC 8th edition staging system were identified in SEER database (2007-2021). Survival outcomes were compared between adjuvant and observation groups. Multivariate Cox and competing risk regression models were built to identify prognostic factors and adjust for covariates in subgroup analyses.

Results: A total of 25919 surgical resected stage IB-IIA NSCLC were enrolled in the study, among which only 3497 (13.5%) received postoperative adjuvant treatment in the real world. The adjuvant therapy rates for stage IB, IIA, and stage IB-IIA patients with high-risk features were 10.9%, 25.0%, and 14.6%, respectively. In the entire cohort, although adjuvant therapy was an independent favorable prognostic factor for overall survival (OS) (HR 0.89, 95%CI 0.84-0.95, P < 0.001), it was not associated with improved lung cancer-specific survival (LCSS) (SHR 1.04, 95%CI 0.97-1.12, P = 0.290). Subgroup analyses revealed that adjuvant therapy was not a favorable prognostic factor for stage IB patients, regardless of the presence or absence of high-risk features; however, it was significantly associated with improved OS (HR 0.75, 95%CI 0.67-0.83, P < 0.001) and LCSS (SHR 0.87, 95%CI 0.76-0.99, P = 0.044) in stage IIA patients. Notably, the survival benefits derived from adjuvant systemic therapy was more prominent in stage IIA NSCLC with high-risk features (OS: HR 0.69, 95%CI 0.60-0.79, P < 0.001; LCSS: SHR 0.76, 95%CI 0.64-0.90, P = 0.001).

Conclusions: Adjuvant therapy was significantly associated with improved OS and LCSS in surgical resected stage IIA NSCLC, especially for those with high-risk features; however, it was not a favorable prognostic factor for stage IB patients, regardless of the presence or absence of high-risk features.



Variable	Count	Percent	OS	HR (95% CI)	P value	P for interaction	LCSS	HR (95% CI)	P value	P for interaction
Tumor size						0.002				0.004
<=30	10815	41.7		1.00 (0.90 to 1.11)	0.945			1.16 (1.01 to 1.31)	0.028	
(30,40]	10314	39.8		0.91 (0.82 to 1.00)	0.060			1.14 (1.00 to 1.29)	0.043	
>40	4790	18.5		0.75 (0.67 to 0.83)	<0.001			0.87 (0.76 to 0.99)	0.044	
Histology						<0.001				<0.001
ADC	16533	63.8		0.90 (0.83 to 0.97)	0.009			1.06 (0.98 to 1.19)	0.120	
SCC	6355	24.5		0.76 (0.67 to 0.85)	<0.001			0.86 (0.74 to 1.01)	0.069	
NEC	1361	5.3		1.49 (1.11 to 2.01)	0.008			1.58 (1.06 to 2.34)	0.025	
ASC	686	2.7		0.78 (0.56 to 1.11)	0.177			0.90 (0.60 to 1.37)	0.630	
Other	992	3.7		0.92 (0.73 to 1.16)	0.486			1.07 (0.80 to 1.45)	0.650	
Stage						0.001				0.001
IB	21129	81.5		0.95 (0.88 to 1.02)	0.142			1.16 (1.06 to 1.26)	0.001	
IIA	4790	18.5		0.75 (0.67 to 0.83)	<0.001			0.87 (0.76 to 0.99)	0.044	
Highrisk						0.577				0.029
No	7567	29.2		0.90 (0.79 to 1.03)	0.120			1.19 (1.01 to 1.39)	0.038	
Yes	18352	70.8		0.86 (0.81 to 0.93)	<0.001			1.00 (0.92 to 1.09)	0.980	
Stage and Highrisk										
IB without Highrisk	5547	21.4		0.95 (0.79 to 1.13)	0.531	0.791		1.24 (1.00 to 1.55)	0.055	0.227
IB with Highrisk	15582	60.1		0.94 (0.87 to 1.02)	0.122			1.12 (1.01 to 1.23)	0.030	
IIA without Highrisk	2020	7.8		0.87 (0.72 to 1.06)	0.163	0.124		1.15 (0.91 to 1.46)	0.230	0.002
IIA with Highrisk	2770	10.7		0.69 (0.60 to 0.79)	<0.001			0.76 (0.64 to 0.90)	0.001	

Keywords: Non-small cell lung cancer, Adjuvant systemic therapy, Lung cancer-specific survival

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.47 Early Treatment Discontinuation of Osimertinib in the Adjuvant Setting: Insights From the ADAURA Study

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Introduction: Osimertinib - a third-generation, central nervous system-active epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) - is recommended as adjuvant treatment for resected stage IB-IIIA EGFR-mutated non-small cell lung cancer (NSCLC), based on significant improvements in disease-free survival (DFS) and overall survival (OS) with 3 years adjuvant osimertinib versus placebo in the phase III ADAURA trial (NCT02511106). Early treatment discontinuation in the adjuvant setting may impact patient outcomes. We performed an exploratory analysis of ADAURA to further examine reasons for early treatment discontinuation.

Methods: Patients with completely resected EGFR-mutated (Ex19del/L858R) stage IB, II or IIIA NSCLC (AJCC 7th edition) were randomised 1:1 to osimertinib 80 mg once daily (n=339) or placebo (n=343) until disease recurrence, treatment completion (3 years), or another discontinuation criterion was met. Patients with early discontinuation of osimertinib (defined as treatment for <34 months) were analysed to assess baseline characteristics, disease recurrence and reasons for discontinuation (including adverse events [AEs]). Data cut-off: 11 Apr 2022.

Results: Overall, 110 patients in the osimertinib arm discontinued treatment early; reasons for discontinuation included: AE (36%), patient decision (31%), disease recurrence (27%) and other reasons (5%). Baseline characteristics of patients with early discontinuation were consistent with the overall population (median age 66 years; 64% female; 38%/31%/31% stage IB/II/IIIA disease). Amongst patients with early discontinuation, 42 (38%) had an AE leading to treatment discontinuation. AEs leading to discontinuation varied, with most Medical Dictionary for Regulatory Activities (MedDRA) preferred terms occurring in ≤2 patients; those reported in >2 patients were all known adverse drug reactions (ADRs) for osimertinib/TKIs and included interstitial lung disease (n=8; five Grade 1 events and three Grade 2 events), electrocardiogram QT prolonged (n=4; three Grade 2 events and one Grade 3 event), pruritus (n=3; one Grade 1 event, two Grade 2 events), decreased appetite (n=3; one Grade 2 event and two Grade 3 events) and diarrhoea (n=3; two Grade 2 events and one Grade 3 event).

Conclusions: Early treatment discontinuation remains a significant issue in the adjuvant setting, often driven by known ADRs, patient withdrawal or disease recurrence. These data highlight the need for proactive AE management to address these challenges. Healthcare providers should ensure thorough communication with patients about the risks and benefits of continuing versus discontinuing treatment, aiming to enhance adherence and optimise patient outcomes.

Keywords: EGFR-mutated NSCLC, Adjuvant, Early discontinuation

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.48 Furmonertinib as Adjuvant Therapy in Postoperative EGFR-Mutated Stage IB-IIA NSCLC With High-Risk Pathological Factors

X-L. Li, J. Fan
Shanghai General Hospital, Shanghai/CN

Introduction: Non-small cell lung cancer (NSCLC) patients with high-risk pathological factors such as micropapillary (MP), solid (S), and spread through air spaces (STAS) have shown poor prognosis in previous studies. Furmonertinib (AST2818) is a novel, promising oral third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), which has demonstrated efficacy in tumors harboring sensitive EGFR mutations and T790M resistance mutation. Here, we investigated the efficacy and safety of furmonertinib as adjuvant therapy in postoperative EGFR-mutated NSCLC patients with high-risk pathological factors.

Methods: Patients who underwent radical lung cancer surgery with both EGFR mutations and MP/S/STAS were enrolled and received furmonertinib 80mg daily. The disease-free survival (DFS), safety and tolerability were evaluated. NCT05165355.

Results: This study has prospectively enrolled 79 patients who were pathologically confirmed adenocarcinoma, EGFR mutation positive (exon 19 deletion/L858R), stage IB-IIA NSCLC. All of them had at least one high-risk pathological factor. There were 56 patients with MP, 14 with S, and 53 with STAS. By the cut-off date of March 28, 2025, all patients were alive and with no radiographic recurrence. The median follow-up time was 24.6 months. During therapy, 17 (21.5%) patients had treatment-related adverse events (TRAEs) of any grade. The most common TRAEs were rash (15, 19.0%), diarrhea (4, 5.1%) and mouth ulcer (1, 1.2%). Only 1 (1.2%) patient had TRAEs of grade 3 or higher.

Conclusions: This is the first prospective study to demonstrate that furmonertinib has good efficacy and a tolerable safety profile as adjuvant therapy in EGFR-mutated early NSCLC patients with high-risk pathological factors who underwent radical lung cancer surgery.

Table. Patient demographic characteristics and safety events.

Variables	Values
Age, years	59 (24, 85)
Sex	
Female	47
Male	32
Type of surgery	
Lobectomy	62
Sub-lobectomy	17
Stage	
IB	59
IIA	20
High-risk factor	
MP	56
S	14
STAS	53
EGFR mutation	
19del	20
L858r	59
AE	
Any AEs	17 (21.5%)
CTCAE ≥ Gr 3	1 (1.2%)
Rash	15 (19.0%)
Diarrhea	4 (5.1%)
Mouth ulcer	1 (1.2%)

Keywords: Early NSCLC, Postoperative adjuvant therapy, EGFR-TKI

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.49 Limited Impact of Adjuvant Chemotherapy in Alk-Positive Stage II-III Adenocarcinoma: A Multicenter CReGYT-03 ALK Study

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Introduction: In 2024, alectinib was approved as adjuvant treatment for patients with non-small cell lung cancer (NSCLC) after resection who harboring a rearrangement in the anaplastic lymphoma kinase (ALK) gene (ALK-positive) based on the results of the ALINA trial in Japan. However, the effect of cytotoxic adjuvant chemotherapy (ACT) has not been fully explored in ALK-positive NSCLC. The aim of this study was to evaluate the role of cytotoxic ACT based on ALK status in patients with stage II-III lung adenocarcinoma (jRCT1050240057).

Methods: We conducted a multicenter retrospective study for patients with lung adenocarcinoma who underwent radical resection between 2011 and 2018 at 27 centers in Japan. Of 1028 patients with pathologic stage II-III (8th edition) lung adenocarcinoma without epidermal growth factor receptor mutation, all of them were tested for ALK status. Among them, 793 patients who underwent anatomical resection with mediastinal lymph node dissection were included in this study. We estimated inverse probability weighting (IPTW) to adjust for confounding variables, including age, sex, smoking status, performance status, and pathological stage associated with the administration of cytotoxic ACT. We evaluated recurrence-free survival (RFS) and overall survival (OS). The median follow-up was 51 months (IQR 31-65 months).

Results: Of 793 patients, ALK-positive adenocarcinoma was detected in 58 patients (7%): 37 (64%) received cytotoxic ACT (ACT group), while 21 (36%) did not (non-ACT group). There were no considerable differences for RFS between those who received cytotoxic ACT and those who did not [5-year RFS: 27% vs. 35%, HR = 0.86 (0.42-1.76)]. However, OS was substantially better in those who received ACT than in those who did not [5-year OS: 90% vs. 69%, HR = 0.19 (0.04-0.81)]. In 80 weighted patient cases (ACT group, 37; non-ACT group, 43), there were no considerable differences for RFS and OS between those who received cytotoxic ACT and those who did not [5-year RFS: 27% vs. 88%, HR = not estimable, and 5-year OS: 90% vs. 100%, HR = not estimable]. Of 735 patients with ALK-negative adenocarcinoma, 414 (56%) received cytotoxic ACT, while 321 (44%) did not. Both RFS and OS were substantially better in those who received cytotoxic ACT compared to those who did not [5-year RFS: 43% vs. 33%, HR = 0.67 (0.56-0.81), and 5-year OS: 72% vs. 57%, HR = 0.55 (0.43-0.71)]. In 828 weighted patient cases (ACT group, 414; non-ACT group, 414), both RFS and OS were substantially better in those who underwent cytotoxic ACT than in those who did not [5-year RFS: 43% vs. 36%, HR = 0.72 (0.60-0.86), and 5-year OS: 72% vs. 60%, HR = 0.61 (0.48-0.77)].

Conclusions: Although this study has limitations due to its retrospective design, the effect of cytotoxic ACT for stage II-III lung adenocarcinoma varied by ALK status. Our study demonstrated that the efficacy of cytotoxic ACT may be limited in patients with ALK-positive adenocarcinoma.

Keywords: non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK), adjuvant chemotherapy

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.50 Aumolertinib as Adjuvant Therapy in EGFRm Stage I-III NSCLC With High-Grade Histological Patterns: 3-Year Dfs Rate Updated

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Introduction: EGFR-mutated (EGFRm) lung adenocarcinoma patients with high-grade histological patterns are known to be associated with poor prognosis. Aumolertinib, the third-generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKI), has achieved potent efficacy for patients with EGFRm NSCLC. Besides, the results of phase III registration trial with adjuvant aumolertinb versus placebo is about to be released soon and aumolertinb will be the third EGFR-TKI comprising indication concerning adjuvant therapy worldwide. Therefore, the aim of this study was to evaluate the efficacy of aumolertinib as adjuvant therapy in resected stage I-III NSCLC with high-grade histological patterns.

Methods: Stage I-III NSCLC patients who were pathologically confirmed with high-grade patterns (micropapillary, solid component or complex glands) and underwent radical surgery were enrolled in the study. EGFRm patients were either assigned into aumolertinib group (group A) receiving aumolertinib (110 mg daily) treatment or observation group (group B). Patients with EGFR mutation negative or unknown were under observation allocated in Group C. The primary endpoint was disease-free survival (DFS) by investigator assessment. The safety was also evaluated.

Results: A total of 144 patients were recruited. 92 patients were EGFRm, of whom, 67 were orally administrated aumolertinb in group A and the rest were only observed in group B. 52 patients with EGFR mutation negative or unknown were under observation in Group C. At data cut-off (December,2024), the median follow-up time was 25.5, 39.1 and 39.0 months in Group A, B and C, respectively. In group C, the 3-year DFS rate was 82%. As for EGFRm patients, the 3-year DFS rate of Group A with 84% was significantly better than that of Group B with 64% (p=0.039). Tumor recurrence only occurred in 6 patients in group A. When stratified by stage and the proportion of high-grade patterns, the 3-year DFS rate of Group A with stage I (p=0.029) and those with 5% high-grade patterns(p=0.0017) were also greatly improved than that of group B. In addition, DFS was also superior in Group A 19DEL patients than in Group B (p=0.012). In terms of the analysis of group B and C (both were observation only), the recurrence ratio in EGFRm patients was higher than those with EGFR negative or unknown. No adverse events of grade≥3 occurred during aumolertinib treatment. 10.4% (7/67) of patients experienced treatment-related adverse reactions, the most common of which were pruritus (4.5%) and rash (3%).

Conclusions: Our study was the first to report adjuvant therapy data for aumolertinib as well as third-generation EGFR-TKIs in NSCLC with high-grade patterns. This updated results further revealed the long-term efficacy and safety of adjuvant aumolertinb and provide a solid proof for real-world practice. Moreover, the study confirmed that patients in stage I and those with≥5% high-grade patterns can benefit from aumolertinib therapy. Continuous follow-up is ongoing to investigate further survival outcomes.

Keywords: Aumolertinib, adjuvant therapy, high-grade histological patterns:

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.51 Safety and Tolerability of Adjuvant Atezolizumab in Pd-L1>50% NSCLC Patients: Real-World Data From the Italian ATLAS Registry

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Introduction: In the IMPower-010 trial, adjuvant atezolizumab demonstrated a significant improvement of disease-free survival along with a tolerable safety profile in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) and high programmed death ligand-1 (PD-L1) expression. We report real-world safety data of adjuvant atezolizumab in surgically resected NSCLC with PD-L1>50% from the Italian ATLAS registry.

Methods: Clinical data and treatment-related adverse events (TRAEs) were retrospectively collected from patients' medical records and electronic healthcare records. TRAEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: Between July 2022 and August 2024, 132 patients from 43 Italian centers received adjuvant atezolizumab and were included in the analysis. The median age at diagnosis was 65 years (range: 35-80). Most patients were male (65.2%) and current/former smokers (90.9%). Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 and 1 in 61.4% and 37.9%, respectively. Adenocarcinoma was the predominant histological subtype (62.1%), with PD-L1 expression ranging between 50% to 89% in 78% and higher than 90% in 22.0% of cases. Molecular analyses were mainly performed using next generation sequencing (63.6%) and all patients were EGFR and ALK wild type. Molecular alterations were identified in 47.7% of cases, with KRAS G12C and non-G12C mutations detected in 15.9% and 18.2% of patients. Lobectomy was performed in 81.1%, pneumonectomy in 6.8%, and both bilobectomy and wedge resection in 6.0% of patients, surgical approach was not reported in 6.1%. According to the 8th TNM staging system, 43.9% had pathological stage IIIA, 40.2% stage IIB, 8.3% stage IIA, and 7.6% stage IIIB. All patients received adjuvant platinum-based chemotherapy. The most common regimens were cisplatin plus vinorelbine (58.3%) and cisplatin plus gemcitabine (24.2%), while 3.9 and 14% of the patients received other cisplatin-based regimens and carboplatin-based combinations, respectively. The median interval from surgery to adjuvant treatment was of 59 days (range 13-270). The median number of adjuvant chemotherapy cycles was 4 (range:1-4). Two patients with pN2 disease underwent adjuvant radiotherapy. With a median follow up of 15.7 months, 54.4% of patients were still receiving adjuvant atezolizumab at the data cut-off. Among those who completed treatment, the median number of cycles was 12.5 (range: 1-20). TRAEs were reported in 33.3%, including skin toxicity (9.1%), diarrhea (8.3%), and increased transaminases (4.5%). Grade ≥3 TRAEs occurred in 15.2%, with diarrhea (3.8%), increased transaminases (2.3%), and enterocolitis (2.3%) being the most frequent. Treatment discontinuation due to TRAEs occurred in 13.6%: diarrhea (5.3%), increased transaminases (2.3%), and enterocolitis (2.3%).

Conclusions: These data are consistent with prior reports confirming the manageable profile of adjuvant atezolizumab in a real-world clinical setting with no new safety signals reported in our analysis.

Keywords: Atezolizumab, Adjuvant, Non–small cell lung cancer

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.52 Clinicopathologic Risk Score to Guide Adjuvant Chemotherapy in Stage IB NSCLC: Toward Integration of AI-Assessed Tumor Immune Signatures

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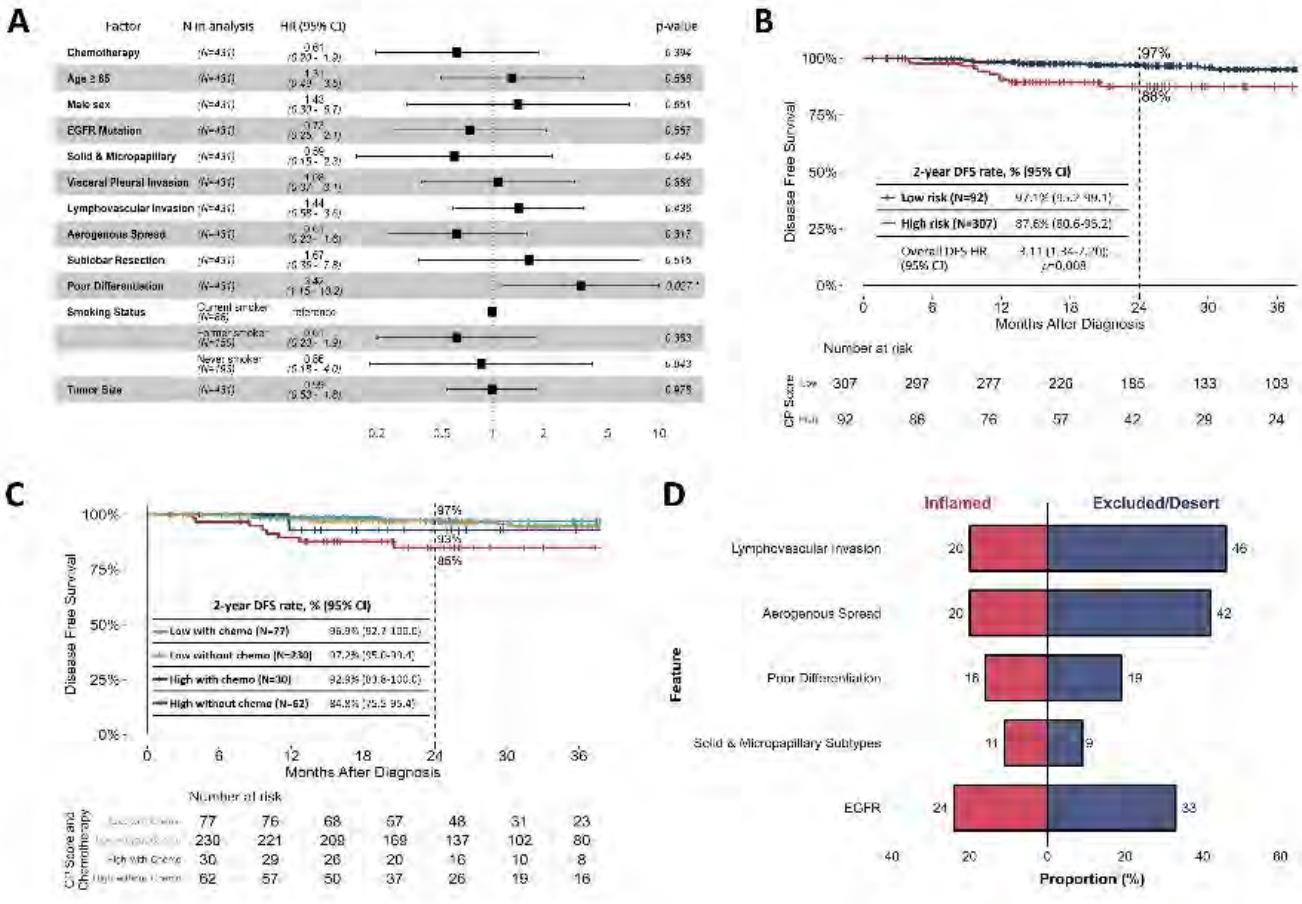
Introduction: Adjuvant chemotherapy is recommended for patients with high-risk features in stage IB non-small cell lung cancer (NSCLC), but the definition of 'high risk' remains inconsistent and unstandardized. We aimed to develop a clinicopathologic scoring system for relapse risk and to explore its association with AI-assessed immune signatures derived from histologic slides.

Methods: We analyzed a retrospective cohort of 431 stage IB NSCLC patients. Clinical and pathologic high-risk features were evaluated for disease-free survival (DFS), and a weighted risk score was constructed using multivariable Cox regression. In an exploratory cohort (n=102), immune signatures including immune phenotype, tumor-infiltrating lymphocytes (TILs), and tertiary lymphoid structures (TLSs) were quantified using Lunit Scope IO and correlated with high-risk features.

Results: Patients who received adjuvant chemotherapy (25% of total) were more likely to have high-risk features such as visceral pleural invasion (p<0.001), lymphatic invasion (p=0.003), and aerogenous spread (p=0.003). Although selectively administered to higher-risk patients, chemotherapy showed a favorable trend in DFS (HR 0.55, p=0.26). Poor differentiation was the strongest independent prognostic factor (HR 3.42, p=0.027), followed by trends for visceral pleural invasion (HR 1.08), lymphovascular invasion (HR 1.44), and sublobar resection (HR 1.67). Based on these findings, a clinicopathologic risk score (range: 0-5) was developed, assigning points to poor differentiation (2), lymphovascular invasion (1), sublobar resection (1), and visceral pleural invasion (1). The score effectively stratified patients into low (0-2) vs. high (3-5) risk groups, with high-risk patients (23% of total) showing significantly worse 2-year DFS (97.1% vs 87.6%; HR 3.11, 95% CI 1.34-7.20, p=0.008), and a C-index of 0.67 for DFS across the entire study period. In subgroup analysis, chemotherapy improved 2-year DFS in high-risk patients (92.9% with vs. 84.8% without chemotherapy), while no meaningful benefit was observed in low-risk group (96.9% vs. 97.2%). In the exploratory cohort, immune-cold phenotypes (excluded/desert) were more common in tumors with high-risk features such as lymphovascular invasion, aerogenous spread, and poor differentiation, suggesting a link between immune evasion and aggressive tumor biology. Inflamed phenotypes demonstrated higher TIL and TLS densities compared to excluded/desert phenotypes. However, these immune signatures were not prognostic in this limited dataset.

Conclusions: Our clinicopathologic relapse risk score effectively stratifies stage IB NSCLC patients and may help identify high-risk patients likely to benefit from adjuvant chemotherapy. The observed correlation between immune signatures and high-risk pathology warrants further investigation as complementary biomarkers.



P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.53 Aumolertinib as Adjuvant Therapy in I-III EGFRm NSCLC : Also Effective in Patients With Multiple Prognostic Risk Factors

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Introduction: In patients with stage I-III EGFRm NSCLC, the 5-year postoperative recurrence rate remains as high as 50% despite achieving local control through radical surgery (R0 resection), resulting in suboptimal long-term survival. Recurrence risk is multifactorial, including high-grade patterns (e.g.,micropapillary, solid component), high-risk relapse factors (e.g., spread through air space,vascular invasion), advanced age (≥70 yr), and comorbidities (e.g., hypertension, diabetes), all of which significantly increase disease progression risk. However, data on optimized adjuvant therapy for EGFRm NSCLC patients with multiple prognostic risk factors remain limited. This study aims to evaluate the efficacy of aumolertinib as adjuvant therapy in this patient cohort and explore the influence of various adverse factors on clinical outcomes.

Methods: Stage I-III EGFRm NSCLC patients who were pathologically confirmed with at least one prognostic risk factor and underwent radical surgery were enrolled in this study ,followed by adjuvant treatment with aumolertinib 110 mg once daily, The primary endpoint was disease-free survival (DFS) by investigator assessment. The safety was also evaluated.

Results: A total of 52 patients were enrolled, with a median follow-up of 31.0 months as of the data cutoff (March 2025). Eight deaths occurred, with 3-year disease-free survival (DFS) and overall survival (OS) rates of 82.8% and 87.4%, respectively. Subgroup analysis based on individual prognostic risk factor (e.g., age >70 vs. ≤70 years, high-grade patterns, high-risk relapse factors and comorbidities) revealed no statistically significant differences in the efficacy of adjuvant aumolertinib across all subgroups. Further stratification by ACE-27 scores indicated that patients with moderate to severe comorbidities (ACE-27 score 2-3) had comparable DFS (p=0.89) and OS (p=0.73) to those with lower comorbidity burdens (ACE-27 score 0-1). Additionally, in patients with ≥ 2 prognostic risk factors , aumolertinib demonstrated consistent efficacy (all P > 0.1, not statistically significant), regardless of the classification or number of risk factors (table 1).No adverse events of grade≥3 occurred during aumolertinib treatment. 21.3% (11/52) of patients experienced treatment-related adverse reactions, the most common of which were rash (9.62%%) and fatigue (7.69%).

Conclusions: Our study was the first to report adjuvant therapy data for aumolertinib as well as third-generation EGFR-TKIs in NSCLC with multiple prognostic risk factors. The results further confirm the long-term efficacy and safety of adjuvant aumolertinib , supporting its clinical applicability in populations with heterogeneous risk profiles. Notably, therapeutic efficacy remained robust regardless of comorbidity severity, age, or cumulative risk burden. Continuous follow-up is ongoing to further investigate survival outcomes.

Table 1. Subgroup analysis based on prognostic risk factors

Prognostic risk factors			n（%,N=52)	DFS P value	OS P value
Count	Classification				
1	Elderly patients	>70	26（50.0%）	p=0.98	p=0.70
		≤ 70	26（50.0%）		
1	High-grade patterns	yes	35（67.3%）	p=0.12	p=0.18
		no	17（32.7%）		
1	High-risk relapse factors	yes	40（76.9%）	p=0.74	p=0.93
		no	12（23.1%）		
1	Comorbidities	yes	14（26.9%）	p=0.89	p=0.93
		no	38（73.1%）		
	ACE-27 scores	0-1	40（76.9%）	p=0.89	p=0.74
		2-3	12（23.1%）		
2	Any 2 prognostic risk factors		/	P>0.1*	P>0.1*
3	Any 3 prognostic risk factors		/	P>0.1*	P>0.1*
4	All 4 prognostic risk factors		5（9.6%）	p=0.53	p=0.56

*: A total of six combinations were analyzed, each with P > 0.1
*: A total of four combinations were analyzed, each with P > 0.1

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.54 The Effect of Adjuvant EGFR-TKI Therapy on the Prognosis of Pathological Stage I Invasive Lung Adenocarcinoma With Sensitive EGFR Mutation

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Introduction: The prognosis of stage I non-small cell lung cancer (NSCLC) remains significant heterogeneity. It is not clear whether adjuvant EGFR-TKI therapy can reduce the recurrence rate and improve survival in patients with stage I disease, especially stage IA.

Methods: This is a retrospective, single-center, observational, propensity score-matched study that enrolled patients with pathological stage I invasive lung adenocarcinoma with EGFR mutation who underwent surgical treatment. The patients were divided into an observation group and an EGFR-TKI group. Inverse probability of treatment weighting (IPTW) was applied to address baseline characteristic imbalances between the two groups. The primary endpoint was relapse-free survival (RFS), and the secondary endpoints was overall survival (OS). RFS and OS were calculated using the Kaplan-Meier method, and the log-rank test was used to compare differences between the two groups. Stratified analysis was performed according to the risk of recurrence determined by tumor characteristics and surgical procedure.

Results: A total of 819 eligible patients were included in the study. After IPTW, 823 patients were included in the analysis, of which 183 (22.2%) patients were in the EGKF-TKI group and 640 (77.8%) patients were in the observation group. For patients with stage I disease, the 5-year RFS was 92.6% (95% CI, 88.4 to 97.1) in the EGFR-TKI group, compared to 77.0% (95% CI, 73.5 to 80.7) in the observation group (HR = 0.26; 95% CI, 0.15 to 0.46; P < 0.001). For patients with stage IA disease, the 5-year RFS was 98.2% (95% CI, 94.8 to 100) in the EGFR-TKI group, compared to 83.2% (95% CI, 78.6 to 88.1) in the observation group (HR = 0.08; 95% CI, 0.01 to 0.57; P = 0.018). For patients with stage IB disease, the 5-year RFS was 87.4% (95% CI, 80.4 to 95.1) in the EGFR-TKI group, compared to 73.5% (95% CI, 68.7 to 78.6) in the observation group (HR = 0.36; 95% CI, 0.21 to 0.63; P < 0.001). Superior RFS was observed with adjuvant EGFR-TKI therapy in most predefined subgroups. There was no significant difference in OS between the two groups of patients with stage I, stage IA, or stage IB disease. In stratified analysis based on recurrence risk, EGFR-TKI therapy improved 5-year OS but not OS in patients with either stage IA or IB disease, regardless of their recurrence risk.

Conclusions: Our study demonstrates that adjuvant EGFR-TKI therapy improves RFS in patients with stage IA and IB invasive lung adenocarcinoma regardless of their recurrence risk, but the difference in OS is not statistically significant. Given the high cost and potential side effects of these drugs, the benefits of improved RFS must be carefully weighed against the lack of a clear survival advantage.

Keywords: EGFR-TKI, lung adenocarcinoma, Adjuvant therapy

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.55 Molecular Profiling of Neo-Adjuvant IO Disclosures Residual Cancer Cells in pCR NSCLC: A Single Cell Analysis of CTONG 1804

S-Y.M. Liu[1], S. Dong[1], S-Y. Liu[1], X-N. Yang[1], R-Q. Liao[1], B-Y. Jiang[1], Q. Wang[2], X-S. Ben[3], J-T. Lin[1], H-H. Yan[1], L-X. Yan[4], Q. Nie[1], H-Y. Tu[1], B-C. Wang[1], J-J. Yang[1], Q. Zhou[1], W-C. Luo[1], C. Huang[1], X. Zhang[5], H. Li[5], J. Wu[5], W-Z. Zhong[1], Y-L. Wu[1]
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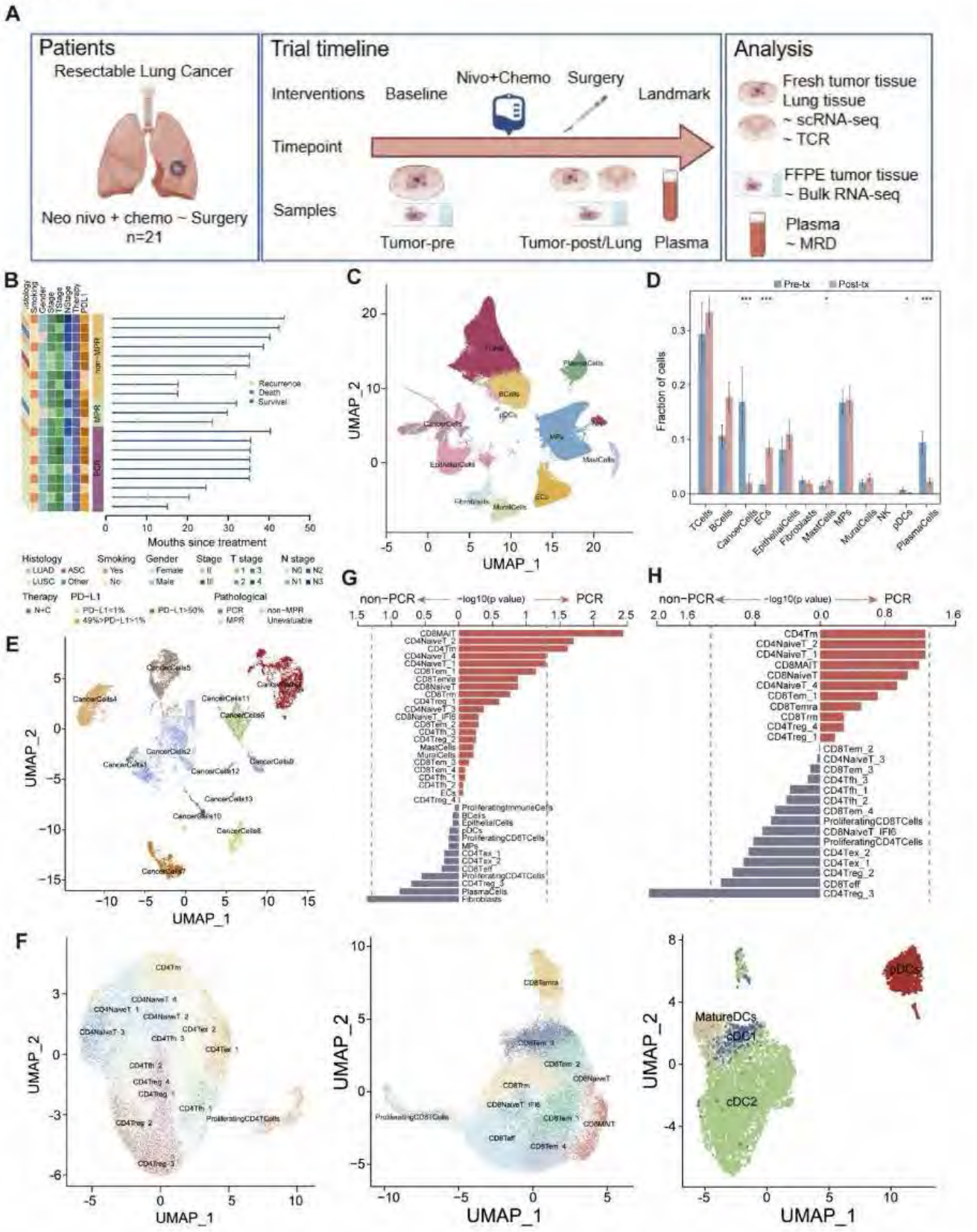
Introduction: We recently reported the clinical findings from a phase II trial of neoadjuvant immunochemotherapy (IO) in untreated patients with resectable non-small cell lung cancer (NSCLC) (CTONG1804). This trial provided an opportunity to investigate the correlation of pathological response and early immune microenvironment during neoadjuvant IO.

Methods: We conducted single-cell RNA sequencing (scRNA-seq) on fresh tumor tissue at pre- and post-IO treatment. Multi-omics sequencing was also used in this exploratory study, that included bulk RNA sequencing and tumor-informed MRD sequencing.

Results: Twenty-one patients were enrolled. The pathological complete response (pCR) rate was 42.9% (9/21). Unexpectedly, a total of 143 cancer cells with genome alterations were identified in six (6/9=66.7%) patients with pCR (Fig 1). Only one pCR patient presented MRD positive within one month after surgery, who had the highest number of cancer cells. These residual cancer cells exhibited reduced proliferative capacity and diminished stem cell-like features but retained epithelial-mesenchymal transition (EMT) markers, suggesting metastatic potential and drug resistance (Fig 2). Elevated antigen presentation pathways, particularly involving CD74-MHC class II, were observed in pCR cancer cells, alongside a significant reduction in tumor neoantigen burden. When comparing the immune cells of different pathological response, we found that conventional dendritic cell type 2 (cDC2) emerged as a critical antigen-presenting cell subtype in pCR patients, enhancing T-cell activation and promoting immune response. Reduced CD4-Treg3 populations correlated with improved treatment outcomes, while CD8-MAIT cells exhibited functional plasticity, transitioning from tumor-promoting to tumor-rejecting phenotypes post-therapy.

Conclusions: Our study highlights the persistence of residual cancer cells even in pCR patients and identifies key immune cell subsets, such as cDC2 and CD8-MAIT cells, that play pivotal roles in modulating anti-tumor response. These findings provide valuable insights into the mechanisms of immune activation and suppression in NSCLC and suggest potential biomarkers and therapeutic targets for optimizing neoadjuvant immunochemotherapy.

Figure 1


A
Patients
Resectable Lung Cancer
Neo nivo + chemo ~ Surgery
n=21
Trial timeline
Interventions
Baseline
Nivo+Chemo
Surgery
Landmark
Timepoint
Samples
Tumor-pre
Tumor-post/Lung
Plasma
Analysis
Fresh tumor tissue
Lung tissue
~ scRNA-seq
~ TCR
FFPE tumor tissue
~ Bulk RNA-seq
Plasma
~ MRD
B
non-MPR
MPR
pCR
Recurrence
Death
Survival
Mouths since treatment
Histology
LUAD
ASC
LUSC
Other
Smoking
Yes
No
Gender
Female
Male
Stage
II
III
T stage
1
2
3
4
N stage
N0
N1
N2
N3
Therapy
N+C
PD-L1
PD-L1<1%
1%>PD-L1>49%
PD-L1>50%
Pathological
PCR
MPR
non-MPR
Unevaluable
C
UMAP_1
UMAP_2
TCells
BCells
PlasmaCells
pDCs
CancerCells
MPs
MastCells
EpithelialCells
Fibroblasts
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Pre-tx
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Fraction of cells
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ECs
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Fibroblasts
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non-PCR
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CD8MAIT
CD4NaiveT_2
CD4Tm
CD4NaiveT_4
CD4NaiveT_1
CD8Tem_1
CD8Temra
CD8NaiveT
CD8Trm
CD4Treg_1
CD4NaiveT_3
CD8NaiveT_IFI6
CD8Tem_2
CD4Tfh_3
CD4Treg_2
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MuralCells
CD8Tem_3
CD8Tem_4
CD4Tfh_1
CD4Tfh_2
ECs
CD4Treg_4
ProliferatingImmuneCells
BCells
EpithelialCells
pDCs
ProliferatingCD8TCells
MPs
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CD4Tfh_1
CD4Tfh_2
CD8Tem_4
ProliferatingCD8TCells
CD8NaiveT_IFI6
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CD4Treg_2
CD8Teff
CD4Treg_3
F
UMAP_1
UMAP_2
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CD4NaiveT_4
CD4NaiveT_1
CD4NaiveT_2
CD4NaiveT_3
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CD8Tem_3
CD8Tem_2
CD8NaiveT
CD8Trm
CD8NaiveT_IFI6
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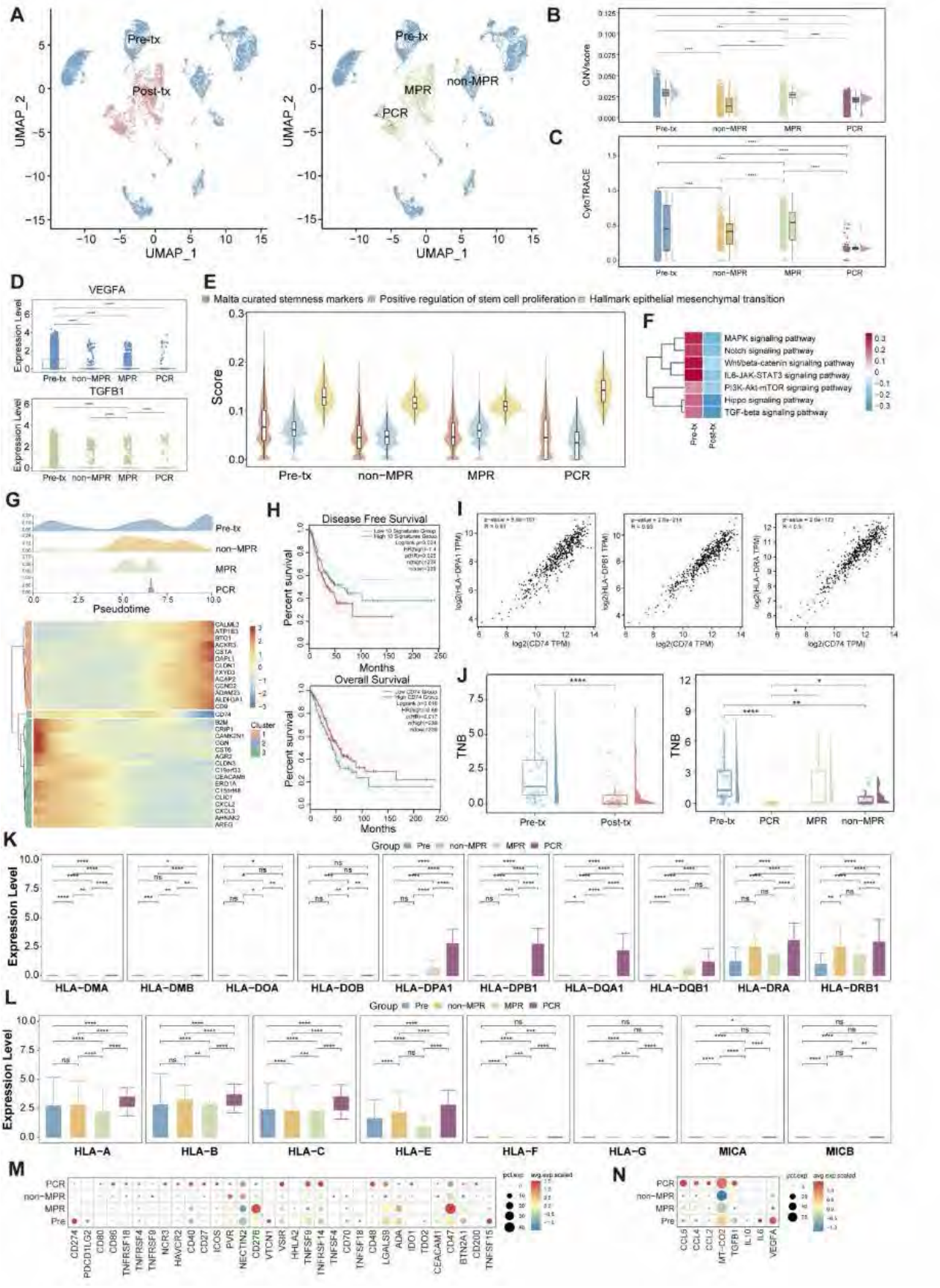
CD8Teff
CD8Tem_4
pDCs
MatureDCs
cDC1
cDC2

Figure 2



Keywords: peri-operative immunotherapy, pCR, residual cancer cells

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.56 Combining Lymph Nodes and Tumor Radiomics Enhances Immunotherapy Efficacy Prediction in Non-Small Cell Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs) are widely used in non-small cell lung cancer (NSCLC), but their application is associated with adverse effects, necessitating the exploration of more effective biomarkers. Numerous studies have demonstrated the unique role of radiomics in early cancer diagnosis, assessment of pathological treatment response, and prediction of lymph node metastasis. Although lymph nodes play a critical role in immunotherapy, current radiomics studies often neglect lymph node radiomic features when predicting ICI efficacy. The relationship between radiomic features of subcarinal lymph nodes and ICI efficacy in NSCLC remains underexplored. This study aims to investigate the association between radiomic features of pulmonary lesions and subcarinal lymph nodes in NSCLC patients and their response to immunotherapy, with the goal of predicting pathological complete response (pCR).

Methods: This study retrospectively analysed NSCLC patients (n=208) who received immunotherapy from January 2016 to December 2020 at Guangdong Provincial People's Hospital, and the external validation cohort consisted of a total of 38 patients from Jiangxi Provincial Cancer Hospital. Radiomic features were extracted by 'PyRadiomics' software package. Five machine learning models were constructed using a two-stage optimisation strategy to filter the features, and their performance was evaluated and compared.

Results: The study included 246 NSCLC patients from two independent centers, divided into a training cohort (TC), internal validation (IV), and external validation (EV) cohorts. The logistic regression model demonstrated optimal performance. The AUC values for the radiomic model combining primary lesions and peritumoral regions were 0.69, 0.54, and 0.44 in TC, IV, and EV, respectively. When incorporating subcarinal lymph node radiomic features, the AUC values improved to 0.72, 0.51, and 0.54. Further integration of peri-lymph node features yielded AUC values of 0.70, 0.69, and 0.52 across the three cohorts.

Conclusions: The multimodal predictive model combining radiomic features from primary lesions, peritumoral regions, subcarinal lymph nodes, and peri-lymph node areas shows potential for predicting NSCLC immunotherapy efficacy. This approach holds clinical significance for guiding therapeutic strategies.

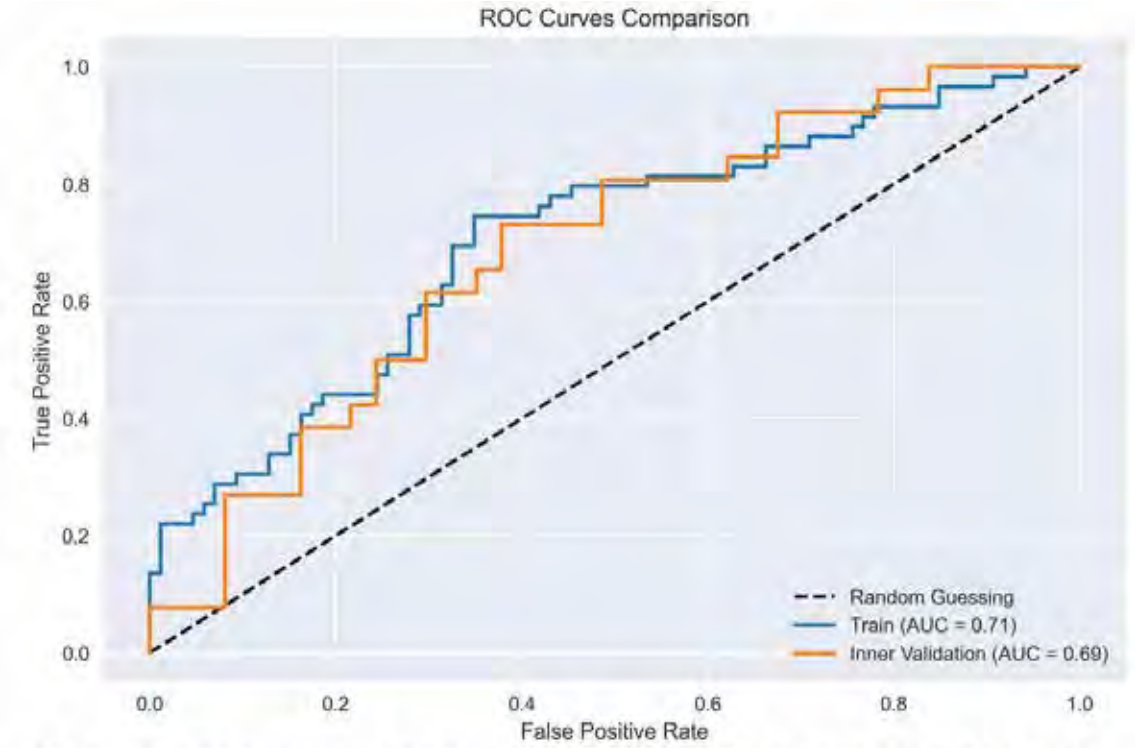

Figure 1. ROC curves of CRM in the Training Cohort and Inner Validation

Keywords: Non-small cell lung cancer, Immunotherapy, Lymph node

P1.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.07.57 Alterations in the Gut Microbiota and Metabolites in Patients With Liver Injury Induced by Third-Generation EGFR-Targeted Drugs

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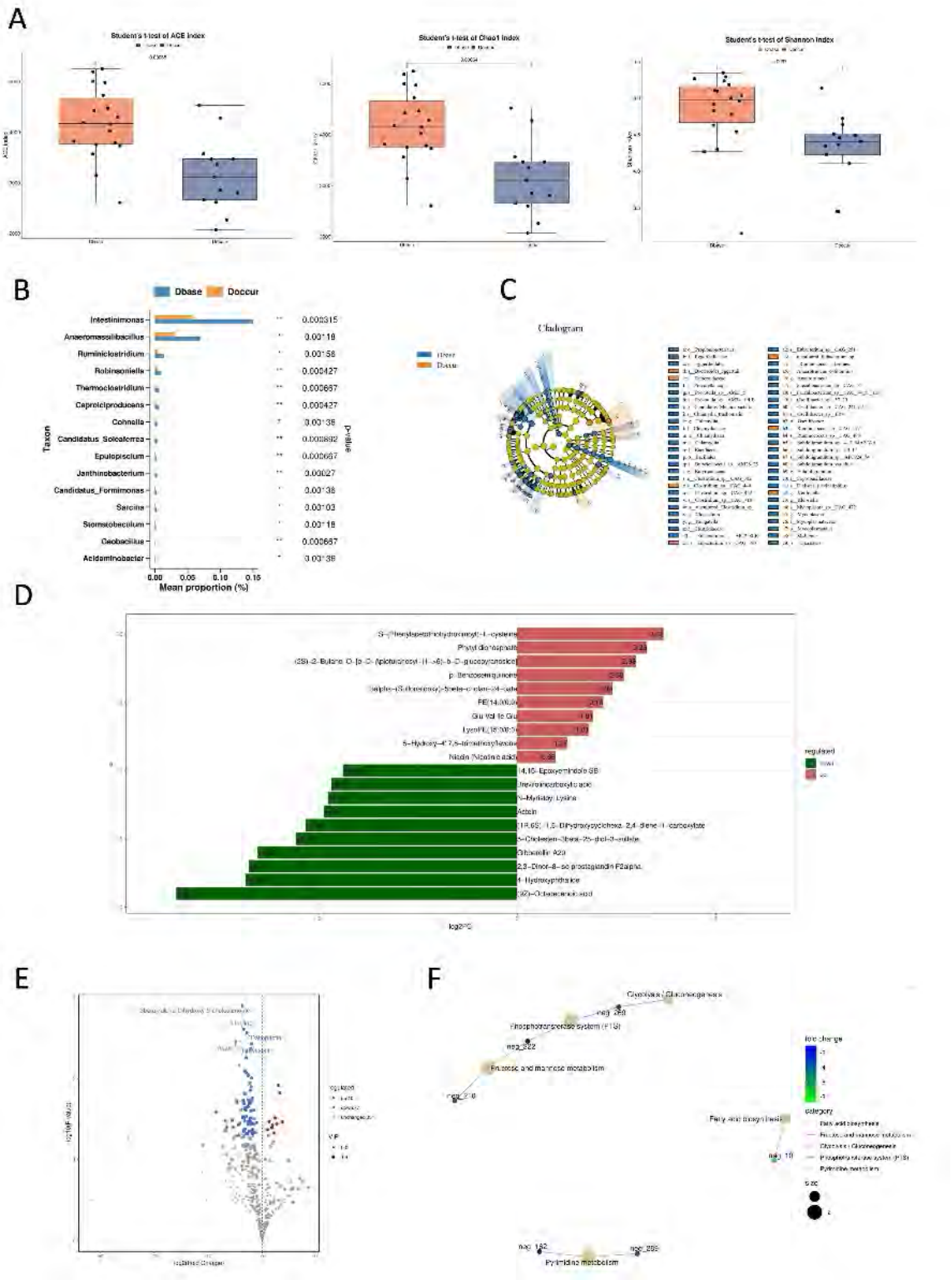
Introduction: Third-generation EGFR-TKI is currently the first-line treatment option for patients with EGFR-mutated NSCLC. Drug-induced liver injury (DILI) is one of the common reasons for drug withdrawal in clinical practice, and there are no specific therapeutic drugs at present. Dysregulation of intestinal microbes can lead to disruption of the intestinal barrier and microbial translocation, while changes in microbial metabolites may cause or aggravate DILI. Therefore, it is of great significance to study the mechanism of intestinal microbes in third-generation EGFR-TKI-related liver injury and explore potential strategies to interfere with drug toxicity by regulating the flora.

Methods: We collected stool specimens from 18 patients with liver injury after third-generation EGFR-targeted therapy at baseline and at the time of liver injury, of which 5 were not collected at the time of liver injury. We conducted metagenomic and metabolomic study sequencing to compare the differences in gut microbiota and metabolites between the two groups of samples.

Results: Among all the samples, there were 18 cases in the Dbase group and 13 cases in the Doccur group. Our analysis revealed significant differences in the gut microbiota and metabolites between the two groups of samples. Species-based α diversity analysis revealed significantly lower ACE, Chao1 (both P=0.00065) and Shannon indices (P=0.0097) in fecal specimens during liver injury compared to baseline, indicating reduced microbial species richness and diversity. We found that the Intestinimonas, Anaeromassilibacillus, Ruminiclostridium, and Robinsoniella decreased in the Doccur group. Metabolomics analysis showed that Octadecenoic acid, 4-Hydroxyphthalide, 2,3-Dinor-8-iso prostaglandin F2alpha, Gibberellin A20, 5-Cholesten-3beta-25-diol-3-sulfate, etc decreased in the Doccur group. KEGG metabolic pathway analysis of the two groups of differential metabolites showed that arabinogalactan biosynthesis, glycolysis, and diterpene biosynthesis had significant differences in synthesis and secretion pathways.

Conclusions: Our findings suggest that the abundance of the gut microbiota and its metabolites in patients with liver injury following EGFR-targeted drugs differ from baseline. Intestinal flora and its metabolites can be used as an effective means to predict the adverse reactions of molecularly targeted drugs.



Keywords: Non-small cell lung cancer, Targeted therapy, Drug-induced liver injury

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.01 First-Line Nivolumab Plus Ipilimumab in Combination With Chemotherapy for Metastatic NSCLC: Real World Data in Italy

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Introduction: Nivolumab plus ipilimumab in combination with 2 cycles of platinum-based chemotherapy is actually a standard of care in the first-line treatment of metastatic non-small cell lung cancer (NSCLC). NICReWo is an Italy-wide, multicenter, observational, ambispective study, designed to collect real-life data during the early post-market authorization approval period of the combination nivolumab plus ipilimumab plus chemotherapy. This is the first report of the retrospective part of the study.

Methods: Data were retrospectively collected starting from January 2022, co-primary endpoints were to evaluate progression-free survival (PFS) and overall survival (OS) in a real world patient population. Secondary endpoints were overall response rate (ORR), duration of treatment and incidence of treatment-related adverse events (AEs). All data obtained for this study were recorded with an Electronic Data Capture (EDC) system using eCRFs (RedCap platform).

Results: 192 patients were enrolled at the time of data cut-off (March 31, 2025) across 9 Italian sites. Median age was 67.9 years old (range: 33-86). The median duration of treatment was 5.67 months (95% CI, 1.81-7.37), corresponding to a median of 6.53 cycles; 51 patients are still ongoing with the treatment without disease progression. After a median follow-up of 20 months (95% CI, 11.0-28.0) the median PFS was 5.5 months (95% CI, 2.8-12.4); 12-months PFS rate was 26.5% (95% CI, 19.3-34.1). Median OS was 9.8 months (95% CI, 4.50-20.1); 12-months OS rate was 45.6% (95% CI, 36.7-54.1). ORR was 29.2%. There were no significant differences in survival based on PD-L1 status (tumor proportional score TPS < 1 versus 1-49%), histology (squamous versus non squamous), presence of liver and brain metastases, KRAS mutational status.Any-grade AEs occurred in 109 patients (56.8%) and Grade ≥ 3 in 21 patients (10.9%). Most common Grade ≥ 3 AEs were neutropenia, colitis and hepatotoxicity. Any-grade immune-related AEs (irAEs) occurred in 68 patients (35.4%) and Grade ≥ 3 in 15 patients (7.8%). Most common Grade ≥ 3 irAEs were colitis and hepatotoxicity. 19 patients discontinued permanently treatment because of toxicity. OS and PFS were significantly higher in patients who have experienced irAEs compared to patients without irAEs, with 12-months OS of 68.1% compared to 12-months OS of 32.1% respectively.Subsequent therapies were administered for 49 patients (25.5%), in particular 19 patients received platinum-based chemotherapy, 16 patients monochemotherapy, 11 patients target therapies and 3 patients radiotherapy.

Conclusions: This study helps address an unmet clinical need for a real world population treated with the combination of nivolumab plus ipilimumab with 2 cycles of platinum-based chemotherapy. This is the first report and survival data are still immature, while the safety profile seems to be in line with was reported in the literature. Our real world study population, compared with patients enrolled in the CheckMate 9LA trial, is characterized by a 3-years higher median age, inclusion also of ECOG PS ≥ 2 patients, higher prevalence of brain metastases, absence of PD-L1 overexpressed patients and lower rate of squamous histology. The prospective part of the study is still ongoing.

Keywords: Non-small cell lung cancer, Immunotherapy, Real world data

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.02 Impact of Prophylactic Use of Cardioprotective L-Carnitine on First-Line Chemoimmunotherapy in Advanced NSCLC: A Cohort Study

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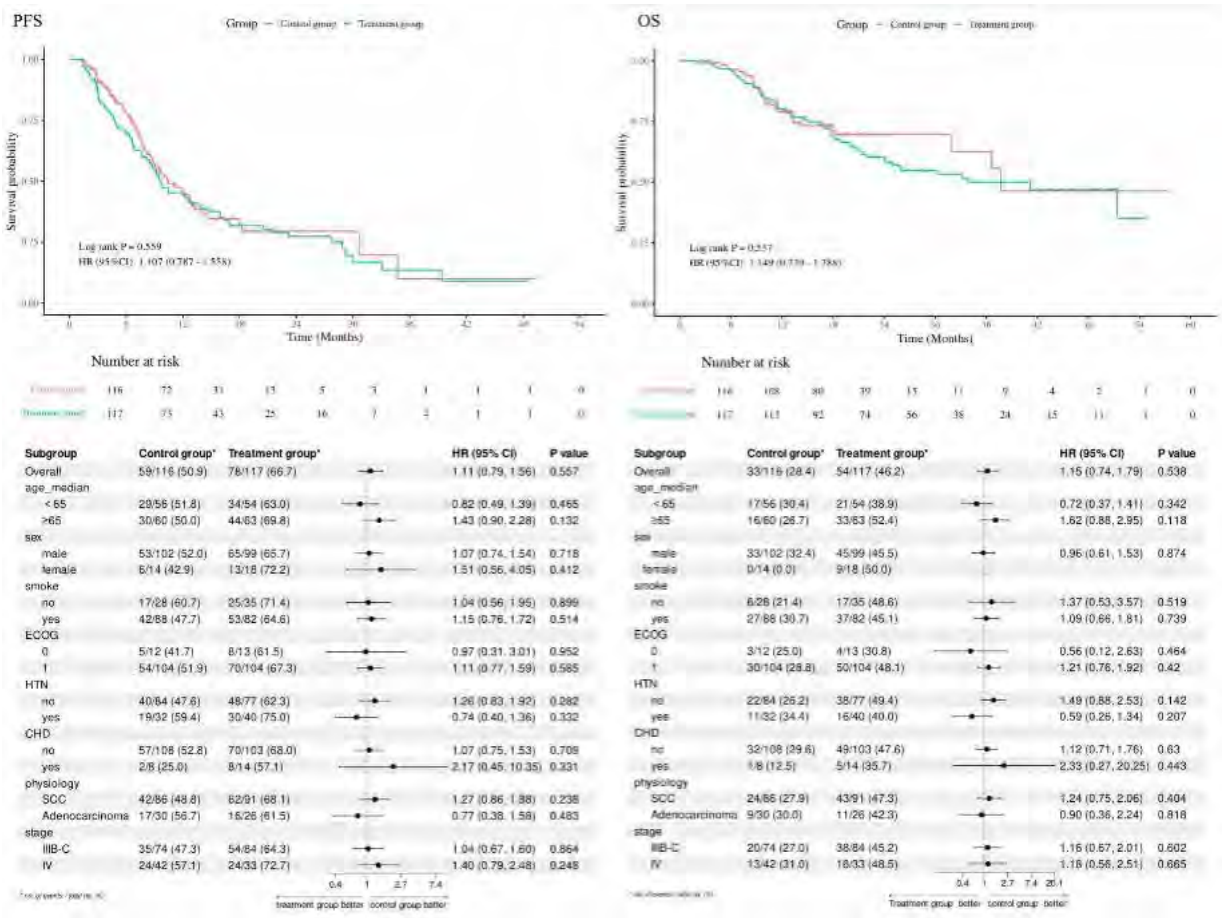
Shengjing Hospital of China Medical University, Shenyang/CN

Introduction: L-Carnitine, a critical mediator of fatty acid metabolism and mitochondrial energy production, has shown potential in modulating metabolic profiles, immune responses, and gut microbiota dynamics. Preclinical evidence suggests its role in mitigating chemotherapy-induced toxicity and influencing tumor microenvironments. This study investigates whether prophylactic L-carnitine supplementation impacts outcomes in advanced non-small cell lung cancer (NSCLC) patients receiving first-line chemoimmunotherapy (PD-1 inhibitor plus platinum-based chemotherapy).

Methods: In this retrospective cohort study, 223 patients with advanced NSCLC treated at Shengjing Hospital between January 2019 and December 2024 were stratified into two groups: the intervention group (n=117) received L-carnitine alongside chemoimmunotherapy, while the control group (n=116) received chemoimmunotherapy alone. Primary endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and safety. The study was approved by the Ethics Committee of Shengjing Hospital.

Results: Baseline covariates, including age, sex, smoking status, hypertension, coronary artery disease, and Charlson Comorbidity Index (CCI), were well-balanced between the two groups. After a median follow-up of 17.7 months, median PFS was comparable between the groups (9.7 vs. 10.4 months; HR=1.11, 95% CI: 0.79-1.56; p=0.56). Median OS was also similar (41.2 vs. 37.7 months; HR=1.15, 95% CI: 0.74-1.79; p=0.54), with 1-year survival rates of 80.3% vs. 78.4% and 2-year survival rates of 60.4% vs. 69.6%, respectively, in the intervention and control groups (all p>0.05). ORR showed no significant difference between the groups (59.8% vs. 60.3%; p=0.99). Subgroup analyses revealed no PFS or OS benefit across clinical variables. Safety profiles were similar between the two groups, with no significant difference in cardiac-related adverse events. Immune-related myocarditis was observed in 6.8% of the intervention group and 8.6% of the control group (p=0.63). No grade ≥3 immune-related myocarditis was observed in either group.

Conclusions: Prophylactic L-carnitine did not provide additional survival benefits or enhance safety in advanced NSCLC patients undergoing first-line chemoimmunotherapy. These findings suggest that routine use of L-carnitine may not be warranted in this context. Prospective studies are necessary to further explore its potential role and identify any specific subgroups that might benefit.



Subgroup	Control group*	Treatment group*	HR (95% CI)	P value
Overall	59/116 (50.9)	78/117 (66.7)	1.11 (0.79, 1.56)	0.557
age_median				
< 65	29/56 (51.8)	34/54 (63.0)	0.82 (0.49, 1.39)	0.465
>65	30/60 (50.0)	44/63 (69.8)	1.43 (0.90, 2.28)	0.132
sex				
male	53/102 (52.0)	65/99 (65.7)	1.07 (0.74, 1.54)	0.718
female	6/14 (42.9)	13/18 (72.2)	1.51 (0.56, 4.05)	0.412
smoke				
no	17/28 (60.7)	25/35 (71.4)	1.04 (0.56, 1.95)	0.899
yes	42/88 (47.7)	53/82 (64.6)	1.15 (0.76, 1.72)	0.514
ECOG				
0	5/12 (41.7)	8/13 (61.5)	0.97 (0.31, 3.01)	0.952
1	54/104 (51.9)	70/104 (67.3)	1.11 (0.77, 1.59)	0.585
HTN				
no	40/64 (47.6)	48/77 (62.3)	1.26 (0.83, 1.92)	0.282
yes	19/32 (59.4)	30/40 (75.0)	0.74 (0.40, 1.36)	0.332
CHD				
no	57/108 (52.8)	70/103 (68.0)	1.07 (0.75, 1.53)	0.709
yes	2/8 (25.0)	8/14 (57.1)	2.17 (0.45, 10.35)	0.331
physiology				
SCC	42/86 (48.8)	62/91 (68.1)	1.27 (0.86, 1.88)	0.236
Adenocarcinoma	17/30 (56.7)	16/26 (61.5)	0.77 (0.38, 1.58)	0.483
stage				
IIIB-C	35/74 (47.3)	54/84 (64.3)	1.04 (0.67, 1.60)	0.864
IV	24/42 (57.1)	24/33 (72.7)	1.40 (0.79, 2.48)	0.248

Subgroup	Control group*	Treatment group*	HR (95% CI)	P value
Overall	33/116 (28.4)	54/117 (46.2)	1.15 (0.74, 1.79)	0.538
age_median				
< 65	17/56 (30.4)	21/54 (38.9)	0.72 (0.37, 1.41)	0.342
≥65	16/60 (26.7)	33/63 (52.4)	1.62 (0.88, 2.95)	0.118
sex				
male	33/102 (32.4)	45/99 (45.5)	0.96 (0.61, 1.53)	0.874
female	0/14 (0.0)	9/18 (50.0)		
smoke				
no	6/28 (21.4)	17/35 (48.6)	1.37 (0.53, 3.57)	0.519
yes	27/88 (30.7)	37/82 (45.1)	1.09 (0.66, 1.81)	0.739
ECOG				
0	3/12 (25.0)	4/13 (30.8)	0.56 (0.12, 2.63)	0.464
1	30/104 (28.8)	50/104 (48.1)	1.21 (0.76, 1.92)	0.42
HTN				
no	22/64 (25.2)	38/77 (49.4)	1.49 (0.88, 2.53)	0.142
yes	11/32 (34.4)	16/40 (40.0)	0.59 (0.25, 1.34)	0.207
CHD				
no	32/108 (29.6)	49/103 (47.6)	1.12 (0.71, 1.76)	0.63
yes	1/8 (12.5)	5/14 (35.7)	2.33 (0.27, 20.25)	0.443
physiology				
SCC	24/86 (27.9)	43/91 (47.3)	1.24 (0.75, 2.06)	0.404
Adenocarcinoma	9/30 (30.0)	11/26 (42.3)	0.90 (0.36, 2.24)	0.818
stage				
IIIB-C	20/74 (27.0)	38/84 (45.2)	1.16 (0.67, 2.01)	0.602
IV	13/42 (31.0)	16/33 (48.5)	1.16 (0.56, 2.51)	0.665

Keywords: L-carnitine, chemoimmunotherapy, non-small cell lung cancer

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.03 Long-Term Efficacy of Immune Checkpoint Inhibitors in Pulmonary Cancer With Rhabdoid Features: A Single-Center Retrospective Analysis

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Introduction: Pulmonary cancers with rhabdoid features (PCRF) are exceedingly rare, with only 44 cases documented. PCRF typically exhibit aggressive behavior and poor prognosis. Molecular data on pulmonary rhabdoid tumors remain scarce, with unreported PD-L1 status, and reports of SMARCA4, KRAS G12D and EGFR exon 19 alterations. The efficacy of immune checkpoint inhibitors (ICIs) is poorly documented in PCRF. Here, we report three patients with PCRF treated with ICIs.

Methods: We retrospectively reviewed of thoracic oncology databases at our institution to identify patients with PCRF treated with ICIs. Informed consent was obtained from all included patients. Clinical data were analyzed and pathology slides were re-evaluated. A comprehensive literature review was performed using PubMed and Google Scholar to identify previously reported cases of PCRF.

Results: We identified three patients treated for PCRF. The first, a 53-year-old male with a 20-pack-year smoking history, presented with epigastric pain and melena. Imaging revealed a right lung mass, bilateral adrenal nodules, mesenteric lymphadenopathy, tonsillar enlargement, and small bowel lesions (stage IVB). Pathological examination confirmed non-small cell carcinoma with rhabdoid features, PD-L1>90%. The patient achieved a complete response to pembrolizumab monotherapy (200 mg every 3 weeks). After 4 years of treatment, the patient developed probable treatment-induced psoriasis, treated with triamcinolone acetonide. Pembrolizumab could be continued. As of today, the patient remains disease-free, seven years after treatment initiation. The second patient is a 64-year-old male with a 50-pack-year smoking history and controlled HIV. Presenting with fatigue and weight loss, imaging revealed lesions in the jejunum, adrenal gland, and lungs (stage IVB). Surgical resection of the jejunal lesion identified an undifferentiated tumor with rhabdoid and epithelioid features. Molecular testing detected a KRAS G12C mutation, PD-L1 100%. Treatment with carboplatin, paclitaxel, and pembrolizumab led to a complete response. After 18 months, isolated adrenal gland activity on the PET-CT prompted stereotactic radiotherapy (36 Gy in 6 fractions). Pembrolizumab was continued, and three and a half years from treatment initiation, the patient remains disease-free. The third patient, a 65-year-old woman with a 30-pack-year smoking history and prior nephrectomy for renal clear-cell carcinoma, presented with a pulmonary nodule and mediastinal lymphadenopathy (stage IIIA). Mediastinal biopsy confirmed non-small-cell carcinoma with rhabdoid features, PD-L1 95%. She underwent a lobectomy and received 4 cycles of adjuvant chemotherapy (carboplatin and pemetrexed). After one year, she presented hypermetabolic mediastinal lymphadenopathy. A biopsy revealed a NSCLC, NOS, PD-L1 3%. She received concurrent chemoradiotherapy (carboplatin and vinorelbine), followed by durvalumab consolidation. One year later, pericardial and pleural effusions developed, cytologically consistent with metastatic renal carcinoma. Despite initiating cabozantinib, she succumbed to disease progression after three months.

Conclusions: Our experience highlights the potential efficacy of ICIs in treating PCRF, particularly with high PD-L1 expression. Notably, this is the first report of prolonged responses to ICIs in these patients. Two patients with metastatic disease achieved durable complete responses and remain disease-free years after treatment. All patients with PCRF had high PD-L1 expression. Further research should focus on the molecular characterization of PCRF and identify therapeutic targets.

Keywords: Rhabdoid Lung Cancer, Immune Checkpoint Inhibitors, Case Serie

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.04 Prediction of Overall Survival in Lung Cancer Patients With Different Organ Metastases: A SEER Population-Based Cohort Study

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Introduction: Distant organ metastasis is a common event in lung cancer (LC). However, the metastatic pattern of different organ of LC and its effect on prognosis have not been comprehensively elucidated. This study aimed to explore the distant metastasis pattern and construct nomograms predicting the metastasis and survival of LC patients using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Lung cancer (LC) data from 586,674 patients diagnosed between 2010 and 2021 were obtained from the SEER database. Patient records were excluded if the lung was not the first primary site, overall survival (OS) was less than 1 month, baseline clinicopathological data were unavailable, survival time was missing, or the patient was younger than 18 years old. The relationship between distant metastatic sites and overall survival was retrospectively analyzed. In addition, 12 machine learning modelswere trained and evaluated to predict occurrence of death based on different metastatic patterns. Model performance was assessed using ROC curves, precision-recall (PR) curves, calibration plots, and decision curve analysis (DCA). The best-performing model was further interpreted using SHAP (SHapley Additive exPlanations), with results visualized through summary plots, bar charts, and circular radar diagrams.

Results: A total of 235,290 patients were finally included for data analysis. 74,526 (31.67%) patients had different degrees of distant metastasis, including 45758(19.45) patients with single organ metastases and 20573(8.74%), 8195(3.48%) multiple (≥3) organ metastases, and 14,3635(61.05%) patients had no distant metastasis. Patient without distant organ metastasis had a significantly longer survival than patients with1 or 2 or 3 or 4 organ metastasis[mOS: 55m (95%CI 54m-55m) vs10m (95%CI 10m-10m), vs 7m (95%CI 6m-7m), vs 6m(95%CI 6m-7m), vs 5m(95%CI 5m-6m), P<0.0001]. Among patients with mono-organ metastasis, the median OS of patients with liver and bone metastasis[mOS: 8m (95%CI 8m-9m)] was significantly shorter than those with brain metastasis (mOS:9m, 95%CI 9m-9m) or lung metastasis(mOS:14m, 95%CI 14m-15m),7 months (95%CI 7m-7m), 6 months (95%CI 5m-6m) respectively, and the difference was significant (P<0.0001); Among those deceased patients(N=151256), 83.26% patients (N=125933) eventually died of lung cancer. In addition, In patients with bone metastasis: GBT achieved the best performance (AUC=0.851,95%CI 0.841-0.862). Top SHAP predictors included year of diagnosis, pathology, treatment status, age, and site of metastasis. In patients with brain metastasis: AdaBoost performed best (AUC=0.851,95%CI 0.841-0.861), with top predictors being year of diagnosis, number of organ metastases, pathology, age, and treatment. In patients with liver metastasis: GBT again showed best performance (AUC=0.850,95%CI 0.835-0.866), with important features including year of diagnosis, pathology, tumor size, age, and treatment. In patients with lung metastasis: GBT was optimal (AUC=0.847,95%CI 0.836-0.859), with SHAP analysis highlighting year of diagnosis, sex, site of metastasis, age, and pathology as key predictors.

Conclusions: Different metastatic patterns at diagnosis in lung cancer are associated with distinct survival outcomes. Patients with liver/bone metastases exhibit significantly shorter overall survival. This study developed novel, machine learning models capable of accurately predicting mortality across organ-specific metastatic patterns, which will aid physicians in making individualized treatment decisions in lung cancer management.

Keywords: Lung cancer, SEER, Organ Specific Overall Survival

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.05 Efficacy and Multi-Omics Insights of Immune Checkpoint Inhibitors in NSCLC With Leptomeningeal Metastasis

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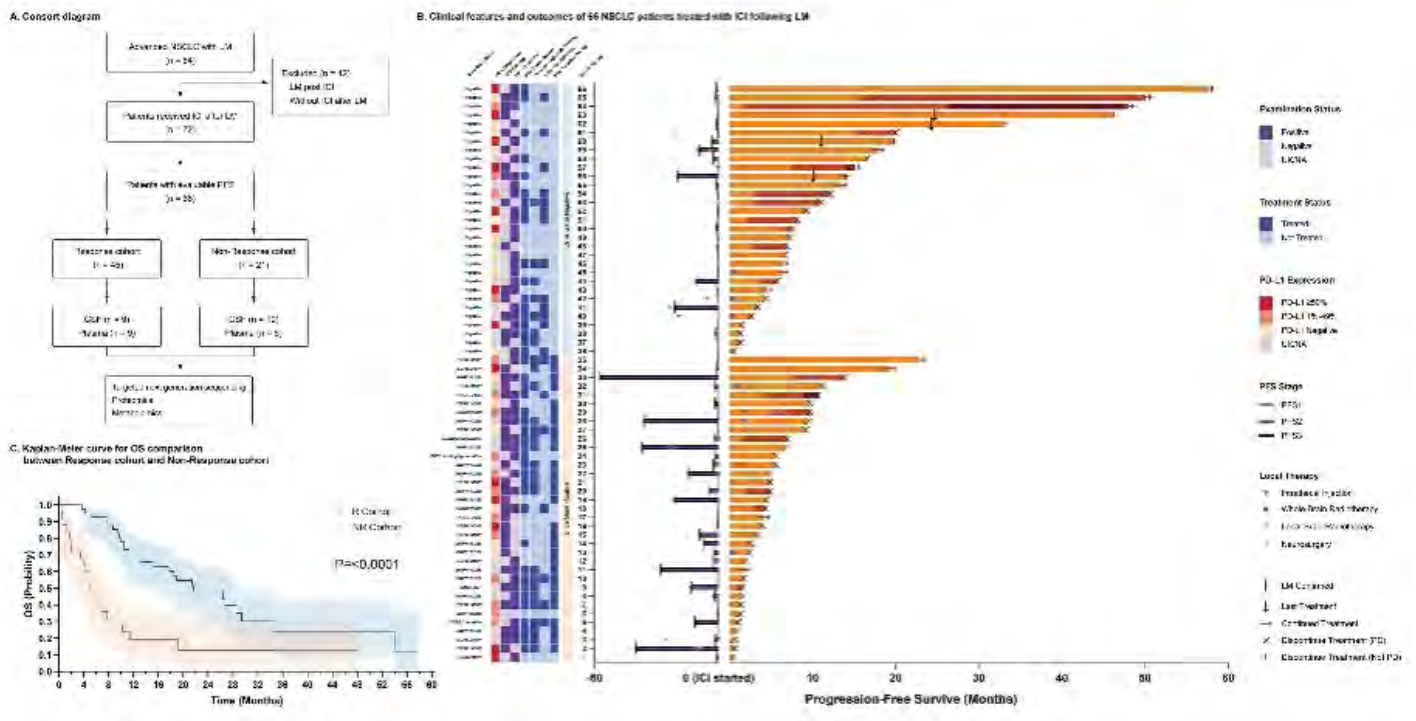
Introduction: Patients with leptomeningeal metastasis (LM) are frequently excluded from clinical trials due to poor overall survival (OS) and compromised performance status. Evidence on immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC) with LM is limited. Hence this real-world study aimed to show the efficacy of ICI treatment for LM and used multi-omic analysis with cerebrospinal fluid (CSF) and plasma to explore potential predictive biomarkers.

Methods: This study enrolled 72 patients with NSCLC and LM receiving ICIs at Guangdong Lung Cancer Institute from December 2017 to April 2024. Clinical information, treatment evaluation and survival outcomes were collected. Patients were stratified into response and non-response cohorts based duration of response. Multi-omic profiling, using proteomic, metabolomic, and next-generation sequencing analyses was conducted on CSF and plasma samples collected before and after ICI treatment.

Results: Among the 72 enrolled patients, 93% demonstrated ECOG PS ≤1, 51.4% harbored driver gene mutations, and 54.2% received ≥2 lines systemic therapy. 28% exhibited neurological symptoms. Subsequently, 84.7% received ICI-based combination therapy. The median OS was 19.2 months (95% CI: 0.6-74.7). Among 66 patients with evaluable progression-free survival (PFS), the median PFS was 4.3 months (95% CI: 0.4-57.6), significantly influenced by age (P=0.02) and driver gene status (P=0.01). Among them, 12 patients achieved long-term benefits from ICIs, with PFS exceeding 12 months, including 3 surpassing 24 months. The response cohort demonstrated markedly prolonged OS compared to non-response cohort (21.7 vs. 4.9 months, P<0.0001). Prior use of antiangiogenic drugs affected response to ICI significantly (p=0.03). Proteomic analysis identified MCP-3, IP-10, IL-13, and GZM as differentially expressed proteins in CSF between responder and non-responder. Notably, elevated MCP-3 levels in both CSF (P=0.02) and plasma (P=0.02) were strongly associated with response. Further analysis revealed significant enrichment in immune cell chemotaxis and migration, chemokine signaling, host defense response, and vascular homeostasis regulation pathways. CSF and plasma exhibit relatively distinct differential metabolites, without consistent enrichment pathways. CSF circulating tumor DNA positive detection was also significantly associated with response (P=0.02) but showed no statistical association with survival.

Conclusions: This study revealed that selected patients with LM derived benefits from ICI combination treatments. Multi-omics analysis identified MCP-3 as a potential efficacy biomarker for ICI treatment. Further prospective studies are warranted to explore the use of ICIs for LM.



Keywords: Immune Checkpoint Inhibitors, Non-Small Cell Lung Cancer, Leptomeningeal Metastasis

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.06 Risk Factors and Prognosis of Immune Checkpoint Inhibitor-Induced Pneumonia in Lung Cancer With Interstitial Lung Disease

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Introduction: Lung cancer patients with interstitial lung disease (ILD) are known to be associated with a higher frequency of immune checkpoint inhibotor (ICI) induced pneumonitis. Even in such a population, ICI treatment sometimes results in long-term survival. This study aimed to determine the risk factors and prognosis of ICI-induced pneumonitis in lung cancer patients with ILD treated with ICIs.

Methods: We retrospectively analyzed 12 lung cancer patients with ILD out of 231 patients treated with ICIs at Kanazawa University Hospital from January 2019 to March 2023.

Results: The patient background was Male/Female: 10/2 cases; Smoking history: all cases; Median age (range): 70 (53-84) years; Histological type: Adenocarcinoma/Squamous cell carcinoma/Small cell lung cancer: 6/4/2 cases; Stage III/IV/postoperative relapse: 3/5/4 cases; 1st / 2nd line treatment: 8/4 cases. The background ILD imaging pattern was UIP: 4 cases, probable UIP: 3 cases, fNSIP: 3 cases, and RB-ILD: 2 cases. ICI-induced pneumonitis was observed in four patients (33%), but there was no Grade 3 or higher pneumonitis. Of the four cases with ICI-induced pneumonitis, 2 cases had honeycomb lung and 1 case had high antinuclear antibody levels, but %VC was better than 80% in all four cases. The proportion of patients with ICI-induced pneumonitis had high SP-D levels compared with patients without ICI-induced pneumonitis (75% and 0% respectively; P = 0.003 by Fisher's exact test). No significant difference was found in LDH, CRP, or KL-6 levels between the two groups. The median overall survival was 27.4 months in patients with ICI-induced pneumonitis and 12.8 months in patients without ICI-induced pneumonitis (p = 0.13).

Conclusions: When ICIs are used for lung cancer patients with ILD, honeycomb lung, and a high SP-D level could be considered risk factors for ICI-induced pneumonitis. The prognosis was not worse in patients who developed mild ICI-induced pneumonitis.

Keywords: Lung cancer patients with interstitial lung diseas, immune checkpoint inhibotor, risk factors

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.07 Impact of Radiotherapy and Immune Checkpoint Inhibitor Combination in Advanced NSCLC: Real-World Data (RWD) Analysis

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Introduction: Immune checkpoint inhibitors (ICIs) have become the standard treatment for advanced non-small cell lung cancer (NSCLC). Radiotherapy (RT) enhances local disease control and has immunomodulatory effects, making its combination with ICIs a potential therapeutic strategy. This study investigates how RT intent (palliative vs. radical) and sequencing with ICIs affect overall survival (OS) and progression-free survival (PFS) in patients from the Spanish Lung Cancer Group's Thoracic Tumor Registry (TTR).

Methods: The TTR is a multicenter, observational cohort study of lung cancer in Spain. This retrospective analysis adhered to the Declaration of Helsinki and was approved by the Ethics Committees of all participating centers. The registry was authorized as a non-interventional study by the Spanish Medicines Agency. A total of 2,179 patients with stage IV NSCLC diagnosed at 66 Spanish centers between March 2009 and May 2023 and receiving ICIs—either as monotherapy or with chemotherapy (CT) in the first or second line—were included.

Results: Among 2,179 patients, 475 (21.8%) received RT—88.0% for palliative intent and 12.0% for radical intent. The most common irradiation sites included bone (45.4%), the central nervous system (33.3%), and the lung (14.4%). The median OS (mOS) was 19.4 months for the ICI group, 17.3 months for the ICI/RTpalliative group, and 27.3 months for the ICI/RTradical group (p=0.002). Compared to the ICI/RTpalliative group, patients treated with ICI (HR=0.80, 95% CI: 0.70-0.91) or ICI/RTradical (HR=0.67, 95% CI: 0.47-0.96) had better survival. The median PFS (mPFS) was 6.0 months for the ICI group, 4.6 months for the ICI/RTpalliative group, and 8.7 months for the ICI/RTradical group (p=0.00022). Patients receiving ICI/RTpalliative had a significant worse prognosis than those in the ICI group (HR=1.29, 95% CI: 1.14-1.45). Regarding treatment sequencing, 14.9% patients received ICI before RT (ICI/RTseq), 39.6% concomitant ICI/RT (ICI/RTco), 35.8% RT before ICI (RT/ICIseq), and 9.7% followed a mixed sequence (ICI/RTmix). The mOS was 19.4 months for the ICI group, 13.3 months for the ICI/RTseq group, 20.3 months for the ICI/RTco group, 15.6 months for the RT/ICIseq group, and 18.7 months for the ICI/RTmix (p=0.00019). Compared to the ICI group, patients receiving ICI/RTseq treatment (HR=1.76, 95% CI: 1.35-2.30) or RT/ICIseq (HR=1.26, 95% CI: 1.03-1.54) were associated with worse survival. The mPFS was 6.0 months for the ICI group, 2.9 months for the ICI/RTseq group, 5.9 months for the ICI/RTco group, 5.1 months for the RT/ICIseq group, and 3.9 months for the ICI/RTmix (p<0.0001). Patients receiving ICI/RTseq (HR=1.92, 95% CI: 1.48-2.48), RT/ICIseq (HR=1.23, 95% CI: 1.03-1.47), or ICI/RTmix (HR=1.56, 95% CI: 1.14-2.13) had a worse prognosis than those in the ICI group.

Conclusions: This study highlights the impact of RT intent and sequencing on survival outcomes in advanced NSCLC patients receiving ICIs. Radical RT and concurrent ICI/RT were associated with improved outcomes, while palliative RT and sequential approaches correlated with worse prognosis. These findings support the need for optimized treatment strategies integrating RT and ICIs to enhance patient outcomes.

Keywords: Thoracic Tumor Registry (TTR), Spanish Lung Cancer Group, real word data

P1.11.08 Peripheral Inflammatory Biomarkers Predict Immunotherapy Retreatment Outcomes in Advanced NSCLC

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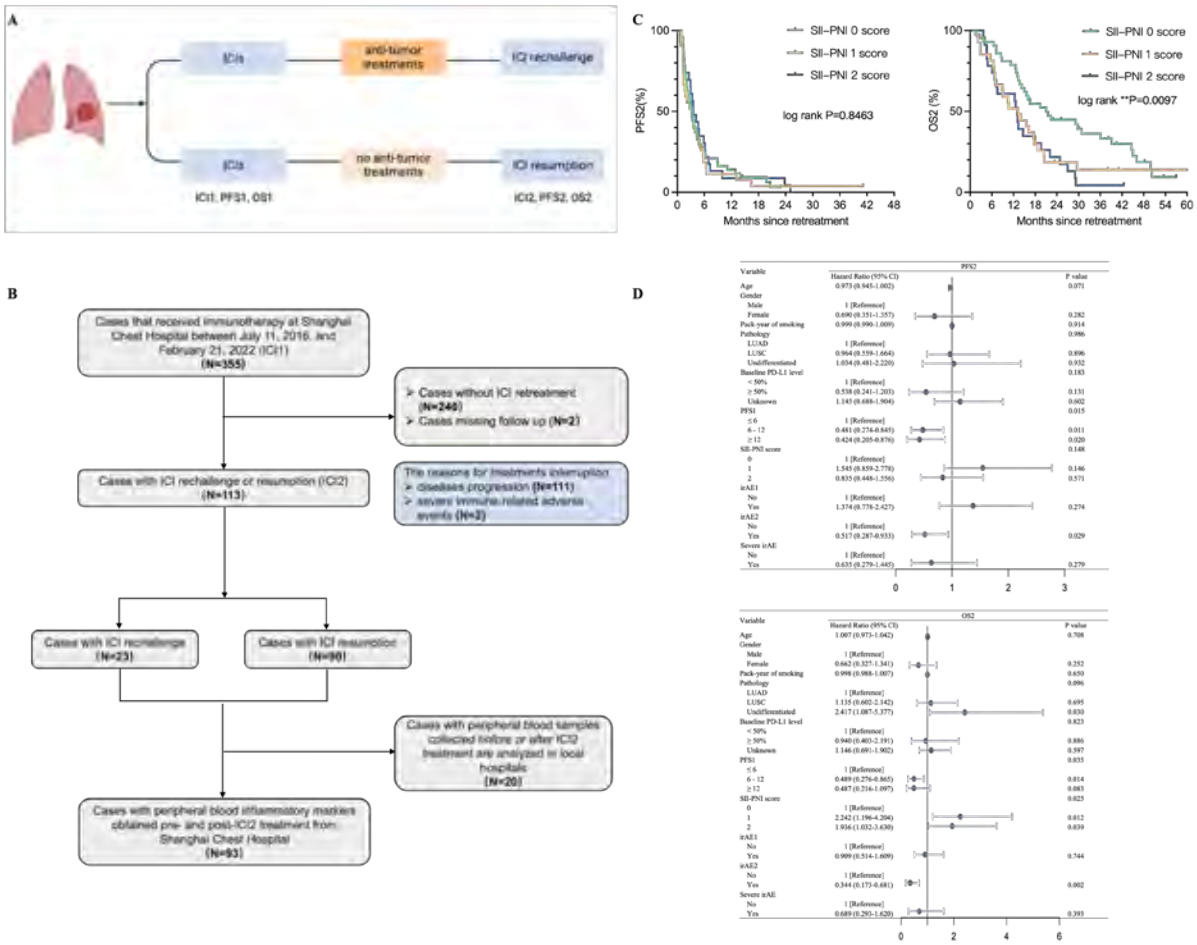
Introduction: The rechallenge of immune checkpoint inhibitors (ICIs) has emerged as a promising therapeutic strategy for advanced non-small cell lung cancer (NSCLC). However, the absence of reliable biomarkers to identify patients most likely to benefit from ICIs rechallenge remains a critical gap in clinical practice.

Methods: This retrospective study included 113 patients with advanced NSCLC who underwent ICI retreatments at the Chest Hospital Affiliated with Shanghai Jiao Tong University School of Medicine between July 2016 and February 2022. The analysis evaluated associations between PD-L1 expression, clinical characteristics, immune-related adverse events (irAEs), and peripheral blood inflammatory markers—including the systemic immune-inflammation index (SII) and the prognostic nutritional index (PNI)—with the efficacy of ICI retreatments.

Results: Progression-free survival after initial immunotherapy (PFS1) was significantly associated with overall survival following ICI retreatments (OS2, P = 0.0020). Notably, PFS1 emerged as a potential predictive marker for patient response to ICI rechallenge (P < 0.001). Patients who experienced irAEs during retreatment demonstrated improved PFS2 (P = 0.0033) and OS2 (P = 0.0006), with severe irAEs correlating with further enhanced survival outcomes (PFS2: P = 0.0156; OS2: P = 0.0361). Moreover, patients with low levels of inflammatory markers, as determined by the combined SII-PNI score, exhibited significantly improved OS2 (P = 0.0097). Multivariate analysis confirmed the SII-PNI score as an independent prognostic factor (P = 0.025), underscoring its utility in stratifying patients based on risk and likely benefit from ICI retreatments. Elevated inflammatory markers were associated with poorer prognosis, suggesting that systemic inflammation contributes to diminished therapeutic efficacy.

Conclusions: These findings highlight the combined SII-PNI score as a novel and clinically valuable biomarker for predicting outcomes in advanced NSCLC patients undergoing ICI retreatments.



Keywords: NSCLC, immune checkpoint inhibitors retreatment, peripheral blood inflammatory facto

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.09 SBRT Combined With Tislelizumab and Granulocyte-Macrophage Colony-Stimulating Factor in Advanced NSCLC Progressing on Immunotherapy

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Introduction: The combination of immunotherapy and chemotherapy has become the first-line standard treatment for advanced Non-Small Cell Lung Cancer (NSCLC). However, effective therapies are limited once immunotherapy resistance develops.Stereotactic body radiotherapy (SBRT) can effectively destroy tumor cells in the radiation area and can mediate an immune response through the abscopal effect. Granulocyte-macrophage colony-stimulating factor (GM-CSF) can also enhance antitumor immune responses by inducing the maturation of dendritic cells (DCs).

Methods: We conducted a Single-Arm Phase II study (ChiCTR2100047048) to assess the efficacy of SBRT in combination with Tislelizumab and GM-CSF for advanced NSCLC patients who have progressed on immunotherapy. This study prospectively recruited 10 eligible patients who initially underwent SBRT (24Gy/3F or 25Gy/5F), followed by a combination therapy with GM-CSF (150 μg for 2 weeks) and Tislelizumab (200mg, Q3w). Subsequently, patients received maintenance therapy with tislelizumab till progression or intolerable toxicity. The primary endpoint was Objective Response Rate (ORR), and secondary endpoints included Progression-Free Survival (PFS), tumors outside the irradiated fields (abscopal response rate, ASR), and safety.

Results: By 1 July 2024, 10 patients had been enrolled, with a median follow-up time of 11.7 months [IQR: 7.18-20.15 months]. The ORR and Disease Control Rate (DCR) were 30% and 70%, respectively. The ASR was 20% and the median PFS was 6.73 months [IQR: 5.48-7.99 months]. For the safety outcomes, mild treatment-related adverse events (AEs) occurred in 60% of patients, and one patient experienced grade ≥3 immune-related rash.

Conclusions: The study suggests that the integration of SBRT with Tislelizumab and GM-CSF may augment immunotherapy efficacy, presenting a promising therapeutic approach for advanced NSCLC patients following immunotherapy resistance.

Keywords: Granulocyte-Macrophage Colony-Stimulating Factor, Immunotherapy resistance, Stereotactic body radiotherapy (SBRT)

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.10 Serum Neopterin and Mortality in Lung Cancer Patients Treated With Immune Checkpoint Inhibitors

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Introduction: The advent of immune checkpoint inhibitors has transformed the management of patients with lung cancer. Immunotherapeutic agents exhibit antitumor activity through the stimulation of immune system, and, in contrast to other targeted therapies, the effect of immunotherapy does not manifest immediately, but only with some delay as time may be needed for the activation of the immune response. Consequently, immunotherapy may fail event in the presence of biomarkers predicting high likelihood of response if the expected survival is shorter than the time needed to obtain a response. Clinical parameters like performance status are commonly used to predict short-term survival, but there is an unmet medical need for laboratory parameters in this setting. Neopterin is a biomarker of systemic immune activation that has been associated with prognosis across the range of solid tumors.

Methods: Serum neopterin, creatinine, C-reactive protein (CRP) and peripheral blood cell count were studied before and during treatment with immune checkpoint inhibitors administered as monotherapy or in combination in 37 lung cancer patients.

Results: Serum neopterin/creatinine ratio (196 ± 73 vs. 387 ± 194 µmol/mol creatinine; p = 0.014), CRP (34.7 ± 31.3 vs.79.7 ± 51.1 mg/l; p = 0.032) and neutrophil count (6.4 ± 2.5 vs. 8.9 ± 2.6 x 109/l; p = 0.048) were significantly lower and hemoglobin was significantly higher (119 ± 27 vs. 106 ± 19 g/l; p = 0.029) in patients who survived for more than 4 months from the start of the therapy compared to patients who died by that time. A significant correlation was observed between serum neopterin/creatinine ratio and CRP (Spearman rank correlation coefficient 0.63; p < 0.0001), hemoglobin (-0.38; p = 0.021), thrombocyte (0.34; p = 0.040), leukocyte (0.34; p = 0.041) and neutrophil (0.36; p=0.029) counts. No significant changes in the parameters examined were observed during the course of therapy.

Conclusions: Serum neopterin/creatinine ratio was almost twice higher in patients who died during the first 4 months of therapy. Neopterin may be useful as a biomarker to identify patients who are unlikely to benefit from immunotherapy.

Keywords: Neopterin, Immunotherapy, Biomarker

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.11 Survival Impact of Pneumonitis in Older Patients With Non-Squamous NSCLC Treated With Pembrolizumab and Pemetrexed: Insights From CJLSG1901

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Introduction: Pembrolizumab combined with pemetrexed has shown efficacy in older patients (aged ≥75 years) with metastatic non-squamous non-small cell lung cancer (NSCLC) and a PD-L1 tumor proportion score (TPS) <50%. However, treatment-related pneumonitis remains a concern, and its impact on clinical outcomes is not fully understood. This post hoc analysis examined the effect of pneumonitis on the efficacy and treatment exposure in the CJLSG1901 study, with a focus on differences in baseline patient characteristics.

Methods: Subgroup analyses were carried out in the CJLSG1901 study to explore the efficacy and safety of pembrolizumab plus pemetrexed in older patients with metastatic non-squamous NSCLC, with a focus on the occurrence of pneumonitis (present vs. absent) after treatment initiation. The 95% confidence interval (CI) of the objective response rate (ORR) was estimated using Clopper-Pearson method. Survival functions were derived through the Kaplan-Meier method, and the median survival time, along with its 95% CIs, was calculated using the Brookmeyer-Crowley method.

Results: Of the 48 patients with metastatic non-squamous NSCLC included in the analysis, 9 (18.8%) developed pneumonitis, comprising 5 (10.4%) with Grade 1-2, and 4 (8.3%) with Grade 3. Patients in the pneumonitis group were predominantly male (88.9% vs. 74.4%). Postoperative recurrence was nearly twice as common in the pneumonitis group (44.4% vs. 20.5%). Patients with pneumonitis had a lower median number of treatment cycles (pemetrexed: 3.0 [range: 1-9] vs. 5.0 [range: 1-28]; pembrolizumab: 3.0 [range: 1-9] vs. 5.0 [range: 1-28]). The ORR was 44.4% (95% CI: 13.7-78.8) in the pneumonitis group and 35.9% (95% CI: 21.2-52.8) in the non-pneumonitis group. The median progression-free survival (PFS) was shorter in the pneumonitis group at 5.5 months [95% CI: 2.6-22.2] compared to 7.8 months [95% CI: 4.8-18.0] in the non-pneumonitis group. In contrast, the median overall survival (OS) was comparable between the groups (19.1 months [4.3-not calculated (NC)] vs. 21.2 months [16.3-NC]).

Conclusions: In conclusion, despite limited treatment exposure, patients who developed pneumonitis exhibited an ORR and OS comparable to those without pneumonitis. However, their PFS was shorter. Differences in patient backgrounds suggest that the risk of pneumonitis may be influenced by preexisting conditions and disease characteristics. This trial was registered at ClinicalTrials.gov (NCT04396457) and the Japan Registry of Clinical Trials (jRCTs041200012).

Keywords: pneumonitis, elderly, pembrolizumab

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.12 Impact of Body Composition on Immunotherapy Response in Non-Small Cell Lung Cancer

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Introduction: Although body mass index (BMI) is a widely used prognostic indicator in non-small cell lung cancer (NSCLC), it fails to distinguish whether differences in immunotherapy response are driven by variations in muscle mass or adipose tissue. To address this limitation, we investigated the association between body composition parameters and clinical outcomes in NSCLC patients receiving immunotherapy.

Methods: This retrospective study involved 473 patients diagnosed with NSCLC between March 2023 and March 2025. Body composition was measured using bioelectrical impedance analysis at at treatment initation, assessing total body fat and muscle mass, as well as their distribution (normalized by height squared). Enrolled patients were followed for at least 6 months to assess clinical outcome. Cox proportional hazards regression models were employed to evaluate the relationship between body composition and progression-free survival (PFS). Logistic regression analysis was conducted to determine the association with the objective response rate (ORR). Additionally, joint effect analyses were performed to assess the combined impact of significant body composition parameters on clinical outcomes. Longitudinal changes in body composition during follow-up were also analyzed to assess their prognostic significance.

Results: A total of 125 patients (110 male [88%]; median age 60 years) were included. 19 body composition parameters were analyzed, among which skeletal muscle index (SMI) and visceral fat area (VFA) showed significant prognostic value. Multivariable Cox regression analysis, after adjusting for age, smoking history, BMI, clinical stage and histological type, demonstrated that a higher SMI (HR=0.42, 95% CI:0.18-0.96 , P=0.041) and a lower VFA (HR=3.32, 95% CI:1.55-7.10, P=0.002) were significantly associated with longer PFS. Additionally, logistic regression analysis indicated that higher SMI (OR=2.93, 95% CI: 1.05-8.18, P=0.041) and lower VFA (OR=0.25, 95% CI: 0.09-0.69, P=0.007) independently predicted the ORR. Joint effect analysis revealed that patients with high SMI but low VFA had an 87% lower risk of disease progression (HR=0.13, 95% CI:0.04-0.38, P<0.001) compared to those with low SMI but high VFA. Furthermore, a reduction in trunk fat mass exceeding 10% during follow-up was associated with poorer PFS (HR=3.54, 95% CI: 1.17-10.71, P=0.025).

Conclusions: Higher SMI and lower VFA were independently associated with improved PFS and better response to immunotherapy in NSCLC patients. These findings highlight that body composition assessment may offer superior prognostic value over BMI and help refine patient stratification for immunotherapy. Further studies are warranted to validate these findings and guide to enhance immunotherapy efficacy in NSCLC.

Keywords: body composition, immunotherapy, non-small cell lung cancer

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.13 A Phase II Study of Camrelizumab Plus Docetaxol in Advanced NCSLC Pre-Treated With Immune Checkpoint Inhibitors and Chemotherapy

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Introduction: Rechallenge of immune checkpoint inhibitors (ICIs) plus chemotherapy has shown promise in treating advanced NCSLC after progression on standard first line treatment of ICI and chemotherapy combination therapy. This study focuses on assessing the efficacy and safety profile of camrelizumab and docetaxol combination therapy as a second-line in patients after progression on standard first line treatment of ICIs plus chemotherapy.

Methods: This study is a prospective multicenter phase II trial, advanced patients who experienced disease progression following first-line ICI and chemotherapy combination therapy. The regimen consisted of camrelizumab (200mg, IV, Q3W) and docetaxol (75mg/m2, IV, Q3w). The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS),objective response rate(ORR)and safety.

Results: As the date cut-off on March 31, 2025, this study included a cohort of 22 patients, all males. The median follow-up time was 11.6m, and the median PFS was 4.0m (95% CI:0.450-7.550). The median OS was not yet reached. The ORR was 11.8%, and the DCR was 75.5%. Reactive cutaneous capillary endothelial proliferation (RCCEP) was the characteristic adverse event associated with camrelizumab. Subgroup analysis indicated that the 13 patients who experience RCCEP derived more benefit from the treatment compared to the 9 patients without RCCEP (6.0m vs 1.9m,HR=0.358, 95% CI: 0.131-0.980,p value=0.046). Among the 16 patients with available PD-L1 TPS expression data, the five patients with PD-L1 TPS≥50% had a median PFS of 12.1m, while the eleven patients with PD-L1<50% had a median PFS of 1.9m (95% CI 1.597-2.203). No significant differences in outcomes were observed between patients with squamous cell carcinoma and those with non-squamous cell carcinoma, or between patients who achieved partial response (PR) versus stable disease (SD) from the front-line treatment.The most common treatment-related adverse effects (TRAEs) were fatigue (72.7%) and RCCEP (59.1%). The most frequent grader 3 or higher TRAEs were decreased white blood cells count (31.8%) and decreased of neutrophils count (31.8%).

Conclusions: Camrelizumab and docetaxol combination therapy may serve as a viable second-line treatment option for NCSLC patients who experience disease progression following front-line ICIs and chemotherapy combination treatment. Patients with PD-L1 TPS≥50% or those who develop RCCEP are more likely to benefit from this treatment. However, the small sample size is a limitation of this study, and further research with a larger cohort is needed to confirm those findings and achieve statistical significance.

Keywords: Camrelizumab, Re-challenge, Second-line

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.14 Depth of Response to Immunotherapy Is Associated With Survival Outcomes in Oligoprogressive NSCLC: A Real-World Data Analysis

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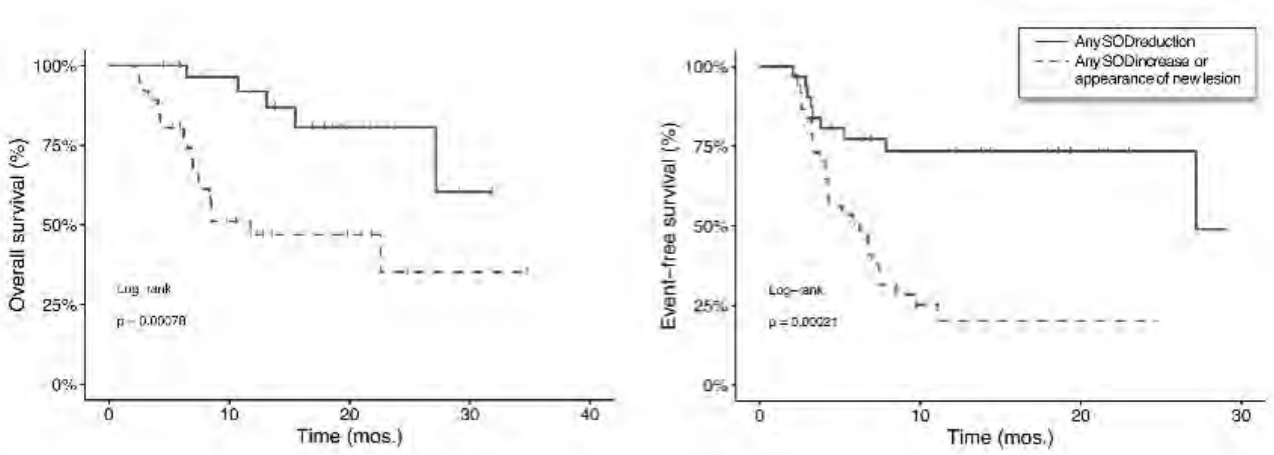
Introduction: Oligoprogressive disease (OPD) is recognized as a distinct clinical presentation with emerging data supporting the use of local ablative therapy (LAT=radiation/surgery) at sites of progression while continuing systemic therapy for non-progressing lesions (NPLs). Limited evidence exists regarding the outcomes of continuing immunotherapy (IO) in patients with OPD. In this real-world analysis, we aimed to investigate whether the "depth" of response (DepOR) to IO, defined as the change in sum of lesion diameters (SOD) across NPLs, correlates with survival outcomes. Characterizing the DepOR in NPLs may guide further disease management.

Methods: We utilized a longitudinal retrospective real-world dataset of patients with metastatic NSCLC without EGFR/ALK alterations receiving anti-PD-(L)1 across 10 US and European institutions. Lesion-level measurements were curated from routine CT scans. Patients with OPD during frontline IO treatment were identified as those with 1-5 extracranial progressing lesions (PLs) with no limit on NPLs. NPLs were longitudinally evaluated for response from the time of OPD until IO discontinuation. PLs were considered potential targets for LAT and were excluded in response evaluation. RECIST measurements were performed on NPLs to estimate the continued treatment effect attributable to IO post-OPD. Best response was determined as the maximum percent change in SOD across NPLs (excluding bone lesions). Time-to-next-treatment (TTNT) and overall survival (OS) were analyzed in patients grouped by varying DepOR.

Results: Among the 586 patients who received frontline IO (from December 2014 to November 2022), 215 (37%) developed OPD. Of these, 70 patients continued IO therapy and had ≥1 follow-up scan available. At the time of OPD, the median (interquartile range [IQR]) duration of frontline IO was 2.6 (2.2, 3.3) months; 55/70 (79%) patients had PLs in known metastatic sites, and 24/70 (34%) had PLs in new sites. The median (IQR) number of NPLs at the time of OPD was 4 (2-6). At the time of best response (median 3.4 months post-OPD), 32/70 (46%) patients experienced any SOD reduction in NPLs, including 11% (n=8/70) with ≥30% reduction. The remaining 38/70 (54%) patients had SOD increase or appearance of new lesion(s). Patients with any SOD reduction in NPLs had significantly improved OS and TTNT (Figure 1).

Conclusions: In this real-world cohort of patients receiving continued IO for oligoprogressive NSCLC, the depth of continued response in NPLs was associated with survival. This finding has clinical implications for monitoring DepOR in NPLs and optimizing interventions, particularly through novel IO combinations.



	OS			TTNT*		
	N	mOS (95% CI), mos.	p-value†	N	mTTNT (95% CI), mos.	p-value†
DepOR category	70		<0.001	70		<0.001
Any SOD reduction	32	NR (27.2, NR)		32	27.2 (27.2, NR)	
Any SOD increase or new lesion	38	11.8 (7.43, NR)		38	6.22 (4.24, 8.52)	

† Log-rank test
*Event defined as initiation of next treatment or death

Figure 1. Kaplan-Meier curves for OS (left) and TTNT (right) stratified by depth of response (DepOR) in NPLs.

Keywords: Oligoprogression, Immunotherapy, Metastatic

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY, SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.15 PD-(L)1 Inhibitors for Treatment of Locally Advanced or Metastatic NSCLC in Asian and Non-Asian Patients: A Meta-Analysis

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Introduction: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide, with higher death rates in Asia than in Europe and North America. Programmed cell death protein-(ligand) 1 (PD-[L]1) inhibitors are effective in NSCLC treatment, but their comparative effectiveness in Asian vs non-Asian populations is unclear.

Methods: A meta-analysis was conducted to assess the efficacy of PD-(L)1 inhibitor monotherapy or combination therapy (with platinum-based chemotherapy or cytotoxic T-lymphocyte-associated protein-4 [CTLA-4] inhibitors) in Asian and non-Asian patients with locally advanced or metastatic NSCLC, and to monitor safety and treatment patterns in the two cohorts using randomized controlled studies. Analyses were based on randomized controlled studies and by first- and second-line (1L, 2L/2L+) therapy. Overall survival (OS) and progression-free survival (PFS) hazard ratios (HRs) were extracted using random effects models. Safety outcomes were described if reported.

Results: Overall, 1431 records were screened, and 1L (n=21) and 2L/2L+ (n=10) studies that had enrolled a total of 10,233 patients with locally advanced or metastatic squamous/non-squamous NSCLC were identified. OS favoured 1L PD-(L)1 inhibitor monotherapy or combination therapy in both Asian (HR=0.70; 95% CI: 0.64, 0.76) and non-Asian (HR=0.71; 95% CI: 0.65, 0.77) patients (Table). Similar findings were observed with PFS in Asian (HR=0.53; 95% CI: 0.47, 0.59) and non-Asian (HR=0.58; 95% CI: 0.53, 0.64) patients. 1L PD-(L)1 inhibitor plus platinum-based chemotherapy and/or CTLA-4 inhibitors and 2L/2L+ PD-(L)1 inhibitor monotherapy were equally effective in Asian and non-Asian populations, but there was a greater magnitude of effect on PFS with 2L/2L+ PD-(L)1 inhibitor monotherapy in Asian (HR=0.57; 95% CI: 0.49, 0.67) than non-Asian (HR=0.73; 95% CI: 0.56, 0.95) patients; this may be related to differences in treatment patterns or prior surgery. Most studies showed low risk of bias using the Cochrane Risk of Bias 2 tool and rank-based Begg test. Safety data were obtained from eight 1L and two 2L/2L+ PD-(L)1 inhibitor studies. There was a higher incidence of treatment-related and immune-related adverse events (AEs) and discontinuations in some Asian populations. This may be linked to regional differences in AE resolution and differences in study periods.

Conclusions: These data demonstrate general consistency of outcomes with PD-(L)1 inhibitors for both Asian and non-Asian patients with 1L or 2L/2L+ locally advanced or metastatic NSCLC. More real-world evidence at the regional level will further confirm long-term clinical benefits and tolerability in specific patient populations.

Table. Survival Outcomes in Asian and Non-Asian Populations With Locally Advanced or Metastatic NSCLC

Outcome	Asian HR [95% CI]	Non-Asian HR [95% CI]	RE Model I^2 (*P* value)
Overall survival			
PD-(L)1 inhibitor 1L monotherapy or combination therapy	0.70 [0.64, 0.76]	0.71 [0.65, 0.77]	25% (.08)
PD-(L)1 inhibitor 1L combination therapy	0.70 [0.63, 0.76]	0.70 [0.62, 0.79]	32% (.06)
PD-(L)1 inhibitor 1L monotherapy or combination therapy (PD-L1 expression ≥50%)	0.50 [0.39, 0.64]	0.64 [0.55, 0.76]	0% (.53)
PD-(L)1 inhibitor as 2L/2L+ monotherapy or combination therapy	0.73 [0.64, 0.83]	0.71 [0.64, 0.78]	0% (.54)
Progression-free survival			
PD-(L)1 inhibitor 1L monotherapy or combination therapy	0.53 [0.47, 0.59]	0.58 [0.53, 0.64]	48% (.003)
PD-(L)1 inhibitor 1L combination therapy	0.53 [0.47, 0.60]	0.60 [0.53, 0.68]	55% (.001)
PD-(L)1 inhibitor 1L monotherapy or combination therapy (PD-L1 expression ≥50%)	0.38 [0.32, 0.44]	0.46 [0.37, 0.56]	4.6% (.40)
PD-(L)1 inhibitor as 2L/2L+ monotherapy or combination therapy	0.57 [0.49, 0.67]	0.73 [0.56, 0.95]	74% (.005)

Abbreviations: 1L, first-line; 2L/2L+, second-line/second-line-plus; CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein-(ligand) 1; RE, random effects.

Keywords: Non-small cell lung cancer, Immunotherapy, Meta-analysis

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.16 Gut Microbiota: Associations Between Composition and Response to Immunotherapy in Non-Small Cell Lung Cancer

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Introduction: Lung cancer (LC) is the leading cause ofcancer-related mortality worldwide. Immune checkpoint inhibitors (ICI) haverevolutionized cancer treatment, but surpass resistance is still a challenge. The gutmicrobiota (GM) impacts cancer immunosurveillance, and its composition has beenassociated with modulating immunotherapy efficacy. We conducted a prospectivestudy (NCT04965129) to evaluate the relationship between the GM and ICIresponse in patients with non-small cell lung cancer (NSCLC).

Methods: NSCLC patients eligible for ICI treatment, in stages III or IV, with ECOG performance status 0-2, and a life expectancy >16 weeks were included. Fecal samples were collected up to 20 days before immunotherapy initiation (T0). A pharmacist conducted monthly visits and weekly telemonitoring to assess drug interactions and provide pharmacotherapeutic follow-up for 16 weeks. The GM was analyzed by 16S rRNA sequencing. Treatment response was evaluated according to RECIST v1.0, considering disease control (DC) as complete response, partial response, or stable disease. Statistical analyses included Mann-Whitney non-parametric tests and Linear Discriminant Analysis (LDA) to identify significant differences in GM composition between ICI responders and non-responders.

Results: We included 27 patients from February 2022 to February 2024: mean age 70.6 years ± 7.5 [SD], predominantly male (59%), with two or more comorbidities (63%), and polypharmacy (74%). Most (85%) had PD-L1 <50, and 37% required pharmaceutical interventions. Around 60% of patients achieved disease control (DC). A total of 81 bacterial species differed significantly between PD and DC ($p<0.05$) groups. No records were identified in the literature relating the interface between GM and ICI response for 74 of these species (91%). In the DC group, an enrichment with health-related Lachnospiraceae (Roseburia spp., Blautia spp.) and Alistipes spp. was observed. All patients with DC were positive for Akkermansia muciniphila versus 33% in PD patients, associating a protective role of these microorganisms in immunotherapy response. Conversely, the genera Acidaminobacter and Anaerovorax predominated (3.78 and 3.38-fold, respectively) in PD patients, related to greater ICI resistance. Analysis of the Poribacteria phylum showed a significant difference between the two types of treatment response ($p = 0.031$), being found in 46% of DC patients and only 8% in PD. Furthermore, Acidaminococcus fermentans was identified in 37.5% of patients in the DC group ($p = 0.0124$) but was absent in all PD participants. Bacteroides caccae ($p = 0.035$) and Prevotella copri ($p = 0.045$) were present in all patients in the study.

Conclusions: GM composition modulates the response to immunotherapy in NSCLC. Our study is pioneering in the evaluation of Brazilian LC patients treated with ICIs. We contribute to the knowledge about the GM and its relevance for precision medicine, aiming for more robust and inclusive biomarkers.

Keywords: Non-Small Cell Lung Cancer, Gut Microbiota, Immunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.17 PD-(L)1 Inhibitors Rechallenge in Patients With Advanced NSCLC Previously Treated With Immunotherapy: A Systematic Review and Meta-Analysis

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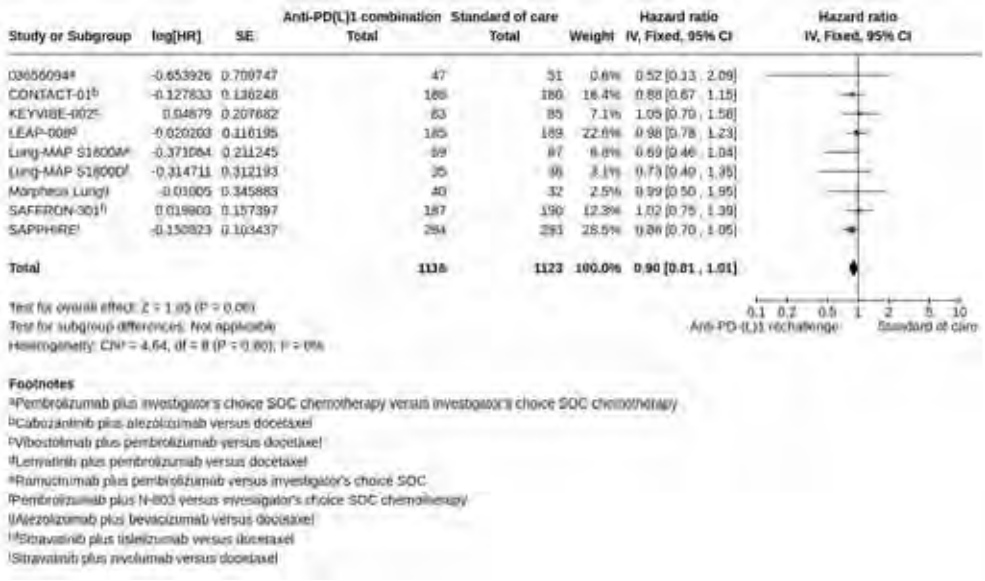
Introduction: Monoclonal antibodies (mAbs) targeting PD-(L)1 improve survival across most NSCLC stages, but resistance—either primary or acquired—remains common. Recent trials have explored PD-(L)1-based re-challenge strategies in advanced NSCLC, often in combination with other agents including other immunotherapies, tyrosine kinase inhibitors (TKIs) and VEGF mAbs, with mixed results.

Methods: The literature search on MEDLINE and EMBASE was performed in January 2025 independently by two groups of authors and eligible studies retrieved by either one or both groups were included. Randomised and non-randomised trials evaluating the safety and efficacy of second or further line of re-treatment with anti-PD-(L)1 mAbs in patients with advanced NSCLC who have previously received the same class of agents and platinum chemotherapy were included. All analyses were performed with RevMan.

Results: Two groups of authors independently identified 2957 and 5830 items, respectively. After removal of duplicates and merging of eligible studies resulting from each iteration of the search strategy, 9 randomised clinical trials were included (NCT03656094, CONTACT-01, KEYVIBE-002, LEAP-008, Lung-MAP S1800A, Lung-MAP S1800D, Morpheus Lung, SAFFRON-301, SAPPHIRE). Experimental treatment consisted of anti-PD-(L)1 combined with chemotherapy (n=2), anti-VEGF mAbs (n=2), tyrosine kinase inhibitors (n=4) and ICIs/immunostimulatory agents (n=2). The control arm consisted of docetaxel (n=6) and investigator's choice SoC chemotherapy (n=3). Most of the included trials enrolled patients independently of the pattern of resistance to anti-PD(L)1 mAbs. Among 1120 and 1123 patients treated with either anti-PD-(L)1-based combinations or SoC, OS was not significantly improved with anti-PD-(L)1-based combinations (hazard ratio (HR) 0.90, 95%CI 0.81-1.01, I2 0%, Figure 1). Similarly, progression-free survival was not significantly improved with anti-PD-(L)1-based combinations (HR 0.92, 95%CI 0.84-1.02, I2 45%) and overall response rate was similar (odds ratio 1.09, 95%CI 0.87-1.36, I2 23%). Additionally, 99 reports from non-randomised clinical trials were identified and further efficacy and safety analyses are ongoing.

Conclusions: Re-challenge with anti-PD-(L)1-based combinations in pre-treated patients did not demonstrate significant improvements in OS and PFS compared to SoC, an outcome that, despite strong biological rationale, remains unexpectedly disappointing. Nonetheless, further investigation is warranted with a focus on refined patient selection and deeper mechanistic understanding.



Footnotes
[a]Pembrolizumab plus investigator's choice SOC chemotherapy versus investigator's choice SOC chemotherapy
[b]Cabozantinib plus atezolizumab versus docetaxel
[c]Vibostolimab plus pembrolizumab versus docetaxel
[d]Lenvatinib plus pembrolizumab versus docetaxel
[e]Ramucirumab plus pembrolizumab versus investigator's choice SOC
[f]Pembrolizumab plus N-803 versus investigator's choice SOC chemotherapy
[g]Atezolizumab plus bevacizumab versus docetaxel
[h]Sitravatinib plus tislelizumab versus docetaxel
[i]Sitravatinib plus nivolumab versus docetaxel

Keywords: NSCLC, Immunotherapy rechallenge, Meta-analysis

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.18 Real-World Characterization of Response Kinetics in Patients With Metastatic NSCLC Receiving First-Line Immunotherapy

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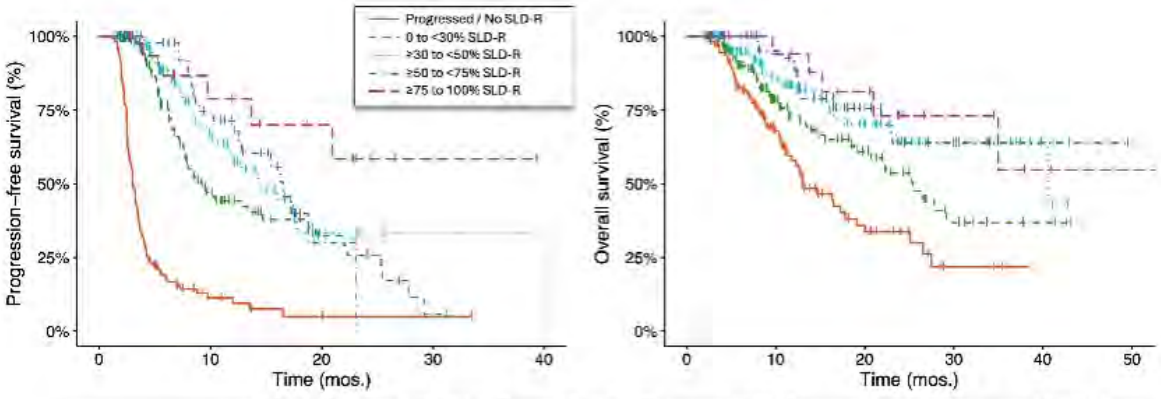
Introduction: Anti-PD-(L)1 is a preferred first-line (1L) treatment for metastatic non-small cell lung cancer (mNSCLC) without driver mutations; however, many patients have inadequate response and experience disease progression. Understanding tumor response dynamics during immunotherapy is critical to identify optimal timing for combination interventions aimed to augment response to anti-PD-(L)1 and improve survival. Here, we characterized the response kinetics of 1L anti-PD-(L)1 in a real-world cohort of patients with mNSCLC and investigated the association of depth of response (DepOR) at 3 months with survival.

Methods: This study utilized a retrospective real-world dataset of patients with mNSCLC undergoing anti-PD-(L)1-based treatment across 10 US and European institutions including radiologist-assessed imaging data. Response was assessed per RECIST v1.1 on routine CT scans. The agreement between 3-month response and best response was assessed using cross-tabulation. The DepOR at 3 months after anti-PD-(L)1 initiation was measured as percent change in the sum of longest diameters (SLD) from baseline. Real-world progression-free survival (rwPFS) and overall survival (OS) were evaluated in patients grouped by varying degree of 3-month DepOR.

Results: A total of 414 patients were identified with evaluable RECIST assessments at both baseline and 3 months after anti-PD-(L)1 initiation. The median (min, max) number of scans per patient in the cohort was 3 (2, 10). Majority of patients achieved best response at 3 months. Deepening of response after 3 months was observed in only 8% of patients. Patients were classified into subgroups based on their 3-month DepOR: 75-100% SLD reduction (SLD-R), 50-<75% SLD-R, 30-<50% SLD-R, 0-<30% SLD-R, SLD increase, and progressive disease. Proportion of patients in each subgroup was 5%, 13%, 25%, 30%, 10% and 18%, respectively. Similar distributions of 3-month DepOR were observed in patients receiving anti-PD-(L)1 monotherapy vs. anti-PD-(L)1/platinum combination therapy. All patient subgroups experiencing SLD reduction at 3-month exhibited significantly improved rwPFS and OS when compared to those with no tumor shrinkage or progression at 3 months (Figure 1). Patients with 50-100% SLD-R had significantly improved rwPFS (p=0.023) and a trend toward better OS (p=0.059) than patients with suboptimal response (0-<50% SLD-R).

Conclusions: This study highlights that patients exhibiting sub-optimal response can be identified early in their treatment trajectory based on 3-month DepOR. Furthermore, if a significant reduction in tumor burden is not achieved at 3 months, it is highly unlikely that further tumor shrinkage will occur. Our findings may inform patient selection for intensification strategies based on the tumor response at 3 months.



		Median rwPFS	Unadjusted rwPFS			Adjusted rwPFS*				Median OS	Unadjusted OS			Adjusted OS*			
Characteristic	N	mPFS (95% CI), mos.	HR	95% CI	p-value	HR	95% CI	p-value	N	mOS (95% CI), mos.	HR	95% CI	p-value	HR	95% CI	p-value	
3-month SLD category	414								414								
Progressed/No SLD-R	114	3.03 (2.73, 3.49)	Ref.	Ref.		Ref.	Ref.		114	13.1 (11.3, 20.3)	Ref.	Ref.		Ref.	Ref.		
0 to <30% SLD-R	124	9.21 (7.73, 16.8)	0.21	0.15, 0.30	<0.001	0.21	0.15, 0.30	<0.001	124	25.4 (20.7, NR)	0.56	0.37, 0.84	0.005	0.63	0.41, 0.97	0.037	
≥30 to <50% SLD-R	102	14.3 (11.8, NR)	0.14	0.09, 0.21	<0.001	0.14	0.09, 0.21	<0.001	102	40.5 (40.5, NR)	0.34	0.21, 0.55	<0.001	0.36	0.21, 0.59	<0.001	
≥50 to <75% SLD-R	55	16.5 (12.6, NR)	0.13	0.08, 0.22	<0.001	0.14	0.08, 0.23	<0.001	55	NR (23.1, NR)	0.27	0.14, 0.52	<0.001	0.28	0.15, 0.56	<0.001	
≥75 to 100% SLD-R	19	NR (13.7, NR)	0.07	0.03, 0.18	<0.001	0.09	0.04, 0.22	<0.001	19	NR (35.0, NR)	0.25	0.10, 0.63	0.003	0.29	0.11, 0.71	0.007	

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio
*Cox models adjusted for histology, PD-L1 status, and IO regimen type

Figure 1. Comparison of patient outcomes across 3-month DepOR subgroups

Keywords: Immunotherapy, Response, Intensification

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.19 Real-World Outcomes of Nivolumab Plus Ipilimumab in Elderly NSCLC Patients (=75): A Retrospective Analysis

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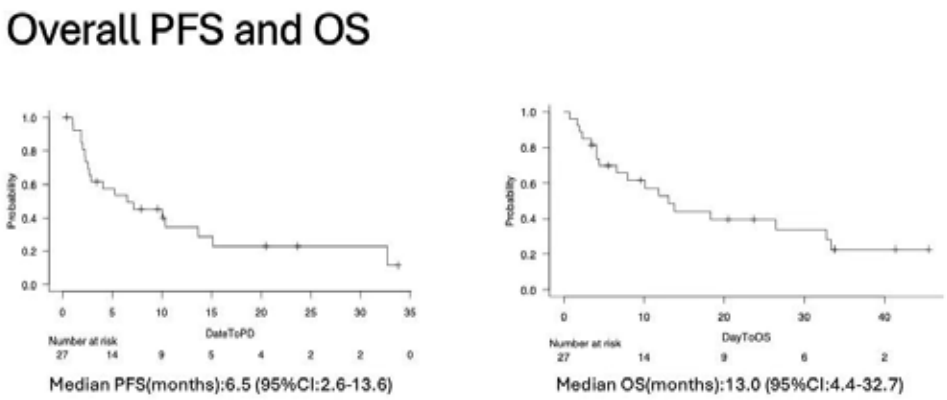
Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of non-small cell lung cancer (NSCLC), offering durable responses. However, elderly patients (≥75years) are underrepresented in clinical trials due to age-related comorbidities and functional decline. Although the combination of nivolumab and ipilimumab has become a standard first-line option based on trials like CheckMate 227, data on its efficacy and safety in elderly populations remain limited.

Methods: We conducted a single-center retrospective observational study to evaluate the clinical outcomes of nivolumab plus ipilimumab in elderly patients with advanced NSCLC lacking driver mutations. Twenty-seven patients aged ≥75 years who received this regimen between February 2021 and October 2023 were included. Clinical data were obtained from electronic medical records. Primary endpoints were progression-free survival (PFS) and overall survival (OS), while secondary endpoints included objective response rate (ORR), disease control rate (DCR), and immune-related adverse events (irAEs). Risk factors associated with progressive disease (PD) as best response were explored using logistic regression, and multivariate analysis was performed with a Cox proportional hazards model.

Results: The median age was 80 years (range 75-90), and 66.7% were male. PD-L1 expression was positive in 8 (29.6%), negative in 18 (66.7%), and unknown in 1 (3.7%). Median PFS was 6.5 months (95% CI: 2.6-13.6), and OS was 13.0 months (95% CI: 4.4-32.7). ORR was 22.2% (6 partial responses), and DCR was 62.9% (11 stable diseases). PD occurred in 10 patients (37.1%). Logistic regression analysis identified never-smoking status as significantly associated with a lower risk of PD (OR = 0.12, 95% CI: 0.01-0.98, p = 0.048), while non-squamous histology showed a trend toward reduced PD risk (OR = 0.17, 95% CI: 0.03-1.09, p = 0.061). The presence of brain metastases significantly increased the likelihood of PD (OR = 24.0, 95% CI: 2.23-260.0, p = 0.009). In multivariate Cox regression analysis, brain metastases remained a significant factor for disease progression (HR = 24.00, 95% CI: 2.21-260.00, p = 0.009). Regarding irAEs, 18 patients (66.7%) experienced any grade, and 11 (40.7%) had grade ≥3 events. Skin rash (n=8), lung injury (n=4), and colitis (n=4) were the most frequent. Grade ≥3 events included lung injury (n=4), arthritis (n=1), adrenal insufficiency (n=1), kidney injury (n=2). One treatment-related death occurred due to pneumonitis.

Conclusions: Nivolumab plus ipilimumab appears to be a feasible treatment for elderly patients with advanced NSCLC, providing meaningful disease control. However, patients with brain metastases may have significantly poorer outcomes.



Keywords: Nivolumab, Ipilimumab, Elderly patients

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.20 Camrelizumab-Based Therapy-Induced RCCEP in Advanced NSCLC Patients: A Pooled Analysis of Two Phase III Registration Trials

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Introduction: Cutaneous immune-related adverse events (irAEs), the most common toxicities of immune checkpoint inhibitors (ICIs), have been reported to positively associate with favorable survival outcomes in ICIs-treated patients with advanced cancer. Reactive cutaneous capillary endothelial proliferation (RCCEP), a distinctive irAE uniquely observed with camrelizumab (PD-1 antibody), may correlate with patient prognosis as well. This pooled analysis aimed to elucidate the clinical features of RCCEP and explore its prognostic relevance in advanced non-small cell lung cancer (NSCLC) patients.

Methods: Individual patient-level data in this pooled analysis were derived from two phase III registration trials, CameL (NCT03134872) and CameL-sq (NCT03668496). The CameL study enrolled patients with stage IIIB-IV non-squamous NSCLC without EGFR or ALK alterations, treated with camrelizumab combined with chemotherapy comprising pemetrexed and carboplatin. The CameL-sq study included patients with stage IIIB-IV squamous NSCLC receiving camrelizumab plus chemotherapy consisting of paclitaxel and carboplatin. Landmark analyses were performed to assess survival outcomes, taking the median time to first RCCEP onset as the time zero-point reference.

Results: RCCEP occurred in 73.4% (292/398) of patients, with a median age of 60.0 years (IQR: 54.0-65.0), the predominance of males (77.4%) and ECOG performance statuses of 0 (25.7%) or 1 (74.3%). The severity of RCCEP was primarily grade 1 (59.3%) and grade 2 (12.6%), with grade ≥3 events accounting for merely 1.5%. Treatment discontinuation due to RCCEP was rare, occurring in only 0.5% (2/398) of patients. The median frequency of RCCEP events was 1.0 (IQR: 1.0-2.0). The median time to first RCCEP onset was 1.48 months (IQR: 0.95-2.27); thus, a 2-month landmark analysis of survival was conducted. Compared with patients who did not develop RCCEP, those who did exhibited longer duration of camrelizumab exposure and increased cumulative exposure to camrelizumab, along with superior clinical outcomes including higher objective response rates (ORR: 71.9% vs. 36.8%), prolonged median progression-free survival (mPFS) [landmark analysis] (13.01 vs. 6.97 months; HR=0.43; 95% CI: 0.31-0.60), and extended median overall survival (mOS) [landmark analysis] (31.70 vs. 12.22 months; HR=0.30; 95% CI: 0.22-0.41).

Conclusions: This pooled analysis confirmed that RCCEP was relatively prevalent yet predominantly mild in severity among advanced NSCLC patients treated with camrelizumab-based regimens. Notably, the emergence of RCCEP positively correlated with enhanced efficacy, evidenced by improved ORR, prolonged PFS and OS, underscoring RCCEP as a potential predictive biomarker for therapeutic efficacy.

Keywords: Camrelizumab, RCCEP, NSCLC

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.21 Target Lesion Necrosis Percentage as a Predictor for Response to Immune Checkpoint Inhibitors in NSCLC: A Retrospective Analysis

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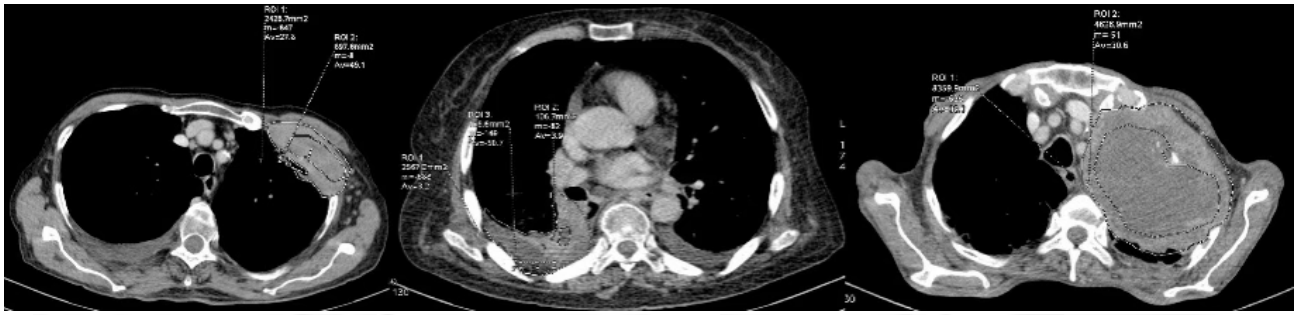
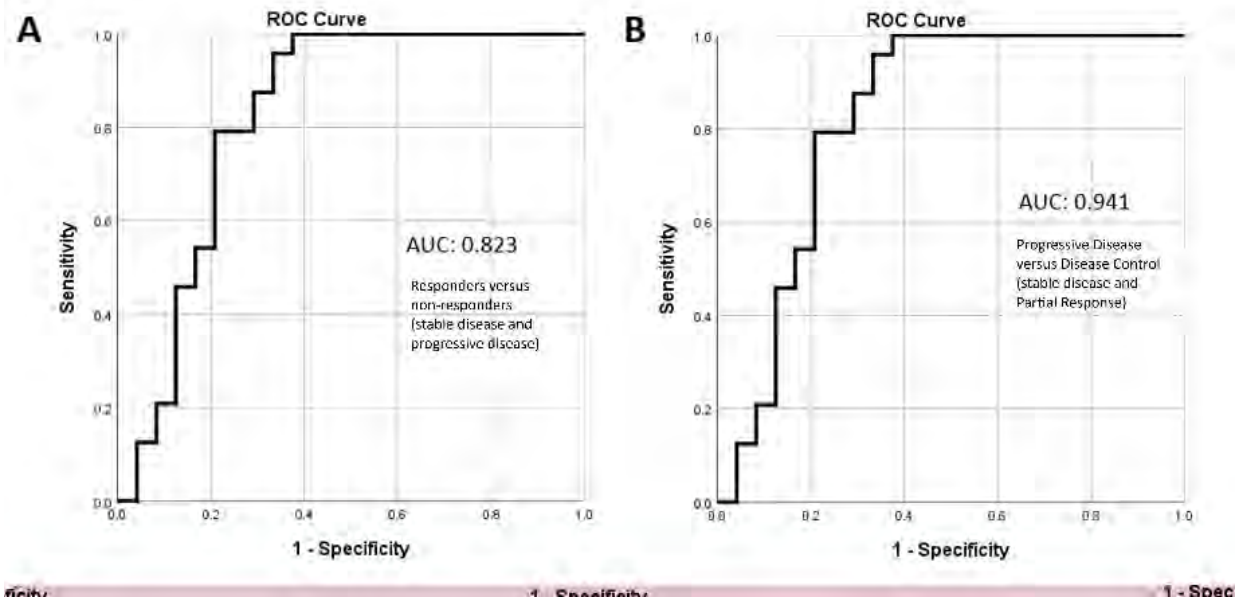
Introduction: Tumor-necrosis is a common finding in computed tomography (CT) scans of non-small-cell-lung cancer (NSCLC) patients and is associated with high tumor grade and poor prognosis. It is hypothesized that high necrosis proportion can indicate inflamed tumor microenvironment which can favor use of immune checkpoint inhibitors.

Methods: This was a retrospective single center study on NSCLC patients (stage IIIB or higher) who progressed/relapsed after first-line therapy and received single-agent Nivolumab. Anonymized contrast-enhanced CT scans done at baseline visit (before starting nivolumab) were used for analysis. Response was classified as per RECIST1.1 criteria and the radiologist (AN) who analyzed the CT scans was unaware of the same. The axial section on CT cuts exhibiting the maximal tumoral cross-sectional area was selected. Tumoral area and necrotic area (both discrete and scattered) were recorded. Necrotic-area was defined based on cut off of hounsfield units less than 50(figure1). Percentage-necrotic-area was compared among responders and non-responders.

Results: 48 subjects with complete follow up data were identified. Majority were males (91.7%), had an ECOG-PS of 1(89.6%), and were stage IV (70.8%). Most common histology was squamous-cell (75%) and adenocarcinoma were 10.4%. Mean age was 60.29±8.6 years and mean necrotic area percentage was 24.75±15.9%. 66.7% (32) patients had disease control of which 75% (24) achieved partial remission (as best response). Percentage-necrosis-area was significantly higher in the responders group [32.92±11.5 versus 16.6±15.7; t(46):4.1; p<0.001; Cohen's D: 13.8] as well as disease control group [9.28±6.2 versus 32.5±13.4; t(46):-6.6; p<0.001; Cohen's D: 11.6] compared to non-responders (stable-disease and progressive-disease combined) and progressive-disease groups, respectively. ROC-AUC for predicting progression was 0.941 with best diagnostic accuracy at 23.18% necrotic-area. ROC-ROC for response prediction was 0.823(figure2).

Conclusions: Measuring necrosis-percentage-area can be used to anticipate response to nivolumab in second line setting. Larger prospective studies are required to confirm our preliminary findings.





Keywords: Necrosis, Nivolumab, Partial Response

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.22 Extracellular Vesicle-Derived LncRNA Signatures in Serum for Diagnosis and Prognosis of Checkpoint Inhibitor-Related Pneumonitis

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Introduction: Checkpoint inhibitor-related pneumonitis (CIP) is a life-threatening immune-related adverse event (irAE) associated with immune checkpoint inhibitors. Due to the absence of specific diagnostic tools, CIP is frequently misdiagnosed or underdiagnosed in clinical practice. This highlights the urgent need for more accurate and non-invasive diagnostic approaches. In this study, we investigate the potential of serum extracellular vesicle (EV)-derived lncRNAs as novel biomarkers for the diagnosis and prognosis of CIP.

Methods: Serum EV lncRNAs from three patient groups—CIP (patients treated with PD-1/PD-L1 inhibitor and with CIP), ICI (patients treated with PD-1/PD-L1 inhibitor and without CIP), and PNE (infectious pneumonia)—were detected via lncRNA sequencing, with selected lncRNAs validated by qRT-PCR in a training cohort (n = 103). The diagnostic (CIP vs. ICI) and differential diagnostic (CIP vs. PNE) models were constructed and assessed for diagnostic performance with Receiver Operating Characteristic (ROC) curves. The results were further validated in an independent validation cohort (n = 74). LASSO regression identified key peripheral blood parameters for comparison and integration with EV-lncRNA models to enhance diagnostic accuracy. Clinical applicability was evaluated via DCA. A prognostic model based on the CIP diagnostic signature was constructed using Cox regression to stratify patients by overall survival (OS) after CIP onset.

Results: Two lncRNAs (TTC9-DT and ITGA2-AS1) were significantly elevated in the CIP group compared to the ICI group and were confirmed as key biomarkers for CIP diagnosis, with TTC9-DT also distinguishing CIP from PNE. In CIP diagnosis (CIP vs. ICI), the CILnc model (TTC9-DT + ITGA2-AS1) achieved high diagnostic accuracy in the training cohort (AUC = 0.945, 95% CI [0.883-1.000]) and was validated in the independent cohort (AUC = 0.983, 95% CI [0.941-1.000]). For differentiating CIP from PNE (CIP vs. PNE), TTC9-DT yielded an AUC of 0.704 (95% CI [0.551-0.857]) in the training cohort and 0.860 (95% CI [0.712-1.000]) in the validation cohort. Through LASSO regression, absolute neutrophil count (NEU), absolute lymphocyte count (LYM), and lactate dehydrogenase (LDH) were identified from routine peripheral blood markers, but their diagnostic efficacy was worse than lncRNA-based models. When combined with specific blood markers, diagnostic performance improved further. The efficacy of CILnc+NEU model was validated for CIP diagnosis (CIP vs. ICI) with AUCs of 0.948 (95% CI [0.887-1.000]) (training cohort) and 0.991 (95% CI [0.965-1.000]) (validation cohort). TTC9-DT+LYM+LDH effectively distinguished CIP from PNE with AUCs of 0.827 (95% CI [0.716-0.939]) and 1.000 (95% CI [1.000-1.000]). Both models demonstrated strong clinical utility, as confirmed by DCA. Additionally, the CILnc+NEU signature effectively stratified CIP patients based on OS after CIP onset (hazard ratio = 12.618, 95% CI [2.766-57.566]).

Conclusions: Serum EV lncRNA-based signatures (CILnc+NEU and TTC9-DT+LYM+LDH) offer specific, non-invasive tools for diagnosing CIP, and they are also potential prognostic markers for CIP patients. These findings may help to promote precise clinical diagnosis and individualized management of CIP.

Keywords: checkpoint inhibitor-related pneumonitis, extracellular vesicles, lncRNA

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.23 Co-Culturing LCOs and Lymphocytes Derived From Pleural Effusion Potentially Implement Personalized Immunotherapy

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Introduction: Identifying lung cancer patients who will respond to immunotherapy remains a significant challenge. Organoid-lymphocyte co-culture represents a potentially valuable tool for improving patient selection. The aim of this study is to establish a co-culture system of human derived lung cancer organoids and lymphocytes derived from pleural effusion, and correlate the results of drug sensitivity testing with real-world clinical efficacy in patients.

Methods: Between October 31, 2021, and May 31, 2024, a total of 328 specimens were collected from 204 patients diagnosed with advanced lung cancer for organoid culture. Co-culture systems were established using lymphocytes and tumor cells isolated from malignant pleural effusions. The ATP bioluminescence tumor chemosensitivity assay (ATP-TCA) was applied to measure changes in cell viability. The expression levels of anti-tumor immune factors in the co-culture system were quantified using the Olink proteomics assay, both before and after treatment. Flow cytometric analysis was also performed to characterize the anti-tumor immune function of T cells.

Results: Compared to malignant pleural effusion lymphocytes (MPELs), we observed a significantly higher proportion of CD11b+ cells within the PBMCs (P<0.001). which may indicate that MPELs is more suitable for constructing organoid lymphocyte co-culture systems than PBMCs. Guided by the above results, a co-culture system of lung cancer organoids (LCOs) and pleural effusion-derived lymphocytes was established. Further, Olink proteomics analysis revealed that pembrolizumab treatment in a co-culture system significantly increased the expression of CD28, IL-12, TNF, PD-L2, and NCR1 (P<0.01). Conversely, the expression of IL-13, IL-5, PD-1, CXCL1, and PTN was significantly decreased (P<0.01). In a separate co-culture system treated with pembrolizumab, a significant increase was observed solely in IL-13 expression. This outcome aligns with the drug sensitivity assay results for this system, which indicated that pembrolizumab was ineffective. Flow cytometry analysis of marking CD8+, CD137+, and CD107a+ T cell showed that compared to peripheral blood, the LCOs pleural lymphocytes co-culture system more accurately reflected the anti-tumor efficacy of T cells. Overall, the analysis showed that the success rate of establishing co-culture system in our study was 29.8% (98/328). The chi-square analysis revealed a statistically significant association between the type of sample taken and the success of establishment (P=0.025). By analysed, the diagnostic threshold (minimum requirement for cell viability reduction) for drug efficacy is 31.93%. ROC analysis showed that the area under the curve (AUC) value was 0.765 (P=0.009). Based on this criterion, under the co-culture system of LCOs and lymphocytes derived from pleural fluid, the consistency between drug sensitivity and clinical efficacy was 78.6% (11/14) and 70.0% (14/20) in the immunotherapy and targeted therapy/chemotherapy groups respectively. The total consistency was 73.5% (25/34), but 37.5% (3/8) under the co-culture system of LCOs and lymphocytes from peripheral blood.

Conclusions: For the first time, we have established a co-culture system of lung cancer organoids (LCOs) and autologous lymphocytes derived from pleural effusion. Notably, drug sensitivity testing in this system demonstrates high concordance with observed clinical efficacy.

Keywords: Immunotherapy, Lung Cancer Organoids, Co-culture

P1.11.24 Real-World Evidence of Primary Resistance to First-Line Chemo-Immunotherapy in Advanced Lung Adenocarcinoma

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Introduction: Despite the unprecedented long lasting-responses observed with immunotherapy (IT) in non-small cell lung cancer (NSCLC), a considerable proportion of patients does not respond to upfront IT-based strategies. Primary resistance to first-line chemo-immunotherapy (CT-IT) still represents an unmet clinical need and an underexplored phenomenon.

Methods: This multicenter retrospective-prospective study included patients diagnosed with advanced lung adenocarcinoma (LUAD) who received first-line CT-IT (cis/carboplatin, pemetrexed, and pembrolizumab) starting from September 4th, 2018, across 33 Italian Centers. This analysis aimed to describe the real-world clinicopathological features and outcomes of patients with primary resistance to CT-IT, defined as RECIST progression (PD) within ≤6 months from treatment initiation and to compare them with those who had a follow-up exceeding 6 months. Both groups had a minimum treatment exposure of 6 weeks as per Society for Immunotherapy of Cancer (SITC) guidelines.

Results: A total of 1068 patients were enrolled by the data cut-off (January 31st, 2023), and 768 of these were included in this analysis. Among the 225 (29.3%) patients who were primary resistant to CT-IT, the median age was 65 years (range, 32-82), 141 (62.7%) patients were male, and 190 (86.4%) were current/former smokers. At univariate analysis, compared with the rest of the study population (n=543), patients with primary resistance had a poorer ECOG PS (ECOG PS ≥2: 9.9% vs 4.5%, p=0.003), a higher percentage of pre-treatment bone metastasis (48.9% vs 31.7%, p<0.001), liver metastasis (15.6% vs 10.3%, p=0.041) and were more likely to have more than three metastatic sites (54.2% vs 37.6%, p<0.001). The most common best response to CT-IT in patients with primary resistance was progressive disease (PD) in 113 (50.4%) cases, compared to a partial response in 338 (62.2%) of the remaining patients (p<0.001). Among patients with primary resistance, those whose best response to CT-IT was PD exhibited even worse baseline clinical features (ECOG PS ≥2: 13.3%, liver metastasis: 16.8%, >three metastatic sites: 59.3%). At the time of PD, a higher proportion of patients with primary resistance continued CT-IT beyond PD (24.0% vs 13.0%, p<0.001). Median duration of treatment (DoT) and median overall survival (OS) were significantly decreased in patients with primary resistance compared to the counterpart (mDoT: 3.8 vs 11.1 months, p<0.001; mOS: 8.3 vs 35.6 months, p<0.001). Furthermore, patients with primary resistance less frequently received a second-line treatment (56.0% vs 66.5%, p=0.005), which consisted of docetaxel in 39 (31.0%) patients and docetaxel plus nintedanib in 31 (24.6%) patients. Of note, patients with primary resistance more frequently achieved progression of disease as best response to second-line therapy (46.0% vs 35.0%, p=0.015).

Conclusions: Baseline characteristics such as ECOG PS ≥2, the presence of bone and liver metastasis and having more than three metastatic sites were significantly more prevalent in LUAD patients with primary resistance to first-line CT-IT. These patients also exhibited a higher likelihood of experiencing PD as the best response to both first-line and second-line therapy, suggesting that special caution should be exercised when treating patients with these unfavorable features.

Keywords: NSCLC, chemo-immunotherapy, primary resistance

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.25 Genomic Characterticers, Survival and Prognostic Analysis of Advanced NSCLC With Kirsten Rat Sarcoma Mutations With Brain Metastases

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Introduction: The brain is a common site of metastasis for lung cancer, however, data on the incidence of brain metastasis, genetic landscape and survival prognosis analysis in patients with KRAS-mutant is limited. Therefore, we conducted this single-center retrospective study to characterize the incidence of brain metastasis in KRAS-mutated patients and to analyze the prognostic factors related to their survival.

Methods: A total of 2,429 patients with advanced non-small cell lung cancer (NSCLC) who were hospitalized at Zhejiang Cancer Hospital from January 2017 to June 2023 were screened. The primary endpoint of the study was the overall survival (OS) . OS was defined as the time from the diagnosis of brain metastasis to the last follow-up or death. Kaplan-Meier methods were used to generate survival curves, and the log-rank test was employed to assess differences. Cox proportional hazards regression was used to evaluate prognostic factors associated with OS.

Results: In analsysis,217 patients with KRAS-mutant were identified, of whom 63 had brain metastasis. The incidence of brain metastasis at diagnosis was 35/217 (16.1%), and the overall incidence of brain metastasis was 63/217 (29.0%). Among the KRAS subtypes, the incidence of brain metastasis for G12C, G12D, G12V, and G12A was 33.9% (20/59), 19.4% (6/31), 28.6% (6/21), and 40.0% (6/15), respectively. The follow-up cut-off date was December 10, 2024, the median OS of 217 patients with KRAS- mutant was 19.4 months (95% CI: 16.9-24.3 months). The median OS of 63 patients with brain metastasis was 15.2 months (95% CI: 13.2-22.1 months), and patients with brain metastasis had significantly shorter median OS compared to those without brain metastasis (15.2 vs. 22.2 months, p = 0.038). There was no significant difference in OS between BM patients with KRAS G12C and those with other subtypes (16.9 vs. 14.9 months, p = 0.27). During the treatment after brain metastasis, 47 patients had received chemotherapy with immunotherapy, 13 patients had received chemotherapy with anti-angiogenic therapy, and 3 patients had only received TKI treatment in clinical research. Those who had received chemotherapy with immunotherapy had longer OS compared to those who did not (16.3 vs. 6.95 months, p = 0.029). Patients who received brain radiotherapy had a tendency towards longer survival compared with those who did not, although the difference was not statistically significant (17.7 vs. 12.5 months, p = 0.15). Univariate and multivariate analysis revealed that the combination of chemotherapy and immunotherapy is an independent prognostic factor.

Conclusions: The incidence of brain metastasis in patients with KRAS-mutant is relatively low. Patients with brain metastasis have a poorer prognosis than those without brain metastasis. Immunotherapy after brain metastasis can improve the overall survival (OS), Univariate and multivariate analysis revealed that the combination of chemotherapy and immunotherapy could improve those patients' prognosis.

Keywords: kirsten rat sarcoma, non-small cell lung cancer, brain metastasis

P1.11.26 Temporal Optimization of Radiotherapy-Immunotherapy Synergy for NSCLC Brain Oligo-Metastases: Prospective Assessment of Prognosis Outcomes

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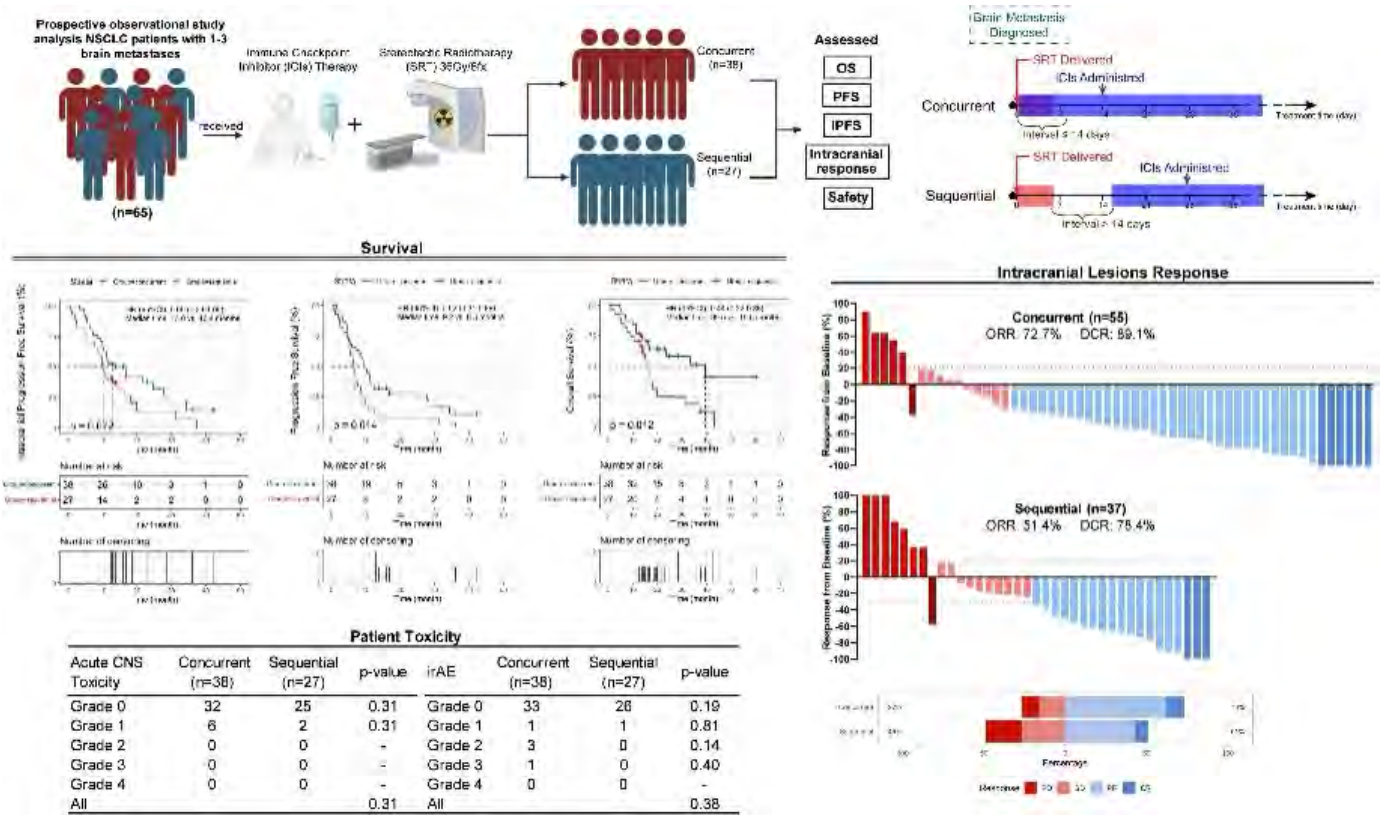
Introduction: Initiating immunotherapy within a specific time window (7-14 days) after radiotherapy may maximize the synergistic effect between antigen release and T-cell activation. This prospective study investigates the optimal sequencing of stereotactic radiotherapy (SRT) combined with immune checkpoint inhibitors (ICIs) in patients with NSCLC brain oligo-metastases, assessing differential clinical responses based on treatment timing.

Methods: From 2018 to 2023, this study enrolled the NSCLC patients with 1-3 BMs who received SRT combined with ICIs. After initial diagnosis of brain metastases, patients first underwent SRT followed by concurrent (interval ≤14 days) or sequential (interval >14 days) ICIs treatment. Based on the temporal interval between the two therapies, patients were followed up, and differences in survival outcomes, intracranial response, and safety profiles were compared between the two cohorts.

Results: Ultimately, this study enrolled 65 patients, including 38 in the concurrent treatment group and 27 in the sequential treatment group. Compared to sequential therapy, concurrent treatment significantly improved overall survival (median OS: 39.5 vs. 16.5 months, hazard ratio [HR]: 0.44, 95% confidence interval [CI]: 0.22-0.85, p = 0.012) and progression-free survival (median PFS: 9.2 vs. 6.5 months, HR: 0.52, 95% CI: 0.31-0.88, p = 0.014). Notably, in patients with PD-L1-positive expression or those with a single brain metastasis, concurrent therapy demonstrated a significant increase in intracranial progression-free survival (median iPFS: 11.0 vs. 9.1 months, HR: 0.41, 95% CI: 0.18-0.98), p = 0.037; 16.7 vs. 9.7 months, HR: 0.61, 95% CI: 0.26-0.99, p = 0.046) compared to sequential treatment. Based on lesion-level assessment of intracranial treatment response, concurrent therapy significantly enhanced the intracranial objective response rate (iORR: 72.7% vs. 51.4%, p = 0.036). No significant differences in treatment-related toxicities were observed between the two groups.

Conclusions: Concurrent SRT and ICIs therapy (interval ≤14 days) significantly improved prognosis outcomes compared to sequential treatment in NSCLC patients with oligo-brain metastases, without increasing treatment-related toxicities. These findings underscore the critical role of initiating immunotherapy a post-radiotherapy window within 14 days to optimize synergistic efficacy, supporting concurrent administration as a preferred strategy for this patient population.



Patient Toxicity

Acute CNS Toxicity	Concurrent (n=38)	Sequential (n=27)	p-value	irAE	Concurrent (n=38)	Sequential (n=27)	p-value
Grade 0	32	25	0.31	Grade 0	33	26	0.19
Grade 1	6	2	0.31	Grade 1	1	1	0.81
Grade 2	0	0	-	Grade 2	3	0	0.14
Grade 3	0	0	-	Grade 3	1	0	0.40
Grade 4	0	0	-	Grade 4	0	0	-
All			0.31	All			0.38

Keywords: Brain Metastases, Stereotactic Radiotherapy, Immunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.27 Optimal Immunotherapy Regimen for STK11 or KEAP1 Mutant Metastatic Non-Small Cell Lung Cancer

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Introduction: Immunotherapy-based regimens have significantly improved outcomes for patients with metastatic non-small cell lung cancer (mNSCLC). However, immunotherapy benefits may be limited in specific subsets of patients with cancers harboring mutations in serine/threonine 11 (STK11) and Kelch-like ECH-associated protein 1 (KEAP1). The optimal immunotherapy strategy for these patients is unknown.

Methods: We reviewed randomized control trials that led to regulatory approval of immunotherapy-based regimens in mNSCLC by the FDA. During our analysis, we only included trials that reported outcomes for STK11 and KEAP1 patients. Since information on STK11/KEAP1 co-mutants was limited, we did not include this information in our analysis. In trials where multiple experimental treatments were tested, we included data on all arms, even if a particular experimental arm did not lead to regulatory approval. We retrieved data regarding outcomes, including overall response rates (ORR), median progression-free survival (mPFS), and overall survival (mOS) for experimental and control arms.

Results: We included 7 randomized trials in our analysis. Keynote 42 was the only included trial evaluating single-agent immunotherapy pembrolizumab in the PDL1-positive population. KEAP1 and STK11 patients had improved ORR and OS with pembrolizumab, but the PFS was not improved. Keynote 189 evaluated chemotherapy plus pembrolizumab and showed improvement in PFS, OS and ORR in the experimental arm. However, combination chemoimmunotherapy with PDL1 antibodies durvalumab and atezolizumab in POSEIDON and IMPOWER 150 underperformed when compared to standard chemotherapy in both KEAP1 and STK11, limiting their role for these patients. Anti-CTLA4 addition to Anti-PD(L)1 improved outcomes in POSEIDON, checkmate 227 and checkmate 9LA trials supporting combination checkpoint blockade, which may abrogate the deleterious effect of STK11 and KEAP1. Lastly, a four-drug regimen of chemotherapy plus bevacizumab and atezolizumab (ABCP) from IMPOWER 150 did not appear to benefit STK11 patients, but KEAP 1 patients did derive benefit.

Conclusions: Though STK11 and KEAP1 mutations in NSCLC are associated with a poor prognosis, these patients can still benefit from immunotherapy-based regimens over chemotherapy alone. We conclude that these patients should receive combination treatments such as pembrolizumab plus chemotherapy or dual checkpoint blockade with or without chemotherapy. Anti-PDL1 antibodies should not be considered interchangeable with pembrolizumab in this patient population. Patients not candidates for combination due to frailty or medical comorbidities may still derive benefit from single agent pembrolizumab if PDL1 is positive.

IO regimen type	Trial	Experimental (E) arm	Control (C) Arm	No. of analyzed STK11 pts (N)	mPFS in STK11 – E vs C arm, HR (CI)	mOS in STK11– E vs C arm, HR (CI)	ORR in STK11 – E vs C arm (%)	No of KEAP1 patients across arms (N)	PFS in KEAP1 - E vs C arm, HR (CI)	OS in KEAP1 E vs C , HR (CI)	ORR in KEAP1 – E vs C arm (%)
Anti-PD-1	KEYNOTE 42	Pembrolizumab	Chemo	33	4.8 months vs 5.1 months, 0.75 (0.36-1.57)	18.1 vs 7.6 months, 0.37 (0.16-0.86)	31.3% vs 5.9%	64	6.1 vs 5.7 months, 0.67 (0.38-1.17)	17 vs 8.9 months, 0.75 (0.42-1.35)	35.5 % vs 18.2 %
Anti-PD-1 + chemo	Keynote 189	Pembrolizumab + chemo	Chemo	54	6 vs 5 months, 0.81 (0.44–1.47)	17.4 vs 8.4 months , 0.75 (0.37–1.50)	31 % vs 17%	68	5.1 v 4.8 months, 0.65 (0.38-1.12)	12.9 v 8.6 months, 0.81 (0.44-1.49)	36% vs 17%
Anti-PDL-1 + chemo	POSEIDON	Durvalumab + chemo	Chemo	66	NR	6.4 vs 10.7 months, 1.19 (0.70-2.05)	NR	29	NR	8.1 vs 8.7 months, 0.77 (0.31-2.15)	NR
	IMPOWER 150	Atezolizumab plus chemo	Chemo	87	3.2 months vs 4.4 months, 1.13 (0.73-1.75)	7.7 vs 9.9 months, 1.01 (0.64-1.58)	NR	86	3.1 v 4.2 months, 1.23 (0.80-1.90)	6.9 vs 11.7 months, 1.51 (0.96-2.37)	NR
Anti-PD-1 + anti-CTLA4	Checkmate 227 (part 1 PDL1>1%)	Ipilimumab + Nivolumab	Chemo	78	NR	NR	NR	38	8.2 v 4.0 months, 0.34(0.14-0.83)	20 v 16.7 months, 0.80(0.65-1.00)	NR
Anti-PD-1 + anti-CTLA4 + chemo	Checkmate 9LA	Ipilimumab + nivolumab + Chemo	Chemo	86	5.4 vs 4.2 months, 0.61(0.37-1.0)	13.8 vs 10.7 months, 0.79(0.48-1.28)	NR	32	8.2 v 4.0 months, 0.34(0.14-0.83)	13.2 vs 5.0 months, 0.51 (0.24-1.08)	NR
Anti-PDL1 + anti-CTLA4 + chemo	POSEIDON	Durvalumab +tremelimumab +chemo	Chemo	72	NR	11.7 vs 10.7 months, 0.80(0.48-1.38)	NR	28	NR	13.7 vs 8.7 months, 0.43 (0.16-1.25)	NR
Anti-PDL1 + anti-VEGF+ chemo	IMPOWER 150	Atezolizumab + bevacizumab + chemo	Chemo plus bevacizumab	97	5.6 vs 4.4 months, 0.68(0.43-1.07)	11.4 vs 11.7 months, 0.92 (0.59-1.44)	NR	83	5.5 vs 4.2 months, 0.58 (0.38-0.88)	12.1 vs 9.9 months, 0.71 (0.44-1.13)	NR

NR, not reported.

Keywords: mNSCLC, STK11, KEAP1

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.28 Nomogram and Effectiveness of Bone-Modifying Agents in Advanced Driver-Negative NSCLC: A Retrospective Real-World Study

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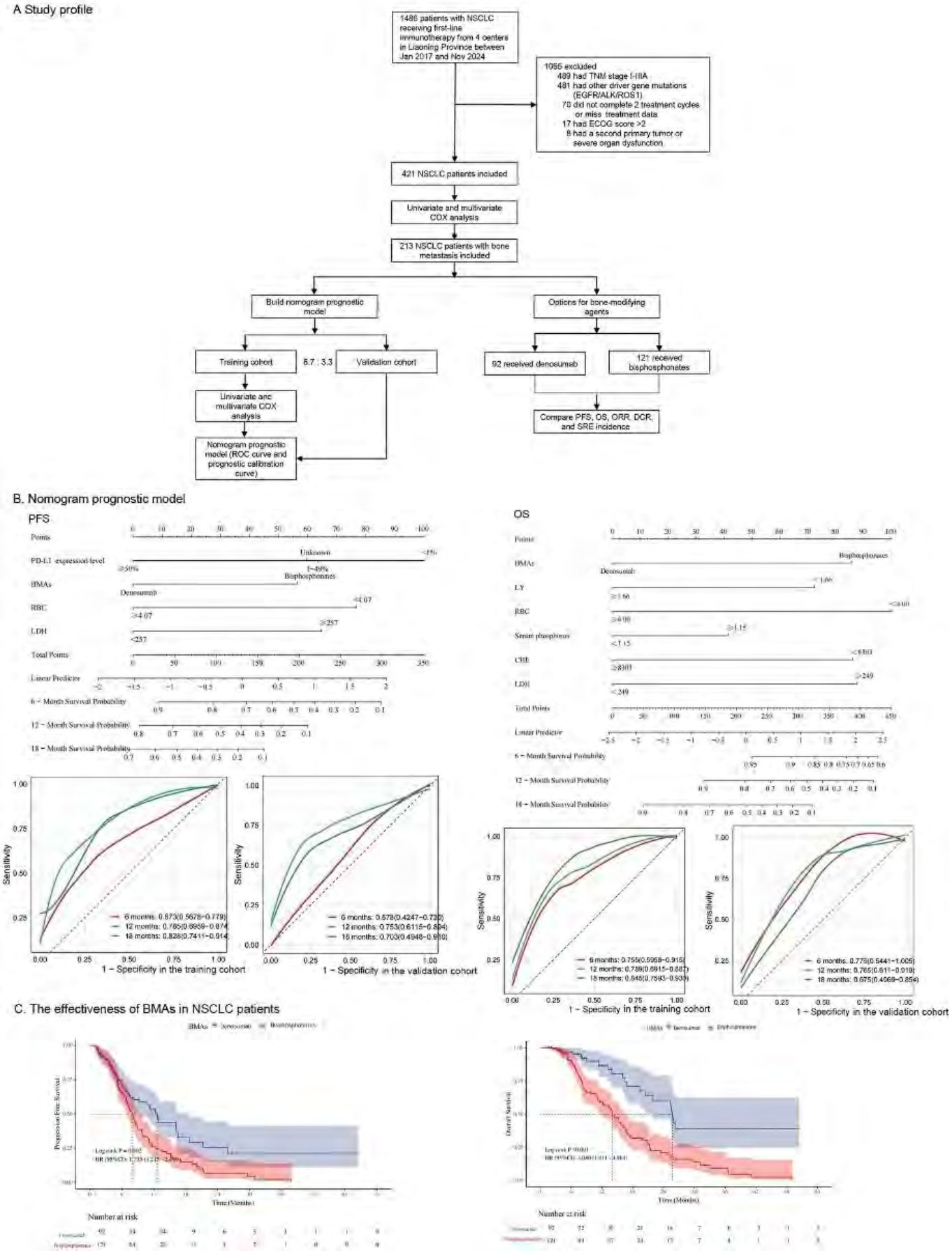
Introduction: This study aims to identify prognostic factors, integrate them into nomograms, and assess the effectiveness of bone-modifying agents (BMAs) in driver-negative NSCLC patients receiving first-line immunotherapy (IO) in real-world setting.

Methods: This retrospective multicenter study included 421 patients with histologically or cytologically confirmed advanced unresectable driver-negative NSCLC who received first-line IO from January 2017 to November 2024. Cox regression analysis was performed to identify independent prognostic factors. Nomograms were developed to predict survival outcomes in NSCLC patients with bone metastasis (BM; the ratio of training and validation cohorts was 6.7: 3.3); the effectiveness of BMAs (denosumab and bisphosphonates) was evaluated in this population.

Results: Among 421 patients with NSCLC, the median follow-up was 16.83 months (95% CI 15.27-18.57), and 213 developed BM; those with BM at baseline had worse survival than those without BM (PFS: 8.63 vs 22.87 months, HR=2.50, p<0.001; OS: 16.83 vs 58.83 months, HR=4.58, p<0.001). Both liver metastasis and BM were significantly independently associated with PFS and OS (all p<0.05). For 213 patients with BM, the nomogram demonstrated good predictive ability of survival; the area under the curve (AUC) in the training group of 6-, 12-, and 18-month PFS was 0.67 (95% CI, 0.57-0.78), 0.79 (95% CI, 0.70-0.87), and 0.83 (95% CI, 0.74-0.91), respectively; the AUC of 6-, 12-, and 18-month OS was 0.76 (95% CI, 0.60-0.92), 0.79 (95% CI, 0.69-0.89), and 0.85 (95% CI, 0.76-0.93), respectively. For patients receiving BMAs, balanced baseline characteristics were observed between the denosumab (n=92) and bisphosphonate (n=121) groups. Both PFS and OS were significantly longer in denosumab than the bisphosphonate groups (PFS: 12.60 vs 8.00 months, HR=1.74, p=0.002; OS: 25.73 vs 14.03 months, HR=3.08, p<0.001). Benefits of the median PFS and OS were observed across the subgroups (almost all p<0.05). No significant difference was observed in ORR and DCR (all p>0.05). A total of 17 of 213 (7.98%) patients experienced skeletal-related events (SREs; denosumab, n=6 [6.52%]; bisphosphonate, n=11 [9.09%]), with no significant difference in the incidence between the two groups. The median time from the start of BMA to SRE was not reached and 40.43 months (95% CI NE) in the denosumab and bisphosphonate groups, respectively (p>0.05).

Conclusions: This study identified the prognostic factors in advanced unresectable driver-negative NSCLC treated with IO and, in patients with BM, proposed a nomogram for estimating survival probabilities and assessed the efficacy of BMAs, offering insights to guide treatment decisions and improve outcomes.



Keywords: NSCLC, immunotherapy, bone metastasis

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.29 ICIs Plus Paclitaxel-Based Chemotherapy Is an Optional Treatment for Transformed SCLC After EGFR-TKI

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Introduction: Small cell lung cancer (SCLC) transformation is one of the acquired resistance mechanisms for epidermal growth factor tyrosin kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC) patients with EGFR sensitive mutations. Etoposide combined with platinum chemotherapy always plays as the first line treatment, while the subsequential line keeps vague.

Methods: Group A was set as aim group, and included patients with SCLC transformation after EGFR-TKI failure and following ICIs plus taxanes-based treatment. In order to analyze whether the addition of ICIs could prolong survival of patients with SCLC transformation, a control group (Group B) was established and included transformed patients who did not receive ICIs treatment after transformation. For the purpose of analyzing the efficacy and survival differences of taxanes-based chemotherapy plus ICIs between patients with and without transformation after EGFR-TKI resistance, we set another control group (Group C: including EGFR-mutant NSCLC patients who did not undergo transformation after EGFR-TKI treatment and received following taxanes-based chemotherapy plus ICIs).

Results: Forty-six patients were enrolled in this study (Group A: N=8; Group B: N=21; Group C: N=17). Seven of eight (7/8, 87.5%) patients in Group A received ICIs plus albumin paclitaxel-based regimens after conventional etoposide/platinum treatment. Patients in Group A tended to achieve a higher DCR than patients in Group B (100% vs 76.2%, p = 0.283), whereas ORRs in these two cohorts were similar (12.5% vs 14.3%, p = 1.000). No significant differences of PFS and OS from the initial diagnosis of advanced stage lung cancer (OS1) were observed between Group A and Group B (median PFS: 5.0 months vs 4.6 months, p = 0.932; median OS1: 54.3 months vs 34.1 months, p = 0.122). OS after transformation in Group A tended to be longer than that in Group B (median OS after transformation: 25.3 months vs 15.0 months, p = 0.055), especially for patients with mono-EGFR-TKI treatment (25.3 months vs 15.0 months, p = 0.010), or without chemotherapy (23.6 months vs 19.1 months, p = 0.045), or without antiangiogenic therapy (23.8 months vs 15.0 months, p = 0.061) before transformation. DCR (100.0% vs 94.1%, p = 1.000) and ORR (12.5% vs 5.9%, p = 1.000) were similar between Group A and Group C with the treatment of taxanes-based chemotherapy and ICIs. Comparable median PFS (5.0 months vs 6.4 months, p = 0.136), median OS1 (54.3 months vs 39.0 months, p = 0.235), and median OS from ICIs implementation (25.3 months vs not reached, p = 0.530) were observed between Group A and Group C.

Conclusions: In EGFR-mutant NSCLC patients with SCLC transformation after EGFR-TKI resistance, ICIs plus taxanes-based chemotherapy is an optional subsequential treatment regimen after conventional etoposide/platinum regimens

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.30 The Efficacy of Immunotherapyfor Patients With Advanced Lung Cancer and Oncogenic Driver Alterations

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Introduction: Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have become a cornerstone in the management of advanced non-small-cell lung cancer (NSCLC) without driver mutations. However, the therapeutic efficacy in NSCLC harboring oncogenic driver alterations remains inadequately clarified. This study aims to elucidate the clinical effectiveness of ICIs for advanced NSCLC with actionable mutations, providing critical insights into their role in genetically defined NSCLC subsets.

Methods: A retrospective analysis was conducted on patients with advanced NSCLC harboring oncogenic driver mutations who received ICIs at Shanghai Chest Hospital between June 2017 and May 2024. De-identified clinical data were analyzed to assess clinicopathologic characteristics, PD-L1 expression at the initiation of ICI therapy, and treatment outcomes, including best response (RECIST 1.1), progression-free survival (PFS), and overall survival (OS). The last follow-up visit occurred on October 15, 2024, with a median follow-up duration of 20.8 months. Additionally, RNA sequencing (RNA-seq) data from The Cancer Genome Atlas (TCGA) were analyzed to characterize the tumor immune microenvironment(TIME) in NSCLC, with a focus on analyzing TIME associated with various genetic alterations.

Results: A total of 407 patients with advanced NSCLC were retrospectively analyzed, harboring the following oncogenic driver mutations: KRAS (n=152), EGFR (n=146), BRAF (n=16), MET (n=28), HER2 (n=31), ALK (n=16), RET (n=13), and ROS1 (n=5). Of these, 146 patients (35.9%) received ICIs after progressing on prior TKI therapy, with the majority belonging to the EGFR subgroup (n=116, 28.5%). Meanwhile, 261 patients (64.1%) received ICIs as first-line therapy, predominantly in the KRAS subgroup (n=146, 35.9%). Across the entire cohort, the median PFS was 17.0 months, while median OS was not reached (NR) at the time of data cutoff. Mutation-specific median PFS was as follows: 31.3 months for BRAF, 31.5 months for RET, 28.3 months for KRAS, 22.2 months for MET, 16.2 months for HER2, 10.2 months for EGFR, and 6.4 months for ALK.Among EGFR-mutant tumors, median PFS differed by mutation subtype but without statistical significance (P=0.9058): 10.07 months for Exon 19 deletion, 9.40 months for Exon 21 L858R mutation, and 13.1 months for other rare EGFR mutations. PD-L1 expression levels did not significantly correlate with PFS in EGFR-mutant patients (P=0.1195). Among KRAS-mutant tumors, no significant difference in PFS was observed between KRAS G12C (n=56) and other rare KRAS mutations (n=96, P=0.6792). However, PD-L1 expression was significantly associated with prolonged PFS (P=0.0181), with PD-L1-positive patients (>=1%) exhibiting a median PFS of 29.4 months versus 15.5 months in PD-L1-negative cases.RNA-seq analysis from TCGA revealed upregulation of immune effector genes (CD8A, IFNG, CD274, GZMB, CXCL9) in KRAS- and BRAF-mutant tumors, whereas EGFR, ALK, RET, MET, and ROS1 alterations were associated with reduced expression. KRAS- and BRAF-mutant tumors also showed higher enrichment of antitumor pathways, particularly CD8+ T cell and immune checkpoint activation signatures. A meta-analysis of 13 studies confirmed the highest ORRs in KRAS- and BRAF-mutant tumors, aligning with our findings.

Conclusions: These findings underscore the differential response to ICIs based on oncogenic driver mutations, highlighting the importance of molecularly guided treatment strategies to optimize patient outcomes.

Keywords: NSCLC, immunetherapy, driver alterations

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.31 Dynamic Monitoring of Circulating Tumor Cells and Single-Cell Sequencing Predict Therapeutic Efficacy in Advanced Lung Cancer

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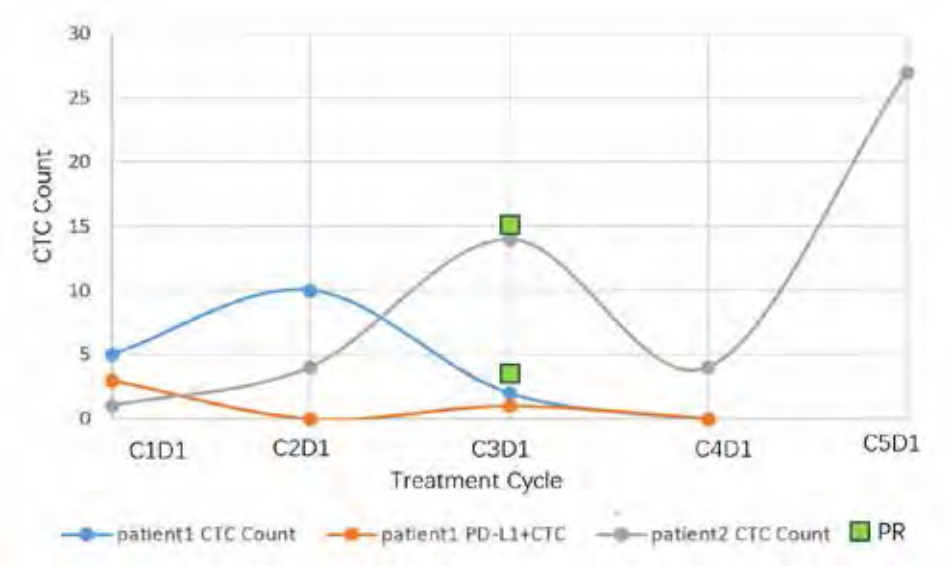
Introduction: Circulating tumor cells (CTCs), as an important biomarker in liquid biopsy, demonstrate the predictive role for prognosis. This study further investigated the clinical application scenarios of CTC dynamic monitoring, single-cell isolation, and next-generation sequencing (NGS) in lung cancer.

Methods: From November 2023 to December 2024, 53 patients with advanced lung cancer (30 NSCLC, 23 SCLC) were enrolled. CTC enumeration and PD-L1 expression were assessed using the CellSearch system at baseline (C1D1) and pre-treatment days of subsequent cycles (C2D1-C5D1). Patients with ≥10 CTCs underwent DEPArray-based single-cell isolation followed by whole-exome sequencing (WES).

Results: CTCs were detectable in 90% (27/30) of NSCLC patients(median count of 3, range from 0 to120). Among them, 33% (10/30) having ≥5 CTCs, and 60% (6/10) of these patients exhibited PD-L1+ CTCs. All SCLC patients exhibited baseline CTCs, with a median count of 38 (range from 1 to over 10,000). CTC clearance after two cycles showed an ORR of 80% (4/5) in NSCLC. In SCLC patients with CTC reduction (baseline ≥5 CTCs declining to <5) observed after one cycle (C2D1) showed response rate of 100% (7/7), significantly higher than 44.4% (4/9, p=0.034) in the non-reduction group. Besides the dynamic change of CTC, we observed that the combining of whole-exome sequencing could enhanced the predictive ability for the efficacy of chemotherapy and immunotherapy in 2 cases of advanced NSCLC(Figure 1).

Conclusions: Dynamics CTC testing could early predicte the efficacy of anti-cancer therapy in lung cancer. Besides, further single-cell NGS sequencing enhanced the predictive yields in NSCLC, large scale validating is ongoing in this field.



Keywords: Dynamic monitoring of CTC, Single-cell sequencing, Predictive biomarkers

P1.11.32 Quality of Life Outcomes from the Phase 3 Study of Atezolizumab + Bevacizumab and Chemotherapy (ATTLAS, KCSG-LU19-04) in EGFR/ALK- Mutated NSCLC

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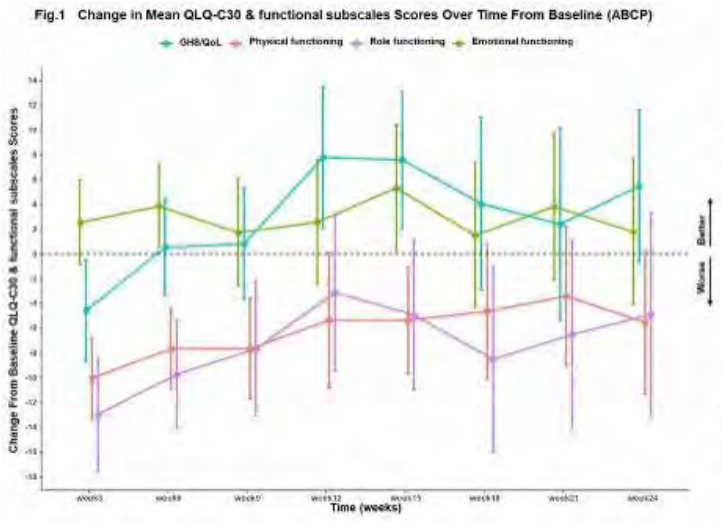
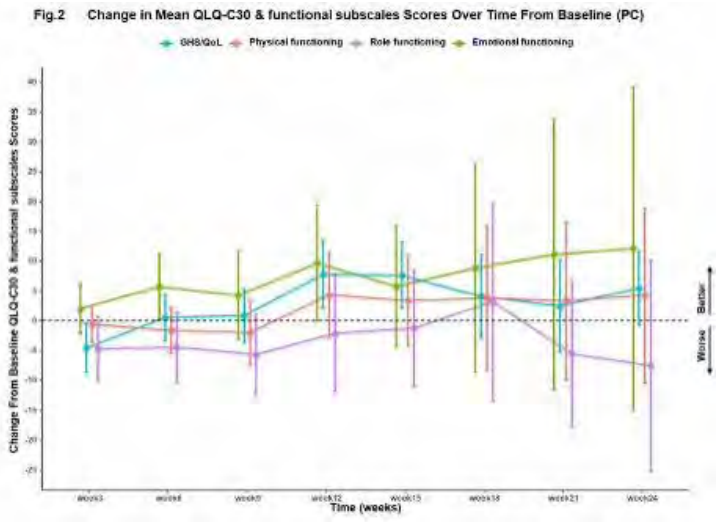
Introduction: In the phase 3 ATTLAS study, the combination of atezolizumab with bevacizumab, paclitaxel, and carboplatin (ABCP), followed by maintenance therapy with atezolizumab plus bevacizumab, demonstrated longer progression-free survival and no new safety concerns compared to pemetrexed plus carboplatin or cisplatin (PC), followed by pemetrexed maintenance, in EGFR- or ALK-mutated NSCLC following tyrosine kinase inhibitor (TKI) failure. Here, we report patient-reported quality of life (QoL) outcomes from this trial.

Methods: Patients received intravenous treatment every 3 weeks until disease progression or loss of clinical benefit. The ABCP regimen consisted of atezolizumab (1,200 mg), bevacizumab (15 mg/kg), paclitaxel (175 mg/m^2), and carboplatin (AUC 5 or 5.5). The PC arm included pemetrexed (500 mg/m^2) with either carboplatin (AUC 5.0) or cisplatin (70 mg/m^2). Health-related QoL was assessed at each cycle using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Key endpoints included changes in global health status/QoL (GHS/QoL) from baseline to weeks 9 and 24, and the median time to deterioration (TTD), defined as a ≥10-point decline in GHS/QoL.

Results: Of 228 patients randomized (2:1), 146 in the ABCP arm and 68 in the PC arm completed at least one QoL assessment. Baseline GHS/QoL scores were similar across arms. The ABCP group showed a slightly greater early decline in GHS and physical functioning scores, but both arms demonstrated trends toward improvement by week 24. Differences in the least squares (LS) mean scores were not statistically significant (Week 9: −4.66 [95% CI, −12.57 to 3.26], P = 0.247; Week 24: −7.39 [−21.72 to 6.94], P = 0.305). QLQ-LC13 results showed more neuropathy, alopecia, and pain in the ABCP arm, suggesting greater treatment-related toxicity. However, cancer-related symptoms (e.g., coughing, hemoptysis, dyspnea) improved more in the ABCP group. Median TTD for GHS/QoL did not differ significantly between arms (P = 0.160).

Conclusions: Despite toxicity-related functional impairment in the ABCP group, overall QoL was not significantly worse compared to the PC group. Improvements in cancer-related symptoms and stable GHS/QoL suggest that ABCP treatment may help maintain QoL while offering survival benefits with appropriate toxicity management.





Keywords: Quality of Life, Non-small Cell Lung Cancer, Atezolizumab Bevacizumab

P1.11.33 The Role of Rhamnose Derived From Gut Microbiome in Modulating the Efficacy of Non-Small Cell Lung Cancer Immunotherapy

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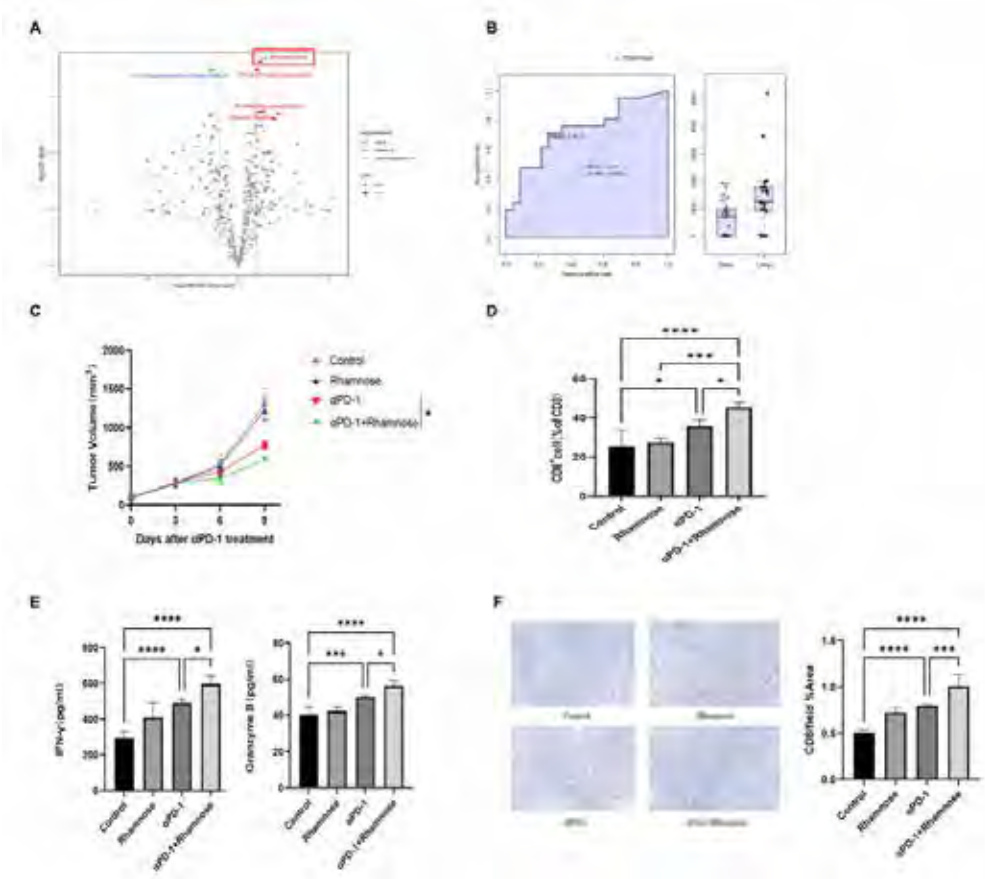
Introduction: In recent years, the relationship between gut microbiota and metabolites and immunotherapy for non-small cell lung cancer (NSCLC) has gradually become a research hotspot. Rhamnose is a monosaccharide that can be secreted by the gut microbiome and has certain potential in regulating immune responses. The mechanism by which Rhamnose regulates the efficacy of immunotherapy for NSCLC is not yet clear. The aim of this study is to explore the mechanism by which gut microbiome metabolite rhamnose regulates the efficacy of immunotherapy for non-small cell lung cancer, providing new ideas for improving the efficacy of immunotherapy for non-small cell lung cancer.

Methods: According to the progression free survival (PFS) of NSCLC patients after immunotherapy, they were divided into a response group (PFS>6 months, R group) and a non-response group (PFS ≤ 6 months, NR group). Baseline fecal samples were collected from patients for non-targeted metabolomics sequencing to screen for rhamnose. Using a mouse lung cancer model, mice were divided into a control group, a rhamnose group, an anti-PD-1 treatment group, and a combination therapy group (rhamnose +anti-PD-1). Observe the changes in tumor volume in different groups of mice. Flow cytometry and immunohistochemical were used to detect changes in tumor infiltrating CD8+T cells in different groups of mice. ELISA was used to detect the expression levels of IFN - γ and Granzyme B in the plasma of different groups of mice.

Results: Non-targeted metabolomics sequencing found that compared with the NR group, the R group had significantly increased levels of rhamnose. In vivo studies on mice showed that compared to the anti-PD-1 monotherapy group, the combination treatment group showed a significant slowdown in tumor volume growth. The results of flow cytometry and immunohistochemical showed that compared with the anti-PD-1 monotherapy group, the infiltration of CD8+T cells in tumor tissues increased in the combination treatment group. According to the ELISA results, the proportion of IFN - γ and Granzyme B in peripheral blood of the combined treatment group also increased, indicating the regulatory effect of rhamnose on systemic immune response.

Conclusions: The efficacy of NSCLC immunotherapy may be related to gut microbiome metabolite rhamnose. Rhamnose enhances the function of CD8+T cells by increasing tumor infiltration and raising the levels of cytokine IFN-γ and Granzyme B.



Keywords: Gut Microbiome, Rhamnose, Immunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.34 First-Line Camrelizumab Plus Chemotherapy in 3004 Patients With Advanced Non-Squamous NSCLC: A Nationwide Retrospective Study

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Introduction: Camrelizumab plus chemotherapy has been approved for the fist-line treatment of advanced non-squamous non-small cell lung cancer (NSCLC) based on the success of the phase 3 CameL study. Recently, the 5-year results from CameL were published. However, long-term outcomes reflecting the effect of this combination strategy in real-world population are warranted.

Methods: This was a nationwide, retrospective observational study of patients with advanced non-squamous NSCLC treated with first-line camrelizumab plus chemotherapy, conducted in China. Baseline characteristics, treatment information, overall survival (OS), and adverse events were reviewed, with indirect descriptive comparisons to CameL.

Results: Between February 28, 2019 and December 29, 2022, a total of 3004 patients from 236 sites initiated treatment. Compared with CameL, the patients in this study were older (median: 65 years vs 59 years; ≥65 years: 51.0% vs. 22.0%). Of these patients, 7.7% of them had an Eastern Cooperative Oncology Group performance status ≥2, while these patients were excluded from CameL. Due to poor tolerance, 5.0% of patients received camrelizumab plus single-agent chemotherapy in this study, while all patients received camrelizumab plus platinum-based doublet chemotherapy in CameL. As of March 5, 2025, the median OS was 25.9 months (95% CI, 24.8-26.8) in 3004 patients, with a median follow-up duration of 25.6 months. In CameL, the median OS was 27.1 months (95% CI, 21.9-31.5) after 5-year results were updated. Of 1002 patients with available safety data in this study, the incidence of any-grade treatment-emergent adverse events (TEAEs) was 78.8%, and 15.7% of patients had grade ≥3 TEAEs.

Conclusions: In real-world setting, more elderly and vulnerable patients received camrelizumab plus chemotherapy. Even under this circumstance, the OS benefit in this study was similar with that in CameL. These large-scale data supported the application of this combination strategy for a broader population in clinical practice. The study is ongoing to enroll more patients and extend follow-up, and 3- to 5-year real-world OS rates will be reported in the future.

Keywords: non-small cell lung cancer, camrelizumab, real-world data

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.35 RATIONALE-303: Long-Term Outcomes With Tislelizumab in Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer

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Introduction: In the final analysis of RATIONALE-303 (NCT03358875), patients with locally advanced or metastatic squamous or non-squamous non-small cell lung cancer (NSCLC) who progressed after platinum-based chemotherapy experienced significantly improved overall survival (OS) with tislelizumab (an anti-programmed cell death protein-1 antibody) vs docetaxel. RATIONALE-303 met its dual primary endpoints of OS in the intent-to-treat (ITT) population and OS in patients with tumour cell programmed death-ligand 1 (PD-L1) expression of ≥25%. We present long-term efficacy outcomes with an additional 30-month follow-up since the final analysis.

Methods: RATIONALE-303 was a global, open-label, randomised, multicentre, phase 3 trial. Patients aged ≥18 years with histologically confirmed, locally advanced or metastatic (squamous or non-squamous) NSCLC who progressed on prior platinum-based chemotherapy were randomised (2:1) to receive intravenous tislelizumab 200 mg or docetaxel 75 mg/m2 every 3 weeks. Co-primary endpoints were OS in the ITT population and PD-L1 ≥25% populations. Secondary endpoints were investigator-assessed progression-free survival (PFSINV), objective response rate (ORRINV), duration of response (DoRINV), and safety.

Results: As of January 18, 2024, median follow-up for OS was 46.5 and 46.7 months for tislelizumab and 41.0 and 41.6 months for docetaxel in the ITT (tislelizumab, n=535; docetaxel, n=270) and PD-L1 ≥25% (tislelizumab, n=227; docetaxel, n=115) populations, respectively (by reverse Kaplan-Meier method). Tislelizumab-treated patients experienced sustained clinical benefit vs docetaxel (Table). Respective median OS was 16.9 vs 11.9 months (stratified HR=0.67; 95% CI: 0.57, 0.80; P<.0001) in the ITT population and 19.3 vs 11.5 months (stratified HR=0.52; 95% CI: 0.40, 0.68; P<.0001) in patients with PD-L1 ≥25%. In the ITT population, median PFSINV was significantly higher with tislelizumab vs docetaxel (4.2 vs 2.6 months [HR=0.64; 95% CI: 0.54, 0.76; P<.0001]); ORRINV (22.6% vs 7.8%) and median DoRINV (13.5 vs 6.1 months) were also higher with tislelizumab vs docetaxel. Tislelizumab-treated patients experienced a lower incidence of grade ≥3 treatment-emergent adverse events (43.6% vs 74.8%) and treatment-related grade ≥3 events (16.1% vs 66.3%) vs docetaxel-treated patients. No new safety signals were identified.

Conclusions: After an additional 30 months' follow-up since the final analysis, previously treated patients with advanced or metastatic NSCLC in the ITT and PD-L1 ≥25% populations of RATIONALE-303 continued to experience a clinically meaningful improvement in OS with tislelizumab vs docetaxel. Tislelizumab-treated patients also had higher response rates, more durable responses, delayed disease progression, and a favourable safety profile compared with docetaxel. These results further support tislelizumab as a treatment option for this patient population.

Table. Efficacy Outcomes in the RATIONALE-303 Trial

	ITT Population		PD-L1 ≥25% Population	
	Tislelizumab (n=535)	Docetaxel (n=270)	Tislelizumab (n=227)	Docetaxel (n=115)
Median OS, months (95% CI)	16.9 (15.2, 19.1)	11.9 (9.6, 13.5)	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)
Stratified HR (95% CI)	0.67[a] (0.57, 0.80)		0.52[b] (0.40, 0.68)	
P value	<.0001[a,c]		<.0001[b,c]	
12-month OS rate, % (95% CI)	62.1 (57.9, 66.1)	49.7 (43.5, 55.7)	67.4 (60.8, 73.1)	48.3 (38.5, 57.4)
24-month OS rate, % (95% CI)	37.3 (33.2, 41.5)	23.9 (18.8, 29.3)	42.7 (36.1, 49.1)	22.4 (15.0, 30.8)
36-month OS rate, % (95% CI)	26.0 (22.3, 29.9)	14.7 (10.6, 19.4)	32.5 (26.4, 38.7)	14.3 (8.3, 21.8)
48-month OS rate, % (95% CI)	20.1 (16.5, 23.9)	11.1 (7.5, 15.6)	26.1 (20.3, 32.2)	9.9 (5.0, 16.8)
60-month OS rate, % (95% CI)	20.1 (16.5, 23.9)	NE (NE, NE)	26.1 (20.3, 32.2)	NE (NE, NE)
Median PFS_{INV}, months (95% CI)	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)	NR	NR
Stratified HR (95% CI)	0.64[a] (0.54, 0.76)		NR	
P value	<.0001[a,c]			
ORR_{INV}, n (%)	121 (22.6)	21 (7.8)	85 (37.4)	9 (7.8)
Median DoR_{INV}, months (95% CI)	13.5 (8.5, 19.4)	6.1 (2.3, 7.2)	NR	NR

Data cutoff: January 18, 2024.
[a]Stratified by histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥25% TC vs <25% TC). [b]Stratified by histology (squamous vs non-squamous) and lines of therapy (second vs third). [c]One-sided stratified log-rank test *P* value.
Abbreviations: CI, confidence interval; DoR_{INV}, investigator-assessed duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; NR, not reported; PD-L1, programmed death-ligand 1; PFS_{INV}, investigator-assessed progression-free survival; TC, tumour cell.

Keywords: NSCLC, RATIONALE-303, tislelizumab

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.36 Strengthening Real World Evidence Generation Through an Expanding Multicenter Canadian Lung Cancer Registry

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Introduction: Real-world evidence (RWE) is increasingly recognized as a vital complement to randomized clinical trials in guiding regulatory and reimbursement decisions. The Food and Drug Administration of the United States (FDA), Health Canada, the European Medicines Agency (EMA) and other regulatory agencies encourage integration of RWE into submissions for new therapeutic indications as well as funding recommendations. The Pan-Canadian Lung Cancer Observational Study (PALEOS) and the Pulse Infoframe Lung Cancer Registry aim to generate critical RWE to meet the needs of regulatory review.

Methods: PALEOS is a multicenter observational registry study being conducted at several Canadian centres collecting both retrospective and prospective real-word data (RWD) on non-small cell lung cancer (NSCLC), following receipt of appropriate ethics and institutional approvals (NCT04706754). The registry captures close to 500 data elements including clinical and demographic variables, diagnostic and molecular profiles, treatment pathways, healthcare utilization patterns and patient reported outcomes (EQ-5D-5L, FACT-L) using both retrospective and prospective methods. Currently, the six initial PALEOS sites centres provide healthcare services to some of the most populous regions in the country and represent a catchment of about thirty percent of the Canadian population, including a mix of urban and rural populations. PALEOS is in the process of engaging additional centers in Canada and internationally for expansion in 2025.

Results: Following activation at the first site in 2019, this lung cancer registry has grown to 2,225 patients as of April 2025. Current registry demographics at first presentation to the cancer centre are: median age at diagnosis of 69 years (range 22-96; n=1684); 48.2% female; and 19.2% stage I, 8.2% stage II, 17.9% stage III, and 58.0% stage IV (n=1381). PD-L1 staining was 29.0%, 31.3% and 39.7% for <1%, 1-49% and ≥50% staining categories, receptively (n=1005). First-line metastatic treatment involving immunotherapy was received by 44.2% of patients (23.1% chemoimmunotherapy, 21.1%, PD-L1 monotherapy), and a further 37.6% received chemotherapy, and 18.2% targeted therapy (n=968). Median follow-up was 18 months for stage I-III patients (range 0-182 months) and 7.6 months (range 0-196 months) for stage IV patients. Median overall survival for stages I, II, III, IV were 46.1, 33.0, 16.4, and 9.7 months, respectively.

Conclusions: PALEOS establishes a robust framework to examine the natural progression, diagnostic and therapeutic approaches, treatment outcomes, and patient reported outcomes in the varied subsets of patients with lung cancer in Canada. It aims to deepen insights into the ways that novel diagnostic tools and treatments inform real-world clinical practice. The project supports the translation of evidence into clinical practice and strengthens data-driven decision-making in multidisciplinary lung cancer care. Moreover, this RWD is collected in a structured registry platform enabled to support regulatory and funding decisions.

Keywords: Lung Cancer, Registry, Real-World Data

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.37 Impact of Immunotherapy on Overall Survival in Advanced Non-Small Cell Lung Cancer: A Real-World Evidence Analysis

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Introduction: Immunotherapy has revolutionized the treatment landscape for advanced non-small cell lung cancer (NSCLC). Since the European Medicines Agency's first approval in 2016, immunotherapy use has extended across all lung cancer histologies and stages. This retrospective analysis from the Spanish Lung Cancer Group's Thoracic Tumor Registry assesses first-line immunotherapy impact on real-world advanced NSCLC patients.

Methods: We analyzed 6,483 patients with advanced NSCLC: 2,803 (43.2%) received immunotherapy and 3,680 (56.8%) did not. We assessed immunotherapy's impact on overall survival (OS) and progression-free survival (PFS), and established correlations between response parameters and long-term survival. We also analyzed clinical characteristics associated with immunotherapy benefit. Kaplan-Meier curves were used for survival analyses with hazard ratios (HRs) derived from Cox proportional hazards models. Statistical significance was set at $p<0.05$.

Results: Baseline characteristics were well-balanced between groups, with predominantly male patients (75.3%), median age of 64 years, and >90% current/former smokers. Most patients had ECOG Performance Status 0-1. Immunotherapy significantly improved OS compared to chemotherapy alone (median OS: 16.3 vs. 10.1 months; HR 0.69, 95% CI 0.64-0.73; $p<0.001$). The 12-month OS rates were 60.7% vs. 43.5%, and 24-month OS rates were 36.3% vs. 23.7% in immunotherapy and control groups, respectively. For PFS, immunotherapy showed modest improvement (median PFS: 9.1 vs. 7.4 months; HR 0.94, 95% CI 0.88-1.00; $p=0.053$). Univariate analysis identified factors associated with OS. Poor prognostic factors in both groups included ECOG PS >1, bone metastases, liver metastases, multiple metastatic sites (>3), and more than three comorbidities. Gender and age were associated with prognosis in the chemotherapy arm but not in the immunotherapy arm. Treatment response strongly predicted survival, with complete response being associated with the most favorable outcomes in both groups.

Conclusions: This real-world analysis confirms that immunotherapy provides significant survival benefits for patients with advanced NSCLC compared to chemotherapy alone. The substantial improvement in median OS demonstrates clinically meaningful benefits of immunotherapy, and treatment response strongly predicts survival.

Keywords: Thoracic Tumor Registry (TTR), Spanish Lung Cancer Group, Real-World Evidence

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.38 Measuring the Effect of Age and Ethnicity on Outcomes in Patients With Advanced Lung Cancer Treated With Immunotherapy: A New Zealand Analysis

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Introduction: Regimens including immunotherapy are the standard first line option for advanced non small cell lung cancer. Pembrolizumab became publicly funded for this indication in New Zealand on 1 April 2023. We investigated the effect of ageing, ethnicity, and other factors on outcome in the New Zealand population.

Methods: This multicentre retrospective cohort study included all patients treated for advanced lung cancer with publicly funded pembrolizumab +/- chemotherapy in part of New Zealand from 1 April 2023 - 31 March 2024. Follow up ended at 1 October 2024. The primary endpoint was time to treatment failure (TTTF). Overall survival was a secondary endpoint.

Results: 125 patients were included with a median age of 68 years (range 48-85). 51 (41%) of patients were New Zealand Māori. The median TTTF was 12.8 months (95% Confidence Interval [CI] = 10.2 to 15.2). Using multivariate analysis, the risk factors for TTTF were age <70 years HR 2.13 (95% CI 1.18 to 3.85, p=.013), non-Māori ethnicity HR 1.78 (95% CI 1.05 to 3.00, p=.031), ECOG 2+ HR 3.08 (95% CI 1.31 to 7.23, p=.010) and high Charlson Comorbidity Index HR 2.67 (95% CI 1.12 to 6.38, p=.027). The risk factors for death were non-Māori ethnicity HR 2.68 (95% CI 1.24 to 5.78, p=.012), ECOG 2+ HR 7.58 (95% CI 2.12 to 27.1, p=.002) and immunotherapy monotherapy HR 2.59 (95% CI 1.33 to 5.06, p=.005). Patients >70 years had no difference in probability of death (p=0.224).

Conclusions: In this cohort of patients, when adjusting for multiple confounders, the duration of treatment was longer for older patients. However, age had no significant influence on survival. Māori patients had a longer duration of treatment and were less likely to die than non-Māori patients. Poor performance status was the greatest overall predictor of death. These results contribute to a growing body of evidence that advancing age has limited influence on overall outcome in patients treated with immunotherapy. That Māori patients had increased survival is encouraging, given this group typically has poorer health outcomes than non-Māori.

Keywords: immunotherapy, age, ethnicity

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.39 The BLIP Score: A Tool for Non-Small Cell Lung Cancer Patients With Brain Metastasesy

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Introduction: Lung cancer is the leading cause of cancer-related mortality, with brain metastases (BMs) worsening prognosis and quality of life. Immune checkpoint inhibitors (ICIs) have transformed the treatment of non-small cell lung cancer (NSCLC), but precise prognostic tools are needed to optimize decision-making.

Methods: The Brain-Lung Immunotherapy Prognostic (BLIP) score was developed using a retrospective cohort of NSCLC patients treated with ICIs at Karolinska University Hospital, Sweden. Prognostic factors were identified through univariate and multivariate Cox regression analyses. Internal validation utilized bootstrap resampling, penalized Cox regression, k-fold cross-validation, and receiver operating characteristics (ROC) analysis. External validation was conducted using an independent cohort from Sotiria Thoracic Diseases Hospital of Athens, Greece.

Results: Among 1844 patients screened, 152 from Karolinska University Hospital and 116 from Sotiria Thoracic Diseases Hospital were included. Key prognostic factors included histology, actionable mutations, age at BM diagnosis, and number of BMs. The BLIP score stratified patients into two prognostic groups: “Good” and “Poor,” with median overall survival (OS) of 15 and 7 months, respectively (hazard ratio [HR]: 0.4; $p < 0.0001$). External validation confirmed these findings, with a significantly lower risk of death for the “Good” group (HR: 0.49; $p = 0.0063$). The model showed robust performance (area under the ROC curve: 0.87).

Conclusions: The BLIP score is a validated prognostic tool for NSCLC patients with BMs receiving ICIs. Incorporating clinical and molecular factors, it improves existing models and supports personalized treatment strategies.

Keywords: brain metastases, prognostic score, personalized cancer therapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.40 The Hidden Impact of Creatinine Clearance Estimation Method on Pemetrexed-Based Chemoimmunotherapy in NSCLC With Low PD-L1 Expression

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Introduction: Pemetrexed-based chemoimmunotherapy (CI) represents a standard regimen for treating advanced non-squamous non-small cell lung cancer (NSCLC). However, its use necessitates caution in individuals with impaired renal function. This study investigated how different methodologies for evaluating renal function influence clinical outcomes in patients with NSCLC exhibiting low programmed death-ligand 1 (PD-L1) expression.

Methods: A total of 352 patients treated between May 2018 and June 2023 were analyzed. Renal function was assessed by both enzymatic and Jaffe methods, and patients were categorized into three groups: Cohort A (Ccr > 50 mL/min by both methods), Cohort B (Ccr > 50 by enzymatic but ≤ 50 by Jaffe), and Cohort C (Ccr ≤ 50 by both methods). Progression-free survival (PFS) was compared between PEM-based and non-PEM-based CI groups before and after propensity score matching (PSM), adjusting for age, ECOG PS, histology, and driver mutation status.

Results: In the overall cohort, PEM-based CI was associated with significantly longer PFS than non-PEM-based CI (median 8.9 vs. 6.9 months, p = 0.003). However, in subgroup analyses, this benefit was clearly observed only in Cohort A (9.4 vs. 7.4 months, p = 0.011). In Cohort B (n = 59), where renal function appeared adequate enzymatically but impaired by the Jaffe method, no significant difference in PFS was observed between treatment groups (6.9 vs. 6.3 months, p = 0.268). Similarly, in Cohort C (n = 29), PFS did not significantly differ between groups (13.8 vs. 6.4 months, p = 0.158), though the sample size was limited. These findings suggest that PEM-based regimens may offer limited benefit in patients with marginal or impaired renal function not detectable by enzymatic assessment alone. After PSM, 178 patients (89 per group) were matched. In the matched cohort, PEM-based CI was associated with slightly longer PFS (8.5 vs. 7.0 months, p = 0.049). In matched Cohort A (n = 132), a similar trend toward improved PFS was seen (8.9 vs. 7.4 months, p = 0.085). In matched Cohorts B and C, the differences in PFS remained non-significant.

Conclusions: These results highlight the clinical relevance of dual-method renal function assessment using both enzymatic and Jaffe techniques. Accurate evaluation is essential for guiding therapeutic decisions and improving treatment efficacy in NSCLC patients with low PD-L1 expression.

Keywords: creatinine clearance, pemetrexed, chemoimmunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.41 Intrapleural Dual Blockade of IL-6 and PD-L1 Reprograms CAF Dynamics and the Tumor Microenvironment in Malignant Pleural Effusion

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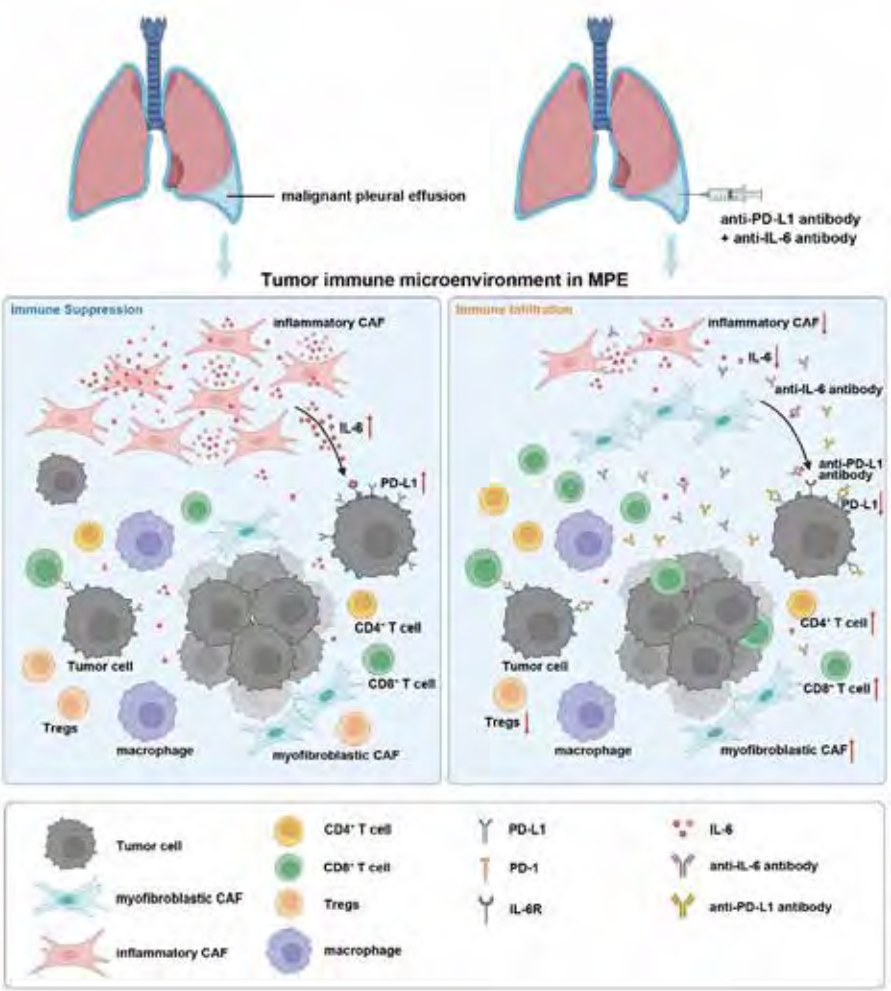
Introduction: Malignant pleural effusion (MPE) is a severe complication in lung cancer, characterized by an immunosuppressive tumor microenvironment (TME) and limited therapeutic options. This study investigates the role of IL-6 in regulating immune suppression and tumor progression in MPE and evaluates the efficacy of dual IL-6 and PD-L1 blockade.

Methods: IL-6 levels were measured in MPE and paired serum samples from lung cancer patients, and correlations with PD-L1 expression and clinical outcomes were analyzed using publicly available datasets. RNA sequencing and immune deconvolution were used to assess immune cell infiltration. CAFs and immune cell infiltration were further evaluated using flow cytometry, immunohistochemistry, and multiplex immunofluorescence. In vitro co-culture systems were employed to simulate the MPE microenvironment and explore IL-6 interactions with CAFs, as well as its regulatory effect on tumor cell PD-L1 expression.

Results: IL-6 levels were significantly elevated in MPE compared to paired serum and correlated with higher PD-L1 expression and poor survival outcomes in lung cancer patients. In the MPE mouse model, combination therapy with IL-6 and PD-L1 blockade reduced MPE volume, tumor burden, and PD-L1 expression, while enhancing T cell infiltration and alleviating TME immunosuppression. IL-6 was found to drive a positive feedback loop with iCAFs, promoting an immunosuppressive environment. In vitro, IL-6 from the MPE upregulated tumor cell PD-L1 expression the IL-6/STAT3 pathway.

Conclusions: This study identifies IL-6 as a critical contributor of immune suppression and tumor progression in MPE. The combination of IL-6 and PD-L1 blockade effectively alleviated immunosuppression and reduced tumor burden, offering a potential therapeutic approach for MPE management.



Keywords: Malignant pleural effusion, IL-6, PD-L1

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.42 Dual Immune Checkpoint Blockade With CTLA-4 and PD-(L)1 Inhibitors in NSCLC: A Reconstructed Patient Data Meta-Analysis

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Introduction: immune checkpoint inhibitors (ICIs) targeting PD-1 or PD-L1, either as monotherapy or in combination with CTLA-4 inhibitors and/or chemotherapy, are the standard of care for patients with advanced non-small cell lung cancer (NSCLC). However, it remains unclear whether dual checkpoint blockade with CTLA-4 and PD-(L)1 inhibitors offers similar efficacy to single PD-(L)1 inhibition or if these approaches yield different outcomes across NSCLC subpopulations.

Methods: We conducted a systematic review and reconstructed individual patient data (IPD) meta-analysis of trials evaluating dual or single immune checkpoint blockade in patients with NSCLC, focusing on studies reporting 5-year survival outcomes or biomarker analyses based on KRAS and/or STK11 mutational status. IPD were extracted and reconstructed by published Kaplan-Meier graphs with respective number at risk at each timepoint using WebPlotDigitizer v5 and the IPDfromKM method, as previously validated.

Results: In total, 6 randomized clinical trials were included in the analyses. Among 2,881 patients with advanced NSCLC, patients who received dual CTLA-4 and PD-(L)1 blockade (n=1,282) achieved similar median OS compared to those who received single PD-(L)1 inhibition (n=1,599) (16.1 versus 16.9 months; HR 0.95, 95% CI, 0.87-1.03, P=0.19), with 3-year OS rates of 29.2% versus 27.0%, respectively, and 5-year OS rates of 19.8% versus 16.3%, respectively. However, among patients with PD-L1 tumor proportion score (TPS) <1%, those who received dual CTLA-4 and PD-(L)1 blockade (n=447), compared to those who received single PD-(L)1 inhibition (n=512), achieved significantly longer median OS (15.5 versus 14.5 months; HR 0.85, 95% CI, 0.74-0.98, P=0.02), with 3-year OS rates of 26.8% versus 18.7%, respectively, and 5-year OS rates of 16.6% versus 9.3%, respectively. Similarly, in patients with NSCLC harboring STK11 mutations, dual CTLA-4 and PD-(L)1 blockade led to significantly longer median OS compared to single PD-(L)1 inhibition (13.9 versus 7.8 months; HR 0.67, 95% CI, 0.49-0.91, P=0.01), with 2-year OS rates of 30.9% versus 22.7%, respectively, and 5-year OS rates of 28.4% versus 13.4%, respectively. No differences in OS between dual CTLA-4 and PD-(L)1 blockade and single PD-(L)1 inhibition were noted among patients with PD-L1 TPS ≥1% (16.5 versus 18.1 months; HR 0.97, 95% CI, 0.88-1.08, P=0.60), TPS 1-49% (15.5 versus 17.3 months; HR 1.02, 95% CI, 0.87-1.20, P=0.77), or TPS ≥50% (19.4 versus 20.3 months; HR 0.96, 95% CI, 0.82-1.12, P=0.62), or based on histology (squamous: 13.6 versus 14.3 months; HR 1.01, 95% CI, 0.88-1.16, P=0.86; non-squamous: 18.3 versus 19.1 months; HR 0.93, 95% CI, 0.84-1.03, P=0.17), KRAS mutational status (KRAS mutated: 20.0 versus 14.8 months; HR 0.84, 95% CI, 0.64-1.10, P=0.20; KRAS wild-type: 16.7 versus 19.9 months; HR 1.10, 95% CI, 0.92-1.31, P=0.29), and in STK11 wild-type tumors (17.4 versus 20.4 months; HR 1.04, 95% CI, 0.87-1.26, P=0.65).

Conclusions: Dual immune checkpoint blockade with CTLA-4 and PD-(L)1 inhibitors, compared to single PD-(L)1 inhibition, is associated with improved OS in patients with advanced NSCLC with PD-L1 TPS <1% and in those harboring STK11 mutations.

Keywords: CTLA-4, immunotherapy, STK11

P1.11.43 Analysis of Characteristics and Predictive Factors for Long-Term Benefit of Immunotherapy in Advanced NSCLC

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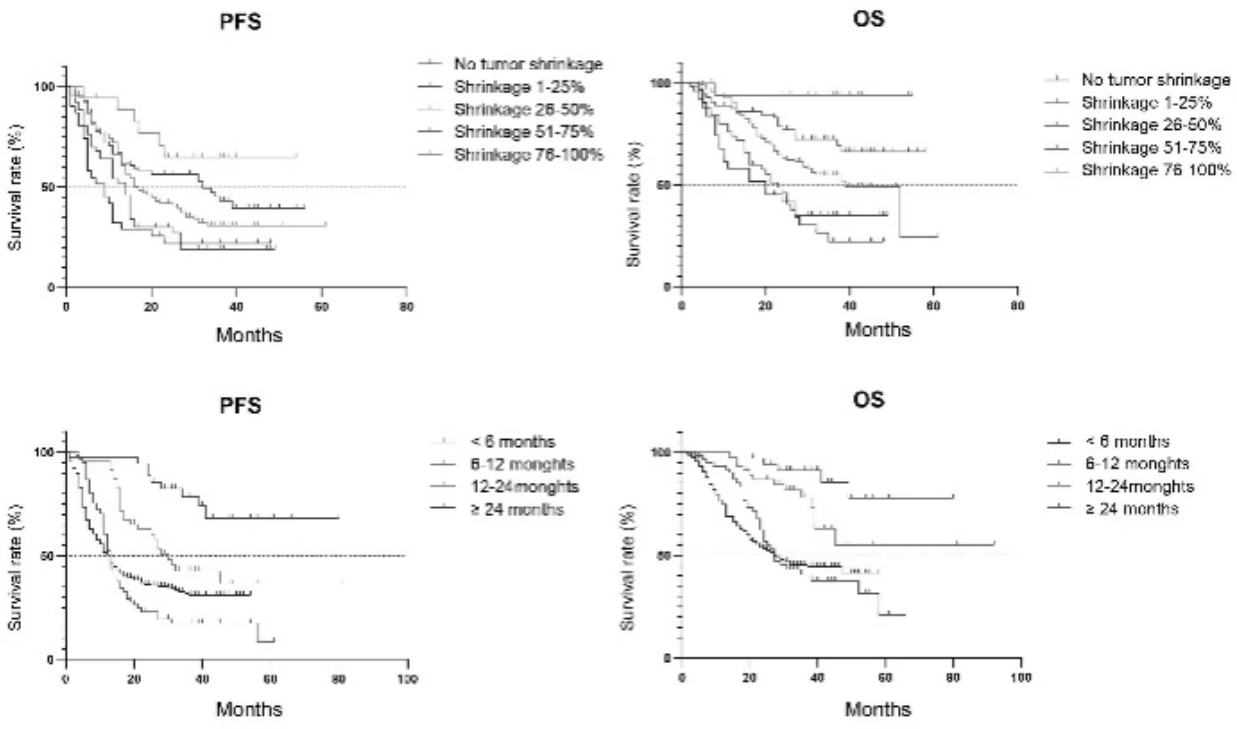
Introduction: Currently, there is a lack of sufficient evidence - based medical evidence regarding the commonalities among the population with long - term benefits from immunotherapy and the predictive factors for efficacy. This study aims to explore the clinical characteristics of patients with advanced non - small cell lung cancer (NSCLC) who show a long - term response to immune checkpoint inhibitors (ICIs) treatment.

Methods: This study retrospectively analyzed 372 patients with advanced NSCLC who received first - line ICIs treatment in our hospital. The patients were divided into two groups according to whether their progression - free survival (PFS) reached 24 months. COX regression analysis was used to evaluate the effects of different depths of response (DepOR) and treatment duration on the patients' survival.

Results: During a median follow-up of 36 months, the median OS for patients with PFS ≥ 24 months has not yet been reached, while the median OS for patients with PFS < 24 months was 19 months. The median PFS for the two groups was not reached and 9 months, respectively. According to the maximum percentage reduction of target lesions compared with the baseline, the median DepOR of the group with PFS ≥ 24 months was significantly better than that of the group with PFS < 24 months (48% vs. 34%, P < 0.001). The PFS and overall survival (OS) of the groups with tumor shrinkage of 26% - 50%, 51% - 75%, and 76% - 100% were significantly better than those of the no tumor shrinkage group. The hazard ratios (HR) for PFS were 0.525, 0.475, and 0.265 respectively; the HR for OS were 0.380, 0.270, and 0.048 respectively. The median time for the tumor to shrink to the maximum extent was 18.4 weeks. Compared with the group with treatment duration < 6 months, the PFS and OS of the 12 - 24 months and ≥ 24 months groups were significantly improved (P < 0.05). The HR for PFS were 0.458 and 0.164 respectively; the HR for OS were 0.335 and 0.133 respectively. Continuing treatment after 24 months of medication did not significantly improve OS (P = 0.148).

Conclusions: The population with long - term benefits from immunotherapy showed a deeper degree of tumor response, and the increase in DepOR showed a step - wise improvement in PFS. Prolonging the duration of immunotherapy significantly improved the patients' survival.



Keywords: NSCLC, ICIs, DepOR

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.44 Efficacy and Safety of Immunotherapy as First-Line Treatment in Metastatic Pulmonary Large-Cell Neuroendocrine Carcinoma

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Introduction: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive cancer with a poor prognosis and limited treatment options. The first-line therapy for advanced LCNEC remains uncertain. This study aimed to evaluate the efficacy and safety of combining PD-1/PD-L1 inhibitors with chemotherapy in the first-line setting for patients with metastatic LCNEC.

Methods: This retrospective study included patients with advanced LCNEC treated with either immunotherapy plus chemotherapy (ICT group) or chemotherapy alone (CT group) as first-line therapy. Data from electronic health records of three hospitals, spanning from January 2015 to October 2024, were analyzed. Outcomes including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were assessed for both groups. Safety was monitored in all patients who received at least one dose of the assigned treatment.

Results: A total of 130 patients were enrolled, with 54 assigned to the ICT group and 76 assigned to the CT group. The median PFS (mPFS) was 7.9 months (95% CI, 4.8-10.9) in the ICT group, compared to 5.3 months (95% CI, 3.7-6.9) in the CT group (hazard ratio [HR], 0.642; 95% CI, 0.438-0.941; p = 0.022). The median OS (mOS) was 15.4 months (95% CI, 6.0-24.8) in the ICT group, compared to 19.5 months (95% CI, 13.5-25.5) in the CT group (hazard ratio [HR], 1.040; 95% CI, 0.659-1.641; p = 0.865). The ORRs in the two groups were 55.6% and 46.1%, respectively (p = 0.286), and the DCRs were 87.0% and 78.9%, respectively (p = 0.234). In the CT group, the mOS for patients who received immunotherapy at second-line or later-line was 19.6 months (95% CI: 13.6-25.6), whereas the mOS for patients who received chemotherapy alone after disease progressed was 12.3 months (95% CI: 6.5-18.1) (p = 0.378). Regarding safety, the most frequent grade ≥ 3 adverse events were neutropenia, leukopenia, anemia, and fatigue, with no significant differences between the two groups. Immune-related adverse events (irAEs) in the immunotherapy group included cutaneous hemangiomas, hypothyroidism, anaphylaxis, and pneumonitis, with no grade 3 or 4 irAEs observed. No new safety signals were observed.

Conclusions: First-line treatment combined with a PD-1/PD-L1 inhibitor was associated with superior PFS for advanced LCNEC, but did not significantly improve OS compared to chemotherapy alone.

Keywords: Pulmonary large-cell neuroendocrine carcinoma, Immunotherapy, First-line treatment

P1.11.45 Real-World Prognosis of Non-Squamous NSCLC Patients With Liver, Bone, or Brain Metastases Treated With Frontline Therapies

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Introduction: Non-small cell lung cancer (NSCLC) commonly spreads to the bone, brain, and liver. Despite advances in therapies, few patients with metastatic NSCLC experience long-term benefit. Metastatic sites have been shown to impact survival, with brain, liver and bone metastases linked to poorer prognosis; however, the effect of metastatic sites on outcomes to treatments is unclear. We used real-world data to assess the influence of metastatic site on outcomes to first line(1L) pembrolizumab(P), chemotherapy(C), or P+C in metastatic NSCLC.

Methods: A retrospective study conducted using the Optum's de-identified Market Clarity Data (Optum® Market Clarity) of adults (≥18 years) with non-squamous, metastatic NSCLC. Eligible patients had ≥1 metastatic site and received P+C, P, or C as 1L therapy between 2017-June 2023. Kaplan-Meier methodology was used to estimate median overall survival (mOS) and 3-year OS by metastatic site and treatment. The ratio of median survival time was calculated by metastatic site using C as reference (REF).

Results: In total, 1,968 patients initiating P+C(44%), P(25%), or C(31%) were included. Median age: 67 years; 45% female. The most common metastatic sites were bone(46%) and brain(42%), followed by liver(17%). Patients receiving P+C and P were more likely to be diagnosed with de novo metastatic NSCLC (72% and 68%, respectively) compared with C(42%). P+C and C patients were similar in age (median: 66 years) and performance status (PS) (77% PS 0-1) compared with P (median: 71 years, 67% PS 0-1). Baseline tumor proportion score for P was more likely to be ≥50% compared with P+C (88% and 33%, respectively). P+C and P patients had a higher likelihood of liver metastases than C patients (19% and 18% vs 12%, respectively), and higher likelihood of bone metastases (51% and 48% vs 37%, respectively). Brain metastases were similar across treatments. Patients who were negative for liver/bone metastases had a numerically longer mOS and 3-year OS vs positive patients across all treatments; the effect was more limited for brain metastases (Table). Longer mOS was observed with P+/- C vs C alone in patients with liver/bone metastases, although the ratio was not statistically significant. No benefit of P+/-C vs C was observed in the metastases-negative treatment groups.

Conclusions: This real-world analysis emphasizes the impact of liver, bone, and brain metastases on prognosis and outcomes to treatment in patients receiving 1L P+/-C. Adding immunotherapy to the C backbone had limited survival benefit, underscoring an unmet medical need in metastatic NSCLC.

Metastases	N	mOS, mo	Ratio of Median Survival (95% CI)	3-Yr Survival, %
LIVER				
POS				
C	73	6.8	REF	23.0
P+C	168	7.2	1.1 (0.8, 1.5)	21.5
P	89	7.6	1.1 (0.8, 1.6)	31.3
NEG				
C	540	17.7	REF	36.8
P+C	690	13.8	0.8 (0.7, 0.9)	31.8
P	408	16.8	1.0 (0.8, 1.1)	37.1
BONE				
POS				
C	228	8.0	REF	20.6
P+C	440	10.0	1.3 (1.1, 1.5)	25.4
P	240	8.5	1.1 (0.9, 1.3)	27.8
NEG				
C	385	26.0	REF	43.3
P+C	418	15.3	0.6 (0.5, 0.7)	34.3
P	257	23.7	0.9 (0.7, 1.1)	44.1
BRAIN				
POS				
C	239	15.0	REF	31.5
P+C	364	11.7	0.8 (0.6, 1.0)	30.0
P	214	16.8	1.1 (0.9, 1.4)	40.0
NEG				
C	374	15.4	REF	37.4
P+C	494	12.4	0.8 (0.7, 1.0)	29.5
P	283	14.4	0.9 (0.8, 1.1)	33.0

Keywords: NSCLC, real-world data, metastases

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.46 RATIONALE-303: Post-Hoc Analysis of Tislelizumab Monotherapy in Previously Treated Non-Small Cell Lung Cancer With Metastases

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Introduction: The global, open-label, randomised, multicentre phase 3 RATIONALE-303 trial (NCT03358875) demonstrated superior overall survival (OS) with tislelizumab (anti-programmed cell death protein-1 antibody) vs docetaxel in patients with locally advanced or metastatic (squamous or non-squamous) non-small cell lung cancer (NSCLC) who progressed after platinum-based chemotherapy. Results are reported on subgroup analyses of patients with metastases, including liver metastases, who historically have poor prognosis.

Methods: Eligible patients aged ≥18 years were randomised (2:1) to receive intravenous tislelizumab 200 mg or docetaxel 75 mg/m2 once every 3 weeks. Efficacy (OS and investigator-assessed progression-free survival [PFSINV] and objective response rate [ORRINV]) and safety outcomes were analysed based on the number of metastatic sites (locally advanced [ie, no metastatic sites], one or two metastatic sites, or three or more metastatic sites) and presence or absence of liver metastases at baseline.

Results: Among the 805 randomised patients (tislelizumab, n=535; docetaxel, n=270), 106 (13.2%) had liver metastases at baseline (tislelizumab, n=73; docetaxel, n=33). As of January 18, 2024 (median study follow-up: 16.6 months for tislelizumab and 10.7 months for docetaxel), sustained OS, PFSINV, and ORR benefit was observed among tislelizumab- vs docetaxel-treated patients, regardless of the number of metastatic sites at baseline (Table 1). OS, PFSINV, and ORR benefit among patients treated with tislelizumab vs docetaxel was maintained in those with and without liver metastases at baseline (Table 2). Safety outcomes were consistent with the known safety profile of tislelizumab, with tislelizumab demonstrating a more favourable safety profile compared with docetaxel across all subgroups (Tables 1 and 2).

Conclusions: This post-hoc analysis of RATIONALE-303 demonstrated a clinically meaningful OS, PFSINV, and ORRINV benefit with tislelizumab vs docetaxel in pretreated patients with locally advanced or metastatic squamous or non-squamous NSCLC, regardless of the number of metastatic sites, including liver metastases.

Table 1. Efficacy and Safety Outcomes by Number of Metastatic Sites at Baseline in the RATIONALE-303 Trial

	Locally Advanced (No Metastatic Sites)		One or Two Metastatic Sites		Three or More Metastatic Sites	
Efficacy Outcomes	**Tislelizumab (n=84)**	**Docetaxel (n=33)**	**Tislelizumab (n=328)**	**Docetaxel (n=172)**	**Tislelizumab (n=123)**	**Docetaxel (n=65)**
Median OS (95% CI), months	24.5 (20.7, 29.5)	14.9 (12.6, 19.3)	17.5 (15.8, 20.0)	12.7 (9.7, 15.2)	11.2 (7.6, 12.9)	7.8 (5.8, 10.5)
Unstratified HR (95% CI)	0.52 (0.33, 0.83)		0.71 (0.57, 0.87)		0.68 (0.49, 0.94)	
Median PFS_{INV} (95% CI), months	8.3 (5.5, 13.1)	3.7 (2.1, 6.9)	4.2 (3.6, 6.2)	2.6 (2.1, 4.0)	2.3 (2.1, 4.0)	2.2 (1.9, 4.0)
Unstratified HR (95% CI)	0.58 (0.35, 0.96)		0.62 (0.50, 0.76)		0.65 (0.46, 0.92)	
ORR_{INV}, n (%) [95% CI]	26 (31.0) [21.3, 42.0]	4 (12.1) [3.4, 28.2]	73 (22.3) [17.9, 27.2]	15 (8.7) [5.0, 14.0]	22 (17.9) [11.6, 25.8]	2 (3.1) [0.37, 10.7]
Safety Outcomes	**Tislelizumab (n=84)**	**Docetaxel (n=33)**	**Tislelizumab (n=327)**	**Docetaxel (n=165)**	**Tislelizumab (n=123)**	**Docetaxel (n=60)**
Patients with ≥1 TEAE, n (%)	83 (98.8)	33 (100.0)	316 (96.6)	163 (98.8)	119 (96.7)	58 (96.7)
Patients with ≥1 TRAE, n (%)	71 (84.5)	32 (97.0)	248 (75.8)	156 (94.5)	85 (69.1)	54 (90.0)
Serious TEAEs, n (%)	21 (25.0)	12 (36.4)	119 (36.4)	48 (29.1)	52 (42.3)	24 (40.0)
TEAEs leading to death, n (%)	1 (1.2)	2 (6.1)	22 (6.7)	5 (3.0)	12 (9.8)	5 (8.3)
TEAEs leading to treatment discontinuation, n (%)	9 (10.7)	8 (24.2)	41 (12.5)	17 (10.3)	17 (13.8)	9 (15.0)

Data cutoff: January 18, 2024.
Abbreviations: CI, confidence interval; HR, hazard ratio; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; PFS_{INV}, investigator-assessed progression-free survival; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 2. Efficacy and Safety Outcomes in Patients With or Without Liver Metastases at Baseline in the RATIONALE-303 Trial

	With Liver Metastases		Without Liver Metastases	
Efficacy Outcomes	**Tislelizumab (n=73)**	**Docetaxel (n=33)**	**Tislelizumab (n=462)**	**Docetaxel (n=237)**
Median OS (95% CI), months	13.4 (7.9, 17.3)	6.8 (4.1, 7.8)	17.6 (15.8, 20.4)	12.9 (11.3, 14.0)
Unstratified HR (95% CI)	0.46 (0.30, 0.78)		0.69 (0.58, 0.82)	
Median PFS_{INV} (95% CI), months	2.1 (2.0, 4.0)	2.0 (1.8, 4.0)	4.3 (4.1, 6.2)	2.9 (2.3, 4.0)
Unstratified HR (95% CI)	0.53 (0.33, 0.85)		0.62 (0.52, 0.74)	
ORR_{INV}, n (%) [95% CI]	11 (15.1) [7.8, 25.4]	2 (6.1) [0.7, 20.2]	110 (23.8) [20.0, 28.0]	19 (8.0) [4.9, 12.2]
Safety Outcomes	**Tislelizumab (n=72)**	**Docetaxel (n=29)**	**Tislelizumab (n=462)**	**Docetaxel (n=229)**
Patients with ≥1 TEAE, n (%)	69 (95.8)	28 (96.6)	449 (97.2)	226 (98.7)
Patients with ≥1 TRAE, n (%)	53 (73.6)	26 (89.7)	351 (76.0)	216 (94.3)
Serious TEAEs, n (%)	30 (41.7)	11 (37.9)	162 (35.1)	73 (31.9)
TEAEs leading to death, n (%)	6 (8.3)	2 (6.9)	29 (6.3)	10 (4.4)
TEAEs leading to treatment discontinuation, n (%)	10 (13.9)	3 (10.3)	57 (12.3)	31 (13.5)

Data cutoff: January 18, 2024.
Abbreviations: CI, confidence interval; HR, hazard ratio; ORR_{INV}, investigator-assessed objective response rate; OS, overall survival; PFS_{INV}, investigator-assessed progression-free survival; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Keywords: NSCLC, RATIONALE-303, tislelizumab

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.47 Clinical Outcomes of Immune Checkpoint Inhibitors Treatment for Postoperative Recurrence in Non-Small Cell Lung Cancer

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Introduction: The efficacy of immune checkpoint inhibitors (ICIs) in the treatment of non-small cell lung cancer (NSCLC) has been widely reported, but specific advantage of ICIs treatment for postoperative recurrence of NSCLC remains unclear. The aim of the study was to evaluate the efficacy of ICIs treatment in patients with postoperative recurrence of epidermal growth factor receptor (EGFR) wild-type NSCLC.

Methods: A retrospective analysis was performed on 1832 patients with stage I-III NSCLC who underwent anatomical lung resection at our institution between 2013 and 2022. One hundred seven patients with wild-type EGFR NSCLC who experienced postoperative recurrence and underwent ICIs treatment or chemotherapy were included. Patients were divided into those who received ICIs treatment with or without chemotherapy (ICIs group, n = 73) and those who received chemotherapy only (non-ICIs group, n = 34). The following information was collected from the medical records: age, sex, brinkman index, surgical procedure, histopathological findings, programmed death ligand 1 (PD-L1) status, mutations in driver genes, performance status (PS) at recurrence, treatment histories, and survival outcomes. This study evaluated the prognosis for postoperative recurrence, including ICIs treatment and other clinicopathological factors.

Results: In the ICIs group (n = 73), 8 patients were treated with ICIs only, 54 combined with platinum-based chemotherapy and 11 with other chemotherapy. In the non-ICIs group (n = 34), 24 patients were treated with platinum-based chemotherapy and 10 with other chemotherapy. With regard to patient background, the proportion of patients with a history of interstitial lung disease (ILD) was significantly lower in the ICIs group (ICIs group 2.8% vs. non-ICIs group 16.7%, p=0.01). Whereas, other factors showed no significant differences between the two groups. The ICIs treatment significantly prolonged survival after recurrence (median survival: ICIs group 38.8 months vs. non-ICIs group 16.4 months, p<0.01). The same significant differences in prognosis were found in cases excluding ILDs (median survival: ICIs group 38.9 months vs. non-ICIs group 17.2 months, p=0.02). In the subgroup analysis of the ICIs group, no significant differences in survival after recurrence were detected between patients with different PD-L1 status (Tumor Proportion Scores: <1%, 1%-49%, ≥50%, p=0.21). Multivariate analysis of all included cases revealed that postoperative distant recurrence at first occurrence (HR=1.75, 95% CI=1.01-3.03, p=0.04) and PS at recurrence (PS1 vs. PS0: HR=2.00, 95% CI=1.08-3.70, p=0.01) was a significant poor prognostic factor for survival after recurrence, and ICIs treatment significantly improved survival after recurrence (HR=0.52, 95% CI=0.30-0.89, p<0.01).

Conclusions: Our results demonstrated that ICIs treatment significantly prolonged survival of postoperative recurrence with wild-type EGFR NSCLC regardless of PD-L1 status, whereas postoperative first distant recurrence and PS at recurrence were associated with poor prognosis.

Keywords: immune checkpoint inhibitors, non-small cell lung cancer, postoperative recurrence

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.48 Scoreit - Is IC3 Similarly Predictive as TC3 for Single Agent PD-1/PD-L1 Immune Checkpoint Inhibition in Metastatic NSCLC (mNSCLC)

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Introduction: The use of immune checkpoint inhibitors (ICI) has led to significant improvements in survival rates in mNSCLC. PD-L1 expression on tumor cells (TC) and immune cells (IC) have been correlated with high response rates, PFS and OS benefit by single agent ICI compared with chemotherapy. However, there are only sparse data on the predictive impact of IC3 (>10% immune cells) with TC<3 (<50% tumor cells) on ICI single agent therapy.

Methods: In a retrospective single center study of the Lungenkrebszentrum Pius-Hospital Oldenburg, 593 NSCLC patients (of all stages) were tested for PD-L1 expression between 2021 and 2023, 269/606 (45%) were identified with high PD-L1 expression and 32% (87/269) of them received PD-1/PD-L1 ICI as palliative first-line monotherapy. The following groups were analyzed: TC3/IC3: 52/269, IC3/TC<3: 76/269 and TC3/IC<3: 141/269 patients. Clinical data including gender, age, smoking status, PD-L1 score and type of ICI therapy were captured. The primary end points were best overall response, overall survival and progression-free survival.

Results: Median age of the 269 patients was 66 years (range 37-88 years), 60% of them were male and 72% were current or ex heavy smoker. In the IC3/TC<3 group, 22 patients were treated with a PD-L1 inhibitor as palliative first-line monotherapy, while 40 patients in the TC3/IC<3 group received a PD-1 inhibitor as monotherapy. Median overall survival was longer in the IC3/TC<3 group with 28.6 months (95% CI: 18.0-39.2 months) versus 13.3 months (95% CI: 2.6-24.0 months) in the TC3/IC<3 group (HR: 0.58; 95% CI: 0.29-1.14], p=0.112). Median PFS was similar in both groups, 8.6 months (95% CI: 2.5-14.6 months) for IC3/TC<3 and 10.1 months (95% CI: 8.3-12.0 months) for TC3/IC<3 (HR: 1.35; 95% CI: 0.67-2.73; p=0.398). Objective response rate was higher for IC3/TC<3 versus TC3/IC<3 (41% vs. 33%; p=0.850).

Conclusions: In metastatic NSCLC, treatment with the PD-L1 inhibitor atezolizumab in patients with PD-L1 expression of IC3/TC<3 led to a descriptively longer OS than treatment with PD-1 inhibitor pembrolizumab or cemiplimab in patients with TC3/IC<3. These data indicate that the predictive value of IC3, irrespective of tumor cell PD-L1 expression, might be similar to TC3. These data will be expanded in a larger prospective registry cohort.

Keywords: Immune Checkpoint Inhibitor, Immune Cell Score, PD-L1

P1.11.49 The Impact of the Lung Microbiome on Checkpoint Inhibitor Pneumonitis: Early Findings From the Australian TRACKER Lung Cancer Biobank

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Introduction: While immune checkpoint inhibitors (ICIs) have revolutionised cancer management, their success has been tempered by immune related adverse events (IrAEs). Checkpoint inhibitor pneumonitis (CIP) is the most common cause of IrAE associated mortality and poses a significant clinical challenge. While there has been extensive research evaluating the impact of the gut microbiome on lung cancer treatment and complications, the impact of the lung microbiome remains a relative unknown. In this study, we aim to characterise the complex microbial - immune microenvironment that drives CIP and look for potential biomarkers and treatment targets in this vulnerable patient population.

Methods: Through the TRACKER lung cancer biobank, an Australian based lung cancer biospecimen repository, bronchial alveolar lavage fluid (BALF) samples were acquired in CIP cases and non-CIP controls. Each BALF sample had matched blank, scope, and oral fluid controls. Following collection, DNA was extracted from samples and sent for 16S rRNA microbial profiling via the Illumina NextSeq™ 2000 platform.

Results: In total, 10 patients (27 samples), comprising 2 CIP and 8 non-CIP patients were included in this initial pilot analysis. Firmicutes, Proteobacteria and Bacteriodota were the most abundant phyla, while Streptococcus (29%), Veillonella (6%) and Gemella (3%) genera demonstrated the highest relative abundance across the samples (Figure1). While relative abundance in Firmicutes, Proteobacteria and Bacteriodiota were similar between CIP and non-CIP cohorts, there was increased relative abundance of Acidobacteriota and Planctomycetota in the CIP cohort (Figure2).

Conclusions: Preliminary results from this small biobank based study demonstrates characteristics of the lung microbiome in patients with CIP. Further analysis on a larger sample cohorts will be conducted to explore the impact of lung microbiome composition on inflammatory responses driving CIP.

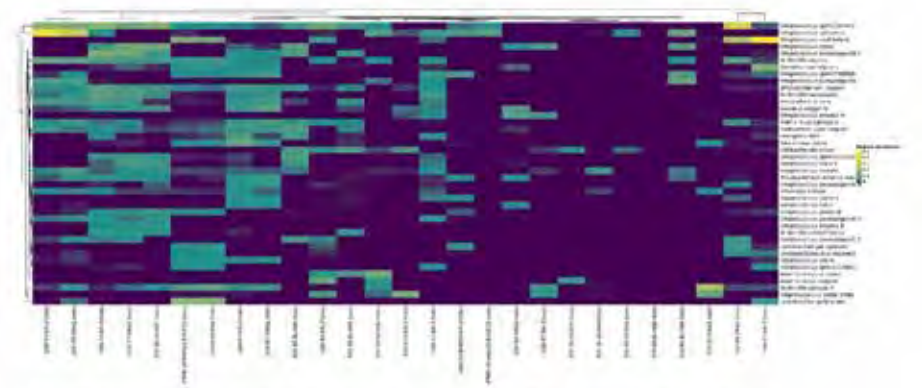

Figure 1: Heatmap depicting phylogenetic distribution across samples. Only species with >1% abundance in at least 2 samples for the top 10 genus were including in this heat map.

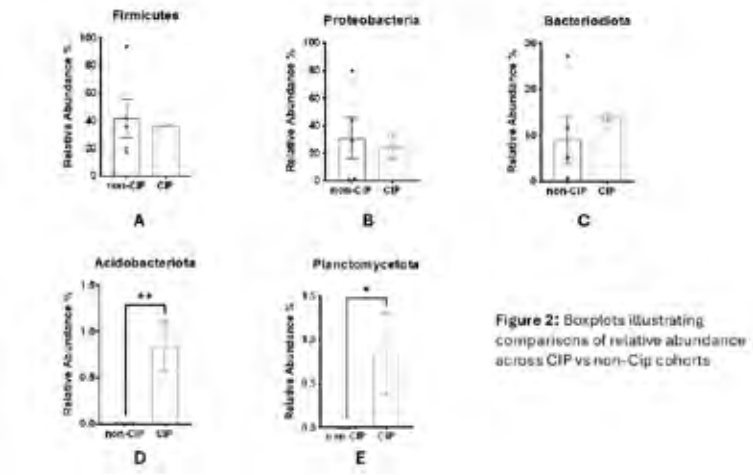

Figure 2: Boxplots illustrating comparisons of relative abundance across CIP vs non-Cip cohorts

Keywords: Checkpoint inhibitor pneumonitis, Lung Microbiome, Immunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.50 Survival Outcomes in Advanced Pulmonary Sarcomatoid Carcinoma Treated With Immunotherapy: An NCDB Analysis

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Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare and aggressive type of non-small cell lung cancer (NSCLC), associated with poor prognosis and resistant to standard platinum-based chemotherapy. Owing to its rarity, survival outcomes in advanced-stage PSC treated with immunotherapy, either alone or in combination with chemotherapy, remain understudied, particularly in comparison to other NSCLCs.

Methods: Demographics, treatment, and survival data for stage IV NSCLC, including PSC, diagnosed between 2015 and 2020 were extracted from NCDB. Univariate survival analysis was conducted using the log-rank test, and Cox multivariate regression was employed to adjust for confounding factors, including age, gender, race, comorbidities, insurance, and treatment facility (academic or community).

Results: A total of 292,751 patients were identified, including 1,039 PSCs and 291,712 other NSCLCs. Of the 515 PSCs that received systemic therapy as the first course of treatment, 229 (44%) received chemotherapy alone, 142 (28%) received immunotherapy alone and 144 (28%) received chemoimmunotherapy. PSC treated with chemotherapy alone had significantly shorter survival than those treated with immunotherapy alone (median overall survival [OS] 6.2 vs 9.7 months, HR 0.82, 95% CI 0.80 - 0.84, p = 0.01) or chemoimmunotherapy (median OS 6.2 vs 12 months, HR 0.83, 95% CI 0.82 - 0.85, p <0.001). Although chemoimmunotherapy was associated with numerically longer survival than immunotherapy alone (median OS 12 vs 9.7 months), the difference was not statistically significant (HR 0.93, 95% CI 0.67 - 1.3, p = 0.3). Among PSC subtypes, spindle cell PSCs demonstrated a survival benefit from immunotherapy compared to chemotherapy (HR: 0.32; 95% CI: 0.15-0.7, p = 0.003), whereas pleomorphic PSCs showed no significant difference (HR: 1; 95% CI: 0.46-2.11, p = 0.8). Compared with other NSCLCs, PSC had significantly shorter survival when treated with chemotherapy alone (median survival 6.2 vs 10.6 months, p <0.001, HR 0.67, 95% CI 0.57 - 0.79). However, no difference in survival was observed between PSC and other NSCLC when treated with immunotherapy alone (median OS 9.7 months vs 11.5 months, HR 0.78, 95% CI 0.56 - 1.11, p = 0.07) or with chemoimmunotherapy (median OS 12 vs 12.9 months, HR 0.87, 95% CI 0.61 - 1.24, p = 0.4).

Conclusions: This study demonstrates that patients with PSC treated with immunotherapy-based treatment achieve better survival outcomes than those treated with chemotherapy alone, with the spindle cell subtype appearing to benefit the most. In the era of immunotherapy, PSC is no longer associated with worse survival outcomes compared to other NSCLC subtypes. Future studies should incorporate biomarkers such as PD-L1 expression and driver mutation status, and evaluate chemotherapy partners in chemoimmunotherapy to better understand treatment response and optimize therapeutic strategies.

Keywords: Pulmonary Sarcomatoid Carcinoma, Immunotherapy, Survival

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.51 Effects of Immune Checkpoint Inhibitors on the Pulmonary Circulation in Lung Cancer Patients

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Introduction: This paper aims to investigate whether ICIs lead to dysfunction of the pulmonary circulation system, to assess the utility of the PAD/AoD as a prognostic predictor, and to discuss related risk factors.

Methods: This retrospective cohort study investigated 461 lung cancer patients treated with ICIs over two years, analyzing changes in pulmonary artery diameter (PAD), aortic diameter (AoD), and the pulmonary artery/aortic diameter (PAD/AoD) ratio through chest computed tomography (CT) at baseline, 3 months, 6 months, 1 year, and 2 years post-treatment, and collecting clinical data to identify risk factors.

Results: The PAD from 25.19 mm to 26.33 mm ($p < 0.001$) and the PAD/AoD ratio from 0.70 to 0.73 ($p < 0.001$) during ICI treatment over a 2-year follow-up period, as early as within the first three months. High-sensitivity troponin I (hs-TnI), α-hydroxybutyrate dehydrogenase (HBDH), creatine kinase (CK), creatine kinase MB (CK-MB), and coagulation indices exhibited significant changes ($p < 0.05$), while cardiac ultrasound result remained unchanged. In subgroup analysis, the severe group demonstrated lower progression-free survival (PFS) (9 months vs. 16 months, $p < 0.001$), overall response rate (ORR) (3.5% vs. 9.1%, $p = 0.004$), and disease control rate (DCR) (48.7% vs. 59.8%, $p = 0.022$) compared to the non-severe group. Meanwhile, the severe PAD/AoD ratio progression(HR 2.144 [95% CI 1.580-2.911] $p<0.001$)and ICI treatment cycle(HR 0.521 [95% CI 0.379-0.717] $p<0.001$)serve as independent predictors of PFS, but immune-related pneumonia(CIP) did not significantly influence the PAD/AoD ratio progression ($p >0.999$).

Conclusions: In lung cancer patients treated with ICIs, pulmonary vascular involvement can occur within the initial three months. Furthermore, severe PAD/AoD ratio progression is a risk factor for PFS, while ICI treatment cycles confer a protective effect on PFS.

Keywords: pulmonary circulation, immune checkpoint inhibitors, lung cancer

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.52 Impact of Disease Progression on Pros in Patients Receiving Cemiplimab/Chemotherapy Versus Chemotherapy for aNSCLC: EMPOWER-Lung 3 Part 2

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Introduction: EMPOWER-Lung 3 part 2 (NCT03409614), a double-blind, placebo-controlled phase 3 study, investigated first-line cemiplimab (anti-programmed cell death 1 [PD-1]) plus chemotherapy versus placebo plus chemotherapy in patients with advanced non-small cell lung cancer (aNSCLC). Clinically meaningful and statistically significant improvements in overall survival (OS) and progression-free survival (PFS) were observed with cemiplimab plus chemotherapy (n=312) versus chemotherapy alone (n=154) (OS: HR 0.65; 95% CI 0.51-0.82; P=0.0003; PFS: HR 0.55; 95% CI 0.44-0.68; P<0.0001). The safety profile was consistent with the previously reported profile for cemiplimab and other PD-1 or programmed cell death-ligand 1 inhibitors in aNSCLC and other tumour types. To evaluate the effects of disease progression on patient-reported outcomes (PROs), we performed post-hoc analyses of patients with and without disease progression, based on both treatment arms combined and for each treatment arm separately.

Methods: PROs were assessed at baseline and Day 1 of each treatment cycle for the first 6 cycles, and then on Day 1 of every third cycle using the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 (QLQ-C30) and Lung Cancer Module questionnaires. The focus of this post-hoc analysis was the QLQ-C30 global health status (GHS)/quality of life (QoL) scale, with higher scores indicating better outcomes. Patients were grouped by their Response Evaluation Criteria in Solid Tumors-based disease progression status (with vs without disease progression) within each treatment arm. Repeated measures mixed-effects analyses were performed to compare overall change from baseline scores while controlling for baseline. Disease progression status at each time point was included as a covariate. Time to onset of definitive clinically meaningful deterioration (TTD) (decrease of ≥10 points) in GHS/QoL was compared between patients with versus those without disease progression using a stratified Cox proportional hazards model with disease progression status included as a time-dependent covariate.

Results: In all patients in the study (both treatment and control arms), an overall change from baseline in GHS/QoL scores significantly favoured patients without disease progression versus those with disease progression (difference in least squares [LS] means: 4.65; 95% CI 2.31-6.99). Similarly, an overall change in GHS/QoL scores significantly favoured patients without disease progression in the cemiplimab plus chemotherapy arm (difference in LS means: 3.97; 95% CI 1.09-6.85) and in the chemotherapy-alone (difference in LS means: 7.61; 95% CI 3.28-11.95) arm, separately. Additionally, in all study patients, a significantly greater delay in TTD in GHS/QoL was observed in patients without versus with disease progression (HR 0.37; 95% CI 0.20-0.68). Similarly, a significantly greater delay in TTD in patients without versus with disease progression was also seen in the cemiplimab plus chemotherapy arm (HR 0.40; 95% CI 0.18-0.87) and in the chemotherapy-alone (HR 0.39; 95% CI 0.13-1.15) arm, separately.

Conclusions: In patients with aNSCLC, overall change from baseline and TTD in GHS/QoL significantly favoured patients without disease progression versus those with disease progression. These results suggest that an increase in PFS may lead to a more favourable overall change from baseline and a greater delay in TTD in GHS/QoL among patients with aNSCLC.

Keywords: Cemiplimab, Advanced NSCLC, Patient-reported outcomes

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.53 Organ-Specific Survival in Metastatic NSCLC Patients Treated With Chemo-Immunotherapy: A Machine Learning-Based Retrospective Analysis

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Introduction: Currently, organ-specific progression-free survival (PFS) and overall survival (OS) in patients with metastatic non-small cell lung cancer (NSCLC) treated with chemo-immunotherapy have not been comprehensively elucidated. This study aimed to evaluate organ-specific metastatic progression patterns, investigate associated survival outcomes, and develop machine learning models to predict prognosis in metastatic NSCLC patients.

Methods: We included NSCLC patients treated with systemic chemo-immunotherapy at MD Anderson Cancer Center between January 2009 and January 2025. Demographic and clinical features, including age, gender, histology, baseline metastatic sites, genomic alterations, prior treatment history, and site of first progression, were collected. Kaplan-Meier analysis was used to compare PFS and OS across progression sites. LASSO-Cox proportional hazards regression was used to identify independent prognostic factors. Real-world PFS and OS were primary outcomes for this study. Disease progression was determined based on pathologic confirmation or clinical progression determined by the treating physician based on imaging reports or through clinical assessment. Twelve machine learning models—including Multilayer Perceptron (MLP), Gradient Boosted Trees (GBT), Random Forest, SVM, Logistic Regression, Naive Bayes, CatBoost, AdaBoost, Bagging, ExtraTrees, LightGBM, and Decision Tree—were trained and evaluated to predict disease progression and mortality. Model performance was assessed using ROC curves, precision-recall curves, calibration plots, and decision curve analysis. SHAP (SHapley Additive exPlanations) was used for model interpretation. Analyses were conducted using GraphPad Prism (v10.1.2), R (v4.0.5), and Python (v3.14).

Results: As of the data-lock date (January 31, 2025), 7,049 NSCLC patients treated with immunotherapy were identified. After excluding 2,717 patients due to positive driver mutations or early-stage treatment, 4,332 stage IV NSCLC patients without targetable mutations were included. Among them, 2,634 (60.8%) progressed at the primary tumor, 1,101 (25.4%) in the lung, 696 (16.1%) in the brain, 630 (14.5%) in the liver, 1,296 (29.9%) in the bone, and 549 (12.7%) in the adrenal glands.PFS and OS were significantly shorter in patients who got liver progression than those who had progression in other sites. median PFS (5.07m, 95%CI 4.60m-6.70m), median OS (11.80m, 95%CI 9.90m-14.53m) (P<0.001). PFS and OS of patients who had progression liver metastases, bone metastases were significantly shorter than those who had no progression at liver metastases(mPFS, 5.07m vs 10.47m, P<0.0001; mOS11.80m vs 27.33m, P<0.0001) and bone metastases(mPFS, 7.77m vs 10.43m, P<0.0001; mOS 17.97m vs 26.03m, P<0.0001), respectively.Among all 12 models, the ExtraTrees algorithm showed the best performance in predicting both disease progression(AUC = 0.935, 95% CI: 0.888-0.971) and mortality (AUC=0.995,95%CI 0.937-0.970). Top SHAP predictors of progression: adrenal metastasis, pathology, age, bone metastasis, and N stage. Top SHAP predictors of mortality: PD-L1 expression, age, line of therapy, non-targetable EGFR mutations, and pulmonary metastases.

Conclusions: In metastatic NSCLC patients receiving chemo-immunotherapy, progression patterns differ significantly by organ site and are closely associated with clinical outcomes. Patients with progression in the liver exhibit the shortest PFS and OS. We also developed novel explainable machine learning models that accurately predict disease progression and mortality, which may aid clinicians in personalizing treatment strategies for advanced NSCLC.

Keywords: Metastatic Non-Small Cell Lung Cancer, Chemo-immunotherapy, Organ specific progression

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.54 Lack of Durable Response to ICI Therapy in Advanced NSCLC: The Role of Circulating Lazy T Cells

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Introduction: Treatment of advanced Non-Small Cell Lung cancer (NSCLC) with immune checkpoint inhibitors (ICIs) leads to long-lasting responses in only 20% of patients. Conversely, 14-37% of patients experience rapid disease progression following ICI therapy. Efforts to investigate the causes of fast tumor progression by dissecting the tumor microenvironment at baseline did not yield any clear clinical biomarkers. Further, real-life longitudinal studies focusing on circulating immune components remain limited, and no specific indexes have been established for clinical monitoring. Previously, we demonstrated that low IFN-γ doses modulate NSCLC plasticity associated with ICI-mediated hyperprogression. However, few is known about the regulation of IFN-γ production by T cells. The goal of this study was to investigate the ability of circulating T cells from advanced NSCLC patients to be stimulated and to produce IFN-γ, comparing long-responder with fast-progressor ICI-treated patients.

Methods: Advanced NSCLC patients undergoing ICIs were enrolled and categorized into patients who responded after 1 year of treatment (long responders-LR) and patients who progressed within the first 3 months (fast progressors-FP). Consecutive blood samples of LR were monitored over time to minimize inter-sample variability and record changes associated to progression. Classical, intermediate, and non-classical monocyte subsets were identified using CD14-PE and CD16-FITC. HLA-DR-APC staining was used to assess antigen presentation capacity. PBMCs isolated from FP and LR patients were cultured with ImmunocultTM medium and hu-IL-2 and stimulated with anti-CD3/CD28/CD2 antibodies. Then, intracellular IFN-gamma level was measured. Plasma soluble factors were measured through human Luminex Discovery Assay.

Results: The expression of HLA-DR resulted lower in classical monocytes compared to intermediate and non-classical counterparts. Notably, FP patients had a more than 50% reduction in HLA-DR expression on intermediate monocytes compared to LR patients. This decrease was also observed in LR patients who later experienced sudden disease progression. Pentraxin PTX3, which can inhibit HLA-DR expression, enhance TGF-β production, and bind CD44, was found to be significantly increased in FP compared to LR patients.LR-derived CD4+ T and CD8+ T cells showed a 2-fold increase in IFN-γ production after three days of stimulation with anti-CD3/CD28/CD2 antibodies, compared to FP T cells. Prolonged exposure to immune stimulators further increased IFN-γ secretion by FP T cells but did not in LR ones. Treatment with nivolumab reduced FP CD4-mediated IFN-γ production, while LR T cells showed increased IFN-γ release under nivolumab treatment. Surprisingly, circulating T regulatory cells resulted slightly higher in LR compared to FP patients. This could indicate a lower intratumor Treg localization in the former. Tregs mainly modulate the immune response through IL-10 and TGF-β1 cytokines. We found a 3-fold increase of TGF-β1 in FP respect to LR, while IL-10 was low or undetectable in both groups.

Conclusions: Advanced NSCLC patients receiving ICI therapy showed longer-lasting therapeutic responses in presence of circulating intermediate monocytes with higher HLA-DR expression. Conversely, elevated PTX3—capable of inhibiting antigen presentation and promoting cancer cell plasticity—was found in FP patients. Despite a slower activation profile, T lymphocytes from FP patients retained the capacity to produce IFN-γ.

Keywords: Interferon gamma, Long Responders, ICI

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.55 Identifying Patients Cured From Metastatic Non-Small Cell Lung Cancer (mNSCLC) With Anti-PD-(L)1 Therapy

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Introduction: Anti-PD-(L)1 therapy can cure patients with advanced cancer, but cure rates remain low in mNSCLC. Identifying patients who are likely to achieve a long-term response could help optimize treatment selection, duration, and surveillance strategies.

Methods: Patients treated with anti-PD-(L)1 therapy across 10 academic institutions and as part of 3 clinical trials were identified. A mixture cure model with a Weibull distribution was used to estimate the cure rate among patients with previously untreated mNSCLC who received anti-PD-(L)1 alone (ICI-mono) or in combination with anti-CTLA-4 therapy (dual-ICI). Unlike the Kaplan-Meier method which assumes all patients may eventually experience the event, a mixture cure model estimates survival by accounting for a cured subgroup that will never experience the event and a non-cured subgroup that follows a traditional survival distribution. Among patients treated across all lines of therapy, pathologic and genomic features were compared between those censored after 3 years of response (considered “possibly cured”), those who progressed after initially responding (acquired-resistance), and non-responders. RECIST v1.1 criteria were used to distinguish between responders and non-responders. Tumor mutational burden (TMB) was z-scored within patients sequenced on the same platform to allow for cross platform comparisons.

Results: A total of 3197 patients were identified, of which 2837 received ICI-mono and 360 received dual-ICI therapy. Estimated cure rates were 11% (95% CI: 8-14%) and 20% (14-26%) among patients treated with front-line ICI-mono (n=912; median PD-L1: 70%, median duration of follow-up: 38 months) and dual-ICI (n=289; 10%; 28 mo). Five year median PFS rates were similar at 11% and 18% respectively. Estimated cure rates were 23% (15-31%), and 43% (31-55%) among responders to front-line ICI-mono (n=280) and dual-ICI (n=114) respectively. There was a significantly higher proportion of complete responders who were “possibly cured” when treated with dual-ICI than with ICI mono (90% vs. 33%, p=0.0011), but no difference in “possible cure” rates between partial responders. There was no difference in PD-L1 expression between “possibly cured” vs. acquired-resistance patients, but there was a significant difference between acquired-resistance patients vs non-responders (ICI-mono: median PD-L1 60% vs. 5%, p=7.2x10-20; dual-ICI: 25% vs. 1%, p=3.9x10-6). Z-scored TMB was significantly higher in “possibly cured” vs acquired-resistance patients, with a larger difference seen in patients treated with dual-ICI (ICI-mono: median z-score: 0.39 vs. 0.15, p=0.0011; dual-ICI: median z-score: 1.2 vs. -0.17, p=0.00064). There was no difference in TMB between dual-ICI treated patients with acquired-resistance vs non-response, whereas a small difference was seen in ICI-mono treated patients. Alterations in FLT4 (VEGFR3) were highly enriched between “possibly cured” patients vs. those who developed acquired resistance to ICI-mono or dual-ICI (odds-ratio=4.3, p=0.0023).

Conclusions: Dual-ICI therapy was associated with a greater proportion of possibly cured patients as compared to ICI-mono in mNSCLC. Higher TMB, particularly in dual-ICI-treated patients, correlated with a greater likelihood of cure. Higher PD-L1, particularly in ICI-mono treated patients, correlated with a greater likelihood of initial response. FLT4 alterations emerged as a potential biomarker of cure, suggesting that lymphangiogenesis may contribute to sustaining immune responses.

Keywords: nsclc, Immunotherapy, cure

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.56 Distinct Predictive Effects of PD-L1 Tps on Immunotherapy Outcomes and Immunophenotype in Squamous Versus Non-Squamous NSCLC

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Introduction: PD-L1 tumor proportion score (TPS) is a key biomarker for immune checkpoint inhibitors (ICIs) efficacy in non-small cell lung cancer (NSCLC). However, its predictive role in squamous (SQ) histology remains unclear, warranting histology-specific investigation.

Methods: Clinicopathologic, genomic, and outcomes data were collected from patients with advanced NSCLC treated with ICIs ± chemotherapy across five international academic centers. Cox regression assessed the association between PD-L1 TPS and survival outcomes to ICIs by histology, adjusting for treatment regimen and line, while spline-based model explored potential non-linear effect across histologic subtypes. Multiplexed immunofluorescence (mIF) on baseline samples quantified immune cell densities, stratifying by PD-L1 TPS and histology. Mutation enrichment analysis explored genomic correlates of response to ICIs ± chemotherapy in SQ NSCLCs.

Results: Among 5148 patients with NSCLC treated with ICIs ± chemotherapy, 909 (17.7%) had SQ histology. Among patients with available PD-L1 TPS, 37.2% had TPS <1%, 30.1% 1-49%, and 32.7% ≥50%. Increasing PD-L1 TPS categories (<1%, 1-49%, ≥50%) were associated with significant stepwise improvements in progression-free (PFS) and overall survival (OS) in NonSQ but not in SQ NSCLCs (Figure 1A). In SQ, only a dichotomized PD-L1 TPS (<1% vs ≥1%) was predictive of longer PFS (adjusted hazard ratio [aHR]: 0.75, p<0.01) and OS (aHR: 0.78, p=0.02), while no difference was observed between TPS 1-49% and ≥50%. Comparing histologies, survival outcomes were similar in TPS subgroups of <1% and 1-49%, but significantly longer in NonSQ vs SQ among patients with TPS ≥50% (PFS aHR: 1.25, p=0.01; OS aHR: 1.50, p<0.01). Spline-based Cox models confirmed the stepwise association between increasing PD-L1 levels and improved survival in NonSQ NSCLCs, but showed a non-linear, plateauing effect beyond 1% in SQ, with no incremental survival benefit (Figure 1B-E). mIF analysis (229 samples: 22 SQ, 207 NonSQ) revealed lower intratumoral CD8+, PD1+, CD8+/PD1+, and FOXP3+ densities in SQ vs NonSQ NSCLCs. Increasing PD-L1 TPS significantly correlated with higher CD8+ infiltration in NonSQ (R=0.25, p<0.01), but not in SQ (R=-0.034, p=0.89), with similar trends across the other markers. In SQ subgroup, KMT2D, MAP3K1 and FANCA mutations were among the genes enriched in responders to ICIs ± chemotherapy (p<0.05).

Conclusions: Increasing PD-L1 levels show stepwise PFS and OS improvements in NonSQ but not in SQ NSCLCs, where TPS acts as a dichotomous (<1% vs ≥1%) rather than continuous predictor. Distinct immunophenotypic and genomic features confirmed this divergence, warranting histology-specific trials and biomarker strategies.

A

	mPFS (months)				mOS (months)			
PD-L1 TPS	**SQ**	***aHR, p***	**NonSQ**	***aHR, p***	**SQ**	***aHR, p***	**NonSQ**	***aHR, p***
<1% vs 1-49%	4.17 vs 6.33	*0.77, 0.01**	4.63 vs 5.82	*0.80, <0.01**	12.6 vs 16.6	*0.79, 0.04**	14.7 vs 18.1	*0.81, <0.01**
<1% vs ≥50%	4.17 vs 6.53	*0.70, <0.01**	4.63 vs 8.25	*0.56, <0.01**	12.6 vs 17.7	*0.77, 0.04**	14.7 vs 27.7	*0.59, <0.01**
1-49% vs ≥50%	6.33 vs 6.53	*0.92, 0.47*	5.82 vs 8.25	*0.70, <0.01**	16.6 vs 17.7	*0.98, 0.86*	18.1 vs 27.7	*0.72, <0.01**

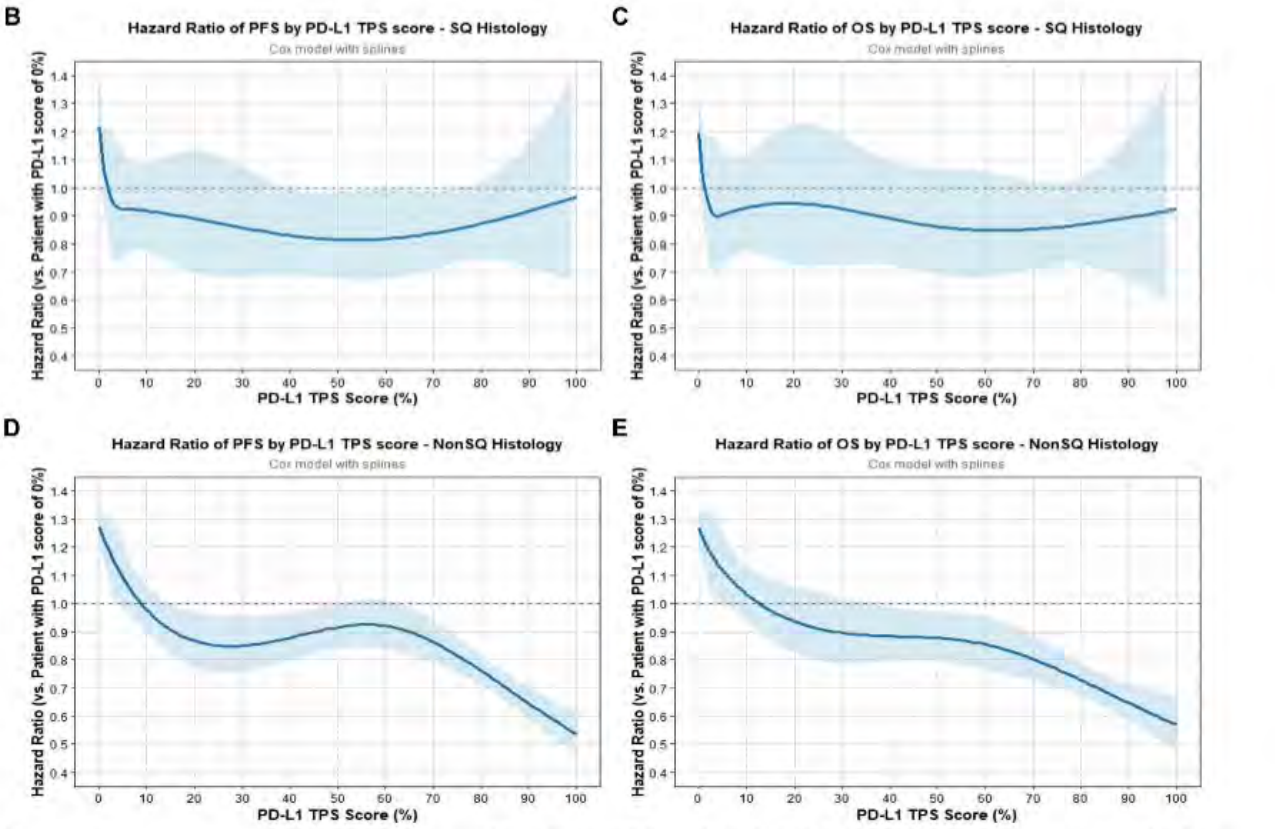

Figure 1: A. Comparative outcomes to ICIs ± chemotherapy between SQ and NonSQ NSCLCs stratified by PD-L1 TPS levels (aHR for treatment regimen and line). **B-E.** Spline-based HR and 95% CIs for PFS and OS of patients with SQ vs NonSQ NSCLC with varying PD-L1 TPS scores, showing a stepwise association between increasing PD-L1 expression and improved outcomes in NonSQ, but not in SQ NSCLCs. HR are calculated as compared to a patient with a PD-L1 score of 0%.

Keywords: Squamous cell carcinoma, PD-L1 expression, Immunotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.57 Association Between CD274 (PD-L1) Gene Expression and PD-L1 Immunohistochemistry in Non-Small Cell Lung Cancer Specimens

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Introduction: The number of immunohistochemistry (IHC)-based biomarkers being developed and validated to guide patient selection for oncology therapeutics is rapidly increasing. However, tumor tissue available for biomarker testing in clinical care is often limited. Multiplex RNA gene expression (GE) for a panel of IHC biomarkers could serve as a screening method, or even a surrogate, for a series of individual IHC tests. As proof of principle, we explored the correlation between CD274 (PD-L1) GE and PD-L1 IHC in non-small cell lung cancer (NSCLC) tissue specimens.

Methods: We queried an institutional database (Foundation Medicine, Inc., Cambridge, MA, USA) of RNA GE and matched PD-L1 IHC results from testing performed from May-September 2024. DNA and RNA co-extracted from FFPE samples were profiled, respectively, using FoundationOne CDx and FoundationOne RNA. PD-L1 IHC was performed with the Dako PD-L1 22C3 PharmDx assay and reported using Tumor Proportion Score (TPS). CD274 (encoding PD-L1) GE (Research Use Only) was quantified from RNAseq data and reported as normalized transcripts per million (TPM).

Results: We identified a cohort of 295 patients diagnosed with NSCLC with available RNA GE and PD-L1 IHC results (TPS 0 = 35.6% [N=105], TPS 1-49 = 36.9% [N=109], TPS ≥50 = 27.5% [N=81]). Three patients had CD274 amplification, all of whom had PD-L1 TPS ≥50; no other pathogenic CD274 alterations were detected. PD-L1 TPS and CD274 expression were positively correlated (Spearman's R = 0.7285, P < .001) and limiting to samples with ≥25% (n=205) or ≥50% (n=96) tumor purity (%TP) strengthened this correlation (R = 0.7485 and R = 0.8022, respectively; P < .001 for both). CD274 expression median [IQR] for clinically relevant TPS thresholds were: TPS 0 58.5 TPM [IQR: 37.2, 98.1]; TPS 1-49 112.1 TPM [IQR: 69.4, 153.8]; and TPS ≥50 276.9 TPM [IQR: 183.6, 399.4] where P < .001 for comparisons across and between all groups. Notably, the IQRs for TPS 0 and TPS ≥50 did not overlap. Moreover, the median difference of expression between TPS 0 and TPS ≥50 further increased when limiting to samples with high %TP: entire cohort (range 5-94% TP) = 218.4; ≥25% TP = 244.3; ≥50% TP = 281.1.

Conclusions: Exploratory analysis demonstrated a positive correlation between CD274 (PD-L1) GE and PD-L1 IHC TPS score, with distinct separation in GE ranges between TPS 0 and TPS ≥50. In the absence of PD-L1 IHC, CD274 GE may be useful to identify NSCLC clinical treatment groups for anti-PD-(L)1 combinations with cytotoxic chemotherapy (TPS 0) versus anti-PD-(L)1 immune checkpoint blockade alone (TPS ≥50). While further clinical correlation is necessary, this serves as a proof of principle for GE as a surrogate for IHC biomarkers. Future investigation is needed to identify clinically relevant expression thresholds for CD274 (PD-L1) for anti-PD-(L)1 immune checkpoint blockade, as well as to explore additional expression biomarkers for antibody-drug conjugates (ADCs) and other novel agents.

Keywords: Gene Expression, PD-L1 IHC, CD274

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.58 Efficacy of First-Line Treatment in Driver-Negative Non-Small Cell Lung Cancer With Liver Metastases : A Bayesian Network Meta-Analysis

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Introduction: This study is designed investigate and determine the optimal first-line treatment options for driver-negative non-small cell lung cancer (NSCLC), and to establish a theoretical foundation for making clinical treatment decisions.

Methods: The present study was prospectively registered within the International Prospective Register of Systematic Reviews (PROSPERO; CRD42025632364). A comprehensive search strategy was employed, encompassing major oncology conferences, Embase, the Cochrane Library, Web of Science, and PubMed. The inclusion criteria for the selected studies were Phase III randomized controlled trials (RCTs) with subjects who had liver metastases from driver gene-negative non-small cell lung cancer (NSCLC). The intervention group received PD-1/PD-L1 inhibitor-based treatment or combination anti-angiogenic therapy, while the control group received chemotherapy only. The primary outcome measure was progression-free survival (PFS), and the secondary outcome measure was overall survival (OS). The Bayesian network meta-analysis was conducted using the “gemtc” and “rjags” packages in R 4.2.3 software.

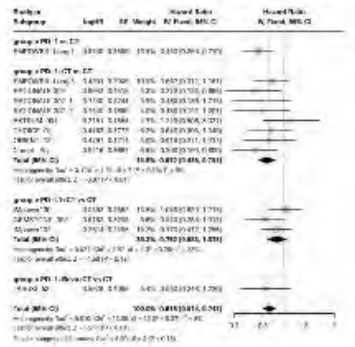
Results: This meta-analysis incorporates data from fifteen clinical trials and 1237 patients. The employment of a PD-1 inhibitor in conjunction with chemotherapy demonstrated a more substantial benefit in terms of both progression-free survival (hazard ratio [HR] = 0.57) and overall survival (HR = 0.68). Furthermore, the PD-1 inhibitor in combination with chemotherapy demonstrated a more favorable outcome in both non-squamous NSCLC (HR=0.37) and squamous NSCLC (HR=0.58). Among the 11 treatment strategies evaluated, the surface under the cumulative ranking curve of camrelizumab plus chemotherapy was 83.06% for PFS and 96.38% for OS.

Conclusions: In treatment-naive patients with driver-negative NSCLC and liver metastases, the combination of a PD-1 inhibitor and chemotherapy provides greater benefits in terms of PFS and OS compared to chemotherapy alone, and camrelizumab plus chemotherapy may be an optimal treatment regimen.

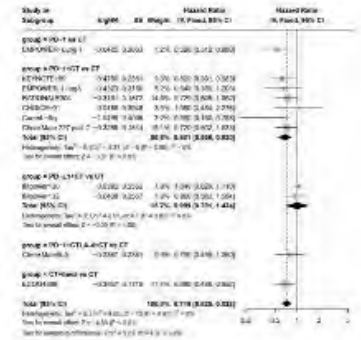
A. Basic characteristics of the included studies

Author	Year	Trial	Number	Experimental arm-I.M	Control arm-I.M	Treatment	Histological Type	Male, %	HR for PFS	HR for OS	Outcome
Shirish Gadgeel	2020	Keynote189	616	66	49	Pembrolizumab+PC vs PC+placebo	nSQ NSCLC	363 (58.93)	-	0.62(0.39-0.98)	PFS、OS、safety
A.Baramidze	2023	EMPOWER-Lung 1	565	48	47	Cemiplimab vs. CT	nSQ NSCLC	313 (87.67)	0.43(0.26-0.71)	0.53(0.31-0.89)	PFS、OS、ORR
A.Baramidze	2023	EMPOWER-Lung 3	466	47	23	Cemiplimab+CT vs. placebo+CT	advanced NSCLC	247 (53.00)	0.66(0.37-1.16)	0.65(0.35-1.20)	PFS、OS、ORR
Howard West	2019	IMpower130	679	69	31	Atezolizumab+CT vs. CT	nSQ NSCLC	400(58.91)	0.93 (0.59-1.47)	1.04 (0.63-1.72)	PFS、OS、safety
Alan Sandler	2006	ECOG 4599	850	90	73	Paclitaxel+Carboplatin+Bevacizumab vs. Paclitaxel+Carboplatin	nSQ NSCLC	463 (54.47)	-	0.68 (0.49-0.96)	OS,PFS,ORR,DCR,Safety
Shun Lu	2021	RATIONALE 304	334	20	17	Tislelizumab + CT vs. CT	nSQ NSCLC	247 (74.0)	0.37 (0.15- 0.90)	0.73 (0.53- 1.05)	PFS
Jie Wang	2021	RATIONALE 307-1	241	15	14	Tislelizumab+ PC vs. PC	SQ-NSCLC	218 (90.45)	0.48 (0.19-1.22)	-	PFS
Jie Wang	2021	RATIONALE 307-2	240	15	14	Tislelizumab + nab-PC vs. PC	SQ-NSCLC	223 (92.92)	0.48 (0.19-1.19)	-	PFS
Luis Paz-Ares	2021	CheckMate9LA	719	68	86	Nivolumab+ ipilimumab +CT vs. CT	advanced NSCLC	504 (70.10)	-	0.79(0.55-0.89)	OS
Caicun Zhou	2024	ASTRUM-004	537	40	17	Serplulimab+CT vs. CT+ Placebo	SQ-NSCLC	488 (90.88)	1.24 (0.51-3.04)	-	PFS、OS、safety、AES
Zhijie Wang	2022	CHOICE-01	465	26	14	Toripalimab+CT vs. CT+Placebo	advanced NSCLC	377 (70.20)	0.64 (0.31 to 1.36)	1.05 (0.50- 2.35)	PFS、AE
Caicun Zhou	2021	ORIENT-12	357	14	13	Sintilimab+GP vs Placebo+GP	SQ-NSCLC	327 (91.60)	0.61(0.27-1.41)	-	PFS
Shengxiang Ren	2021	Camel-Sq	389	21	19	Camrelizumab+CT vs. Placebo+CT	SQ-NSCLC	359 (92.29)	0.39 (0.19-0.80)	0.35 (0.16-0.77)	PFS
Caicun Zhou	2022	GEMSTONE-302	479	39	18	Sugemalimab+CT vs. Placebo+CT	advanced NSCLC	383 (79.96)	0.54(0.29-1.02)	-	PFS
Makoto Nishio	2020	IMpower132	578	37	36	Atezolizumab+PC vs. PC	nSQ NSCLC	384 (66.4)	0.77(0.47-1.25)	0.96(0.58-1.58)	PFS、OS
S. Sugawara	2021	TASUKI-52	550	19	20	Nivolumab+Bevacizumab+Placebo vs. PC	nSQ NSCLC	411 (74.73)	0.55(0.25-1.23)	-	PFS
H. Borghaei	2023	CheckMate 227 part 2	755	86	82	Nivolumab+CT vs. CT	metastatic NSCLC	530 (70.20)	-	0.72(0.50-1.03)	OS、PFS、ORR、safety

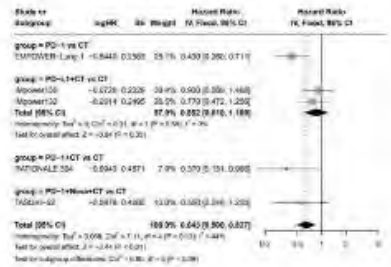
B. The impact of different treatment regimens on PFS



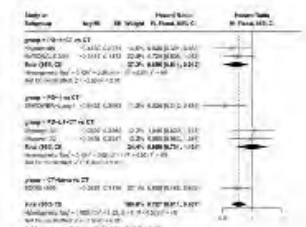
C. The impact of different treatment regimens on OS



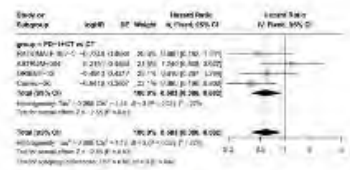
D. Forest plot of PFS in non-squamous NSCLC



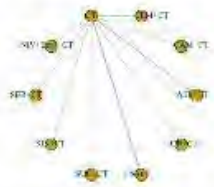
E. Forest plot of OS in non-squamous NSCLC



F. Forest plot of PFS in squamous NSCLC

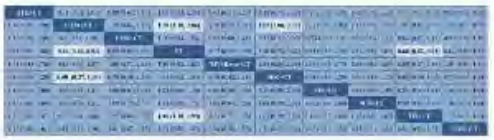


G. Network relationship diagram of PFS



H. Network relationship diagram of OS

I. League diagram of PFS



J. League diagram of OS

Keywords: Meta-analysis, Non-small cell lung cancer, Liver metastases

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.59 Effect of IFNG Expression Levels on Real-World Survival Outcomes in Patients With Metastatic Non-Small Cell Lung Cancer Receiving Immunotherapy

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Introduction: Despite advances in immunotherapy for metastatic non-small cell lung cancer (NSCLC), a significant proportion of patients do not respond to immune checkpoint inhibitors (ICIs). Identifying effective prognostic biomarkers that are independent of squamous and nonsquamous histology is critical for optimizing treatment strategies in NSCLC. Interferon gamma (IFNG) has emerged as a potential marker for predicting immunotherapy outcomes due to its role in immune modulation.

Methods: We retrospectively evaluated metastatic NSCLC patients treated with first-line ICIs or ICI plus chemotherapy with an ECOG performance status of 0 or 1 at the time of initial diagnosis. Patients were identified from the ConcertAI linked with Caris Life Sciences data, a U.S.-based, de-identified, patient-level dataset that integrates EHR-based clinical data with exomic, transcriptomic, and whole slide imaging data. Patients were grouped based on high and low IFNG expression, defined as the top and bottom quartiles of expression (transcripts per million, TPM). Survival analyses, including Kaplan-Meier estimates and Cox proportional hazard models, were performed, stratified by histological subtypes of adenocarcinoma (N = 414) and squamous cell carcinoma (N = 147), and by IFNG expression levels.

Results: We evaluated 561 patients who met the selection criteria. High IFNG expression was associated with significantly longer median overall survival (OS), regardless of histological subtype. The median OS for high IFNG expression was 26.7 months in adenocarcinoma (N = 111) and 27.6 months in squamous cell carcinoma (N=38). In contrast, low IFNG expression corresponded to a median OS of 15.1 months in adenocarcinoma (N = 99) and 12.9 months in squamous cell carcinoma (N = 42). Cox regression analysis confirmed that low IFNG expression was significantly associated with higher mortality risk (Hazard Ratio [HR] = 1.8, 95% CI = 1.35-2.4, P < .001). Histological subtype did not independently predict OS (p > 0.05).

Conclusions: High IFNG expression is associated with improved survival outcomes in metastatic NSCLC patients treated with ICIs or ICIs plus chemotherapy as first-line therapy independent of histological subtype. These findings suggest the potential utility of IFNG as a prognostic biomarker to guide therapy decisions in higher-risk NSCLC and tailor treatment strategies in this patient population.

Keywords: NSCLC, Immunotherapy, IFNG

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.60 Interstitial Lung Abnormalities and MUC5B Polymorphism in Immune Checkpoint Inhibitor Pneumonitis

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Introduction: Interstitial lung disease (ILD) is a significant risk factor for both immune checkpoint inhibitor (ICI)-related and radiation-induced pneumonitis. Interstitial lung abnormalities (ILA), observed in 10-12% of smokers, are radiological findings associated with an increased risk for progression to ILD. ILD can lead to chronic lung inflammation and fibrosis, often worsening over time due to aging or smoking. A polymorphism in the promoter region of MUC5B (rs35705950-T) is strongly linked to idiopathic pulmonary fibrosis, the most common idiopathic ILD. In population studies, the presence of this polymorphism—specifically, each copy of the MUC5B (rs35705950-T) variant was associated with a 2.8-fold increase in the odds of lung abnormalities compared to those with other major MUC5B alleles. However, its association with and impact on ICI pneumonitis outcomes remain unclear.

Methods: We conducted a case-control study using two metastatic NSCLC cohorts, consisting of over 700 patients treated with anti-PD-(L)1 therapy with or without anti-CTLA-4. The study included 24 cases of ICI pneumonitis, diagnosed by a multidisciplinary team, and 48 matched controls from the same cohort. Controls were selected based on propensity score matching per age and smoking status and had available pretreatment CT scans ILA assessment. We analyzed single nucleotide polymorphism for MUC5B genotyping to determine the presence of the MUC5B rs35705950-T polymorphism and its correlation for pneumonitis risk. We analyzed the correlation between the maximum pneumonitis grade (per CTCAE), clinical outcome and radiologic resolution patterns (full, partial, or no resolution) in patients with ICI pneumonitis in relation to the MUC5B rs35705950-T polymorphism.

Results: The rs35705950-T polymorphism was associated with an approximately five-fold increased risk of ICI- pneumonitis (OR 4.6, 95% CI 1.5-15.8) ILAs were identified in 47% of ICI- pneumonitis cases versus 15% of controls, conferring a five-fold increase in pneumonitis risk (OR 4.9, 95% CI 1.7-14.6). However, MUC5B (rs35705950-T) polymorphism was not associated with pneumonitis severity, clinical outcome or its likelihood of radiologic resolution.

Conclusions: The rs35705950-T polymorphism and pretreatment CT scan findings of ILA significantly increase the risk of ICI-P in NSCLC but do not seem to affect clinical outcomes of ICI pneumonitis. Further studies are needed to validate these findings across diverse populations and improve predictive models.

Keywords: Pneumonitis, Interstitial Lung Abnormality, MUC5B polymorphism

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.61 Effects of Probiotic Duration and Type on Immunotherapy Efficacy in Non-Small Cell Lung Cancer With or Without Antibiotics

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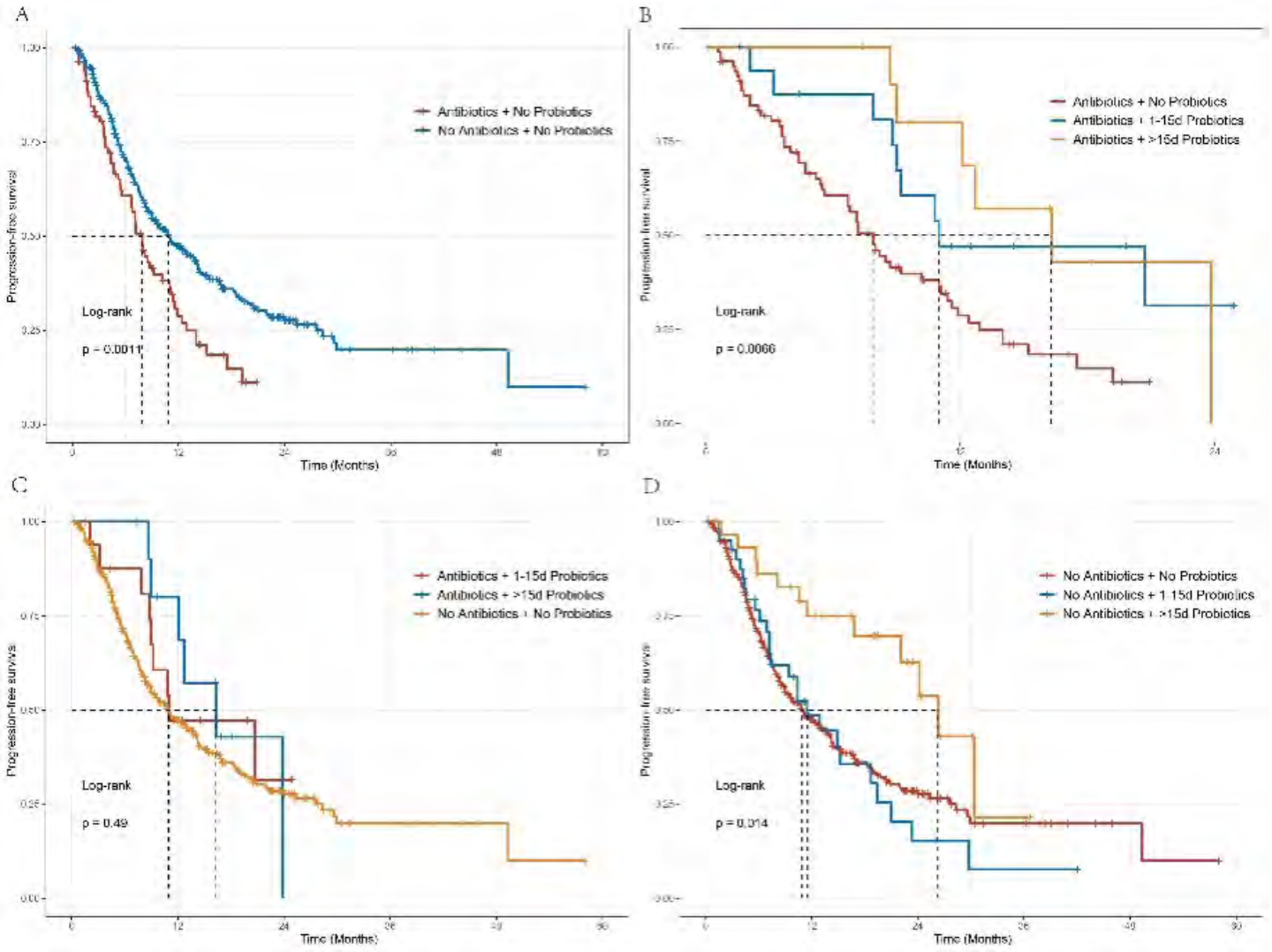
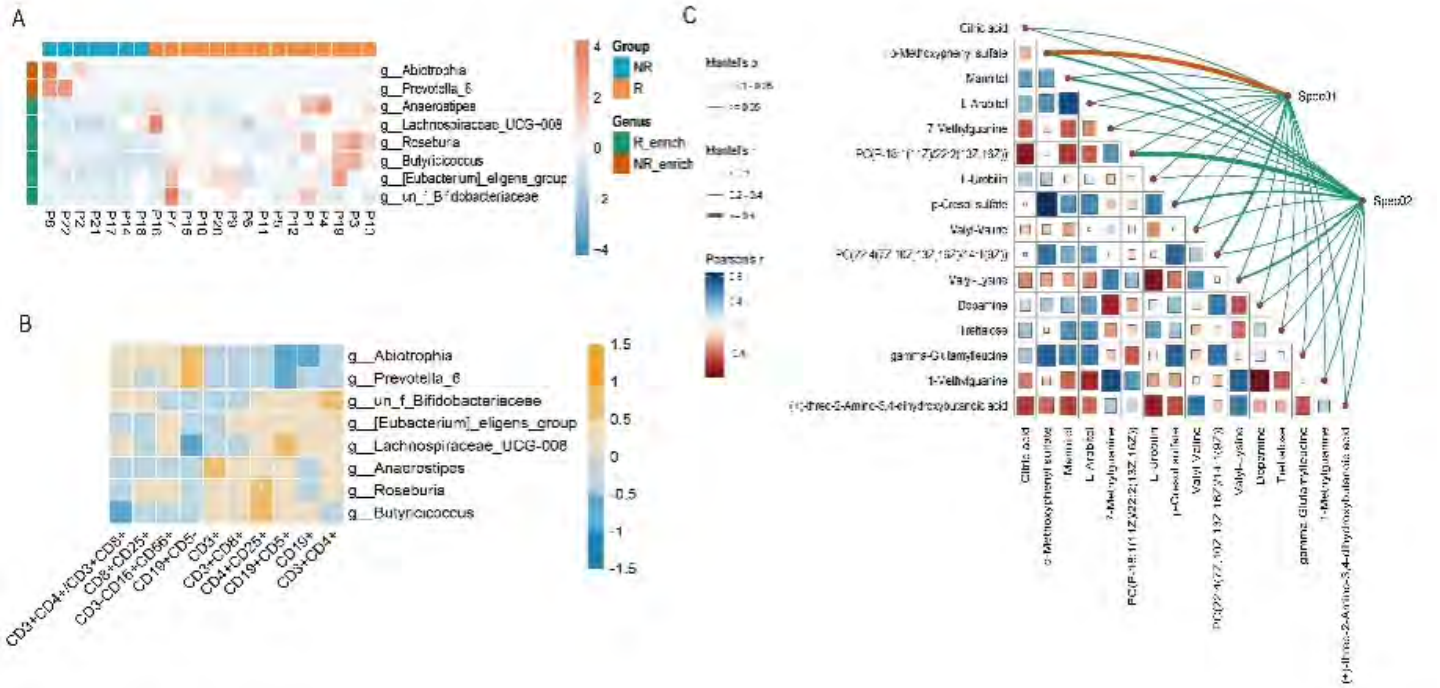
Introduction: In non-small cell lung cancer (NSCLC) patients, antibiotics impair immunotherapy efficacy, while probiotics can enhance it. The relationship between the duration of probiotics and the restoration of immunotherapy efficacy compromised by antibiotics, as well as its potential to enhance immunotherapy outcomes in antibiotic-naive patients, remains unclear. Furthermore, more probiotic types and their mechanisms for improving immunotherapy efficacy need to be identified and elucidated.

Methods: This multicenter study enrolled wild-type NSCLC patients. Clinicopathological features were recorded, focusing on antibiotic and probiotic use and duration. Baseline fecal and blood samples were collected. Gut microbiota were analyzed via 16S rRNA sequencing, and serum metabolites were analyzed through untargeted metabolomics. Flow cytometry was used to explore potential mechanisms.

Results: 524 wild-type NSCLC patients were enrolled in the study, with fecal samples collected from 22 patients. Patients receiving antibiotics alone exhibited poorer PFS and OS. For those receiving antibiotics, the use of probiotics, regardless of duration, led to improved PFS and OS, which were comparable to those of patients in the No antibiotics + No probiotics group. Among the patients who did not receive antibiotics, those who were treated with probiotics for more than 15 days showed improved PFS. Patients with enriched gut microbiota in un-f-Bifidobacterium and roseburia showed better PFS. The frequency of peripheral Th cells was positively associated with the abundance of un-f-Bifidobacterium. There was also a positive correlation between o-Methoxyphenyl sulfate and the gut microbiota that exhibited better immunotherapy efficacy.

Conclusions: Antibiotics weaken immunotherapy efficacy in wild-type NSCLC patients. Probiotics, regardless of duration, restore this compromised efficacy. For antibiotic-naive patients, taking probiotics over 15 days can improve immunotherapy efficacy. Certain probiotics, including un-f-Bifidobacterium and Roseburia, may be potential candidates for improving the efficacy of immunotherapy.





Keywords: Non-small Cell Lung Cancer, Probiotic, Gut microbiota

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.62 Deep Learning Histopathology Model for PD-L1 (TPS) and Immunotherapy Outcome Prediction in Non-Small Cell Lung Cancer

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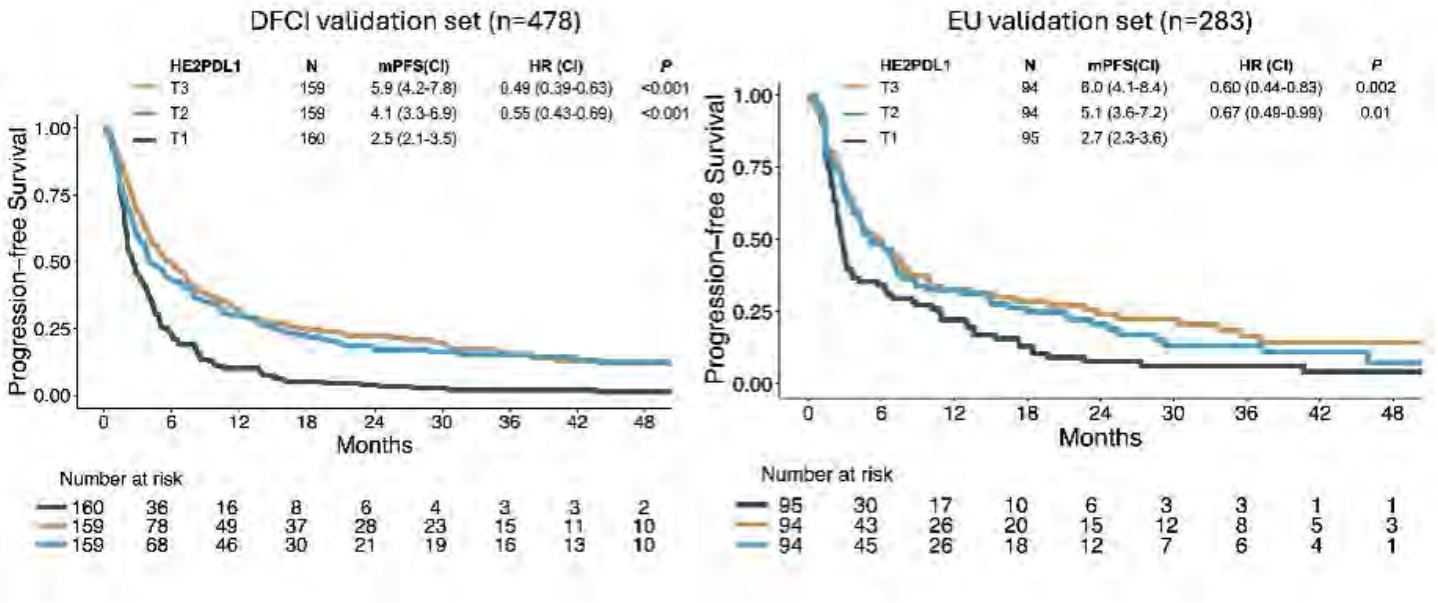
Introduction: PD-L1 expression, assessed by immunohistochemistry (Tumor Proportion Score, TPS), is the key predictive biomarker for managing immunotherapy in advanced lung cancer. We aimed to develop an AI-based model for predicting PD-L1 status directly from H&E images and evaluating its association with immune checkpoint inhibitor (ICI) outcomes.

Methods: We developed a fully automated deep learning model (HE2PDL1) composed of three stages: 1)Tumor detection: A supervised convolutional neural network was trained on 40k H&E image patches (270x270 px) from 624 patients (36% early-stage, 64% late-stage) to identify tumor epithelial regions. 2) Feature extraction of tumor regions was performed using a pathology foundation model (Conch_v1). 3) PD-L1 classification: A transformer-based multi-instance learning model was fine-tuned to classify whole-slide H&E images into three PD-L1 categories (<1%, 1-49%, ≥50%) using immunohistochemistry (TPS) as reference.The model was trained, tuned and evaluated on stage I-IIIA NSCLC patients from the TNM-I trial (NCT03299478; n=720). For external validation, the model was deployed on two independent advanced-stage NSCLC cohorts treated with ICI monotherapy: US cohort (DFCI, n=478) and European multicenter cohort (EU, n=283).

Results: For tumor classification, the model achieved macro F1 score of 0.92 on an external set of 6k images from176 patients (early and late stage). PD-L1 distribution in the overall cohort (n=1481) was: negative 25%, intermediate 32%, and high 43%. In the early-stage development set, the model achieved mean AUC of 0.73 (95% CI: 0.69-0.77) for identifying PD-L1-high tumors in internal 10-fold cross-validation. External validation in two independent cohorts (DFCI and EU) yielded AUCs of 0.75 (0.71-0.80) and 0.67 (0.61-0.73), respectively. HE2PDL1 predictions differentiated ICI objective response with AUCs of 0.69 (0.63-0.73) and 0.60 (0.53-0.66) in the two validation cohorts. A stepwise (tertile-based) increase in HE2PDL1 probability scores was associated with improved progression-free survival following ICI in both external cohorts (Figure), with similar trends observed for overall survival.



Conclusions: The HE2PDL1 deep learning model offers a fast, cost-effective surrogate for PD-L1 IHC testing in NSCLC, using standard H&E slides. It may support treatment decisions when tissue is limited (e.g., small biopsies with no residual material for IHC), staining is inconclusive, or rapid results are needed. Its strong performance across two large independent ICI-treated cohorts suggests value in routine diagnostics.

Keywords: NSCLC, Immunotherapy, Deep Learning

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.63 Shifts of Mutational Signatures Reveal Response Variability to Pembrolizumab-Based Immunotherapy in NSCLC Patients

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Introduction: Immune checkpoint inhibitors, such as pembrolizumab, have revolutionized NSCLC treatment. However, response to immunotherapy remains highly variable and understanding the genomic adaptations is crucial for optimizing the therapy outcomes. In this study, we performed targeted next-generation sequencing (NGS) on tumor (T) and longitudinal liquid biopsy (LB) samples to investigate dynamic mutational changes in NSCLC patients with different responses to pembrolizumab. Analyzing mutational signatures and key driver mutations over follow-up, we aimed to uncover molecular mechanisms associated with durable response or resistance to therapy.

Methods: Within this study, we collected T and LB1 samples before treatment initiation, followed by additional longitudinal LB samples (LB2, LB3, etc.) approximately every 2-3 months during clinical follow-up until therapy completion. Targeted NGS libraries (SureSelect CD Glasgow Cancer Plus Panel, Agilent Technologies, UK) were sequenced on the NovaSeq XPlus system (Illumina, USA) in 2×150 bp read mode. Data preprocessing, including alignment and variant calling, was performed using AGeNT, BWA-MEM, MUTECT2, and VEP, while downstream variant analysis and visualization were conducted using the R package Maftools. This study was funded by the Polish National Centre for Research and Development (LIDER/46/0237/L-12/20/NCBR/2021).

Results: We sequenced 293 samples (77-T, 78-LB1, 55-LB2, 34-LB3, 26-LB4, 23-LB5) from 78 patients (45 males, 33 females; median age: 67±8) treated with pembrolizumab in monotherapy (n=26) or in combination with chemotherapy (n=52) (median PFS: 4 months). Among them, 23 patients were long responders (PFS >12 months), while 55 were short responders (PFS ≤12 months). Mutational analysis showed 70% concordance between T and LB1 samples, with TP53 and KMT2C/D being the most frequently mutated genes in both tissue and liquid biopsy samples. KRAS mutations co-occurring with STK11 (three cases) and KEAP1 (one case) mutations were observed exclusively in short responders. In both T and LB1 samples, short responders showed significant enrichment of the COSMIC_3 signature (associated with HR-related DNA-DSB repair defects), whereas long responders had COSMIC_2 signature (APOBEC), which was significantly associated with TP53 mutations. Over time, both groups transitioned to COSMIC_6 (DNA mismatch repair defects) and COSMIC_30 (unknown etiology) at 3 and 6 months of treatment, respectively. By 12 months (LB4), short responders reverted to COSMIC_3, while long responders retained COSMIC_6 and COSMIC_30, which persisted in LB5. These shifts correlated with the early elimination of TP53 mutations in long responders and their gradual decrease in short responders, as well as the persistence of a KMT2C/DNMT3A-mutated clone, which frequency fluctuated over time.

Conclusions: The dynamic shifts in mutational signatures during treatment reflect ongoing tumor evolution under pembrolizumab pressure, revealing distinct genomic adaptation patterns between long and short responders. Long response was associated with a pre-treatment APOBEC signature and the early elimination of TP53 mutations, potentially supporting the maintenance of adaptive mutational profiles. Conversely, short responders initially exhibited a mutational shift but eventually reverted to their original HR-related DNA-DSB repair defect signature, suggesting an inability to preserve adaptive genomic changes under treatment.

Keywords: NSCLC, Immunotherapy, mutational signatures

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.64 Vision Foundation Model to Predict Immunotherapy Treatment Response in Lung Cancer Patients

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Introduction: Immunotherapy is an advanced approach for treating lung cancer patients. Accurately predicting treatment response allow clinicians to better select patients benefitting from treatment. This study developed an artificial intelligence (AI) approach to predict immunotherapy response in patients with stage-III-IV locally-advanced-non-small-cell lung cancer (NSCLC) using large vision foundation model (VFM), integrating longitudinal computed tomography (CT) imaging and tumor mutational burden (TMB) to predict durable clinical benefit (DCB) defined as no progressive disease within 6 months of treatment initiation.

Methods: A transformer based VFM was created using large and diverse 3D-CT sourced from public and institutional datasets using self-supervised learning. The VFM was refined using 10-fold stratified cross validation using 200 patients with NSCLC to predict DCB. A longitudinal AI model using pretreatment CT (pCT) and CT scan acquired 9 weeks as well as pCT AI model were created. Subset of 153 patients with available TMB were combined with the image to create an AI-TMB model. Performance metrics including AUROC, specificity, and sensitivity. Kaplan-Meier survival analysis was performed to evaluate overall-survival (OS) and progression-free survival (PFS).

Results: The longitudinal-AI-model was the most accurate (AUC-0.89±0.07, sensitivity-0.87±0.09, specificity-0.86±0.16) and was associated with PFS ($p < 0.0001$, Harrell's c-index:0.713) and OS ($p < 0.0001$, c-index: 0.703) using uni- and multivariable cox regression shown in Table 1. AI-TMB model was slightly less accurate (AUC: 0.83 ±0.16, sensitivity: 0.83±0.20, specificity:0.83±0.16) and was also associated with PFS ($p = 0.0001$, c-index: 0.63) and OS ($p = 0.0005$, c-index: 0.639). pCT only model was the least accurate. Figure 1 shows the Kaplan-Meier curves computed by dichotomizing patients into low- versus high-risk groups using probability of predicting DCB with a cut-off of 0.5.

Conclusions: VFM could combine longitudinal-CT as well as CT-TMB to accurately predict immunotherapy response. Further analysis on other institutional cohorts is needed to evaluate model generalization capabilities.

Figure 1. Overall Survial and Progression-Free Survial Analysis

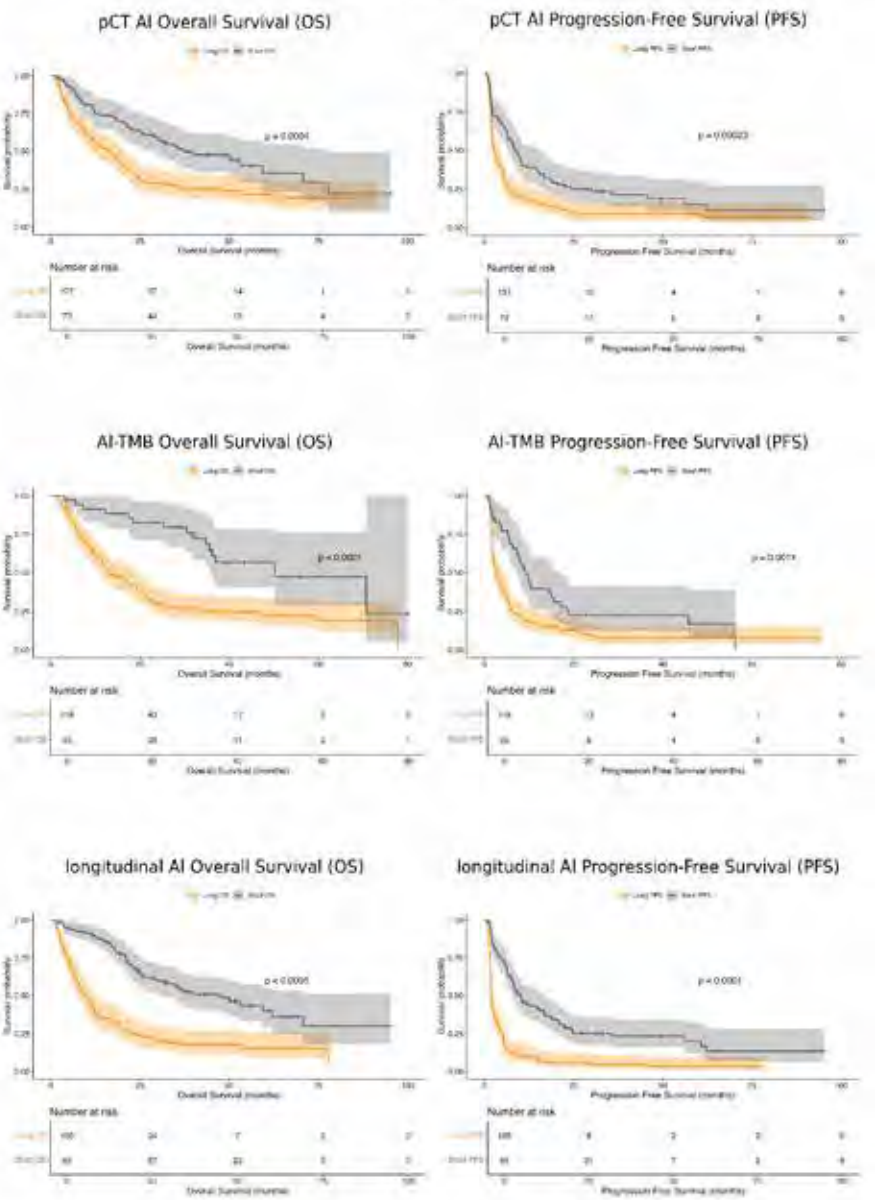

Table 1. Association with (a) Progression free survival (PFS) and (b) overall survival (OS). Multivariable analysis was adjusted for age, sex, smoking status (never, former, current), treatment (monotherapy versus combination), and lines of prior treatments

(a)

Method	Univariable analysis			Multivariate analysis			
	Hazard ratio	CI 95%	p-value	Hazard ratio	CI 95%	p-value	c-index
AI-TMB	3.28	1.84, 5.84	<0.0001	3.58	1.93, 6.64	0.00005	0.648
pCT	3.06	1.87, 5.01	<0.0001	2.745	1.639, 4.60	0.0012	0.632
Longitudinal	5.71	3.72, 8.78	<0.0001	6.354	4.10, 9.84	<0.0001	0.713

(b)

Method	Univariable analysis			Multivariate analysis			
	Hazard ratio	CI 95%	p-value	Hazard ratio	CI 95%	p-value	c-index
AI-TMB	4.92	2.47, 9.77	< 0.0001	5.85	2.77, 12.34	3.6e-6	0.692
pCT	3.63	2.05, 6.41	< 0.0001	2.86	1.58, 5.18	0.0005	0.639
Longitudinal	4.82	3.02, 7.69	4.3e-11	5.349	3.31, 8.65	7.8e-12	0.703

Keywords: Immnotherapy, Artificial Intelligence, Response Prediction

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.65 Ivonescimab Versus Pembrolizumab for PD-L1-Positive NSCLC: A Subgroup Analysis of HARMONi-2 by Tumor PD-L1 Expression Lev

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Introduction: HARMONi-2 (NCT05499390), a phase 3 randomized trial in China compared ivonescimab, a novel bispecific antibody targeting programmed cell death-1 (PD-1) and vascular endothelial growth factor (VEGF), with pembrolizumab as monotherapy in 398 patients with PD-ligand-1 (PD-L1)-positive (tumor proportion score [TPS] ≥1%) advanced non-small cell lung cancer (NSCLC). In the primary analysis, treatment with ivonescimab resulted in a statistically significant improvement in progression-free survival (PFS) compared with pembrolizumab (hazard ratio [HR] 0.51 [95% CI 0.38-0.69]; one-sided P<0.0001) and PFS was broadly consistent across prespecified subgroups of patients. The objective of this subgroup analysis was to further assess efficacy and safety outcomes by level of tumor PD-L1 expression based on TPS.

Methods: HARMONi-2 was a randomized, double-blind phase 3 trial that enrolled adults with locally advanced or metastatic PD-L1-positive NSCLC without EGFR mutations or ALK translocations and had not received previous systemic therapy. Patients were randomly assigned (1:1) and received intravenous ivonescimab 20 mg/kg or pembrolizumab 200 mg every 3 weeks for up to 24 months; randomization was stratified by PD-L1 TPS expression, histology, and clinical stage. Efficacy and safety endpoints reported in primary analysis of HARMONi-2 were evaluated in this subgroup analysis of patients with PD-L1 TPS 1-49%, TPS ≥50%, and TPS ≥90%.

Results: The ivonescimab treatment group included 115 patients with PD-L1 TPS 1-49%, 83 patients with TPS ≥50%, and 27 patients with PD-L1 TPS ≥90%. The pembrolizumab treatment group included 115 patients with PD-L1 TPS 1-49%, 85 patients with TPS ≥50%, and 28 patients with PD-L1 TPS ≥90%. At the January 29, 2024, data cutoff, median follow-up was 8.7 months. The unstratified HR (95% CI) for PFS was 0.54 (0.37-0.78) in patients with PD-L1 TPS 1-49%, 0.48 (0.29-0.79) in patients with TPS ≥50%, and 0.47 (0.16-1.36) in patients with TPS ≥90%. In the ivonescimab treatment group, the overall response rate (ORR) in patients with TPS 1-49% was 43%, 60% in patients with TPS ≥50%, and 63% in patients with TPS ≥90%. In the pembrolizumab treatment group, the ORR was 31%, 48%, and 64%, respectively. Serious treatment-related adverse events (TRAEs) occurred in 23 (20%) patients in the ivonescimab group versus 13 (11%) patients in the pembrolizumab group in the TPS 1-49% subgroup, 18 (22%) vs 19 (22%) patients in the TPS ≥50% subgroup, and 8 (31%) versus 7 (25%) patients in the TPS ≥90% subgroup. Grade ≥3 hemorrhage AEs were similar in patients in the ivonescimab treatment group: 1 (1%) patient in the TPS 1-49% subgroup, 1 (1%) patient in the TPS ≥50% subgroup, and 1 (4%) patient in the TPS ≥90% subgroup and were similar to the rates seen in patients in the pembrolizumab treatment group: 0 versus 1 (1%) versus 0 patients, respectively.

Conclusions: Although the study was not powered to analyze efficacy by PD-L1 subgroups, this analysis shows overall evidence of numerically better PFS benefit and higher response rate with manageable safety profile for ivonescimab compared to pembrolizumab across all PD-L1 subgroups.

Keywords: PD-L1 subgroup, ivonescimab, pembrolizumab

P1.11.66 Cost-Effective Machine Learning for Predicting Survival in NSCLC Patients on Immunotherapy: Insights From the APOLLO11 Study

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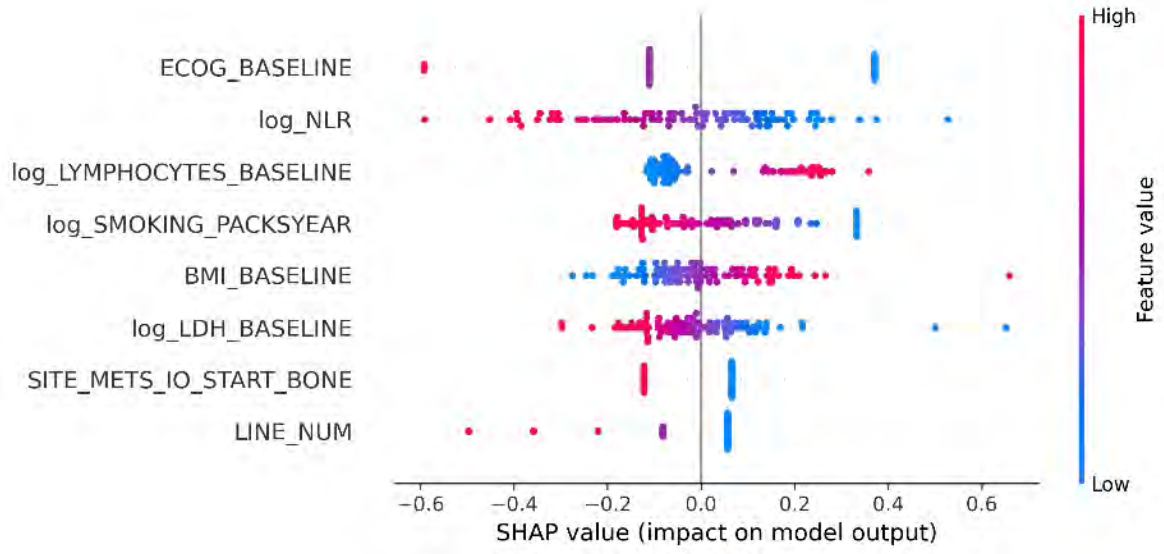
Introduction: Accurately predicting the efficacy of immunotherapy (IO) in individuals with non-small cell lung cancer (NSCLC) remains a key challenge in personalized care. Reliable prognostic tools are critical to support informed decision-making, particularly given IO's potential to offer improved quality of life compared to chemotherapy. Recent advances in machine learning (ML) applied to real-world clinical and laboratory data show promise in enhancing the prediction of IO outcomes and guiding treatment strategies.

Methods: We analyzed data from 1,130 individuals with stage IIIB-IV NSCLC treated with immunotherapy across ten Italian institutions participating in the APOLLO11 study (NCT05550961). Machine learning (ML)-based survival analysis (Cox-ML and other survival models) was used to evaluate overall survival (OS), while classification models (logistic regression and random forest) were developed to predict which patient will have a very poor prognosis (defined as OS<6 months). The dataset was divided into training and internal test sets, with one centre reserved as an external validation set to assess model generalizability. To prioritize the identification of individuals most likely to benefit from IO, we implemented cost-sensitive learning strategies. These adjustments were designed to minimize false negatives ensuring that those with potential benefits would be correctly identified and not excluded from IO treatment. Explainability methods were applied to identify and validate the most influential features across models.

Results: The best classification model achieved an AUC of 0.72 on the test set. On external validation, the model achieved an AUC of 0.80, indicating good generalizability across centres. SHAP analysis highlighted high ECOG performance status, high neutrophil-to-lymphocyte ratio (NLR), and low lymphocyte count as the strongest predictors of very poor prognosis. Models outperformed established biomarker PDL1 (AUC 0.65) and EPSILON score (AUC 0.50) on the test set. For survival prediction, the best-performing model was Cox-ML achieving c-index values of 0.72 and 0.64 on internal test and external validation sets, respectively.

Conclusions: The application of AI methodologies enhanced predictive performance, underscoring the value of RWD, including clinical parameters and laboratory results, and highlighting opportunities for further optimization. Explainability outputs aligned with established prognostic scores such as LIPI and EPSILoN. Given the lack of reliable tools to guide immunotherapy decisions, where choices often rely on subgroup analyses and assumptions, these models show the potential of leveraging routinely collected data to provide practical, scalable decision support in real-world settings through a cost-efficient approach that uses simple ML methods and standard clinical data.



Keywords: NSCLC, immunotherapy, explainable AI

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.67 VEGFR1/PD-L1 CAR-T cell treatment of solid tumor-derived malignant pleural effusion/ascites

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Introduction: Malignant pleuraleffusion/ascites (MPE/MA) is a frequent and disabling complication in patientswith advanced-stage cancers. Previously, we reported that PD-L1 wassignificantly upregulated on tumor and immune cells in MPE/MA, and designed aPD-L1-targetd chimeric switch receptor (PD-L1 CSR), which could enhance thetumor environmental fitness of 2nd generation CAR-T cells. Here, we found that vascular endothelialgrowth receptor 1 (VEGFR1) was broadly and strongly expressed on disseminated tumor cellsin MPE/MA (63 solid tumor patients in total, including 14 lung cancers, 11breast cancers, 6 stomach cancers, and 22 ovarian cancers). This dual targeting rationale promptedthe design of PD-L1 CSR-modified VEGFR1-specific CAR-T cells (VEGFR1/PD-L1CAR-T) to address immunosuppressive and angiogenic tumor microenvironments.

Methods: Preclinicalvalidation demonstrated potent antitumor activity of VEGFR1/PD-L1 CAR-T cellsagainst pleural and abdominal metastatic tumors in murine models. Subsequently,a 3+3 dose escalation, investigator-initiated phase I clinical trial was conducted. Thirteensolid tumor patients with MPE/MA were enrolled, among which six patients (5 NSCLC) were diagnosed with MPE. Patients receivedweight-adjusted infusions of VEGFR1/PD-L1 CAR-T cells, with safety and efficacyoutcomes evaluated.

Results: Treatment achieved 100% MPE control, with transient low-grade fever and mild cytokine elevation as the sole adverse events. The current results supported the potential of VEGFR1/PD-L1 CAR-T as a novel therapeutic for patients with MPE/MA.

Conclusions: These results underscore the feasibility and therapeutic potential of dual-targeted VEGFR1/PD-L1 CAR-T cells for managing MPE/MA, warranting further clinical investigation in advanced solid malignancies.

Keywords: CAR-T cell treatment, malignant pleural effusion/ascites, VEGFR1/PD-L1

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.68 Multi-Omic Profiling Identifies Key Factors Associated With Response to Ivonescimab (AK112) in Non-Small Cell Cance

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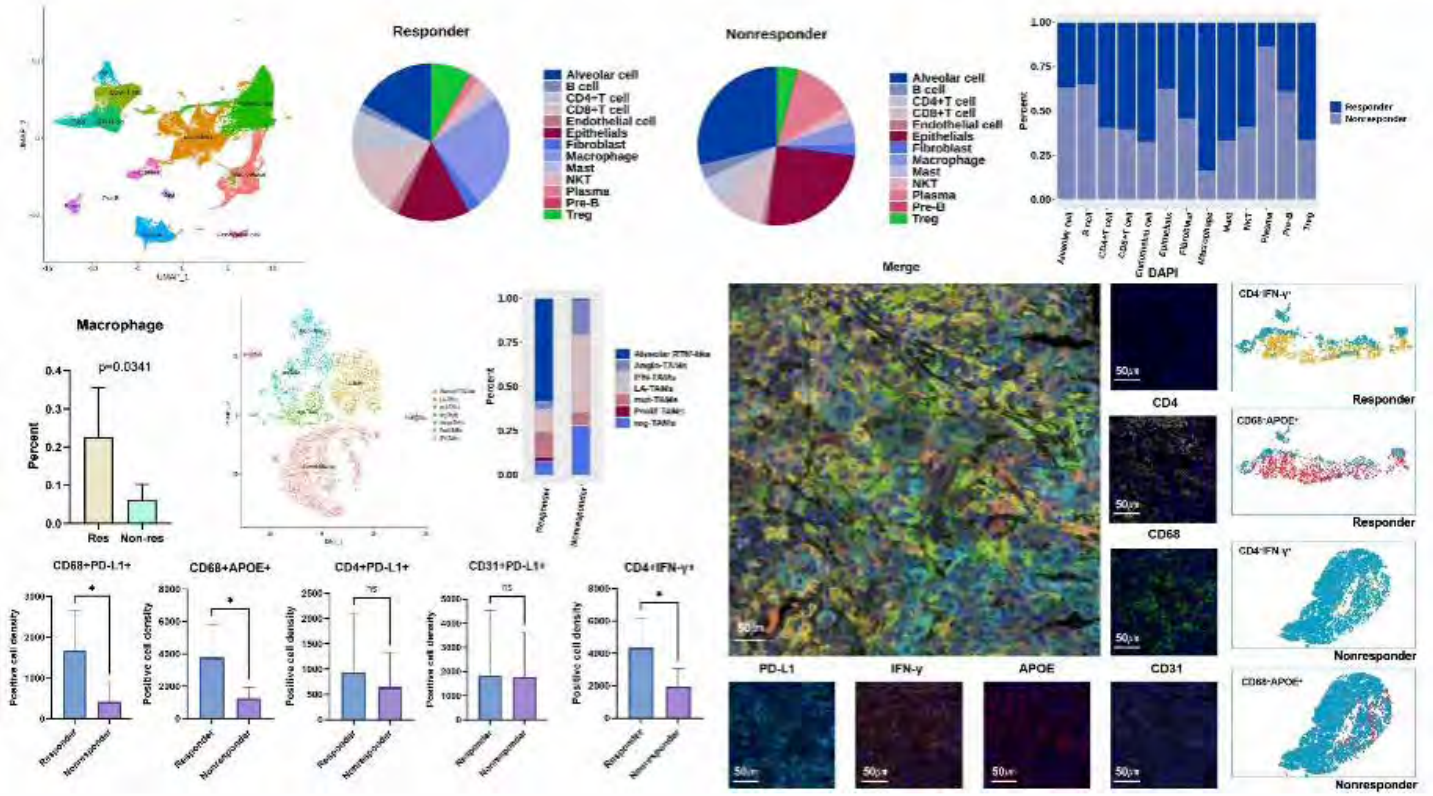
Introduction: Monotherapy with immune checkpoint inhibitors has shown limited efficacy in non-small cell lung cancer (NSCLC). Ivonescimab (AK112), a bispecific antibody targeting PD-1 and VEGF, demonstrated promising results in the Phase 3 HARMONi-2 trial. This study aims to identify predictive biomarkers for AK112 efficacy and explore immune escape mechanisms within the tumor microenvironment (TME).

Methods: This retrospective study included 56 NSCLC patients treated with AK112 between May 2021 and July 2024. Blood biomarkers were analyzed for their predictive value, and a model was developed. The TME immune landscape was evaluated using single-cell transcriptomics, TCR sequencing, multiplex immunohistochemistry, and flow cytometry

Results: Biomarkers such as NLR, MLR, PLR, ApoE, and PD-L1 were found to be associated with treatment response. Among these, PD-L1 exhibited the highest predictive accuracy (AUC 0.623). A predictive model incorporating these biomarkers accurately forecasted the objective response rate (ORR) (AUC 0.742) and progression-free survival (PFS) (P = 0.0081). Single-cell RNA analysis revealed differences in immune cell populations, with APOE+ macrophages correlating with better responses. The proximity of immune cells to tumor vasculature was found to influence treatment efficacy. Flow cytometry further confirmed the pivotal role of APOE+ macrophages in the treatment response.

Conclusions: Blood biomarkers effectively predict the outcomes of AK112 treatment in NSCLC. The developed predictive model provides valuable prognostic insight. APOE+ macrophages play a critical role in the drug's efficacy, and TME analysis offers key insights for developing personalized treatment strategies. This study emphasizes the importance of individualized approaches in NSCLC treatment.



Keywords: Immunotherapy, Ivonescimab, NSCLC

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.69 Efficacy of Immunotherapy ± Chemotherapy in Metastatic NSCLC with KRAS, STK11, or KEAP1 Mutations: A Network Meta-Analysis

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Introduction: Mutations in KRAS, STK11, and KEAP1 are associated with poor prognosis in metastatic non-small cell lung cancer (NSCLC), yet optimal treatment strategies for these subgroups remains unclear. This Bayesian network meta-analysis (NMA) comprehensively evaluates the comparative efficacy of PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, and chemotherapy (CT), alone or in combination, in these molecular subgroups of patients.

Methods: We conducted a systematic review and NMA following PRISMA guidelines, including randomized controlled trials from PubMed, Cochrane, Embase, ClinicalTrials.gov, and major conference proceedings up to February 2025. Studies assessed the following first-line systemic therapies in advanced NSCLC with confirmed KRAS, STK11, or KEAP1 mutations: 1) PD-1/PD-L1 inhibitors; 2) PD-1/PD-L1 inhibitors + CT; 3) PD-1/PD-L1 + CTLA-4 inhibitors; 4) PD-1/PD-L1 + CTLA-4 inhibitors + CT; 5) CT. Outcomes were progression-free survival (PFS) and overall survival (OS). Bayesian random-effects models generated hazard ratios (HRs) with 95% credible intervals (CIs). Treatment rankings were assessed using surface under the cumulative ranking curve (SUCRA).

Results: The analysis included 8 trials (10 publications) encompassing 7,220 patients, of which 4,455 (61.7%) were mutation-evaluable (10.89% KEAP1, 12.37% STK11, 16.25% KRAS). For KEAP1-mutant tumors, PD-1/PD-L1+CTLA-4 inhibitors+CT showed superior OS versus CT alone (HR 0.48, 95% CI 0.25-0.91) and ranked highest, while PD-1/PD-L1 inhibitors+CT was most effective in wild-type. In STK11-mutant NSCLC, PD-1/PD-L1 inhibitors monotherapy significantly improved OS versus CT (HR 0.56, 95% CI 0.35-0.87; SUCRA top-ranked), contrasting with wild-type where PD-1/PD-L1 inhibitors+CT was superior. For KRAS-mutant disease, PD-1/PD-L1 inhibitors monotherapy (HR 0.42, 95% CI 0.21-0.85) and PD-1/PD-L1+CTLA-4 inhibitors+CT (HR 0.63, 95% CI 0.44-0.89) both outperformed CT alone, with monotherapy ranking highest; in KRAS G12C, PD-1/PD-L1 inhibitors monotherapy showed particularly striking benefit (HR 0.28, 95% CI 0.09-0.9). In wild-type tumors, PD-1/PD-L1 inhibitors+CT consistently ranked highest. PFS SUCRA results corroborated these findings.

Conclusions: This analysis suggests mutation-specific therapeutic responses. Better results were observed with PD-1/PD-L1+CTLA-4 inhibitors+CT for KEAP1-mutant, PD-1/PD-L1 inhibitors monotherapy for STK11- and KRAS-mutant (especially G12C), and PD-1/PD-L1 inhibitors+CT for wild-type NSCLC. These results highlight the importance of biomarker-driven selection of checkpoint inhibitors in the first-line setting in patients with KRAS, STK11, and KEAP1 alterations.

Keywords: Non-small cell lung cancer, Network meta-analysis, Immune checkpoint inhibitors

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.70 Immune Cell Infiltration and Spatial Associations in the Tumor Microenvironment Following Dual ICI or ICI-Chemotherapy

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Introduction: Immune checkpoint inhibition (ICI) with anti-PD-L1 inhibitors alone or in combination with anti-CTLA4 inhibition (dual-ICI) or with chemotherapy (ICI-chemo) induces complex changes in the tumor microenvironment (TME). The effects of these distinct treatment combinations on tumor-immune composition are poorly understood. Imaging mass cytometry (IMC) enables analysis of cell compositions and spatial associations in pre- and post-ICI lung tumor samples to elucidate differential immune responses and cellular interactions across treatment strategies.

Methods: Tumor samples from lung cancer patients receiving dual-ICI or ICI-chemo were collected. IMC was used to profile cell types and their spatial interactions within the TME. Statistical analyses were performed to identify significant differences in cell infiltration and spatial associations between treatment groups and response categories.

Results: Post-treatment samples from both treatment groups exhibited significantly higher infiltration of neutrophils, NK cells, and dendritic cells compared to pre samples ($p < 0.05$), indicating immune activation. However, Tregs were significantly elevated in the dual-ICI group ($p < 0.0005$) but not in the ICI-chemo group. Cellular heterogeneity analysis further showed that ICI-chemo samples had higher immune cell infiltration in both pre- and post-treatment samples, while epithelial cells were more abundant in dual-ICI post-treatment samples ($p < 0.0005$). Progressive disease (PD) in the dual-ICI group was associated with elevated epithelial cells and Tregs compared to responders, while PD in the ICI-chemo group was significantly associated with reduced monocytes, macrophages, and CD8 T cells ($p < 0.05$). Multicellular spatial analysis identified eight distinct spatial neighborhood structures. In post-treatment dual-ICI samples, one neighborhood exhibited high infiltration of B cells, dendritic cells, CD4 T cells, and CD11b+ myeloid cells, forming a robust and complex immune neighborhood. However, a shift in this neighborhood was observed in post-ICI-chemo samples, where only B cells and dendritic cells remained prominent, with CD4 T cells and CD11b+ myeloid cells no longer present. Additionally, cell-cell interaction patterns differed, with dual-ICI post-surgical samples showing active interactions among immune and stromal cells, while ICI-chemo post samples displayed avoidance patterns among B cells, dendritic cells, and NK cells with other cell types. Notably, epithelial cells in dual-ICI post samples exhibited an avoidance pattern with immune and stromal cells, while in ICI-chemo post samples, epithelial cells demonstrated active interactions with these cell types.

Conclusions: Dual-ICI or ICI-chemo induces distinct immune responses and spatial cellular arrangements in the TME. Dual-ICI is associated with epithelial cell persistence, higher Treg infiltration, and active immune-stromal cell interactions, though epithelial cells exhibit avoidance of these interactions, potentially contributing to progressive disease. In contrast, ICI-chemo promotes higher immune cell infiltration and altered spatial organization, with epithelial cells actively interacting with immune and stromal cells. These findings highlight the importance of spatial dynamics and cell-cell interactions in shaping treatment outcomes, offering insights for optimizing treatment strategies in cancer.

Keywords: Immunotherapy, Immune check point inhibitor, ICI-Chemotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.71 RMT in Non Small Cell Lung Cancer

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Introduction: Multiple studies have shown that gut microbiome composition may modulate response to immune checkpoint inhibitors (ICI). Recent clinical trials in melanoma demonstrated safety and feasibility of fecal microbiota transplant (FMT) in combination with ICI. No study has demonstrated the safety and efficacy of FMT derived from healthy donors in patients receiving combination ICI and platinum-based chemotherapy. We report the preliminary safety and efficacy of restorative microbiota therapy (RMT) from the open-label safety-run-in portion of the randomized double-blind phase II Trial of RMT or placebo in combination with durvalumab and tremelimumab with chemotherapy in advanced Non-Small Cell Lung Cancer (NSCLC).

Methods: Patients with treatment-naïve locally advanced or metastatic NSCLC without actionable genomic alterations were enrolled. Eligible study participants received RMT, a standardized oral encapsulated formulation of freeze-dried microbiota derived from healthy donors manufactured by the University of Minnesota Microbiota Therapeutics Program. RMT was given weekly for 16 weeks and patients received the combination of durvalumab, tremelimumab and platinum doublet chemotherapy per the POSEIDON clinical trial. The co-primary endpoints were the safety and tolerability (NCI CTCAE v 5) and the efficacy using progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Blood and stool were collected at frequent intervals. 16S ribosomal RNA (rRNA) sequencing was performed on the stool specimens and measures of diversity, and relative abundance were estimated. The present study reports the open-label safety component of the study participants who received RMT from a single donor.

Results: Ten participants were included in the analysis of safety and efficacy. Median age was 62 years (range 53-75 years), 55% were female and all patients had adenocarcinoma histology. Median follow-up time was 15 months (range 2-24 months). The most common AE probably or possibly related to RMT were diarrhea, bloating, constipation, anorexia, and fever. Grade ≥3 AE probably or possibly related to RMT and chemoimmunotherapy was 17%. There were no cases of bacteremia or treatment-related deaths. Four patients remain on the study treatment. Confirmed objective response rate was 50% (95% CI: 24, 76) and the median PFS was 5.3 months (95% CI 1.6, NE). Exploratory analysis of 16S rRNA sequencing data (N=9) showed that the relative abundance of Collinsella was higher in responders compared to non-responders.

Conclusions: We report that the combination of microbiota therapy with chemoimmunotherapy appears to be safe with no new toxicity signal. Preliminary efficacy is promising, and the randomized double-blind placebo-controlled study is ongoing. Early data suggest that Collinsella in the stool is associated with treatment response.

Keywords: Non small cell lung cancer, Immunotherapy, Gut microbiome

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.72 Phase II Study of Combination Azacitidine and Entinostat and Nivolumab in Patients With Metastatic Non-Small Cell Lung Cancer

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Introduction: Emergence of resistance to immune checkpoint blockade (ICB) mandates the development of strategies for ICB sensitization. Epigenetic targeting agents with ICB represent a novel combinatorial approach to enrich anti-tumor immunity in non-small cell lung cancer (NSCLC). Hypermethylation of DNA promoter regions by DNA methyltransferases (DNMT) and histone deacetylation by histone deacetylases (HDAC) are two key epigenetic regulatory mechanisms, with preclinical studies showing that HDAC and/or DNMT inhibition can induce susceptibility to ICB and inhibit tumor growth. Herein, we will present results of completed arms from a clinical trial of combination epigenetic therapy with concurrent nivolumab.

Methods: Patients with previously treated metastatic NSCLC were enrolled into this multi-institutional platform phase II study (NCT01928576). Treatment arm assignment was defined by prior ICB treatment status and related disease response. Arm D enrolled ICB-naïve patients; Arm E enrolled patients with ICB-refractory disease (progression within 6 months of ICB initiation); and Arm F enrolled ICB-pretreated patients (stable disease ≥ 6 months on prior ICB therapy). Study treatment for all patients was combination azacitidine (40 mg/m2 subcutaneous days 1-5, 8-10), entinostat (4 mg by mouth days 3 and 10) and nivolumab (3 mg/kg IV days 1 and 15) for 6 cycles, followed by nivolumab alone. The primary endpoint of the study is overall response rate (ORR) by Arm. Secondary endpoints include time to progression (TTP), 24-week progression-free survival (24 wk-PFS), median overall survival (mOS) and safety and tolerability.

Results: Between September 2017 and January 2022, 40 patients enrolled in the trial to Arm D (n=14), Arm E (n=7) and Arm F (n=19) respectively. ORR was 21% (95% CI: [5-51%]) on Arm D, 14% [0-58%] on Arm E and 11% on Arm F [1-33%]. Median TTP was 7.8 months on Arm D, 4.9 months on Arm E and 3.8 months on Arm F. 24wk-PFS in Arm D was 57% [36-90%], in Arm E was 29% [9-92%], and in Arm F 42% [25-71%]. mOS for Arm D was 24.6 months, for Arm E 5.0 months and 12.1 months for Arm F. One patient on Arm E experienced two dose-limiting toxicities attributed to study treatment (dyspnea, vomiting); one treatment-related serious adverse event (trSAE) was seen on Arm D, and 5 trSAEs were reported in two patients on Arm E.

Conclusions: Concurrent combination epigenetic therapy with ICB was safe for patients with previously treated advanced NSCLC regardless of prior ICB exposure. This combination was encouragingly efficacious in the post-ICB setting. Patients treated on Arm F were found to have promising clinical benefit following previous disease progression on standard treatment approaches. Further correlative evaluation, including in-depth genomic and transcriptomic analyses, are ongoing to accurately identify patients most likely to benefit from this therapeutic approach. Final integration of these translational studies with clinical outcomes will work to identify the biologic effect of epigenetic therapy in re-shaping the tumor microenvironment to personalize this epigenetic combinatorial approach.

Keywords: epigenetics, immunotherapy combinations, clinical trial

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.73 Tiragolumab Plus Atezolizumab and Bevacizumab in Immunotherapy-Refractory, Pd-L1+, Advanced Non-Squamous Non-Small Cell Lung Cancer

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Introduction: Treatments for checkpoint inhibitor immunotherapy (CPI)-refractory advanced non-small cell lung cancer (NSCLC) are limited. Inhibition of vascular endothelial growth factor (VEGF) has demonstrated synergy in combination with PD-(L)1 blockade in both CPI-naïve and -refractory NSCLC. Blockade of T-cell immunoglobulin and ITIM domain (TIGIT) has also shown synergy when combined with anti-PD-(L)1 CPI, and translational work indicates tumor infiltration with immune inhibitory cells (regulatory T-cells, macrophages) are critical to anti-tumor efficacy of anti-TIGIT CPI. This suggests TIGIT-based therapies may be best-positioned for CPI-resistant/refractory disease in which these cell populations are commonly enriched. Here we present interim data from a multi-cohort single-arm phase 2 trial of tiragolumab (anti-TIGIT) plus atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) in immunotherapy-refractory, PD-L1+, advanced non-squamous NSCLC (NCT04958811).

Methods: In cohort A of this study, patients with advanced PD-L1+ (tumor proportion score (TPS) ≥ 1%), EGFR/ALK/ROS1 wild-type, non-squamous NSCLC with progression on prior anti-PD-(L)1-based CPI are treated with tiragolumab 600 mg IV with atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV every 3 weeks until progressive disease or unacceptable toxicity. The primary endpoint is investigator-assessed objective response rate (ORR) according to RECIST v1.1, utilizing a Simon 2-stage design in which a null ORR of 4% is tested against a one-sided alternative of 20%. A sample size of 21 patients provides 80% power with a one-sided type 1 error rate of 5% to determine a true ORR of 20%. Key secondary endpoints are investigator-assessed progression-free survival (PFS), overall survival (OS) and safety (assessed by frequency of treatment-emergent adverse events [TEAEs]). Pre- and on-treatment blood and tumor specimens are being collected for translational analyses.

Results: In stage 1 of the Simon 2-stage design, 12 patients were enrolled. Median age was 63.5 years, 58% of patients were female, and 75% had a history of current or prior smoking. Median number of prior lines of therapy was 1 (range: 1-3) and 58% had PD-L1 high (TPS ≥ 50%) disease. The investigator-assessed ORR was 25% (95% confidence interval (CI), 9.0 - 53.0) with a disease-control rate of 83% (95% CI, 55.0 - 95.0). At a median follow-up of 10.7 months, the median PFS was 4.8 months (95% CI, 2.6 - Not Reached [NR]) and the median OS was 21.5 months (95% CI, 7.7 - NR). Nine patients (75%) experienced a grade ≥3 TEAE, of which hypertension (2 patients - 15%) and pneumothorax (2 patients - 15%) were most common. In both instances, pneumothorax occurred spontaneously in setting of documented bullous emphysema and was adjudicated unrelated to therapy. Four patients (33%) experienced a grade ≥3 treatment-related adverse event, among which hypertension (15%) was most common.

Conclusions: Tiragolumab plus atezolizumab and bevacizumab demonstrates a promising efficacy signal with favorable toxicity profile in patients with advanced PD-L1+, CPI-refractory, non-squamous NSCLC. Based on these data, and per protocol, the study will proceed to the second stage of the Simon 2-stage design. Planned tissue and blood correlates will explore immunologic, molecular, and pathologic response features to identify patient subsets most likely to benefit from this approach.

Keywords: immunotherapy, TIGIT, VEGF

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.74 Phase Ib Study of Golidocitinib Plus Anti-PD-1 in Anti-PD-1 Treated Advanced NSCLC: Dose-Escalation Safety Using BOIN Design

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Introduction: Resistance to first-line immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC) leads to limited treatment options and poor prognosis. Preclinical and early clinical data have shown synergistic effects between JAK inhibitors and anti-PD-1, suggesting a promising therapeutic strategy in this population. Our study evaluates Golidocitinib, a selective JAK1 inhibitor, in combination with Anti-PD-1 in patients with locally advanced or metastatic NSCLC who progressed after first-line Anti-PD-1 therapy. The study aims to determine the safety, tolerability, and preliminary efficacy of this combination, addressing a critical unmet need in overcoming immune resistance. The dose-exploration phase employs a Bayesian Optimal Interval (BOIN) design to determine the recommended expansion phase combination dose.

Methods: This study is a phase Ib, single-center, single-arm exploratory clinical study. The BOIN design to establish a safe dose of Golidocitinib with anti-PD-1. Patients received oral Golidocitinib at either 75 mg or 150 mg once daily, combined with an anti-PD-1 (200 mg, intravenous, every 3 weeks). Dose-limiting toxicities (DLTs) were evaluated over a 28-day period (first cycle plus 7 days) to establish the combination dose, with 3-6 patients(pts) per dose level. Following dose escalation, the study transits to an expansion phase at the selected dose to assess antitumor efficacy, with the primary endpoint of objective response rate (ORR) per RECIST 1.1 criteria. Secondary endpoints included progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety.

Results: In the BOIN dose-escalation phase, 6 patients were enrolled: 3 received Golidocitinib at 75 mg daily and 3 at 150 mg daily, each combined with anti-PD-1. No DLTs were observed in either cohort during the 28-day DLT assessment period, indicating good tolerability and safety. Grade 2 adverse events (AEs) were observed as neutropenia (2 pts), hypertriglyceridemia (2 pts), leukopenia (1 pt), thrombocytopenia (1 pt) and proteinuria (1 pt) in 4 patients. Additionally, one patient reported a cardiac-related Grade 2 AE (manifested as atrial fibrillation, rapid ventricular rate and aberrant conduction). No adverse events greater than Grade 2 were reported. Based on the BOIN algorithm and absence of DLTs, the 150 mg dose was selected as the combination dose. The study will now expand to enroll a total of 30 patients to further evaluate safety and efficacy, focusing on ORR as the primary measure of antitumor activity.

Conclusions: The combination of Golidocitinib at 150 mg daily with anti-PD-1 was well-tolerated in immune-resistant NSCLC patients, with no DLTs observed in the dose-escalation phase. These preliminary results support progression to the expansion phase, where safety and therapeutic potential will be further explored. This approach holds promise as a novel strategy to overcome resistance to prior ICIs therapy in NSCLC population. Ongoing enrollment and data collection will provide deeper insights into its clinical utility.

Keywords: NSCLC, Anti-PD-1 Treated, Golidocitinib Plus Anti-PD-1

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.75 A Phase 2 Study of PCSK9 Inhibitor, Alirocumab, and PD1 Inhibitor, Cemiplimab, in Advanced Immunorefractory Metastatic NSCLC

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Introduction: For most NSCLC patients, overcoming immunotherapy resistance remains a critical challenge. In preclinical models, PSCK9 mediated immune checkpoint inhibitor (ICI) resistance by degrading MHC1 molecules. Further, PCSK9 inhibition synergized with anti-PD1 antibody to induce cytotoxic CD8+ T cell activation and intratumoral penetration to enhance anti-tumor activity.

Methods: TOP 2201 is a phase II, single arm trial designed to evaluate the clinical activity and safety of alirocumab (PCSK9 inhibitor) in combination with cemiplimab (anti-PD1 antibody) in patients whose tumors were ICI resistant. The primary endpoint is objective response rates (ORR). Secondary endpoints include progression free survival (PFS), overall survival (OS), duration of responses (DOR), disease control rates (DCR) and safety. Correlative objectives include biomarker analysis to identify predictors of response.

Results: Forty patients were enrolled between May 2023 and November 2024 (data cut off). The ORR in the intention-to-treat (ITT) population was 14.7%. When stratified by histology, the ORR was 36.4% in squamous and 3.6 % in non-squamous histology. The DCR in the study population was 83.2%. Amongst responders, the median DOR was 9.9 months (95% CI, 4.2 - 15.8). The median PFS was 3 months (95% CI, 2.6 - 5.5) for the ITT population. By histology, the median PFS was 5.5 months (95% CI, 0.8 - 17), and 2.8 months (95% CI, 2.1 - 4.1) for the squamous and non-squamous respectively. In the ITT population, the median OS was 7 months (95% CI, 3 - 13); the 6-month and 12-month OS rates were 61% and 49.5% respectively. By histology, the 6-month OS rate was 82% for squamous and 54% for non-squamous, while the 12-month OS rate was 71.6% and 40.4% for squamous and non-squamous respectively. Exploratory analysis revealed that the presence of oncogenic alterations in PIK3CA/AKT1/PTEN was significantly associated with improved outcomes. The ORR of patients with alterations in PIK3CA/PTEN/AKT1 was 50% (95% CI, 24 - 73) whereas in patients without these alterations the ORR was 0%. The median DOR in the presence of the alterations was approximately 10 months (95% CI, 4.2 - 15.8). When stratified by the presence alterations, the median PFS was 14.9 months (95% CI, 0.8 - 17) vs 2.7 months (95% CI, 0.8 - 17) in the altered vs unaltered groups respectively. The presence of PIK3CA/PTEN/AKT1 alteration predicted a statistically significant improvement in PFS with a HR of 0.26 (95% CI, 0.13 - 0.5; p 0.0012). There was trend towards improved OS in the altered versus unaltered group, but it did not reach statistical significance, HR 0.4 (95% CI, 0.16 - 0.99; p 0.07). There were no unexpected safety signals.

Conclusions: Alirocumab added to cemiplimab was well tolerated and reversed immunotherapy resistance in a subset of patients. Notably, patients with squamous histology demonstrated improved ORR and survival benefit compared to non-squamous histology. The response pattern seen with alterations in PIK3CA/PTEN/AKT1 suggest that PIK3CA/PTEN/AKT1 could be biomarkers of response to PCSK9-based combinations. Confirmation of these findings are needed in larger studies. The impact of PIK3CA/PTEN/AKT1 alterations on PCSK9 biology is being investigated in preclinical models.

Keywords: Immunoresistant, PCKS9, NSCLC

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.76 Bevacizumab Plus Serplulimab and Chemotherapy for EGFR-TKI-Resistant Non-Squamous Non-Small Cell Cancer: A Phase2Study

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Introduction: Although the quadruple regimen combining bevacizumab, immunotherapy, and platinum-based doublet chemotherapy has become a primary treatment option for EGFRmut non-squamous non-small cell lung cancer (nsq-NSCLC), its clinical benefits in EGFR-TKI-resistant populations remain controversial. Therefore, we initiated a phase 2 study to investigate the feasibility, efficacy, and safety of bevacizumab (HLX04) combined with serplulimab (HLX10) and standard chemotherapy in EGFR-TKI-resistant nsq-NSCLC patients.

Methods: This is a multicenter, single-arm phase 2 trial (NCT06334757). The main inclusion criteria are adults aged 18-70 years with EGFRmut nsq-NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, documented disease progression after first- to third-generation EGFR-TKI therapy (≤2 lines), and no history of immunochemotherapy exposure. Eligible patients receive 4-6 cycles of HLX04 (7.5 mg/kg, day 1) plus HLX10 (300 mg, day 1), in combination with standard chemotherapy consisting of pemetrexed and carboplatin every 3 weeks, followed by maintenance therapy with HLX04 plus HLX10 and pemetrexed until progression, unacceptable toxicity, or up to 2 years (35 cycles). After considering both safety profiles and socioeconomic burden, the bevacizumab dose of 7.5 mg/kg was selected for this study. The primary endpoint is the objective response rate (ORR). The secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to response (TTR), duration of response (DoR), and safety.

Results: This study enrolled 46 patients from nine centers across China. The median age was 59 (range: 36 - 70); 63.0% were female, 73.9% were non-smokers, 95.7% had an ECOG PS of 1, and 54.4% had brain metastases. Thirty-four patients (73.9%) failed on prior first-line EGFR-TKI treatment. Thirty-three patients (71.7%) previously received a third-generation EGFR-TKI only. One patient had a confirmed complete response, and 21 had partial responses, resulting in an ORR of 47.8% (95% CI: 32.9 - 63.0%) and achieving the predefined target of 45.0%. The DCR was 87.0% (95% CI: 73.7 - 95.1%). As of March 4, 2025, the median follow-up was 8.8 months. A total of 25 PFS events were reported, with a median PFS of 7.7 months (95% CI: 7.0 - NR) and a 6-month PFS rate of 68.3% (95% CI: 55.8 - 83.6%). The median TTR and DoR were 1.5 months (95% CI: 1.4 - 2.8) and 6.2 months (95% CI: 5.3 - NR), respectively. OS data remained immature, with three deaths reported. Subgroup analyses revealed that patients without brain metastases were more likely to achieve better efficacy, with an ORR of 52.4% vs. 44.0% and a median PFS of 9.5 vs. 7.1 months. No statistically significant differences in PFS were observed among patients stratified by prior therapy lines or EGFR-TKI agents. The incidence of any grade of adverse events (AEs) was 80.4% (37/46). Seventeen (37.0%) patients experienced grade ≥3 AEs; neutrophil count decreased (12/46, 26.1%) was the most frequent, followed by white cell count decreased (9/46, 19.6%) and platelet count decreased (8/46, 17.4%).

Conclusions: These findings indicated that a dose-reduced bevacizumab regimen combined with serplulimab and platinum-based doublet chemotherapy exhibited promising efficacy and manageable safety for patients with EGFR-TKI-resistant nsq-NSCLC.

Keywords: EGFR-TKI-Resistant, Immunochemotherapy, nsq-NSCLC

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.77 A Comprehensive Analysis of Front-Line Regimens for Stage IV Non-Squamous Non-Small Cell Lung Cancer: A 13-Year Experience

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Introduction: Advances in immunotherapy and targeted therapy have reshaped the standard of treatment for stage IV non-squamous (NS) non-small cell lung cancer (NSCLC). However, there is a paucity of real-world data comparing the previous standard of treatment to modern regimens. In this retrospective study we analyzed the overall survival (OS) in stage IV NS NSCLC treated with standard chemotherapy (CTX) compared to modern regimens.

Methods: We conducted a retrospective analysis of de novo stage IV NS NSCLC at time of diagnosis treated at Cleveland Clinic, OH from 1/2010-12/2022. Baseline variables including age at diagnosis, sex, race, performance status, smoking history, PDL1 testing and molecular profiling were collected along with treatment regimens. Treatment response was assessed using RECIST 1.1 response criteria. OS was calculated from date of first therapy. Multivariable cox hazard regression (CPH) was used to adjust for confounding. We compared two groups: 1) immunotherapy (IT), CTX-immunotherapy (CTX + IT) and targeted therapies which were grouped as “modern therapies” and 2) conventional CTX.

Results: We identified 1,518 patients with NS NSCLC, of which 97% had adenocarcinoma (N = 1471). Median age at diagnosis was 65 (IQR 58-73). 51% of the patients were female, 82% were white and 42% were current smokers. Treatments administered included conventional CTX (744, 49%), IT (186, 12%), CTX+IT (318, 21%), and targeted therapy (270, 18%). The most common regimens were carboplatin + pemetrexed/paclitaxel (N = 502, 80%) and bevacizumab + carboplatin + pemetrexed/paclitaxel (N = 127, 20%) for CTX, pembrolizumab (N = 167, 89%) for IT and carboplatin + pemetrexed + pembrolizumab (N = 153, 41%) for chemo-IT. Overall response rate was 58% with median follow-up of 47.5 months. The 2 and 5-year OS were 30% (95%CI 28-33) and 12% (95%CI 10-14). On multivariable CPH, modern regimens improved OS by 28% compared to conventional CTX (HR 0.72, 95%CI 0.65-0.81, p < 0.001). In the conventional CTX group, bevacizumab + carboplatin + pemetrexed/paclitaxel was associated with improved OS compared to carboplatin + pemetrexed/paclitaxel (HR 0.75, 95%CI 0.59-0.94, p = 0.012) and pemetrexed was superior to paclitaxel (HR 0.79, 95%CI 0.63-0.99, p = 0.047). Using multivariable CPH, front-line Osimertinib (N = 81) was associated with improved OS compared to erlotinib (N =93) in EGFR mutated NS NSCLC (HR 0.59, 95%CI 0.42-0.84 p = 0.003) but not afatinib (n=26) (HR 0.80, 95%CI 0.48-1.33, p = 0.013). In ALK mutated NS NSCLC, multivariable CPH showed that front-line crizotinib (N =20) was associated with worse OS than alectinib (N = 28) (HR 4.4, 95%CI 1.87-10.6, p < 0.001)

Conclusions: In the largest retrospective study of stage IV NS NSCLC, we confirmed that modern regimens improved OS by 28% compared to conventional CTX. Despite that, long term survival remains poor and further research is needed.

Keywords: Adenocarcinoma, Immunotherapy, Chemotherapy

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.78 NAI, An IL-15 Superagonist, A New Class Of Lymphocyte Stimulating Agent (LSA) Prolongs OS In NSCLC By Reversing Lymphopenia

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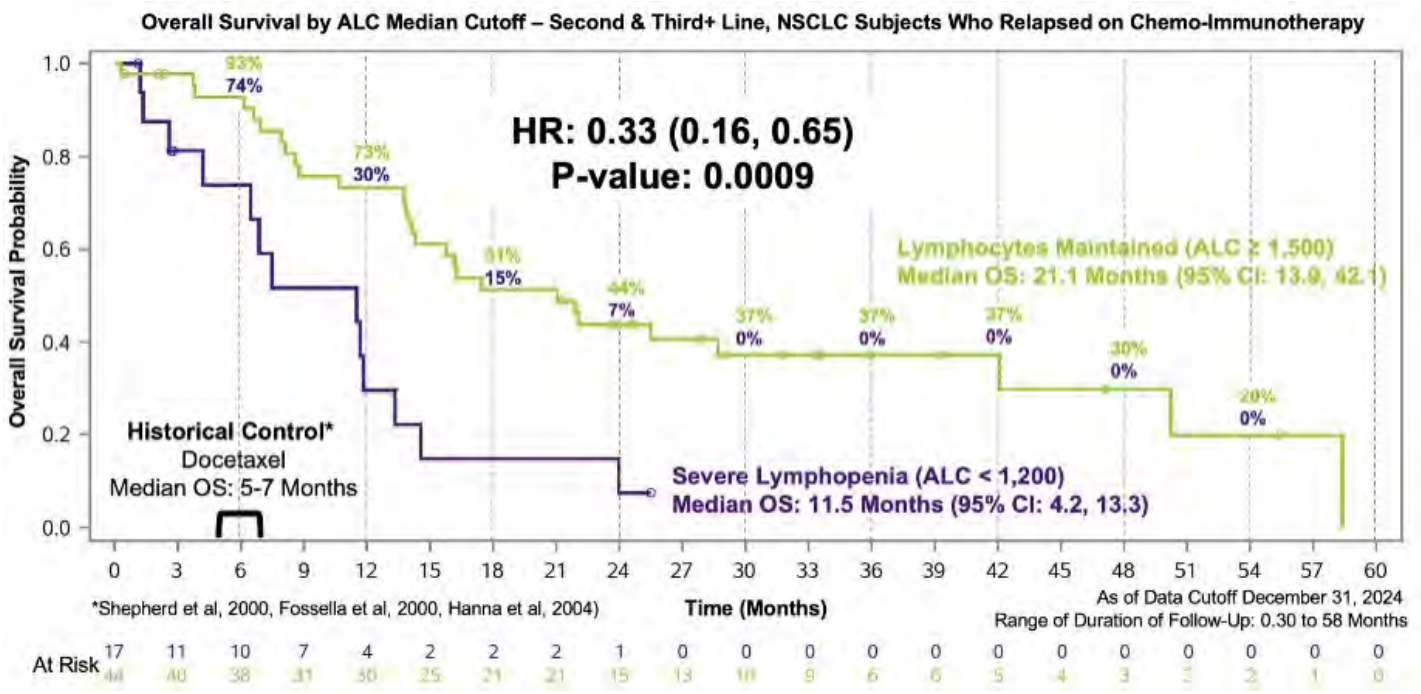
Introduction: Prior to the approval of Nogapendekin alfa inbakicept (NAI), an IL-15 superagonist which stimulates lymphocytes important in immunogenic cell death (Natural killer cells, CD4+ CD8+ T cells and memory T cells), no treatment existed to address lymphopenia as measured by the absolute lymphocyte count (ALC) in the CBC differential. Severe lymphopenia (ALC<1,000), associated with the adverse effects of chemotherapy, radiation, steroids and CPI, significantly lowers overall survival in NSCLC. While absolute neutrophil count (ANC) is widely used to identify neutropenic fever risk, ALC has been largely ignored by clinicians since no therapy existed to treat lymphopenia. To test the hypothesis that NAI, a novel immunotherapy and first-in-class lymphocyte stimulating agent (LSA), prolongs OS by reversing lymphopenia and maintains median ALC≥1,200, a Phase 2 study was conducted wherein patients with NSCLC with acquired resistance to CPI therapy were treated with the same CPI+NAI, a chemo-free combination (QUILT-3.055 NCT03228667). The effect of reversing lymphopenia and maintaining ALC≥1,500 was studied to examine the hypothesis that proliferating NK and T cells with improved ALC results in prolonged OS.

Methods: The change in ALC (absolute cell count and percentage change from baseline) with NAI and CPI during study and its relationship to median OS was the primary endpoint for LSA. Statistical differences between the OS in patients who failed to achieve ALC≥1,000 versus those who overcame severe lymphopenia (ALC<1,000) and those who maintained ALC≥1,500 were measured.

Results: The median OS for 2nd line (51%) and 3rd line+ (49%) was 14.3 months (95% CI 11.7, 17.4) with 23 of 86 subjects alive at data cutoff (Dec 2024). With NAI, 69/86 (80%) exceeded the median ALC 1,200 with a median OS of 15.8 months (12.6, 21.9). Of these 69 subjects, 44/69 (64%) maintained an average ALC≥1,500 throughout study therapy with median OS 21.1 months (13.9, 42.1) and significantly prolonged (HR: 0.33 [0.16, 0.65], p=0.0009) compared to subjects who failed to achieve ALC 1,200 with median OS 11.5 months (4.2, 13.3).

Conclusions: For the first time, ALC is an actionable accessible biomarker to recognize and treat lymphopenia induced by chemotherapy, radiation, steroids and immunotherapy and to prolong OS with NAI. Lymphopenia is addressed for the first time with availability of this new class of lymphocyte stimulating agent (LSA), NAI. When ALC is maintained ≥1,500 with NAI, the immune system is effectively activated (chemo-free), and median OS is significantly prolonged at 21.1 months, HR: 0.33 (95% CI:0.16,0.65) P=0.0009.



Keywords: nogapendekin alfa inbakicept, Lymphopenia, overall survival

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.79 A Meta-Analysis on Anti-PD-1/L1 With or Without Anti-VEGF Plus Chemotherapy in EGFR-Mutant or ALK-Rearranged NSCLC Progressing on TKIs

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Introduction: Non-small cell lung cancer (NSCLC) is commonly diagnosed at an advanced stage with a high predilection for distant metastasis. Despite available treatment options for epidermal growth factor (EGFR)-positive and anaplastic lymphoid kinase (ALK) fusion-positive disease in the advanced and metastatic stage, the prognosis remains dismal on progression with limited treatment options after the use of tyrosine kinase inhibitors (TKI). Although studies have shown that immune checkpoint inhibitors (ICI) have limited benefit for oncogene-driven lung cancer, with more associated adverse events when given after TKIs, several trials have been conducted with conflicting results. This systematic review and meta-analysis examined the efficacy and safety of anti-PD-1/L1 among patients with metastatic non-small cell lung cancer progressing after targeted therapy.

Methods: A systematic search was done using PUBMED, Cochrane, and Clinicaltrials.gov for articles published until March 23, 2025 to examine the effect and safety of anti-PD-1/L1 with or without anti-vascular endothelial growth factor (VEGF) plus chemotherapy after progression on prior TKIs compared with chemotherapy and placebo in locally advanced or metastatic NSCLC. Phase III randomized controlled trials (RCT) which included patients with advanced NSCLC who progressed on TKI treatment for EGFR mutation or ALK translocation with no previous chemotherapy were included. The outcomes investigated were progression-free survival (PFS), overall survival (OS), and > grade 3 treatment-related adverse events (AEs). Data on PFS, OS, and AEs were extracted from the included studies. Hazard ratios (HR) for survival and relative risk (RR) for the adverse events with 95% confidence intervals (CI) were pooled from the included studies and summarized using RevMan 5.3.

Results: This pairwise meta-analysis included five phase III RCTs (CheckMate 722, ATTLAS-KCSG-LU19-04, HARMONi-A, KEYNOTE-789, and ORIENT-31) with 1, 812 patients. Anti-PD-1/L1 with chemotherapy improved PFS compared with chemotherapy and placebo (HR 0.76; 95% CI 0.66, 0.88) and OS (HR 0.86; 95% CI 0.75, 1.00). Anti-PD-1/L1 with anti-VEGF and chemotherapy improved PFS compared with chemotherapy and placebo (HR 0.52; 95% CI 0.44, 0.62) with no effect on OS (HR 0.99; 95% CI 0.78, 1.26). OS data was not yet available for HARMONi-A due to the short-term follow-up, hence, excluded from OS analysis. There were more associated > grade 3 treatment-related AEs on the use of anti-PD-1/L1 with or without anti-VEGF plus chemotherapy compared with chemotherapy and placebo (RR 1.26; 1.03, 1.54). There was no observed heterogeneity for all outcomes except for the occurrence of adverse events (I2 67%).

Conclusions: Anti-PD-1/L1 with chemotherapy improved PFS and OS, while anti-PD-1/L1 with anti-VEGF and chemotherapy improved PFS with no effect on OS. The use of anti-PD-1/L1 with anti-VEGF and chemotherapy was associated with a higher risk of > grade 3 treatment-related AEs, thus, warrants careful monitoring. Anti-PD-1/L1 with or without anti-VEGF plus chemotherapy is a novel and promising approach for NSCLC patients with EGFR mutation or ALK translocation progressing on prior TKIs. Longer follow-up of the included trials is recommended.

Keywords: anti-PD1 and anti-PDL1, VEGF, EGFR and ALK

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.80 Tumor-Derived Complement Factor B Drives Tumor Growth and Anti-PD-1 Resistance in STK11-Mutant Lung Adenocarcinoma

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Introduction: Loss-of-function STK11 mutations occur in 15-20% of lung adenocarcinomas (LUAD) and correlate with immunotherapy failure and poor outcomes. C3 production was increased in human STK11-mutant versus STK11-wild-type LUAD, and high C3 mRNA expression in STK11-mutant LUAD was associated with worse survival. Stk11 deletion (STK11-KO) in syngeneic murine CMT167 tumors (a spontaneous KrasG12V murine LUAD tumor model) resulted in increased neutrophil and reduced T cell infiltration and anti-PD-1 resistance similar to human STK11-mutant LUAD. C3 deletion in STK11-KO tumors resulted in dramatic inhibition of tumor growth and enhanced sensitivity to anti-PD-1 in immunocompetent mice but had little effect following CD8 depletion or in nude mice, pointing to tumor-derived C3 promoting immune evasion. Comparison of gene expression in STK11KO and STK11KO-C3KO tumor showed that C3 modulates expression of multiple complement genes including complement Factor B (CFB), which is required for alternative complement pathway activation through the alternative pathway (AP) C3 and C5 convertases. We hypothesized that tumor-derived CFB promotes growth and anti-PD-1 resistance in STK11-mutant tumors.

Methods: We used transient CRISPR-Cas9 RNP transfection to generate CMT167-STK11KO tumor cells with CFB deletion (CMT167-STK11KO-CFBKO) while avoiding the immunogenic effects of lentiviral based systems. We compared the subcutaneous tumor growth of CMT167-STK11KO-CFBKO and CMT167-STK11KO LUAD cells in immunocompetent mice to evaluate the effect of tumor-derived CFB in vivo. Iptacopan is an oral CFB inhibitor approved for paroxysmal nocturnal hemoglobinuria. We evaluated whether Iptacopan could overcome in-vivo anti-PD-1 resistance of CMT167-STK11KO tumors.

Results: Knockout of CFB resulted in robust inhibition of STK11KO tumor growth in immunocompetent mice. Combination treatment with CFB inhibitor Iptacopan and anti-PD-1 reduced STK11KO tumor growth and extended survival of mice.

Conclusions: Our results extend our prior findings of tumor-derived C3 promoting immune evasion in STK11-mutant LUAD and identify tumor-derived CFB in promoting tumor growth and immune check point inhibitor (ICI) resistance. These results identify tumor-derived C3 and CFB as a novel signaling axis to target in STK11-mutant LUAD and point to the potential role of the alternative complement pathway in tumor immune evasion. These results also provide rationale for an early phase clinical trial of CFB inhibitors such as Iptacopan to enhance anti-PD-1 effectiveness in patients with STK11-mutant LUAD.

Keywords: Lung Cancer, STK11, Complement pathway

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.81 Low-Dose Nivolumab With Platinum Doublet Chemotherapy in Patients With Advanced Central Squamous Cell Lung Cancer (SCAR)

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Introduction: Immune-checkpoint-inhibitors (ICI) have revolutionized the management of NSCLC. Despite the survival evidence, access to ICI remains limited especially in low- and middle-income countries due to prohibitive cost. Low dose ICIs have been studied in anecdotal cases and shown to have non-inferior results, though prospective and robust trials are missing. Nivolumab achieves 70-90% PD-1 occupancy at a dose level of 0.1-0.33mg/kg. With a half-life of 25 days we hypothesized that 20mg flat-dose of Nivolumab will continue to demonstrate meaningful clinical benefit in patients of NSCLC. Based on the prior results of low-dose nivolumab with chemotherapy in head-neck tumors and results of exploratory analysis of CheckMate-227 part-2, we selected cases of central-squamous-tumors for our study.

Methods: It was a single-arm, open-label, phase-2 clinical trial on treatment naïve NSCLC patients with squamous-histology. Inclusion criteria included, current-smokers, target lesion present in central-area (defined as within inner one third section from the major airways) with stage IIIB or higher and not amenable for definitive surgery/chemoradiotherapy. Primary-endpoint included objective-response-rates (ORR) and secondary endpoints included progression-free-survival, overall-survival and disease-control-rates.

Results: Over six months, 29 patients were screened, and 19 were enrolled. Of these, 18 were males, with a mean pack-year history of 28.3±10, and mean age 61.32±7.9 years (table 1). ECOG performance status of 2 and stage IIIB were seen in 52.6% (each). Eleven had chronic obstructive pulmonary disease. Main bronchi involvement was noted in 84.2%, and tracheal infiltration in 21%. After a median follow up of 128 days, 8 (42.1%) patients progressed and 6 (31.6%) died. 12 (63.1%) patients had a decrease in target lesion size of which 10 had >30% decrease suggestive of Partial Remission (as per RECIST 1.1). 4 patients had stable disease, and one had progressive disease, as best response. 4 patients died before first imaging for response assessment. ORR was 52.6% and DCR was 73.7%. 9 patients demonstrated an improvement in Karnofsky Performance Status of minimum 10 points. None of the patients reported any immune-related-adverse-events.

Conclusions: ORR in our study was lower than that of Nivolumab with chemotherapy arm of Checkmate227 part-2 squamous sub-group (60% versus 52.6%) but still better compared to only chemotherapy arm (52.6% versus 32%). The initial results of SCAR trial show encouraging results favouring the use of low dose nivolumab in central squamous cell NSCLC cases.

Table 1: Baseline clinical and outcome related characteristics of the study population. BMI: Body mass index; TNM: Tumor Node Metastasis; ECOG: Eastern cooperative oncology group; COPD: Chronic obstructive pulmonary disease; IRAE: Immune related adverse events.

Variables		**N (%)**
Age (years)		61.32±7.9
Smokers (Current)		28.3±10
BMI (kg/m^2)		19.48±7.7
Males		18 (94.7)
Stage (as per VIII TNM Staging Manual)	IIIB	10
	IIIC	2
	IVA	5
	IVB	2
ECOG Performance Status	0	1
	1	8
	2	10
Comorbidities	COPD	10 (52.6)
	Coronary Artery Disease	5 (26.3)
	Hypertension	2 (10.5)
Mean Tumor Size (Target Lesion), centimetres		6.2±2
Best Response	Partial Remission, mean % change	10 (52.6), 54%
	Stable Disease	4 (21.0)
	Progressive Disease	1 (5.2)
Death		6 (31.6), 4 without assessment
IRAE		0

Keywords: Cost effective, Nivolumab, Squamous Cell

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.82 Study of THIO Sequenced With Cemiplimab in 3rd Line Immune Checkpoint Inhibitor-Resistant aNSCLC: Improvement in PFS

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Introduction: Despite advancements in third line treatments, long-term survival for advanced non-small cell lung cancer (NSCLC) remains suboptimal, with median survival follow-up of only 5.8 months. (1) Treatment options for immune checkpoint inhibitor (ICI)-resistant patients are limited. THIO, a telomere-targeting agent that modifies telomeres in cancer cells, demonstrates improved progression-free survival (PFS) independent of PD-L1 expression.

Methods: NCT05208944 is a phase 2, multicenter, open-label study that enrolled 79 patients with advanced NSCLC who relapsed after 1-4 prior treatments, including ICIs. In the third line therapy 22 patients treated with THIO (60, 180, or 360 mg) were evaluated for (PFS) and their prior PD-L1 expression at the time of study enrollment (C1D1).

Results: In the third line therapy 17 out pf 22 patients (77%) surpassed the benchmark value, and in the 180 mg dose group (n=10) it reached 24.1 weeks. The response to THIO and cemiplimab, demonstrated by partial response (PR) and stable disease (SD) was independent of baseline PD-L1 status. This indicates that THIO can be effective across patients regardless of their PD-L1 status as cemiplimab alone provides survival benefit to advanced NSCLC patients with PD-L1 tumor expression of at least 50% (2).

Conclusions: THIO demonstrates clinically meaningful PFS improvement in third line patients with advanced NSCLC, independent of PD-L1 status. The improved (PFS) observed in patients treated with THIO in sequential combination with an immune checkpoint inhibitor (ICI), compared to standard chemotherapy, supports its potential to expand treatment options for ICI-resistant advanced NSCLC.

Keywords: NSCLC, metastatic, Immune checkpoint Inhibitor-resistant

P1.11.83 Ivonescimab Versus Pembrolizumab for PD-L1-Positive NSCLC: A Subgroup Analysis of HARMONi-2 by Tumor Histology

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Introduction: Ivonescimab is a novel, investigational bispecific antibody against programmed cell death-1 (PD-1) and vascular endothelial growth factor (VEGF). The phase 3 HARMONi-2 (NCT05499390) trial compared ivonescimab with pembrolizumab as monotherapy in 398 patients with PD-ligand-1 (PD-L1)-positive (tumor proportion score [TPS] ≥1%) advanced non-small cell lung cancer (NSCLC) in China. In the primary analysis of HARMONi-2, progression-free survival (PFS) was significantly longer for patients treated with ivonescimab compared with pembrolizumab (hazard ratio [HR] 0.51 [95% CI 0.38-0.69]; one-sided P<0.0001) and was consistent across prespecified subgroups of patients with squamous and non-squamous histology. The objective of the current analysis was to further assess efficacy and safety outcomes by histology subgroup.

Methods: Patients enrolled in HARMONi-2 were adults with locally advanced or metastatic PD-L1-positive NSCLC without EGFR mutations or ALK translocations, who had not received previous systemic therapy. Patients were randomly assigned (1:1) and received intravenous ivonescimab 20 mg/kg or pembrolizumab 200 mg once every 3 weeks for up to 24 months; randomization was stratified by PD-L1 TPS expression, histology, and clinical stage. Efficacy and safety endpoints reported in the primary analysis of HARMONi-2 were evaluated in this subgroup analysis of patients with squamous and non-squamous NSCLC.

Results: The ivonescimab treatment group included 90 patients with squamous and 108 patients with non-squamous histology; the pembrolizumab treatment group included 91 patients with squamous and 109 patients with non-squamous histology. A further analysis has been conducted by PD-L1 TPS level for PFS. At the January 29, 2024, data cutoff, median follow-up was 8.7 months. The unstratified HR (95% CI) for PFS was 0.50 (0.33-0.76) in patients with the squamous histology and 0.55 (0.36, 0.84) in patients with the non-squamous histology. In the subset of patients with TPS 1-49%, the PFS HR was 0.51 (0.30-0.87) in patients with the squamous histology and 0.43 (0.21-0.88) in patients with the non-squamous histology, while in patients with TPS ≥50% the PFS HR was 0.43 (0.21-0.88) in patients with the squamous histology and 0.49 (0.25-0.96) in patients with non-squamous histology. In the ivonescimab treatment group, the overall response rate (ORR) in patients with the squamous histology was 53% and in patients with the non-squamous histology was 47% versus 31% and 45%, respectively, in the pembrolizumab treatment group. Serious treatment-related adverse events (TRAEs) occurred in 17 (19%) patients in the ivonescimab group versus 17 (19%) patients in the pembrolizumab group in patients with the squamous histology and 24 (22%) versus 15 (14%) patients with the non-squamous histology, respectively. Importantly, the rates of Grade ≥3 hemorrhage were similar in patients with squamous and non-squamous histology in the ivonescimab treatment group: 0 versus 2 (2%) patients respectively, and were similar to the rates seen in patients in the pembrolizumab treatment group: 1 (1%) versus 0 patients, respectively.

Conclusions: The analysis of histology subgroups from the HARMONi-2 study shows consistently numerically greater PFS benefit and response rate and a manageable safety profile for ivonescimab compared to pembrolizumab.

Keywords: Squamous NSCLC, Non-squmous NSCLC, ivonescimab

P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.84 Phase II Trial of Tislelizumab Combined With Anlotinib and 2-Cycle Chemotherapy as First-Line Treatment for Advanced NSCLC

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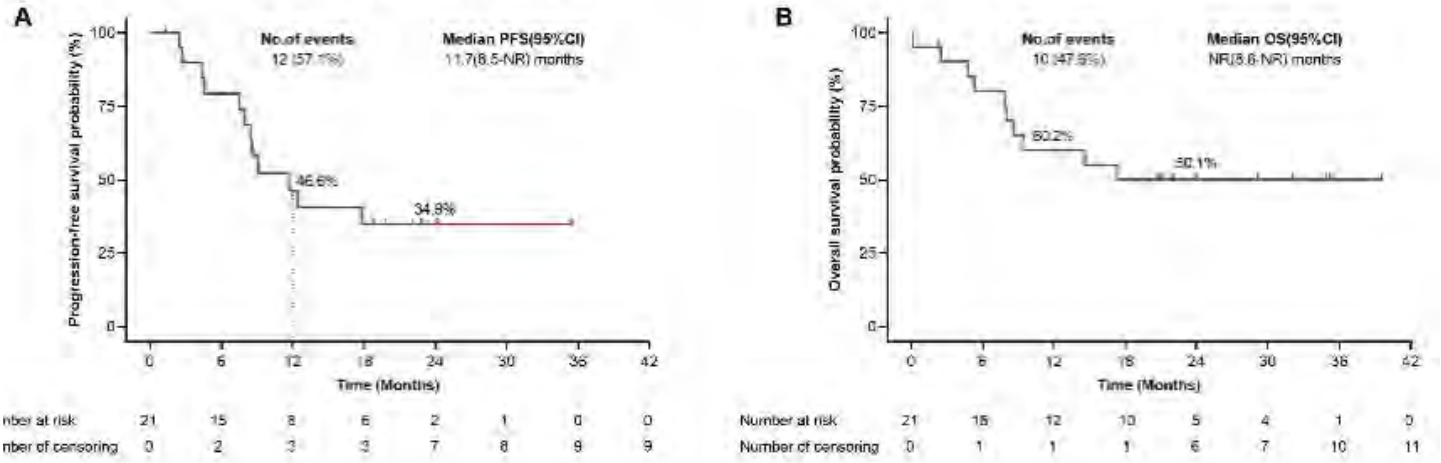
Introduction: First-line chemo-immunotherapy has demonstrated remarkable survival benefits in advanced NSCLC. However, disease progression remains a persistent challenge, the median progression-free survival (PFS) is approximately 6~ 9 months. The design of this Phase II study, which combines immunotherapy, anti-angiogenic therapy, and short-course chemotherapy, aims to reduce the toxicity of chemotherapy while maximizing the synergistic anti-tumor effect that is greater than the sum of its parts, achieving a "1 + 1 + 1 > 3" effect.

Methods: This was a single-arm, single-center, exploratory study. Patients eligible for enrollment had previously untreated, histologically confirmed locally advanced NSCLC who were not amenable to curative surgery or radiotherapy (stage IIIB, IIIC) or metastatic (stage IV) NSCLC (per AJCC 8th edition). Patients received tislelizumab (200 mg, Q3W) plus anlotinib (12 mg, QD, d1-14, Q3W) and platinum-based chemotherapy for 2 cycles, then they continued maintenance therapy with tislelizumab plus anlotinib until disease progression, intolerable toxicity, or a maximum duration of 2 years was reached. The primary endpoint was progression free survival. Second endpoints included overall survival, object response rate, duration of response, disease control rate and safety.

Results: Between July 2021 and November 2023, a total of 21 patients were enrolled, with a median age of 64 years. Among them, 15 patients were non-sq NSCLC and 6 patients were sq-NSCLC. The majority of patients (90.5%) were at stage IV, and most patients (85.7%) had an ECOG PS of 1. As of March 7, 2025, the median follow-up duration was 24 months (range: 21-34) and the median treatment cycle for both tislelizumab and anlotinib was 10 (range: 3-32). The median PFS was 11.7 months (95%CI:8.5-NR), with 1-year and 2-year PFS rates of 46.6% and 35%, respectively. The median OS was not reached (95%CI:8.6-NR), and the 1-year and the 2-year OS rate were 60.2% and 50.1%, respectively. The ORR was 66.7%, DCR was 100%, and the median DOR was 7.6 months. The incidence rate of any-grade TRAE was 19.04%. No grade ≥3 TRAEs and irAE were observed.

Conclusions: Tislelizumab plus anlotinib and 2-cycle chemotherapy as first-line treatment for advanced NSCLC demonstrated promising efficacy with a tolerable safety profile. It might provide a new treatment strategy to prolong the survival benefits for advanced NSCLC patients.

Figure. Kaplan-Meier plots for PFS (A) and OS (B)



P1.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.11.85 Overall Survival With Nivolumab Plus Relatlimab With Platinum-Doublet Chemotherapy in Metastatic NSCLC From RELATIVITY-104

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Introduction: PD-1 and LAG-3 are distinct immune checkpoints upregulated in NSCLC that contribute to T-cell dysfunction. RELATIVITY-104 is a proof-of-concept, randomized, phase 2 study of first-line nivolumab + relatlimab (a human LAG-3-blocking antibody) + platinum-doublet chemotherapy (PDCT) versus nivolumab + PDCT in metastatic NSCLC. In Part 2 of the study, patients in the nivolumab + relatlimab + PDCT arm had higher ORR in the all-randomized population and a trend toward improved clinical benefit in the prespecified stratification factor subgroup of tumor PD-L1 expression ≥1%, which was further enriched in nonsquamous histology. The safety profile was generally manageable. Here, we report overall survival (OS), patient-reported outcomes (PROs), and exploratory translational analyses from Part 2 of RELATIVITY-104.

Methods: Adults with previously untreated stage IV/recurrent NSCLC, ECOG PS ≤1, and no targetable mutations were eligible. In Part 2, patients were randomized 1:1 (stratified by tumor PD-L1 expression, histology, and ECOG PS) to receive nivolumab 360mg + relatlimab 360mg + PDCT or nivolumab 360mg + PDCT, Q3W. ORR per BICR was the primary endpoint. Secondary endpoints included PFS per BICR, ORR/PFS by biomarker subgroups, and safety. Exploratory analyses were OS, translational analyses from the tumor, and PROs.

Results: With a median follow-up of 12.65 months (range, 0.03-28.42; database lock, 2 May 2025), PFS continued to favor nivolumab + relatlimab + PDCT versus nivolumab + PDCT in patients with tumor PD-L1 expression ≥1% and nonsquamous NSCLC (HR [90% CI], 0.68 [0.46-1.01]). In the all-randomized population, the OS HR (90% CI) was 1.04 (0.82-1.32). OS benefit was observed with nivolumab + relatlimab + PDCT in prespecified subgroups, including patients with tumor PD-L1 expression ≥1% and nonsquamous NSCLC (HR [90% CI], 0.60 [0.38-0.94]; table). In the nonsquamous NSCLC subgroup, relatlimab and nivolumab activity was linked to natural killer (NK) cells; high expression of a NK-cell-activating receptor gene signature in baseline tumors was associated with PFS and OS benefit. The safety profile of nivolumab + relatlimab + PDCT remained consistent with previous reports. PRO results will be presented.

Conclusions: Nivolumab + relatlimab + PDCT demonstrated a trend toward improved OS versus nivolumab + PDCT in the tumor PD-L1 ≥1% and nonsquamous NSCLC prespecified subgroups. These results from the first randomized phase 2 study of a LAG-3 blocking antibody-containing regimen in first-line metastatic NSCLC support further investigation of nivolumab + relatlimab + PDCT in the phase 3 RELATIVITY-1093 study.

Table. OS results from Part 2 of RELATIVITY-104

	Nivolumab + relatlimab + PDCT		Nivolumab + PDCT		OS HR (90% CI)
	n	Median OS, mo (90% CI)	n	Median OS, mo (90% CI)	
All randomized	158	12.6 (10.8–16.2)	151	16.6 (11.6–20.8)	1.04 (0.82–1.32)
Tumor PD-L1 expression					
<1%	70	10.6 (7.5–13.8)	67	19.9 (11.5–23.8)	1.39 (0.97–1.99)
≥1%	79	16.2 (11.3–NR)	71	13.6 (8.8–18.4)	0.78 (0.56–1.11)
Histology					
Squamous	51	10.8 (8.3–13.8)	47	13.6 (10.4–20.8)	1.23 (0.82–1.83)
Nonsquamous	107	15.5 (11.5–23.4)	104	17.2 (10.5–22.9)	0.95 (0.71–1.28)
Tumor PD-L1 expression and nonsquamous					
≥1%	50	NR (14.6–NR)	48	17.0 (8.1–19.6)	0.60 (0.38–0.94)
1–49%	28	NR (11.3–NR)	20	7.4 (5.3–18.4)	0.46 (0.25–0.86)
≥50%	22	NR	28	19.1 (8.8–NR)	Not calculated[a]

[a]HR not calculated due to an insufficient number of events (<10 per arm).
NR, not reached.

Keywords: Immunotherapy, Relatlimab, Nivolumab

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.01 Sociodemographic Factors in Access to Robotic-Assisted Oncologic Lung Resection, a United States (US) National Cancer Database Analysis

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Introduction: Robotic-assisted thoracoscopic surgery (RATS) has gained traction in the surgical management of non-small cell lung cancer (NSCLC), with potential benefits in postoperative pain and outcomes. However, equitable access to RATS remains unclear. We evaluated national patterns in RATS utilization and assessed whether sociodemographic disparities in access vary by geographic region in the United States (US).

Methods: We conducted a retrospective cohort study using the National Cancer Database (2010-2021), identifying adults with clinical stage I-IIIa NSCLC who underwent RATS or video-assisted thoracoscopic surgery (VATS). Patients with missing approach data were excluded. A multivariable logistic regression analysis using backwards selection was performed to examine the relationship between RATS approach and sociodemographic variables of interest. The model was fit with all variables with p<0.20 in the univariate analyses of patients with an MIS approach with <10% missing data. An interaction term between race and geographic location was included in the model to examine differing relationships between race and approach by region.

Results: Among 162,080 patients (62.8% VATS, 37.2% RATS), RATS utilization increased over time, surpassing VATS volume in 2019. Patients were primarily female (57%), white (82%), non-Hispanic (96%), with Medicare insurance (64%). Uninsured patients had lower odds of receiving RATS (OR=0.88, 95% CI 0.78-0.98, p=0.026), while Medicaid status showed no difference (OR=1.00, 95% CI 0.95-1.06, p=0.95). Patients in Medicaid expansion states had significantly lower odds of RATS (OR=0.80, 95% CI 0.77-0.83, p<0.001). Notably, racial disparities in RATS access varied by region: Black patients had lower odds of RATS in the South Atlantic and East North Central regions, but higher odds in East South Central and West South Central (OR 1.22) regions (Figure 1). Hispanic or Latino patients had lower odds in the East North Central region, but higher odds in New England and the Pacific.

Figure 1: Statistically significant findings from multivariable logistic regression predicting robotic approach among minimally invasive oncologic lung resections in the NCDB 2010-2021 (n=150,900), as compared to white non-Hispanic patients.

Conclusions: Access to robotic lung cancer surgery remains uneven across sociodemographic and geographic lines. These findings underscore the importance of addressing system-level barriers to advanced surgical technologies to ensure equitable access. As RATS continues to expand globally, ensuring equitable adoption will be critical to preventing downstream disparities in lung cancer care and outcomes.

Keywords: Robotic Surgery, Disparities, Lung Resection

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.02 Socioecological Factors Associated With Lung Cancer Clinical Trial Enrollment: Real-World California Cancer Registry Data

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Introduction: In the United States, less than 5% of participants in oncology clinical trials (OCTs) are from diverse race/ethnic backgrounds (i.e., Hispanic and Black), highlighting the need to identify modifiable socioenvironmental and clinical factors that may drive racial/ethnic disparities in OCTs participation. To fill this gap, we aimed to identify whether policy-, health system-, and patient-factors are associated with OCTs enrollment using data from a diverse population-based cohort of lung cancer cases in Los Angeles County, California.

Methods: We analyzed retrospective data from the California Cancer Registry/Los Angeles Cancer Surveillance Program between 2002-2021. Variables were operationalized: Outcome: OCT enrollment (not enrolled vs enrolled). Exposures: The policy- (Pre-2014 FDA plan to enhance the collection and availability of demographic subgroup data vs Post-2014, and COVID), Health system- (facility designated cancer center status: None vs All three, CoC-only, Multiple, NCI-only), and Patient-factors (Charlson comorbidity score [0 vs 1, 2, 3+], and insurance status [Private vs Medicaid, Medicare, Other]). Multivariable logistic regression model was used to explore these associations.

Results: Almost 1% (n=599/68,245) of our cohort was enrolled in OCT. Enrollees were mostly non-Hispanic White (NHW) (64.8%), Medicare-insured (60.3%), comorbidity-free (46.1%), and seeing at a CoC facility (62.1%). In unadjusted models, racial/ethnic minorities were less likely to be enrolled in OCT than NWH patients (Table). After adjusting for covariates, no statistically significant associations between race/ethnicity and OCT were found (Table). For the policy factor, we found that, during COVID, patients were 82% (OR=0.18, 95%CI: [0.10, 0.30]) less likely to be enrolled in OCT compared to the Pre-2014 FDA plan. For the health system, those that were seen at a CoC/NCI/NCCN facility were significantly more likely to be enrolled in OCT (All three=5.57[3.69, 8.33], CoC-only=5.64[4.29, 7.53], Multiple=8.12[5.67, 11.67], NCI=3.39[2.27, 5.02]) compared to those not being seen in any of those facilities. For our patient factor, we found an inverse association between comorbidity categories and OCT enrollment (1=0.72[0.59, 0.88], 2=0.51[0.37, 0.69], 3+=0.25[0.16, 0.37]). Similarly, compared to private insurance, having Medicaid was associated with a 53% (0.47[0.30, 0.72]) less likely to be enrolled in OCT, while Medicare was associated with a 92% (1.92[1.55, 2.38])increased likelihood of OCT enrollment compared to private insurance.

Conclusions: Using population-based data, our findings underscore that racial/ethnic disparities in OCT enrollment could be mitigated by addressing where individuals get cancer care, broadening comorbidity restrictions, and expanding cancer care research facilities in underserved areas.

Table: Multivariable association of policy-, and health system-, and patient-factors with the likelihood of oncology clinical trial enrollment among lung cancer patients from the California Cancer Registry/ Los Angeles Cancer Surveillance Program CSP (2002-2021)

Variables	CT Participation (N=68,245) Crude OR(95%CI)	CT Participation (N=59,668) aOR(95%CI)
Policy		
FDA action plan (Ref= Pre-2014 FDA)		Ref
Post-2014-2020 FDA	1.18(0.98,1.41)	0.75(0.55, 1.02)
(2020-2021)Covid	**0.46(0.30, 0.68)**	**0.18(0.10, 0.30)**
Health System		
Healthcare facility approved(Ref = None)		
All Three approved	**11.39(7.70, 16.72)**	**5.57(3.69, 8.33)**
CoC approved facility	**8.40(6.47, 11.10)**	**5.64(4.29, 7.53)**
Multiple Approved	**10.80(7.70, 15.19)**	**8.12(5.67, 11.67)**
NCI approved	**7.79(5.29, 11.41)**	**3.39(2.27, 5.02)**
Patient		
Race/Ethnicity(Ref = Non-Hispanic White)		
Non-Hispanic Black	**0.76(0.58, 0.93)**	1.20(0.87, 1.62)
Hispanic	**0.52(0.39, 0.67)**	0.91(0.67, 1.21)
Non-Hispanic Asian/Pacific Islander	**0.53(0.39, 0.69)**	0.89(0.69, 1.14)
Charlson comorbidity score (Ref=0)		
1	**0.62(0.51, 0.75)**	**0.72(0.59, 0.88)**
2	**0.39(0.28, 0.52)**	**0.51(0.37, 0.69)**
3+	**0.15(0.10, 0.22)**	**0.25(0.16, 0.37)**
Unknown	**0.50(0.38, 0.64)**	1.05(0.79, 1.37)
Insurance Status (Ref = Private)		
Medicaid	**0.43(0.27, 0.63)**	**0.47(0.30, 0.72)**
Medicare	**1.24(1.04, 1.47)**	**1.92(1.55, 2.38)**
Other	**0.37(0.21, 0.59)**	**0.51(0.28, 0.86)**

Notes:
Crude OR = Unadjusted Odds Ratios; aOR = Adjusted Odds Ratios, Ref=Reference, FDA = Food and Drug Administration.
Model adjusted for sex, age, year of diagnosis, marital status, education, SES status, cancer stage, treatment modality, in addition to all variables outlined in this table.
Facility certification designation: California Commission on Cancer (CoC), California National Comprehensive Cancer Network (NCCN), NCI-designated cancer center (NCI)
Multiple includes CoC and/or National Cancer Institute (NCI) and/or NCCN.
Insurance Other includes Indian/Public Health Services and county funded/military/uninsured
Bolded represents statistical significance.

Keywords: clinical trial disparities, lung cancer, population data

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.03 Stage Iv Nonsquamous Non-Small Cell Lung Cancer (NSCLC) Biomarker Testing Disparities and Outcomes: A Population-Based Stu

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Introduction: Recognizing disparities in guideline-concordant EGFR and/or ALK biomarker testing is crucial to improve outcomes for patients newly diagnosed with stage IV nonsquamous NSCLC. This informs targeted interventions focused on populations least likely to receive biomarker testing, optimizing resource allocation. Despite the critical importance of biomarker testing, the rates and factors associated with testing is unknown.

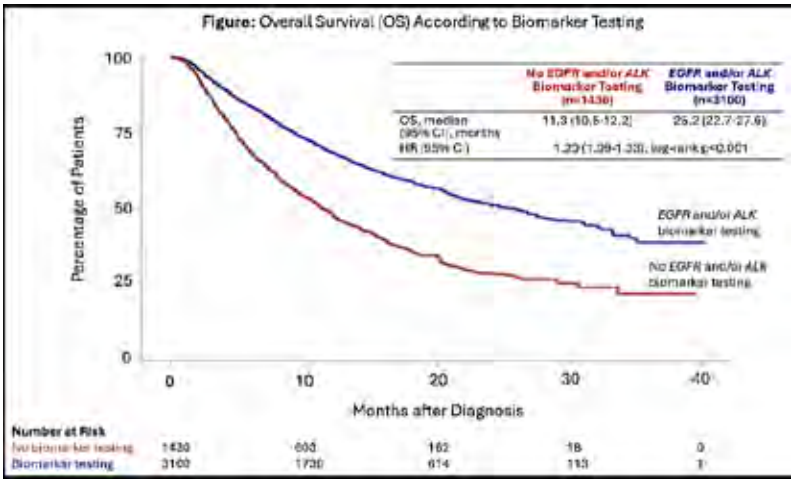
Methods: This population-based cohort study used records from the California Cancer Registry to identify patients newly diagnosed with stage IV nonsquamous NSCLC between 2021 to 2022. Patients who received no systemic NSCLC treatment were excluded. Multivariable logistic regression was used to examine characteristics associated with biomarker testing. Multivariable Cox proportional hazards regression was used to compare overall survival (OS) between patients with and without biomarker testing.

Results: Among 4,530 identified patients, 1,430 (32%) had no EGFR and/or ALK biomarker testing reported. Patients residing in the lowest tertile of neighborhood socioeconomic status (SES) were less likely to receive biomarker testing (odds ratio 0.69, 95% confidence interval [CI] 0.57-0.84). Similarly, patients who were older, male, and had comorbid conditions were less likely to receive testing (Table). Patients without biomarker testing had a shorter median OS (11.3 versus 25.2 months, p<0.001) and increased hazard of death (hazard ratio (HR) 1.20, CI 1.09-1.33) than those with biomarker testing (Figure).

Conclusions: Nearly one-third of patients with NSCLC in this large cohort study did not receive guideline recommended biomarker testing and had significantly decreased OS. To our best knowledge, this is the largest study to date to define guideline-concordant biomarker testing disparities among patients with stage IV nonsquamous NSCLC. Targeted interventions to improve EGFR and/or ALK biomarker testing should focus on older adults, male patients, and those residing in low SES neighborhoods.

Table: Multivariable Logistic Regression of *EGFR* and/or *ALK* Biomarker Testing

Characteristic	Odds ratio (95% CI)	p-value
Age ≥50 (reference: <50)	0.51 (0.37-0.70)	<0.001
Male sex (reference: female)	0.62 (0.54-0.71)	<0.001
Race and ethnicity (reference: non-Hispanic White)		
Asian or Pacific Islander	2.43 (2.03-2.92)	<0.001
Hispanic	1.21 (0.99-1.47)	0.059
Non-Hispanic Black	0.88 (0.68-1.14)	0.317
Neighborhood SES (reference: highest tertile)		
Lowest tertile neighborhood SES	0.69 (0.57-0.84)	<0.001
Middle tertile neighborhood SES	0.76 (0.65-0.89)	0.001
Comorbid medical conditions	0.72 (0.59-0.87)	0.001
Insurance status (reference: private insurance)		
Federal government insurance (Medicare)	0.97 (0.83-1.13)	0.707
State government insurance (Medicaid)	0.93 (0.74-1.15)	0.495
State and federal government insurance (Medicare/Medicaid)	1.41 (1.01-1.96)	0.043
Metastatic disease site		
Brain (reference: no brain metastases)	1.37 (1.18-1.59)	<0.001
Liver (reference: no liver metastases)	0.97 (0.80-1.17)	0.739



Keywords: biomarker testing, goal-concordant care, disparities

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.04 Prioritizing Lung Cancer Screening in Middle-Income Countries: A Feasibility-Need Framework to Guide Implementatio

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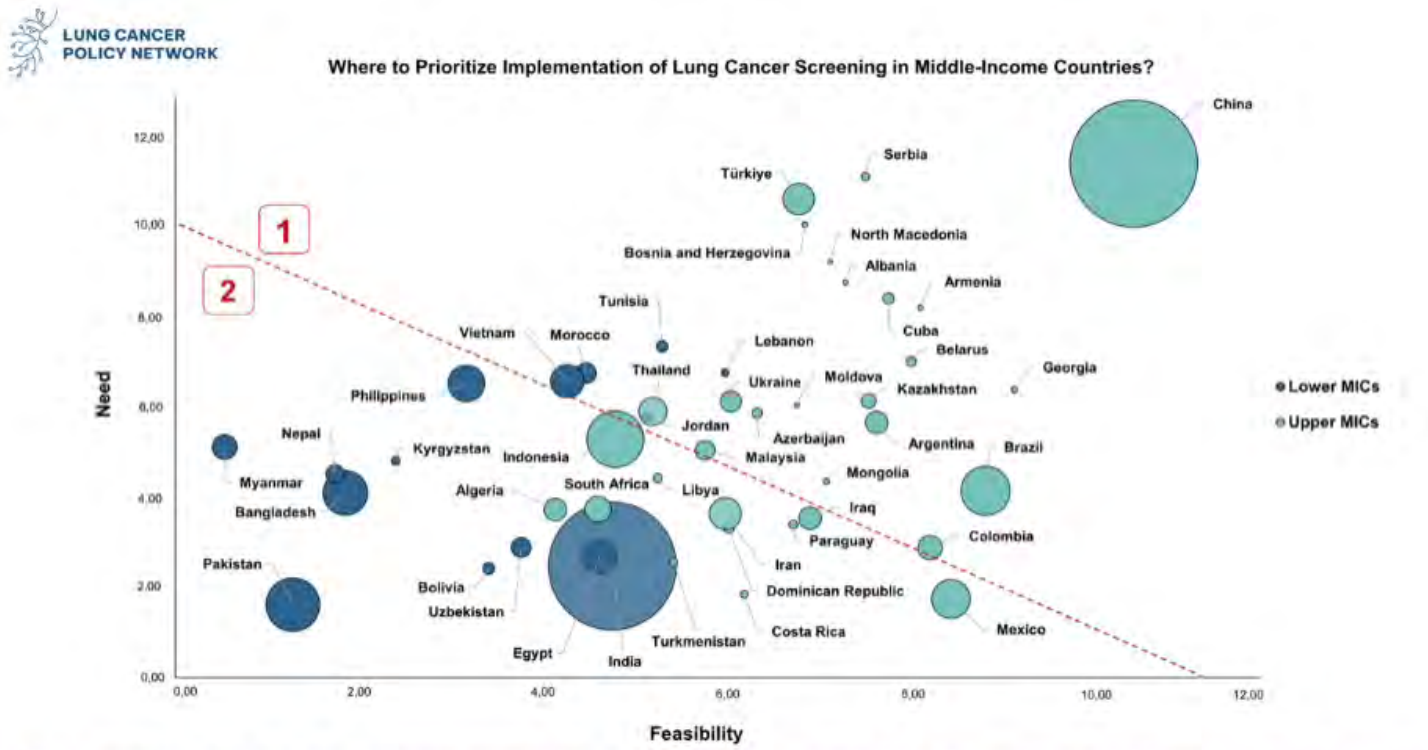
Introduction: A feasibility-need framework applied across 105 middle-income countries (MICs) identifies China, Vietnam, Türkiye, and several Balkan countries as top priorities for lung cancer screening (LCS) implementation. This data-driven, policy-focused approach integrates lung cancer burden and system readiness to determine where screening is both urgently needed and realistically feasible. Lung cancer remains the leading cause of cancer-related mortality worldwide, with 65.3% of deaths occurring in low- and middle-income countries. While most high-income countries are progressing toward reduced lung cancer mortality through national screening programs, many MICs face rising burdens from growing smoking rates and late-stage diagnoses. Low-income countries were excluded due to more urgent health priorities, including infectious disease control.

Methods: A comparative analysis of LCS need and feasibility was conducted using a weighted scoring system based on epidemiological and healthcare infrastructure indicators. Need scores were based on lung cancer mortality and incidence rates, five-year prevalence, cumulative risk of new cases, smoking prevalence, and life expectancy. Feasibility scores incorporated healthcare expenditure, CT scanner availability, number of physicians and radiologists, existing LCS studies, and GDP per capita, reflecting each country's capacity to execute screening. Countries with populations under 2 million and total scores below 2 (on a scale 1-10) were excluded due to insufficient justification for national screening efforts. Data were sourced from GLOBOCAN (IARC), WHO, JTO, LCPN, and national databases.

Results: Forty-six MICs met the inclusion criteria. Two focus clusters emerged: (1) High-Need, High-Feasibility; and (2) High-Need, Low-Feasibility. China was ranked highest in the overall readiness, but it still requires introduction of a national, structured screening program with guideline adherence, targeting the right risk groups. Türkiye, Serbia, Bosnia and Herzegovina, Albania, and North Macedonia exhibited the highest LCS need, but face a shortage of trained healthcare professionals needed to run screening programs. Vietnam, Kazakhstan, and Brazil show promise through active national research and piloting efforts. Indonesia and the Philippines demonstrated urgent need but limited feasibility, requiring foundational investments before introducing screening.

Conclusions: China, Vietnam, Türkiye, and the Balkan countries emerge as MICs where LCS could yield the greatest public health impact. However, workforce limitations, financing gaps, and lack of regulatory structures remain key barriers. Targeted investment and evidence-informed policy design are essential to unlock LCS potential in MICs. This feasibility-need framework can inform international and national NCD strategies and guide global collaboration. Ongoing qualitative interviews with national experts will further refine feasibility assessments and guide country-specific recommendations for LCS implementation.



*Data Note: This chart ranks lung cancer screening in middle-income countries based on need (lung cancer burden & screening demand) and feasibility (economic & infrastructure readiness). Bubble size reflects the population of each country. A diagonal line separates **High-Need, High-Feasibility Cluster (1)** and **High-Need, Low-Feasibility Cluster (2)**. Values on the axes are arbitrary and used for comparative visualization.*

Keywords: Lung Cancer Screening (LCS), Middle-income countries (MICs), Feasibility-Need Framework

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.05 Evolution of Neoadjuvant Treatment for Non Small Cell Lung Cancer (NSCLC) in Brazil: An Analysis From the Brazilian Lung Cancer Registry

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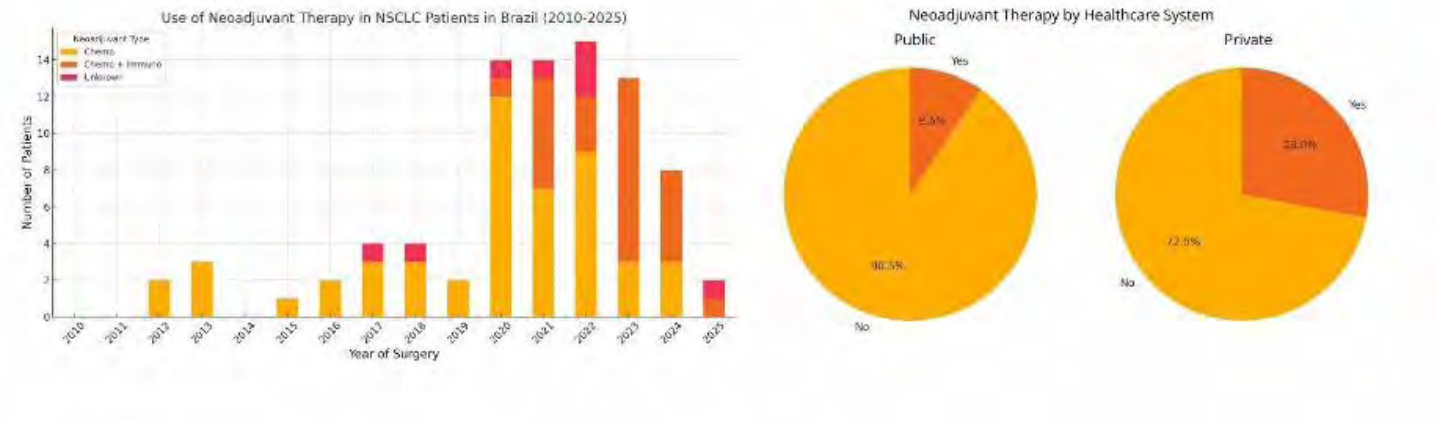
Introduction: Neoadjuvant therapy has emerged as a promising strategy in managing locally advanced NSCLC, allowing tumor downsizing, early micrometastasis treatment, and potentially improved resectability. In 2022, the Brazilian regulatory agency approved nivolumab with chemotherapy for resectable NSCLC, marking the first immunotherapy approved for neoadjuvant use in Brazil. However, its routine availability in the public healthcare system remains limited and is currently restricted to clinical trials. This study aimed to analyze factors associated with neoadjuvant therapy use, treatment profiles, and survival outcomes in Brazil.

Methods: Data were drawn from the Brazilian Lung Cancer Registry, a multicenter database including patients undergoing lung cancer surgery since 2010. Patients with clinical stage IIA-IIIB (8th edition), excluding carcinoid tumors, considered eligible for neoadjuvant therapy per NCCN/ESMO guidelines were selected. Demographic and clinical variables were collected, and appropriate statistical tests were applied with $p<0.05$ as the significance level.

Results: Of 3,132 patients, 680 met inclusion criteria; 106 (15.58%) were excluded due to missing neoadjuvance data. Among the remaining, 84 (12.35%) received neoadjuvant therapy and 490 (72.06%) did not. Age, sex, race, ECOG, and comorbidity index were similar between groups. Neoadjuvant use was more common in the private sector (27.95% vs. 9.47%, $p<0.001$) and in advanced stages (IIIA/IIIB: 69.88% vs. IIA/IIB: 33.332%, $p<0.001$). Utilization increased markedly from 2020. Of treated patients, 61.45% received chemotherapy alone and 30.12% received chemoimmunotherapy. Mean surgical time was longer with neoadjuvant therapy (269.04 vs. 247.83 min, $p=0.076$), and robotic-assisted surgery was more frequent (22.62% vs. 10.25%, $p=0.006$). Histology also differed, with fewer squamous cell carcinomas and more "other" types in the neoadjuvant group ($p=0.037$). Downstaging was more common with neoadjuvance (52,56% vs. 35,15%, $p=0.049$). Survival did not differ significantly across stages IIA-IIIB.

Conclusions: Neoadjuvant therapy use in Brazil is still limited, with significant disparities between public and private systems. Patients treated in the private sector were nearly three times more likely to receive neoadjuvant therapy, reflecting unequal access to multimodal care. Its adoption increased notably after 2020, likely driven by emerging evidence and regulatory approval. Although associated with more downstaging and greater use of high-complexity techniques such as robotic surgery, no survival benefit was demonstrated. Differences in histology and surgical complexity suggest potential selection bias. These findings underscore the urgent need to reduce institutional and socioeconomic barriers to ensure equitable access to guideline-recommended care. Future studies should assess long-term outcomes and explore strategies to expand availability, particularly in the public health system.

context.



Keywords: Neoadjuvant Therapy, Health Disparities, Real-World Data

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.06 Who Gets a Biopsy? Disparities in Histological Confirmation and Survival Among Lung Cancer Patients

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Introduction: Histological confirmation is essential for lung cancer diagnosis and treatment selection, yet a subset of patients—particularly those with advanced disease—are diagnosed based solely on clinical or radiological suspicion. Some patients may present at an advanced stage and poor performance status, making a diagnostic procedure impractical. However, the rapid advancement of targeted therapies and immunotherapy for NSCLC makes histological confirmation increasingly critical for optimal treatment decisions. Some patients may be incorrectly excluded from the diagnostic process, thereby missing the opportunity for potentially life-prolonging therapies. This study aimed to analyze demographic and survival disparities among lung cancer patients based on whether a diagnostic confirmation was made.

Methods: We extracted all lung cancer cases from the SEER Research Data, 17 Registries (November 2022 submission), between 2000-2020. Patients were categorized as histologically confirmed or diagnosed solely by clinical/radiological suspicion. We examined demographic, socioeconomic, and geographic factors associated with non-confirmation. A subgroup analysis was conducted on metastatic patients. Kaplan-Meier estimates were used for survival comparisons, and chi-square tests evaluated correlations between categorical variables.

Results: Among 972,813 lung cancer patients, 78,913 (8.1%) were diagnosed without histological confirmation. This percentage decreased only slightly over time. Patients more likely to be diagnosed without confirmation were older, female, unmarried, lower-income, and living in rural areas (all $p < 0.001$). These disparities persisted in metastatic patients, where 7.4% (41,429 patients) lacked histological confirmation, including 6.0%, 10.9%, and 26.1% of patients aged 65-74, 75-84, and ≥85, respectively.

Patients in rural versus metropolitan areas (11.3% vs. 7.5%) and patients with an income <$50,000 vs >$75,000 (10.3% vs 7.4%) had higher rates of non-confirmation (both $p<0.001$).

Patients with a histologically confirmed diagnosis had significantly better survival (median survival: 11 months vs. 2 months, $p < 0.001$), including among metastatic patients (5 months vs. 1 month, $p < 0.001$). Among metastatic patients without histological confirmation, less than 25% survived beyond 3 months. The majority of patients died from lung cancer in both groups, further emphasizing that those without biopsy confirmation were not simply dying from comorbidities.

Conclusions: A significant proportion of lung cancer patients, including those with metastatic disease, do not undergo biopsy confirmation, raising concerns about missed treatment opportunities. The presence of socioeconomic and geographic disparities in biopsy rates suggests that some of these cases may be preventable. Additionally, the high early mortality rate in non-confirmed patients highlights the need for earlier recognition of symptoms and improved access to timely diagnosis. Efforts should focus on reducing disparities, enhancing diagnostic workflows, and ensuring all eligible patients receive histological confirmation for appropriate treatment selection.

Footnote: This abstract was reviewed using ChatGPT for grammar and language refinement

Keywords: Diagnostic confirmation, Lung cancer, Disparity

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.07 Comparing Baseline Characteristics of NSCLC Patients Receiving Radiotherapy in Real-World Practice and Clinical Trials

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Introduction: NSCLC populations display diverse baseline patient characteristics (BPCs) due to differences in co-morbidities, risk factors and anatomical factors. Clinical trials typically recruit fitter patients who can better tolerate experimental treatment toxicities, limiting the generalisability of study findings. In the context of NSCLC radiotherapy, the characteristics of patient excluded from trials remain under-reported. This study compares the BPCs of patients treated at our centre with those reported in clinical trials and benchmarks them against data from other institutions.

Methods: BPCs of consecutive patients with NSCLC treated with curative-intent radiotherapy between 2013-2023 at a tertiary centre were extracted from a real-world data platform. Data included age, sex, ECOG PS, suitability for concurrent chemotherapy (CC), stage, and histological confirmation. BPCs were compared with published large (n=400+) institutional real-world series, and with eligibility criteria of phase II-III clinical trials evaluating conventional/mildly hypofractionated (CONV) and stereotactic (SABR) radiotherapy, published 2013-2023.

Results: Data from n=5,075 patients (n=3509 CONV, n=1566 SABR) from our centre were analysed. Median age 73 years; stage I 40%, stage II 27%, stage III 33%; CC received by 12% CONV. Eight institutional series were identified (two European, three US for CONV (n=3541), one European SABR n=7279). CONV patients were older at our centre compared with European and US cohorts respectively (age 72 vs 69 vs 66 years), less fit (ECOG 0-1 52% vs 77% vs 77%) and had lower rates of tissue diagnosis (81% vs 86% vs 100%). CC suitability was similar to Europe but lower than US (12% vs 10% vs 76%) (Table 1). SABR patients were less fit compared with the European cohort (ECOG 0-1 38% vs 74%) but had higher rates of tissue diagnosis (53% vs 34%), and similar age (75 vs 73 years). Twelve landmark trials were identified (eight CONV (n=2532), four SABR (n=453)) compromising: five European, five US, one Canadian, one Australian studies. At our centre, 31% patients met the eligibility for ≥1 trial. The eligibility was met by median 9.3% patients (IQR 9.3-16) for CONV trials, 42% (IQR 36.5-42) for SABR trials.

Conclusions: Pronounced differences in BPCs were observed between European and US real-world cohorts. A minority of European patients meet the eligibility for recent landmark clinical trials, primarily due to ECOG, tissue diagnosis and CC suitability. To enhance the generalisability and impact of future research, collaborative groups, funders, and industry partners should prioritise studies that are applicable to a broader patient population.

Table 1 – Comparison of baseline characteristics in patients receiving curative-intent radiotherapy: single-centre experience versus real-world European and US cohorts and landmark clinical trials

	European Centres			US Centres			Clinical Trials (Weighted Means)
	Christie 2013–2023 Unpublished UK	Walls ClinOnc 2024 UK	Olloni JTOCRR 2024 Denmark	Speirs JTO 2017 Missouri	McFarlane IJROBP 2021 Michigan	Atkins IJROBP 2021 Massachusetts	
No of Patients	3509	478	644	416	1302	748	2532
Median Age, years	72	70	68	64	67	65	64
Gender, %							
Female	47	47	47	43	49	49	65
Male	53	53	53	57	51	51	35
ECOG PS, %							
0–1	52	58	91	86	68	88	93
2+	40	42	9	14	32	12	7
Stage, %							
II	27	NR	12*	1	15	11	1
III	44		82	99	85	89	99
Histology Confirmation, %	81	86	NR	100	NR	100	100
Concurrent Chemotherapy, %	12	10	NR	79	85	58	95

* = stage I patients included in this value

Keywords: Clinical trial access, Radiotherapy, Real-world data

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.08 Routine Self-Administration of a Nursing Demographic Survey to Patients Starting TKIs Identifies At-Risk Individuals

H. Vlahos, K. Rafique, L. Everest, F. Al-Agha, C. Brown, L.J. Zhan, A. Nafees, E. Tsang, S. Raptis, S. Barghout, K. Khan, D. Patel, B. Guiab, N.S. Clarkson, A. Burke, C. De Guia, P. Bradbury, F. Shepherd, A. Sacher, L. Eng, N.B. Leighl, G. Liu
Princess Margaret Cancer Centre, Toronto/ON/CA

Introduction: As oral tyrosine kinase agents (TKIs) become more prevalent as treatment in metastatic non-small cell lung cancer (NSCLC), it remains unclear the impact of out-of-pocket costs such as travel, affecting patients in a universal healthcare system. These burdens can act as a barrier to care as well has having impacts on quality of life. We piloted a nursing self-administered demographic questionnaire for outpatients starting EGFR TKI inhibitors.

Methods: Since 2020, we piloted a survey for patients with EGFR-mutant NSCLC starting first-line TKIs. It collected demographic data, out-of-pocket costs, travel distances, and number of clinic visits. Surveys were completed in clinic rooms before oncology appointments. This initial analysis focused on feasibility and descriptive data from baseline questionnaires in a single-centre CARMA-BROS study at Princess Margaret Cancer Centre (NCT04151342).

Results: FEASIBILITY: No concerns were raised around completing the survey. Language proved to be an issue in some patients, however, this was often mitigated by someone accompanying the patient. During COVID-19, patients were seen less often in clinic, leading to missing follow-up surveys. However, this had no impact on baseline analysis. Baseline completion rate exceeded 85%. DESCRIPTIVE ANALYSIS: In 178 patients with metastatic EGFR NSCLC, median age at diagnosis was 66 [inter-quartile range, IQR 57-74] years, 63% were female, 71% were never-smokers, 73% were of Asian ethnicity; 94% had adenocarcinomas; 81% were diagnosed initially in Stage IV. Socio-demographics showed 31% had annual household income of under CDN $30,000, while another 20% had income of CDN $30,000 to $59,000, only 20% declined to answer; 24% had a job change since diagnosis (retirement or stopping work). Out-of-pocket non-transport spending demonstrated that a proportion of individuals with more than CDN $80 of out-of-pocket spending due to their cancer was 30%. Of those, median annual spending was CDN $1580 [IQR: CDN $580 to CDN $3300]. The most common reasons for spending were for medications (17% of patients) and home renovations (6%). Travel to and from the cancer centre was assessed; 74% came by car, while 14% came by taxi and 11% came by public transit. The median distance travelled was 25km (IQR: 12km to 35 km). Median annual number of clinic visits was 22 [IQR: 12 to 40].

Conclusions: Patients completing this survey either independently or with caregivers was feasible. A minority of patients had either significant annual out-of-pocket spending costs and/or distance travelled to come to clinic for management of their EGFR TKI therapy. Over 50% had low annual household incomes of < CDN $50,000. These findings identify surveyed patients' logistical and financial burdens. Moreover, it identified individuals who may benefit from extra nursing and interdisciplinary support. With success of this pilot, the next implementation goals are to translate the questionnaire into multiple languages and share it digitally on a mobile app/tablet for patients/caregivers to complete at the initiation of TKIs. We aim to establish a formal process where this data is used to assess and support patient experiences as they begin EGFR TKI therapy.

Keywords: Tyrosine Kinase Inhibitors, Barriers to Care, Nursing

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.09 The Impact of Out-Of-Pocket Costs, Travel Distances and Clinic Visits on Quality of Life for Patients on TKIs

K. Rafique, H. Vlahos, L. Everest, F. Al-Agha, C. Brown, L.J. Zhan, A. Burke, C. De Guia, A. Nafees, E. Tsang, S.R. Raptis, S. Barghout, K. Khan, D. Patel, B. Guiab, N.S. Clarkson, N.B. Leighl, P. Bradbury, F.A. Shepherd, A. Sacher, L. Eng, G. Liu
Princess Margaret Hospital, Toronto/ON/CA

Introduction: The increasing use of oral tyrosine kinase inhibitors (TKIs) for metastatic non-small cell lung cancer (NSCLC) has raised important questions regarding the impact of barriers—such as travel distance, frequency of clinic visits, and out-of-pocket expenses—on patient quality of life within the universal healthcare system. Nurses can play a key role in mitigating these barriers through counseling, telehealth, and care coordination. We evaluated the association between out-of-pocket costs, travel distances, and number of clinic visits on health utilities, and EQ-5D-5L component questions in patients starting EGFR TKIs.

Methods: From 2020 onwards, we piloted a survey for patients with metastatic EGFR mutation starting on first-line EGFR TKI, that included: demographic data, out of pocket costs, travel distances, clinic visits, and EQ-5D-5L. Canadian-based health utilities were derived from EQ-5D-5L. Associations of out of pocket costs, travel distances, or clinic costs with health utilities of EQ-5D-5L questions were analyzed using Spearman's rho. This was a single center CARMA-BROS study analysis at Princess Margaret Cancer Centre (NCT04151342).

Results: In 175 patients with metastatic EGFR-mutated NSCLC, median age at diagnosis was 65 [inter-quartile range, IQR 57-74] years, 63% were female, 71% were never-smokers, and 73% were of Asian ethnicity; and 94% had adenocarcinomas; 82% were diagnosed initially in Stage IV. In terms of socio-demographics, 31% had annual household income of under CDN $30,000, while another 20% had income of CDN $30,000 to $50,000, and only 20% preferred not to answer; 24% had a job change since diagnosis (mostly retirement or stopping work). In terms of out-pocket non-transport spending, proportion of individuals with more than $80 of out-of-pocket spending due to then cancer was 30%. Associations between two barriers of care, i.e., annual out-of-pocket costs and number of clinic visits annually were each associated with health utility scores, and the majority of components that form the health utility, including a number of mild-to-moderate correlations with anxiety-depression and functional status (e.g. ability to perform usual activities, self-care, and mobility). Additionally, travel distance was not associated with overall health utility but was associated with pain and discomfort scores.

Conclusions: In TKI-treated patients, barriers-to-care were associated with quality-of-life, including symptoms and functional status aspects. This highlights the importance of nursing-led assessments to identify such barriers in these patients through nursing-based questionnaires. Next steps are to develop tools to support patients with these barriers, through the development of standardized social work, pharmacy, and nursing support triggers.

Table: Spearman's rho correlation of Barriers of Care and EQ-5D health utilities individual questions

			Health Utility Spearman's rho (95% CI)					
		n pts	Total Score	Anxiety and Depression	Mobility	Self-Care	Usual Activities	Pain and Discomfort
All out-of-pocket costs	Spearman's rho (95% CI)	175	**-0.19** (-0.33, -0.15)	**0.22** (0.07, 0.36)	0.13 (-0.03, 0.28)	**0.16** (0.01, 0.32)	0.14 (-0.01, 0.28)	**0.16** (0.01, 0.30)
	p-value		**p=0.01**	**p=0.003**	0.08	**0.03**	0.06	**0.04**
All out-of-pocket costs (non-zero costs)	Spearman's rho (95% CI)	52	**-0.31** (-0.54, -0.05)	**0.26** (0.01, 0.50)	**0.27** (0.00, 0.50)	**0.29** (0.05, 0.53)	**0.22** (-0.03, 0.47)	**0.18** (-0.11, 0.46)
	p-value		**p=0.02**	**0.003**	**0.05**	**0.04**	0.12	0.20
Travel Distances	Spearman's rho (95% CI)	154	-0.05 (-0.19, 0.10)	0.07 (-0.07, 0.23)	-0.07 (-0.23, 0.07)	-0.02 (-0.20, 0.15)	0.03 (-0.12, 0.19)	**0.17** (0.02, 0.32)
	p-value		0.53	0.34	0.34	0.78	0.66	**0.03**
Number of cancer centre visits	Spearman's rho (95% CI)	175	**-0.28** (-0.42, -0.14)	**0.20** (0.06, 0.34)	**0.16** (0.01, 0.31)	**0.24** (0.08, 0.40)	**0.33** (0.17, 0.47)	**0.15** (0.01, 0.30)
	p-value		**p<0.001**	**0.006**	**0.03**	**0.001**	**<0.001**	**0.04**

Keywords: Health Disparities, Nursing, Tyrosine Kinase Inhibitors

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.10 Treating Without Guidelines: Management and Outcomes of Lung Cancer During Pregnancy

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Introduction: Lung cancer diagnosis during pregnancy is uniquely challenging due to the lack of treatment guidelines and the requirement for a careful balance between maternal treatment and fetal safety. However, with the increasing incidence of lung cancer in young women, we expect an increase in the number of lung cancer diagnoses during pregnancy. This systematic review evaluates clinical characteristics, diagnostic approaches, treatment timing, and maternal and fetal outcomes in these complex cases reported in the literature to date.

Methods: A comprehensive literature search of PubMed, Embase, and Scopus (1948-2024) identified 4,411 studies. After removing duplicates and irrelevant studies, 446 articles were screened, and 96 cases that met the inclusion criteria, specifically, the co-occurrence of pregnancy and lung cancer, were selected for analysis. Non-English studies were excluded. Variables included patient demographics, diagnostic modalities, cancer staging, treatment regimens, therapy timing, and outcomes. Statistical analysis was performed using Stata 15.1.

Results: The patients' median age was 33 years (SD ±4.97), ranging from 18 to 42 years. Advanced-stage disease (Stage III or IV) was diagnosed in 65% of cases, primarily through imaging, pleural fluid cytology, and histopathological evaluation. Chemotherapy regimens, such as cisplatin (29.5%) and paclitaxel (9.0%), were administered in 22.8% of cases during pregnancy, with a mean gestational timing of 21.8 weeks (SD ±10.4). Targeted therapies, including EGFR inhibitors (e.g., gefitinib and osimertinib), were used in 18% of cases, with 31.6% initiated postpartum. Surgery, predominantly lobectomy, was performed in a small number of cases (6.2%).Cancer stage was significantly associated with fetal outcomes ($p < 0.0001$), with Stage IV linked to higher rates of preterm delivery and pregnancy termination. The timing of chemotherapy was not significantly associated with fetal outcomes. However, granular data about chemotherapy administration is missing ($p = 0.25$). Tobacco use correlated with advanced-stage cancer ($p = 0.0006$), with 16% of tobacco users presenting at Stage IV. ALK fusions (32.9%) and EGFR mutations (21.4%) were the most common alterations seen in this cohort of pregnant patients with lung cancer. Live births were observed in 47% of cases. Regarding pregnancy outcomes, full-term deliveries (24.7%), preterm deliveries (29%), and pregnancy terminations (18%) were the most common outcomes. Fetal demise occurred in 1.08%, and in rare cases, 14.7% of fetal metastases were histopathologically confirmed.

Conclusions: Lung cancer during pregnancy, particularly in advanced stages, presents significant clinical challenges. Chemotherapy use in the second trimester and targeted therapies postpartum showed favorable maternal outcomes while minimizing fetal risk. These findings emphasize the importance of early diagnosis, tailored treatments, and the urgent need for standardized guidelines to manage these complex cases. Clinical Implications: This review underscores the critical need for a multidisciplinary approach involving oncologists, obstetricians, and neonatologists in managing pregnant patients with lung cancer. The collaborative effort of these professionals is essential in developing individualized treatment plans based on cancer stage, mutation status, and gestational timing, thereby optimizing maternal and fetal outcomes.

Keywords: Lung Cancer, Pregnancy, Disparities

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.11 Clinical and Molecular Characterization of Lung Cancer in Never-Smokers Identified Through an Incidental Nodule Program

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Introduction: Lung cancer in never-smokers represents a growing clinical concern, now ranking among the top ten causes of cancer-related mortality in high-income countries, despite the absence of tobacco exposure. Early detection remains challenging, as no structured population-based screening exists for this subgroup. However, incidental pulmonary nodules detected through imaging studies offer a unique opportunity to diagnose these cancers at earlier stages. This study aimed to describe the clinical, morphological, and molecular profile of lung cancer in never-smokers diagnosed through an incidental nodule detection program.

Methods: We conducted a retrospective descriptive analysis of patients diagnosed with lung cancer via a pulmonary nodule detection program between January 2023 and December 2024. Only never-smokers were included. Variables collected included age, sex, clinical stage (0-4), nodule characteristics (density, border, size, and location), PD-L1 expression (<1%, 1-49%, ≥50%), and presence of oncogenic driver mutations (EGFR, ALK, KRAS, ROS1, BRAF, and others). Results labeled as "unknown," "not performed," or missing were grouped as "unknown."

Results: Of the 25,358 CT scans reviewed, 2,200 nodules were identified as suspicious for malignancy. A total of 237 patients enrolled in the nodule program, with 80 cases confirmed as lung cancer. Among these, 26 patients (32.5%) were never-smokers.

- Demographics: Mean age was 65.8 years (SD ± 16.9); 77% were female.

- Stage at diagnosis: Stage 0 (8%), Stage I (35%), Stage II (15%), Stage III (4%), Stage IV (38%).

Nodule characteristics:

- Density: solid (88%), ground-glass (8%), part-solid (4%)

- Border: regular (88%), irregular (12%)

- Location: left lower lobe (31%), right lower lobe (23%), right upper lobe (19%), left upper lobe (19%), middle lobe (8%)

- Mean size: 35.2 mm (SD ± 23 mm)

PD-L1 expression:

- <1%: 9 (82%)

- 1-49%: 2 (18%)

- ≥50%: 0 (0%)

- Unknown/not performed: 15 (58%)

Driver mutations:

- Detected in 13 (50%) patients

- Not detected: 5 (19%)

- Unknown/not performed: 8 (31%)

Conclusions: Our findings reinforce the value of incidental imaging in enabling earlier diagnosis of lung cancer in never-smokers. Despite the absence of targeted screening, this route shows promise in identifying cases at potentially curable stages. A significant proportion of tumors harbored actionable driver mutations, particularly among stage IV cases, underscoring the urgent need for improved access to molecular testing, even in early-stage disease. This study adds to growing evidence that lung cancer in never-smokers may constitute a distinct clinical and molecular entity, warranting tailored diagnostic and therapeutic strategies.

Keywords: non smokers, incidental nodles, lung screening

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.12 Unwarranted Variation in Lung Cancer Care in Perth, Western Australia: A Lung Cancer Clinical Quality Data Platform Report

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Introduction: Lung cancer is one of Australia's most common cancers and the leading cause of cancer death and cancer-associated burden of disease. Unwarranted variation in lung cancer care is described across Australia; interventions to systemically identify and address this are urgently required given the impending implementation of the government-funded National Lung Cancer Screening Program (NLCSP) in July 2025. The aim of the Lung Cancer Clinical Quality Data Platform (LUCAP) is to improve the safety and quality of lung cancer care through the utilisation of routine clinical data; this report describes findings over a twelve-month period.

Methods: Between September 2022 and December 2024, adult patients with suspected and confirmed thoracic malignancy referred to four tertiary hospitals in metropolitan Perth, Western Australia were recruited. Routine clinical data were prospectively captured, including demographics, appointment dates, investigations, multidisciplinary meeting (MDM) outcomes, and treatment modalities. Data were benchmarked against standards established by the Australian Optimal Care Pathway and national Clinical Quality Indicators (CQIs). Censor date was 09 February 2025.

Results: Over the project duration, 1261 participants were recruited, amongst which 1089 thoracic malignancies were diagnosed. There were 976 participants diagnosed with lung cancer; the median age was 71 years, 453 (46%) were female sex, and 320 (33%) reported current tobacco use. Table 1 summarises key CQIs over twelve months. No hospital met standards for timely lung cancer care, and additionally there was evidence of significant unwarranted variation between sites (CQIs 1, 3, 8). Variance in genomic testing rates was identified (CQI 6) and may reflect variable practice across public and private pathology providers. Rates of MDM discussion were universally high, however the quality of documentation varied (CQIs 11, 12, 13). Rates of treatment provision were high (CQIs 16, 17, 22, 23) for participants diagnosed with both early and late-stage disease.

Conclusions: There is evidence of unwarranted variation across the continuum of lung cancer care in metropolitan Perth; a minority of patients commenced treatment within target timeframes. Variation in the proportion of participants with complete genomic testing and timely PET/CT staging are of particular concern given the increasing complexity of thoracic oncology. Additional funding for staffing and infrastructure, as well quality improvement initiatives, will be required to fully realise the benefits of NLCSP implementation.

Table 1. Clinical quality indicators, October 2023-September 2024

	CQI #	Tumour	Target	All	SCGH	FSH	RPH	SJOGM	P value
Number of participants diagnosed with lung cancer	N/A	SCLC, NSCLC	N/A	512	138	132	123	119	N/A
Referral to first appointment ≤14 days Median days (IQR)	1	SCLC, NSCLC	≥80%	50% 16 (8,28)	30% 20 (14,32)	43% 15 (12,24)	65% 7 (4,25)	63% 11 (6,26)	<0.001
Referral to first diagnostic procedure ≤28 days Median days (IQR)	2	SCLC, NSCLC	>90%	54% 28 (17,46)	56% 24 (20,43)	50% 28 (21,43)	53% 27 (12,59)	61% 20 (12,38)	0.324
Referral to first treatment ≤42 days Median days (IQR)	3	SCLC, NSCLC	≥60%	17% 76 (54,111)	12% 76 (55,111)	12% 78 (56,110)	17% 84 (51,137)	30% 63 (41,89)	0.003
Discussed at least once at MDM prior to treatment (%, n)	11	SCLC, NSCLC	≥85%	94% 433/461	94% 122/130	91% 106/116	98% 110/112	92% 95/103	0.142
ECOG performance status documented (%, n)	12	SCLC, NSCLC	≥95%	89% 454/512	83% 114/138	99% 130/132	98% 121/123	75% 89/119	<0.001
Complete clinical TNM stage documented (%, n)	13	SCLC, NSCLC	≥95%	79% 404/512	78% 107/138	80% 106/132	71% 87/123	87% 104/119	0.015
Stage IV NSCLC, had adequate genomic testing* (%, n)	6	NSCLC	>95%	86% 110/128	96% 27/28	97% 29/30	96% 26/27	65% 28/43	<0.001
FDG PET/CT within 6 weeks of first curative-intent treatment (%, n)	8	SCLC, NSCLC	>95%	34% 105/305	30% 27/91	25% 20/80	43% 32/74	43% 26/60	0.033
Any anti-cancer treatment (%, n)	16	SCLC, NSCLC	≥80%	92% 469/512	96% 142/148	90% 119/132	92% 113/124	88% 105/119	0.167
Surgical resection, Stage I-II NSCLC (%, n)	17	NSCLC	≥60%	59% 102/172	55% 27/49	56% 24/43	58% 19/33	68% 32/47	0.548
Systemic therapy administered, Stage IV NSCLC (%, n)	22	NSCLC	≥50%	74% 95/128	68% 19/28	67% 20/30	82% 22/27	79% 34/43	0.430
Systemic therapy administered, SCLC (any stage) (%, n)	23	SCLC	≥80%	78% 39/50	82% 9/11	86% 12/14	83% 15/18	43% 3/7	0.116

SCGH: Sir Charles Gairdner Hospital, FSH: Fiona Stanley Hospital, RPH: Royal Perth Hospital, SJOGM: St John of God Midland Public and Private Hospital.
* PD-L1 for Squamous Cell Carcinoma, and PD-L1, EGFR, ALK and ROS for non- Squamous Non-Small Cell Lung Carcinoma

Keywords: lung cancer, clinical quality indicator, unwarranted variation

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.13 Biomarker Testing Timeliness for Patients With Lung Cancer

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Introduction: Complete and timely biomarker testing is a key step for selecting optimal treatment and clinical trial eligibility in patients with lung cancer. Despite this, racial and socioeconomic disparities in biomarker testing have been previously reported. This study evaluates biomarker testing timeliness for patients with lung cancer at an urban tertiary care safety-net hospital.

Methods: We conducted a retrospective review of next-generation sequencing (NGS) reports performed by an external vendor by tissue, blood, or both sampling methods for patients with a primary lung cancer at University of Illinois Hospital from December 2018 through March 2025. For patients who had multiple NGS tests done during their treatment course, only the initial NGS report was included in this analysis. Key variables were time from tissue or liquid biopsy to report, time from NGS test order to report, and the presence of an actionable molecular biomarker associated with an FDA approved therapy. Patient demographic and clinical data were obtained through retrospective review of the electronic medical record. Independent two-sample t-tests were performed to compare mean turnaround time from sample collection and order placement to NGS report. Association between race and NGS turnaround time were assessed using chi-square tests of independence.

Results: A total of 436 patients underwent NGS testing by either tissue (157; 36.0%), blood (78; 17.9%), or combination sampling (201; 46.1%). The cohort consisted of 50.9% male, 49.1% female, 64.7% Black, 22.8% White, 10.7% Hispanic, and 8.8% Asian. Histological distribution was 69.4% adenocarcinoma, 18.3% squamous cell carcinoma, 6.9% NSCLC-NOS, and 5.3% small cell carcinoma. Mean turnaround time from sample collection to NGS reporting was significantly shorter for liquid versus solid tumor (12.8 vs 38.6 days, $p<0.01$). Similarly, mean turnaround time from order placement to report was significantly shorter for liquid versus solid tumor (12.3 vs 21.1 days, $p<0.01$). There was no statistically significant association between race and turnaround time from sample collection to report for either solid tumor ($p=0.27$) or liquid biopsies ($p=0.52$). The distribution of turnaround times (≤14 days, 14-30 days, >30 days) did not differ significantly across racial groups. The percentage of patients with a molecular biomarker associated with an FDA-approved therapy by histology was 48.4% (adenocarcinoma), 25.8% (NSCLC-NOS), 8.7% (small cell carcinoma), and 7.6% (squamous cell carcinoma).

Conclusions: At our urban tertiary care safety-net hospital, liquid biopsy yielded significantly faster turnaround times than solid tumor biopsy for next-generation sequencing ($p<0.01$). While biomarker racial disparities have previously been reported, no significant racial differences were observed in the timeliness of biomarker reporting in our cohort. Nearly half of the patients with adenocarcinoma harbored actionable molecular alterations, highlighting the importance of comprehensive and timely molecular testing to guide precision oncology in diverse populations.

Keywords: Biomarker, Equity, Lung

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.14 Regional Disparities in Late-Stage Lung Cancer Outcomes in Sweden - Insights From Population-Based Data

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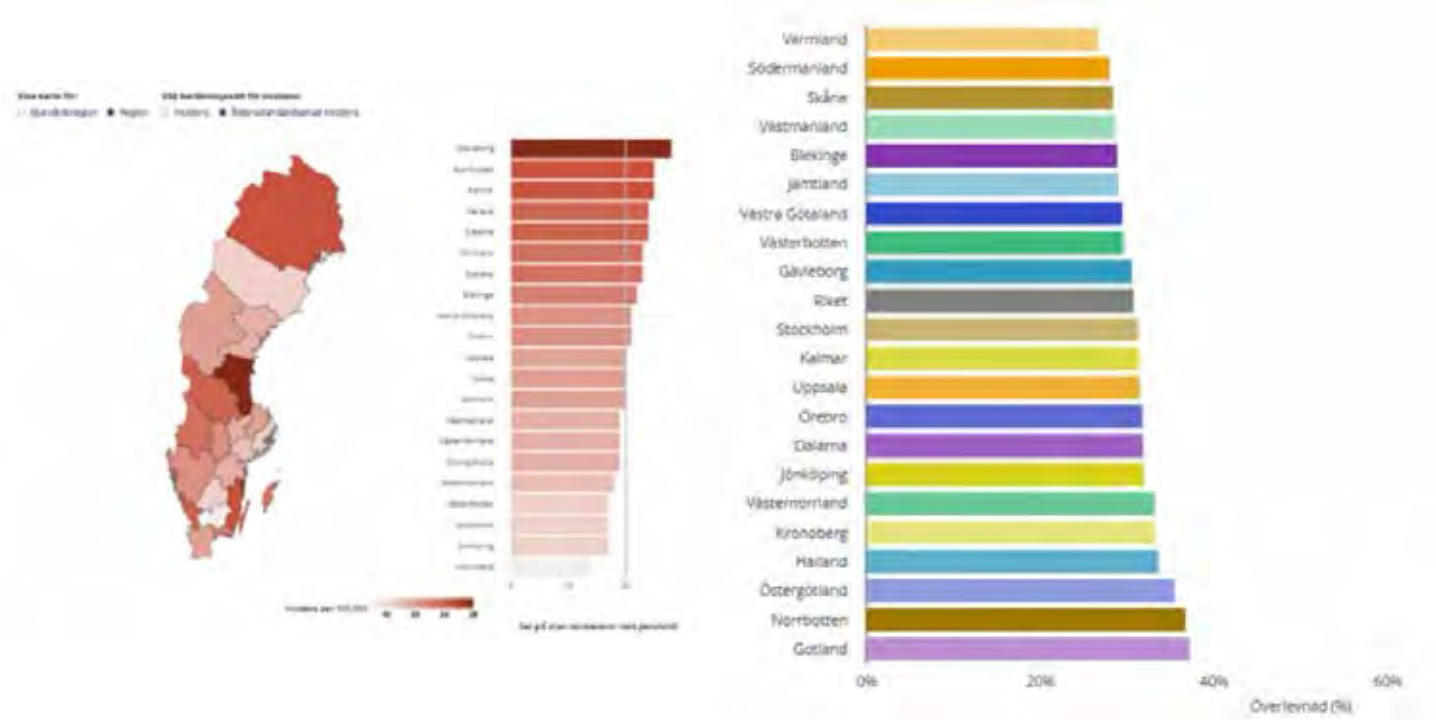
Introduction: Lung cancer is often diagnosed late in the disease process, with detrimental impacts on patient outcomes. Using the recently launched VizCan platform with population-based cancer data offers a unique opportunity to improve lung cancer care through an enriched understanding of which factors that result in differences in cancer care. This study aims to examine potential regional differences in incidence, survival, and mortality in stage IV lung cancer.

Methods: VizCan is an interactive visualization platform open for everyone to use (https://vizcan.epistat.se). It includes 18 different cancer types. The study focuses on lung cancer and includes all patients identified via ICD-10 codes in the Swedish Cancer Registry (SCR) from 2014 onwards. Reporting to the SCR, managed by the National Board of Health and Welfare, is mandatory. Patient outcomes include age-standardized incidence, overall survival (OS), relative survival (RS), and age-standardized mortality.

Results: Between 2014 and 2022, a total of 37,206 patients were diagnosed with lung cancer. Almost 50% (n=18,437) were diagnosed in stage IV. The majority were older (mean age=71) and women (53%). The age-standardized incidence varied from 14 to 28 per 100,000 person years between different regions (Figure 1). The one-year OS and RS estimates differed between regions (26.7% to 37.2% for OS (Figure 2) and 27.0% to 37.2% for RS, respectively). Age-standardized mortality generally decreased over time, but also showed variations between regions. For instance, mortality in 2022 varied between 9 to 21 per 100,000 person years in different regions.

Conclusions: Regional differences exist in late-stage lung cancer incidence, survival, and mortality in Sweden, despite a declining mortality trend. The high proportion of patients diagnosed in stage IV underscores the need for earlier detection and improved access to timely and equitable care. Equal access to targeted interventions through regional quality improvements may help reduce disparities and enhance lung cancer outcomes



Keywords: disparities, epidemiology, outcomes

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.15 Social Vulnerability and Survival Outcomes in Stages I-II Lung Cancer: A Predictive Nomogram-Based Analysis

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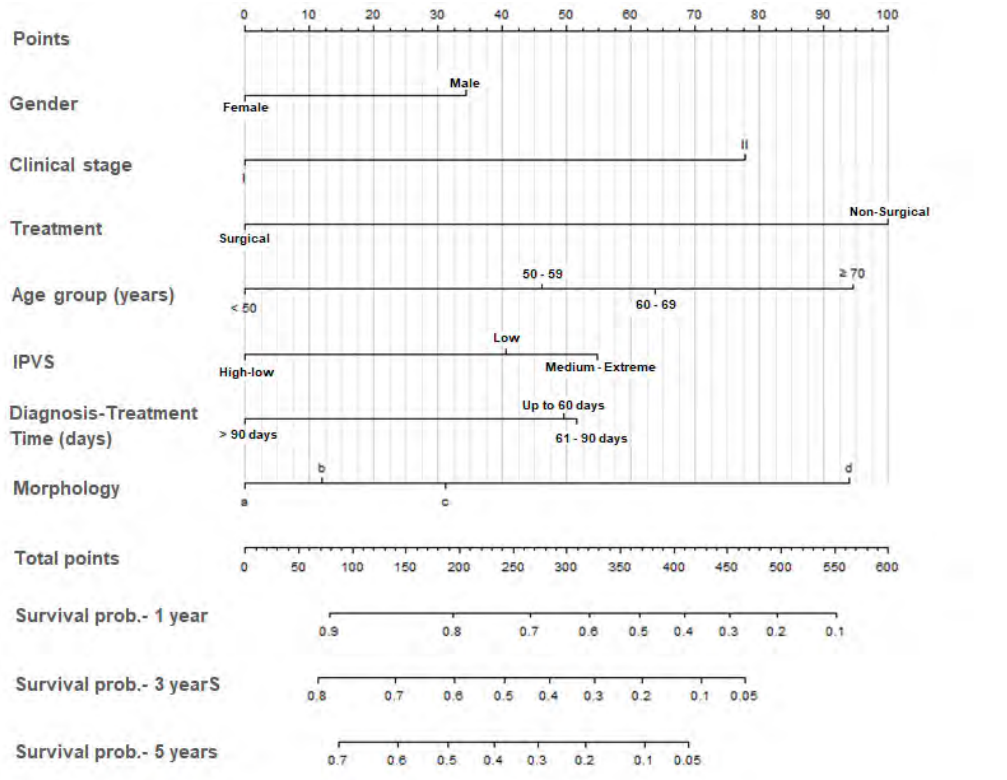
Introduction: Social vulnerability profoundly affects access to surgical treatment and survival outcomes in early-stage lung cancer. This study focuses on the development of a predictive nomogram that incorporates the Índice Paulista de Vulnerabilidade Social (IPVS -São Paulo Index of Social Vulnerability) as a critical determinant of disparities in patient management.

Methods: Data from 1,345 patients with stage I-II lung cancer diagnosed between 2000-2013 were analyzed. Kaplan-Meier survival analysis and Cox regression models assessed the impact of IPVS, treatment modality, and other clinical factors on survival. A nomogram was constructed using a multivariate Cox model to predict 1-, 3-, and 5-year survival probabilities, emphasizing PVS as a primary factor influencing surgical access and outcomes. The nomogram's predictive accuracy was evaluated using the C-index and AUC values.

Results: Patients in higher IPVS categories (IPVS 3) exhibited significantly lower rates of surgical treatment (p<0.001), with a mortality hazard ratio (HR) of 1.65 (95% CI: 1.34-2.04) compared to those in IPVS 1. Non-surgical treatment was the strongest predictor of mortality (HR=2.03, 95% CI: 1.76-2.35, p<0.001). Other significant factors included male gender (HR=1.25, 95% CI: 1.07-1.45) and age ≥70 years (HR=1.84, 95% CI: 1.45-2.31). The constructed nomogram incorporated IPVS, treatment modality, stage, age, gender, and histology, assigning a weighted impact to each factor. The nomogram (Fig. 1) demonstrated moderate predictive accuracy, with a C-index of 0.66 (95% CI: 0.64-0.68) and AUC values of 0.72, 0.74, and 0.73 for 1-, 3-, and 5-year survival, respectively. The tool revealed that higher IPVS levels correlated with delayed or absent surgical intervention, directly reducing survival probabilities.

Conclusions: The predictive nomogram highlights the Paulista Index of Social Vulnerability as a central determinant of disparities in surgical access and outcomes in early-stage lung cancer. By quantifying the impact of IPVS and other clinical factors, the nomogram serves as a valuable tool to guide targeted strategies for addressing inequities and improving access to life-saving surgical care.



DATABASE: 1,252 patients overall; 11 cases without IPVS information
*a. Adenocarcinoma + Neuroendocrine carcinoma; b. Large cell carcinoma; c. NSCLC Carcinoma+Squamous cell carcinoma; d. SCLC Carcinoma

Keywords: Lung cancer, social vulnerability, Survival

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.16 Racial and Ethnic Disparities in Receipt of Guideline Concordant Treatment for Early-Stage NSCLC in Los Angeles County

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Introduction: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in California. Black patients experience the highest mortality rates (39 per 100,000) compared to Non-Hispanic White (NHW) (34 per 100,000), Asian/Pacific Islanders (A/PI) (23 per 100,000), and Hispanic patients (17 per 100,000). The most modifiable factor contributing to these differences is the receipt of guideline-concordant treatment (GCT), with surgical resection or radiation therapy recommended for all medically operable patients with stage I-II NSCLC. Despite rigorous clinical evidence supporting these guidelines, a higher proportion of Non-Hispanic Black (NHB) and Hispanic patients do not receive GCT compared to NHW patients. This study analyzed differences in receipt of GCT across racial and ethnic groups, leveraging data from a robust, population-based cohort of all early-stage NSCLC cases diagnosed in Los Angeles County.

Methods: Patients diagnosed with early-stage NSCLC (tumors <4cm, no lymph node involvement, and no metastases) between 2012-2022 were identified from the Los Angeles County Cancer Surveillance Program. Using a logistic regression model, we evaluated the association between race and ethnicity and receipt of guideline concordant treatment, adjusting for confounders including age, sex, socioeconomic status, insurance type, marital status, and tumor size. Outcomes were defined as receipt of GCT (surgery or radiation only), while non-GCT included no treatment or any combination of multiple treatments.

Results: A total of 2,857 patients with early-stage NSCLC were identified of which 57.3% were NHW, 8.9% were NHB, 14.2% were Hispanic, and 18.8% were A/PI. Patients with early-stage NSCLC were on average 69.6 years of age, majority female (63.2%), and had an average tumor size of 1.9 cm. While most patients (87.4%) received GCT, NHB patients had the highest proportion of non-GCT treatment (18.0%) followed by Hispanic patients (15.8%). NHB patients had significantly higher odds of not receiving GCT compared to NHW patients (OR: 1.54, 95% CI: 1.05-2.26; $p<0.05$). No statistically significant differences in GCT receipt were observed for A/PI or Hispanic patients compared to NHW patients. However, the disparities in non-GCT between Hispanic vs. NHW patients were largely explained in stepwise regression models by socioeconomic factors (crude OR: 1.59 [1.17-2.17] vs. fully SES-adjusted model OR: 1.26 [0.90-1.177]).

Conclusions: Addressing disparities in GCT for patients diagnosed with early-stage NSCLC is critical to improving survival outcomes. Future studies identifying factors influencing a patient's decision to receive GCT and a physician's decision to recommend and adhere to GCT guidelines is needed to understand the complexity of treatment decision-making.

Keywords: Population-based science, Cancer Care Quality, Disparities

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.17 Financial Distress and Concerns Prior to Cancer-Directed Treatment Among Patients With NSCLC

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Introduction: In recent years, significant progress has been made in the development of novel biomarkers and therapies for non-small cell lung cancer (NSCLC). However, the clinical benefits of this progress have not been equally distributed across all patient groups, partly due to adverse social conditions associated with poor health outcomes (i.e., health-related social needs). Previously published studies have shown that NSCLC survivors are more likely to have unmet supportive care needs, be unemployed, and experience financial hardship. Given the growing evidence of the associations of social adversity to poor health outcomes and the increasing costs of cancer care, we evaluated the prevalence of financial distress prior to the initiation of cancer-directed therapy among patients with NSCLC.

Methods: This multi-site prospective study enrolled adults with NSCLC initiating cancer-directed treatment into one of two cohorts: Cohort A enrolled patients with early-stage NSCLC receiving a curative intent treatment, and Cohort B enrolled patients with advanced NSCLC receiving noncurative intent treatment. Patients completed social needs and financial toxicity survey assessments prior to treatment initiation (baseline) and at 1, 3, and 6 months. Study enrollment is ongoing. We conducted an interim exploratory analysis of 56 patients enrolled in the study (aggregate of cohorts A and B) as of March 2025, who completed a baseline assessment. Data was summarized using descriptive statistics.

Results: Among 56 patients, 53.8% identified as female, 61.5% were aged 60-79, and 28.8% were aged 40-59. Regarding their NSCLC, 35.7% had early-stage disease and 64.3% had advanced disease. 34.7% of patients reported an annual household income of $24,999 or less. Prior to the initiation of cancer-directed therapy, 41.7% of participants reported experiencing financial concerns over the past week, and 38.3% expressed concerns about being able to take care of themselves. Over half (52.9%) of the patients reported not having enough money in savings, retirement, or assets to cover the costs of their treatment. Furthermore, 31.8% reported being “very much” concerned about potential financial challenges arising from their illness or treatment. Most patients (44.8%) reported dissatisfaction with their current financial status and 41.2% felt “not at all” in control of their financial situation. Participants commonly felt frustrated they couldn’t work or contribute as much as they usually did (14.9% quite a bit, 29.9% very much).

Conclusions: In this prospective cohort of patients with NSCLC, patients commonly experienced financial distress and concerns prior to the initiation of cancer-directed therapy. Early identification of financial concerns could help identify supportive resources for patients undergoing cancer treatment and help mitigate some of the adverse social conditions associated with poor health outcomes.

Keywords: financial distress, social needs, financial toxicity

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.18 Victorian Lung Cancer Registry Impacts on Multi-Disciplinary Lung Cancer Meeting Presentation

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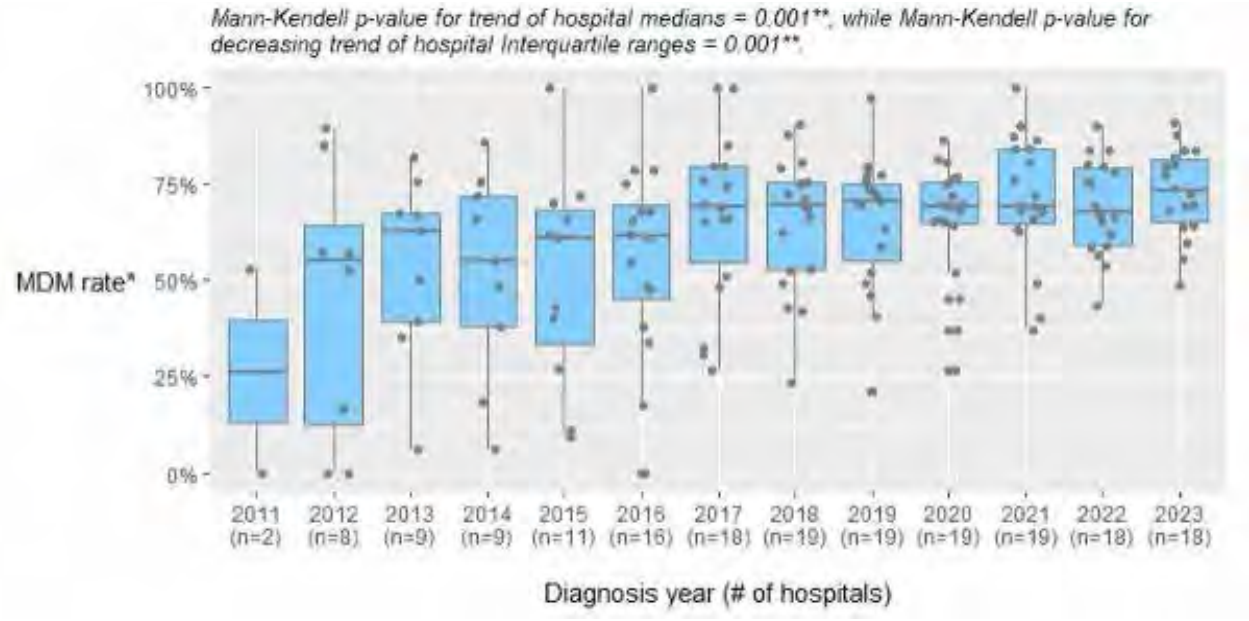
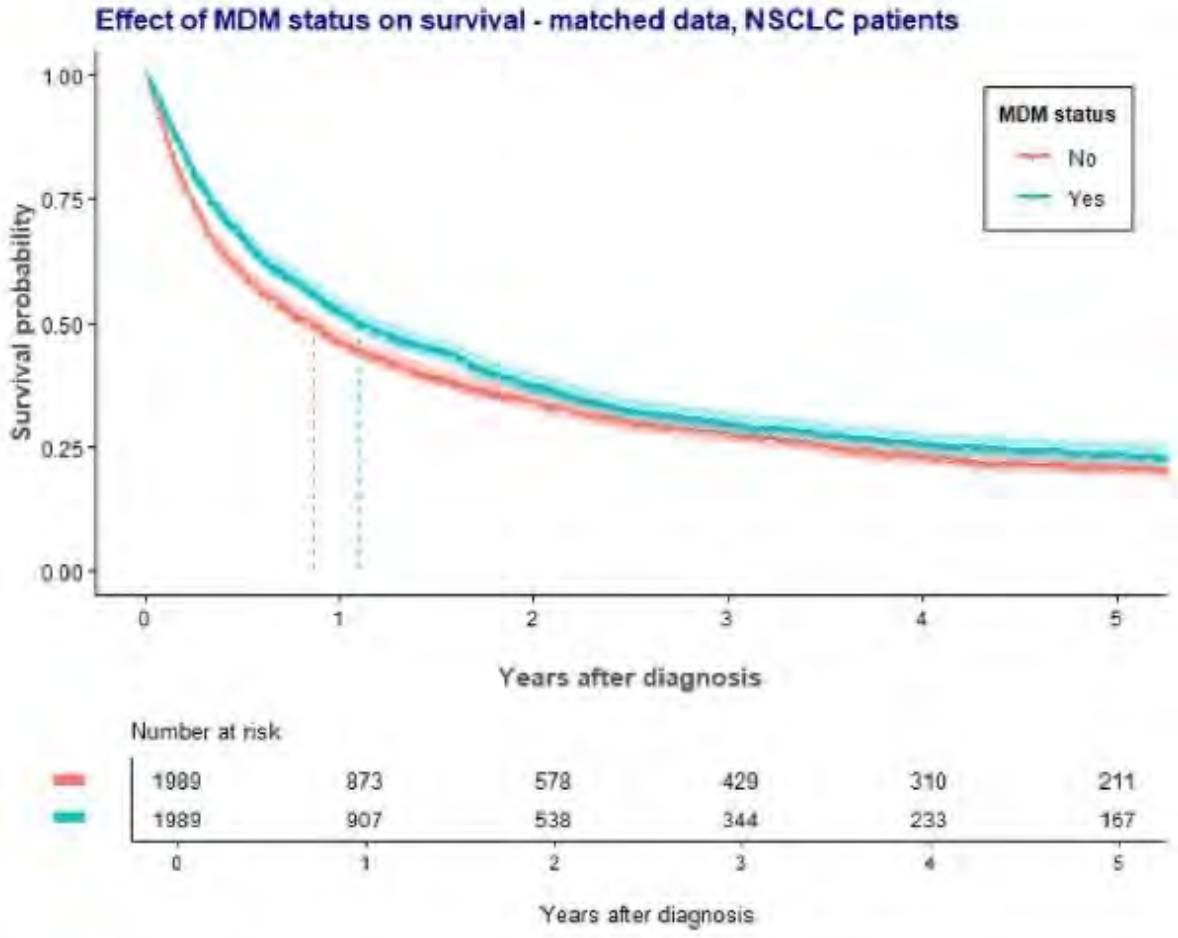
Introduction: Lung cancer is an heterogeneous and complex disease requiring multidisciplinary input for optimal management planning, with guidelines recommending all patients be discussed in a multidisciplinary setting. Multidisciplinary discussion (MDM) aims to enhance evidence-based management, improve treatment access and optimise complex management plans.

Methods: We aimed to assess the extent and impacts of MDM discussion in patients with lung cancer described by the Victorian Lung Cancer Registry (VLCR) from 2011-2024 in Victoria, Australia. We identified MDM presented and non-presented patients and assessed dependant management outcomes and survival impacts.

Results: 18,597 patients were included of whom 67% had evidence of presentation to a lung cancer MDM, with MDM presentation increasing from 59.1% to 80.6% during the study period Figure 1. MDM presentation was associated with significantly higher levels of provision of Guideline Concordant Treatment (GCT) in NSCLC (52.9% vs 42.3%, p<0.001), non-GCT and lower levels of no treatment (13.4% vs 24.6%, p<0.001). Modifiable factors which may increase MDM presentation included higher age, stage IV disease and treatment in a private hospital. Propensity matched survival analysis in NSCLC revealed a median survival of 1.1 years (1.0-1.3 years, p<0.001) for MDM presented vs non presented individuals 0.86 years (0.76-0.94), providing a 12% reduction in mortality hazard (HR 0.88(0.82-0.95), p<0.001) Figure 2.

Conclusions: Clinical Quality Registries enable assessment of the appropriateness and effectiveness of healthcare implementation in population-based complex disease domains and inform quality improvement initiatives within learning health systems. MDM presentation increased by 20% during this study period providing significant management optimisation and survival advantage





MDM status	N	1 year survival (95% CI)	5 year survival (95% CI)	Median survival, years (95% CI)	Hazard ratio (95% CI)	P-value
No	1,989	46.4% (44.2-48.6)	20.9% (19-22.9)	0.86 (0.76-0.94)	Ref.	Ref.
Yes	1,989	52.5% (50.3-54.9)	23.4% (21.2-25.8)	1.1 (1.0-1.3)	0.88 (0.82-0.95)	<0.001***

Keywords: Multidisciplinary meeting, Clinical quality registry

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.19 Impact of Race and Ethnicity on the ENGAGE-Derived Lung Cancer Screening Recommendations: Implications for Risk Assessment

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Introduction: The ENGAGE framework optimizes lung cancer screening based on age, sex, and smoking related risk factors, for ever-smoked individuals at a personalized-level. The inclusion of race and ethnicity in risk prediction models is controversial. We adapted the PLCOm2012 risk model and integrated it into ENGAGE to evaluate the influence of race and ethnicity on the ENGAGE-derived lung cancer screening schedules.

Methods: We developed and validated three versions of Cox proportional hazards regression models for lung cancer risk differing by the levels of race and ethnicity included (6-race, 3-race, no-race) and one model to predict death from causes other than lung cancer using data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). The developed risk models incorporate all PLCOm2012 covariates but converted smoking intensity and body-mass index (BMI) from continuous to categorical variables. The competing causes of death model includes all PLCOm2012 covariates except family history of lung cancer plus sex, diabetes, cardiovascular disease, stroke, and hypertension. We integrated these risk models into ENGAGE and generated personalized screening schedules for the National Lung Screening Trial (NLST) participants who were randomized in the low dose computed tomography (LDCT) arm and were adherent to annual screening. We compared the performance of ENGAGE across the different versions of the risk models (6-race PLCOENGAGE2025, 3-race PLCOENGAGE2025, no-race PLCOENGAGE2025) and the original ENGAGE that uses the Bach risk model, in terms of the number of screen-detected cases, number of screening exams, and number of false-positive results.

Results: The PLCOENGAGE2025 models demonstrated good and comparable discrimination, calibration, and validation in both PLCO and NLST data. Screening schedules derived from ENGAGE performed better when based on PLCOENGAGE2025 compared to the Bach risk model. The ENGAGE version utilizing the Bach model reduced screening exams by 81% and false-positive results by 84%, while delaying screen-detected lung cancer diagnoses by 2.8% relative to the NLST results. ENGAGE-derived schedules based on the PLCOENGAGE2025 race-specific models outperformed those using the PLCOENGAGE2025 no-race model for Black individuals, resulting in more screen-detected cases and higher mortality reduction (Figure 1).

Conclusions: Incorporating race and ethnicity into lung cancer risk models enhances the effectiveness of screening in a mixed-race population which justifies its consideration in risk prediction models. ENGAGE-derived schedules maintained comparable effectiveness to annual screening despite reducing the number of screening exams and false-positive results.

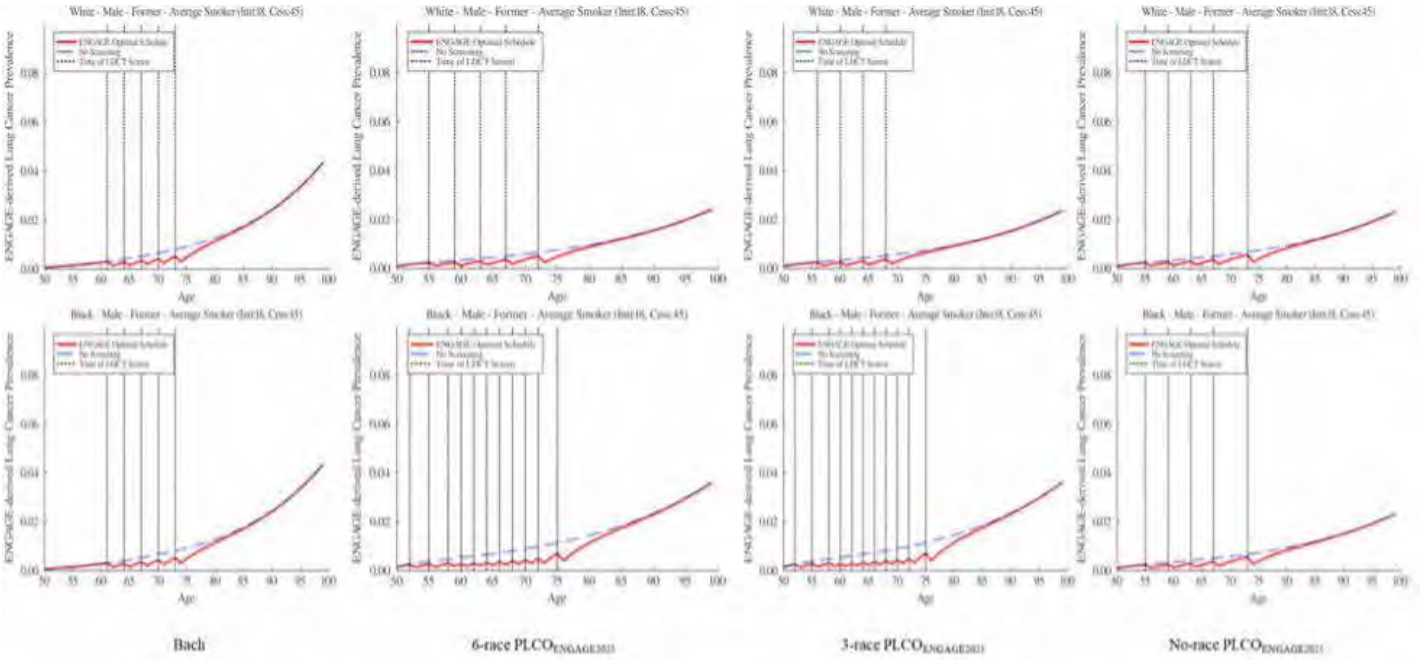

Figure 1. ENGAGE lung cancer screening schedule for a male former average smoker with overweight, some college education, no chronic obstructive pulmonary disease, no family history of LC, no personal history of cancer, and no comorbidities. The first row represents the Non-Hispanic White population, and the second row represents the Non-Hispanic Black population. Risk models considered include the 6-race PLCO$_{ENGAGE2025}$, 3-race PLCO$_{ENGAGE2025}$, no-race PLCO$_{ENGAGE2025}$, and Bach model.

Keywords: racial disparities, lung cancer screening, ENGAGE framework

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.20 Optimal Lung Cancer Outcomes for People From Rural and Remote Areas: An Overview of the Problem and a Research Program to Reduce Disparities

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Introduction: People living in rural and remote communities have higher smoking rates and lung cancer diagnoses than their metropolitan counterparts. Tobacco use is a significant risk factor, contributing to approximately 90% of lung cancers in males and 65% in females. Additionally, age-standardised mortality rates for lung cancer increase with geographical remoteness. People with cancer from rural and remote areas often experience delays in diagnosis and treatment. Accessing infrastructure such as CT imaging and radiation therapy can pose a challenge in these regions, impacting timely and effective lung cancer diagnosis and care. Addressing these disparities and inequities in rural and remote areas requires dedicated research. This abstract presents an overview of the Equitable Cancer Outcomes across Rural and Remote Australia (ECORRA) program, which aims to improve cancer outcomes through targeted strategies and interventions.

Methods: The ECORRA program consists of three funded projects in progress conducted across several states of Australia. We will describe: 1) ECORRA Trial: A national stepped-wedge trial to embed a co-designed implementation package to reduce time to diagnosis and time to treatment for people with cancer in rural and remote communities; 2) ECORRA Optimal Care Pathway: The development of a rural and remote specific Optimal Care Pathway, a nationally endorsed standard for the delivery of timely, quality care; which will complement the existing tumour Optimal Care Pathways such as lung cancer; 3) ECORRA Victoria: A statewide survey to identify and compare the predictors of delays to diagnosis and treatment between rural and metropolitan Victorians. All projects are active and include people with lung cancer.

Results: This program of work represents strong partnerships across academic institutions, clinicians, health services, policymakers and community organisations. A consumer advisory group of 18 people from rural and remote areas has been appointed to contribute across the program. A fit for purpose governance structure has been established and endorsed, with national site visits underway. Responses to four public government consultations have been submitted and PhD projects aligned to the program have commenced. Ethical requirements for all necessary components of the program have been lodged and approved. For the ECORRA Trial, national quantitative surveys and qualitative interviews are underway to inform development of the implementation package, with 60-100 interviews with a diverse range of health care professionals providing cancer care and consumers to be completed by the time of this presentation. Over 30 professionals and people with lived experience of cancer have informed the first draft of the Optimal Care Pathway, which will undergo national public consultation later in 2025.

Conclusions: The ECORRA program represents an interdisciplinary investment to reduce cancer inequities across rural and remote communities through integrated research and policy approaches. Supported by both state and federal funding, the program aims to drive meaningful improvements in cancer care. Key results relevant to lung cancer treatment and outcomes will be presented, and the next steps will be outlined. Approaches to scalability and sustainability will be presented, to drive lasting impact for people affected by lung cancer from rural and remote areas.

Keywords: rural, health services, equity

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.21 Gender Disparities in Remote Patient Monitoring: Analysis From 973 Lung Cancer Patients Treated Across 42 Sites in France and Belgium

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Introduction: Gender disparities in cancer care and outcomes are increasingly evident, affecting incidence, treatment access, and survival. Multiple phase III trials have established remote patient monitoring (RPM) with ePROs as a standard, improving morbidity and quality of life. RPM also offers a unique opportunity to assess baseline social determinants of health (SDOH) and symptom burden. This study examines gender-based differences in RPM use and outcomes among lung cancer patients.

Methods: The RPM process included medical prescription, weekly symptom monitoring (PRO-CTCAE), and alerts to healthcare providers (HCP) for severe or worsening symptoms. Data from 973 lung cancer patients treated at 42 sites in France and Belgium between January 2022 to December 2024 were analyzed. Gender-specific differences in demographics, tumor characteristics, treatment modalities, symptoms and social determinants of health (SDOH) were evaluated.

Results: Among 973 lung cancer patients, descriptive statistics were as follows: 44% female (F) and 56% male (M), mean age 65.1 (F) vs. 66.4 years (M) (p = 0.05); metastatic disease in 67.9% (F) vs. 61.5% (M); 49.8% of patients had non-oncogene-addicted NSCLC, 37.8% had oncogene-addicted NSCLC and 8.7% had a SCLC. Unfavorable SDOH were similar across groups except alcohol consumption frequency (F:12.7% vs. M: 29.5% p<0.001). Female exhibited higher adherence to weekly questionnaire (F: 84.3% vs. M:81.5%, p<0.001) and shorter time to process them (median response time (hours) [Q1-Q3] (M: 10.6 [1.4,57.2], F: 9.2 [1.3,49.3], p=0.004). At baseline, female patients experienced higher symptoms burden (PROs grade ≥ 3 symptoms) including anorexia, nausea, vomiting, diarrhea, constipation (F: 45.7% vs. M: 34.5%, p<0.001) and unfavorable physical function related symptoms including pain, performance status (PS), fatigue (F: 59% vs. M: 46.9%, p<0.001). Female patients had higher rates of symptom improvement after alerts (≥ 1 grade reduction, PRO-CTCAE of 93.8% (M) vs. 97.5% (F), p=0.032) compared to males. Imbalances in symptom burden appeared mitigated at 12 weeks, with non-significative remaining differences.

Conclusions: Female patients showed a higher burden for digestive symptoms and unfavorable physical function. Female patients exhibited higher degree of symptom improvement following RPM alerts, suggesting that baseline differences could be alleviated by RPM. Gender-specific differences underscore the need for tailored RPM strategies to ensure more equitable clinical outcomes.

Keywords: Gender disparities, Remote Patient Monitoring (RMP), electronic Patient Reported Outcomes (ePRO)

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.22 Concordance of HER2 Protein Overexpression by IHC and ERBB2 Gene Amplification by NGS in Lung Cancer

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Introduction: Recently approved HER2-directed antibody drug conjugate - trastuzumab deruxtecan (T-DXd) for HER2+ solid tumors specifically targets the HER2 protein on the surface of cancer cells. Broad-based, next generation sequencing (NGS) testing is standard for those with advance non-small cell lung cancer (NSCLC). While there is a known strong correlation between HER2-overexpression (OE) and ERBB2 gene amplification (amp) in other malignancies such as breast cancer, little is known of the correlation in lung cancers. Moreover, if only ERBB2-amp is assessed by NGS without evaluation for HER2-OE by IHC, patients may be misidentified and not be able to receive appropriate treatment for HER2-OE advanced NSCLC such as T-DXd. This study aims to assess the concordance between HER2-OE and ERBB2-amp, among lung cancer patient samples evaluated simultaneously by IHC and NGS tests.

Methods: We examined tissue samples tested by Neogenomics Laboratories of individual lung cancer patients who received the NeoTYPE® Lung Tumor (NTP) profiling between May 2023-June 2024. As part of NTP, HER2-OE was assessed by IHC (clone 4B5) using ASCO/CAP breast scoring algorithm. HER2-OE criteria was met if samples were IHC 2+/IHC 3+. ERBB2-amp was obtained by NGS and considered positive if the copy number variant gain was ≥2.8 (qualitative assay with 88% sensitivity and 82% specificity). The proportion of samples with overlapping HER2 IHC and ERBB2 NGS test results were reported. The association between HER2 IHC and NGS ERBB2-amp tests was examined using chi-square and concordance using spearman's rank correlation tests.

Results: Of the 2,960 samples included, 28.2% (n=836) met the HER2-OE criteria and 22.2% (n=657) tested positive for ERBB2-amp (Table). An overlap between HER2-OE and positive ERBB2-amp was observed in only 10.0% (n=294) of the samples. A statistically significant association was found between the HER2 IHC and ERBB2-amp test results (p-value<0.001), with a trend toward increasing rate of positive ERBB2-amp from IHC 0 to IHC 3+ (correlation coefficient 0.19, p-value<0.001). However, ERBB2-amp was negative among 66.6% of IHC 2+ (529/794) and 31.0% of IHC 3+ (13/42) samples.

Conclusions: The concordance between HER2-OE and positive ERBB2-amp was observed only in about one-tenth of the samples. Nearly one in three samples from the IHC 3+ and two out of three samples from the IHC 2+ group were missed if patients were only tested with NGS. These findings highlight the importance of incorporating HER2 IHC into routine diagnostic workup for lung cancer patients to accurately identify patients eligible for HER2-directed therapy such as T-DXd.

Keywords: HER2 IHC, NGS ERBB2, Concordance

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.23 Role of Lung Microbiome on Precise Diagnosis of Patients With Checkpoint Inhibitor Pneumonia: Result From a Prospective Cohort Study

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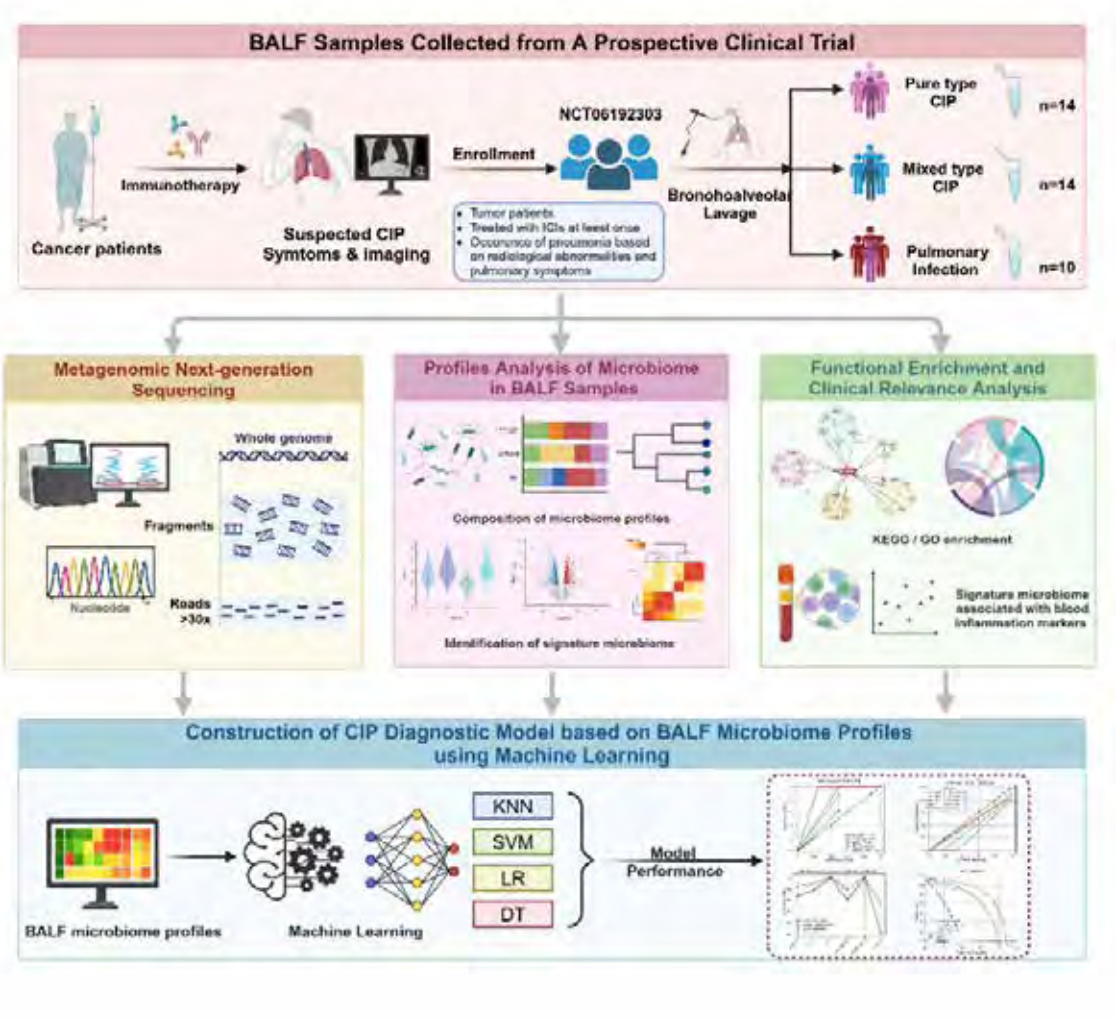
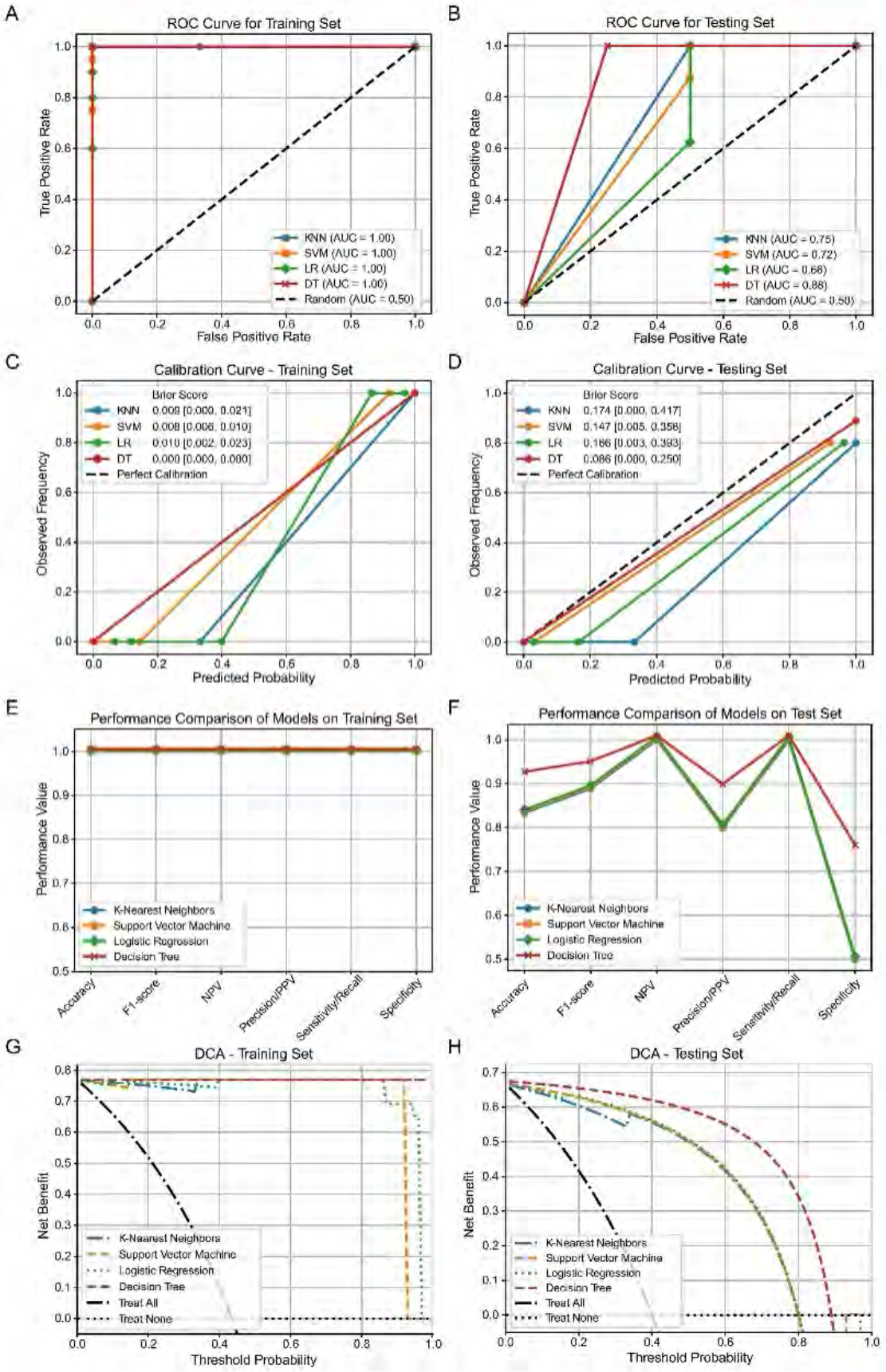
Introduction: Checkpoint inhibitor pneumonia (CIP) is a lethal immune-related adverse event in cancer patients receiving immunotherapy. This study aims to characterize the lung microbiome in CIP patients and evaluate its diagnostic potential.

Methods: In a prospective clinical trial (NCT06192303), bronchoalveolar lavage fluid samples (BALF) were obtained from 38 patients presenting clinical symptoms and radiographic evidence of pneumonitis following immunotherapy. The cohort included 14 cases of pure-type CIP (PT-CIP), 14 cases of mixed-type CIP (MT-CIP), and 10 cases of pulmonary infection (PI). Metagenomic next-generation sequencing (mNGS) of BALF was employed to delineate the lung microbiota profiles. Using linear discriminant analysis effect size, we discerned characteristic microbiota among the three groups and further explored the associations of signature microbiota with host immune-inflammatory markers. Functional enrichment analyses revealed potential metabolic reprogramming and differences in biological functions between CIP and PI patients. Finally, leveraging four machine-learning models, we ascertained the value of BALF microbiota profiles in diagnosing CIP.

Results: The composition of lung microbiota differed significantly between CIP and PI patients. Microbial taxa, such as Porphyromonas, Candida, Peptostreptococcus, Treponema, and Talaromyces, exhibited distinct abundance patterns across the three groups. Correlation analysis revealed a significant positive correlation between Candida abundance and host immune-inflammatory markers, such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, monocyte-lymphocyte ratio, systemic immune inflammation index, while Porphyromonas demonstrated negative correlation. Compared to the PT-CIP patients, the lung microbiota of PI patients exhibited a more diverse biological and metabolic profile. Additionally, machine learning models based on BALF microbiota profiles could accurately diagnose CIP, with the decision tree model showing the best diagnostic performance (AUC: 0.88).

Conclusions: Our study unraveled the characterization of the lung microbiota profiles across distinct CIP subtypes and established a diagnostic model for CIP based on the decision tree. These findings emphasize the value of BALF mNGS in improving the diagnosis of CIP.





Keywords: Checkpoint inhibitor pneumonia, Metagenomic next-generation sequencing, Machine learning

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.24 Mixed Methods IASLC Global Survey and Provider Interview Study of Us NSCLC Biomarker Testing Practices and Clinical Processes

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Introduction: Biomarker testing has become essential for non-small cell lung cancer (NSCLC), but optimal testing is not yet performed universally, nor is the pathway to achieving this clear. We used mixed methods to explore not only testing practices but also associated workflows/processes in diverse settings across the United States.

Methods: We utilized U.S. data from the 2024 IASLC Global Survey (IGS) on Biomarker Testing and structured interviews with thoracic oncology providers to understand current U.S. practices and their context. An interim analysis of the first 15 interviews was performed in NVivo 14 to identify both common themes and unique practices.

Results: There were 287 IGS U.S. respondents from 39 states and 15 interview participants, representing 11 sites across 8 states. Both IGS and interview data included majority academic centers (64% and 62%, respectively), but interview data included more community sites (16% versus 31%). Oncologists predominated in IGS (49%), whereas thoracic surgeons comprised the majority of interviewees (53%). Table 1 summarizes participant characteristics and key findings regarding current practices, workflows, and barriers to best practice testing. Biomarker practices varied widely, particularly for early-stage testing. IGS respondents universally reported cost among the top 3 barriers, compared to only 3 interview participants. While most interviewees reported no cost considerations in their biomarker testing decision-making, they did commonly report delays due to the Medicare “14-day rule” (non-reimbursement for in-patients) and need for universal insurance coverage, both ultimately cost-related, as barriers. Turnaround time (TAT) was identified as a top 3 barrier in all IGS groups except for pathologists, and among interviewees, who noted variability in workflows, lack of defined role responsibilities/ownership, and bottlenecks due to staffing shortages as causative factors. Although 50% of IGS respondents reported reflex testing, including 53% of community, only 27% of interview sites and none of the community/other sites had reflex protocols. Interestingly, sites with reflex testing frequently identified it as a facilitator and/or target for improvement nationally, and yet only 33% of participants at sites without reflex did so.

Conclusions: Cost, TAT, and tissue remain the most important barriers to biomarker testing in the U.S. Although most key themes were similar between interview and IGS U.S. results, the in-depth interviews uncovered several important differences and revealed significant heterogeneity in practices and needs. Additionally, these findings suggest the need for greater assessment in real-world settings to identify and implement tailored solutions.

type (site)	specialty	who & % tested†	NGS utilization	who orders	reflex status	TAT	barriers/targets for improvement
Interviews							
academic (A)	surgery	total: 80-90%, early: not-specified advanced: 90%	~100%	oncology PA	pseudo-reflex *(onc orders for all their pts)*	2w	
academic (C)	surgery	all adeno cIB+ some squam cII+	100%	oncology & surgery	none	3-4w	14-day rule, reflex, lack of a focused panel (esp for early stage), national guideline → insurance coverage
academic (E)	surgery	resectable: 66% advanced: 100% get some form of testing	100%	oncology, surgery if resected	none	2-3w	reflex, TAT, tissue
academic (F)	surgery	total: 66% early: 25% advanced: almost all	all stages >I; may spot order for stage I	pathology	true reflex	10-14d	TAT, pathways for resectable v unresectable (delay in testing after surgery v delay in getting in for IP biopsy)
academic (D)	oncology	early: 80% advanced: 100%	NGS for reflex; mostly NGS for ordered	pathology	true reflex	10d (calendar)	TAT, patients missed with reflex, 14-day rule, awareness in community
academic (F)	oncology	total: 80-90% advanced: 100%	all stages except IA	pathology	true reflex	3-4w	knowledge/education, provider fatigue, reflex, implementation in community, ownership, tissue, TAT
academic (D)	pathology	total: 100% squams: if requested	all NSCLCs, including atypical carcinoids	pathology mostly, all others can	true reflex	2-3w	cost (incl reimbursement hassles e.g. frequent peer-to-peer), tissue, buy-in
academic (F)	pathology	unknown but reflex testing on all stage IB+	all NSCLCs	pathology	true reflex	9d-2w	relationship between pathology dept & independent molecular lab, funding (for equipment, space, staff)
U-affiliated (B)	surgery	early: 90%, T2+, any N advanced: 100%	100%	pathology mostly	true reflex	PCR: 1d NGS: 2-3w	14-day rule, TAT, reflex
community (I)	surgery	early: 20% advanced: 90%	varies by hospital but not a lot of NGS	oncology	none	1-2w	no defined/unified team in community private practice setting: coordinating care in this setting
community (K)	surgery	total: 80% select IB (EGFR only), all IIA+	all advanced stages, IIA+	preferentially oncology	none	10-14d (calendar)	TAT, cost, ownership/ordering provider, defined protocol
community (G)	oncology	adenos: 80-100% squams: depends on provider	depends on provider	oncology	none	10-14d (calendar)	tissue, practice standardization, TAT
community (K)	oncology	early: 80% advanced: 100% adenos, squams at progression	all stages	oncology	none	liquid: ≤7d tissue: 10-14d	reflex, uniform uptake
other (J)	surgery	total (early and advanced): 100%	~100%	everyone	none	7-10d (calendar)	TAT, tissue, uniform buy-in/uptake
other (H)	oncology	unknown, possibly 100% for all stages	stage 1B+	oncology, except surgery if early stage	none	10-14d (business)	buy-in outside of oncology, logistics in different systems/settings, partnership with pathologists
2024 International Association for the Study of Lung Cancer (IASLC) Global Survey on Biomarker Testing							
academic	193 (64%)	all stages*: 90%	early: 42% advanced: 52%		52% reflex		1. cost (24%) 2. tissue (23%) 3. TAT (22%) 4. awareness (14%) 5. access to testing & TT (9%)
community	49 (16%)	all stages*: 82%	early: 36% advanced: 47%		53% reflex		1. TAT (31%) 2. tissue (25%) 3. cost (18%) 4. access to testing & TT (14%) 5. awareness (8%)
other	62 (20%)	all stages*: 81%	early: 38% advanced: 32%		39% reflex		1. awareness (29%) 2. TAT (25%) 3. cost (23%) 4. tissue (12%) 5. access to testing & TT (8%)
20 (7%)	surgery	all stages*: 72%	early: 21% advanced: 41%		64% reflex		1. cost (64%) 2. awareness (40%) 3. TAT (33%) 4. access to testing & TT (31%) 5. tissue (25%)
139 (49%)	oncology	all stages*: 95%	early: 43% advanced: 53%		44% reflex		1. TAT (28%) 2. tissue (20%) 3. cost (19%) 4. awareness (12%) 5. access to testing & TT (8%)
42 (15%)	pathology	all stages*: 86%	early: 47% advanced: 64%		72% reflex		1. tissue (36%) 2. cost (31%) 3. awareness (15%) 4. access to testing & TT (14%) 5. TAT (12%)

NGS, next generation sequencing; TAT, turnaround time (order to result); adeno, adenocarcinoma; squam, squamous cell carcinoma; onc, oncology; U-affiliated, university-affiliated community; IGS, IASLC Global Survey; TT, targeted therapy; *non-squamous histology; †early/advanced refer to stage

Keywords: biomarker testing, non-small cell lung cancer, practice improvement

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.25 Cost-Effectiveness of Initial Pan-TRK IHC Followed by RNA-NGS for NTRK Fusion Detection in Patients With NSCLC in China

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Introduction: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in various adult and pediatric tumors, including approximately 0.24% of non-small cell lung cancer (NSCLC) cases. NTRK testing is recommended for metastatic NSCLC to guide targeted therapy. Various detection methods exist, each with differing costs and effectiveness.

Methods: A decision tree model was constructed from a health system perspective in China to simulate patients with NSCLC and evaluate the costs and health outcomes of next-generation sequencing (NGS) and pan-TRK immunohistochemistry (IHC) followed by RNA-NGS confirmation (pan-TRK IHC+RNA-NGS) . Diagnostic performance data were sourced from literature and validated by pathologists and clinicians. Data on clinical efficacy, treatment costs, and utility for progression-free survival (PFS) were obtained from open databases and literature. Expert interviews provided turnaround time and testing costs. The time horizon included the duration of NTRK testing and the PFS period associated with the medication. Both one-way and probabilistic sensitivity analyses were conducted to assess the model's robustness.

Results: The analysis considered two scenarios based on regional variations in NTRK testing in China: Scenario1:For 10,000 patients with NSCLC, the NGS testing alone produced 5278.9 life years (LY) and 3750.6 quality-adjusted life years (QALY) at a total cost of $61,811,372, whereas the pan-TRK IHC +RNA-NGS testing strategy yielded 5280.2 LYs and 3751.7 QALYs at a lower total cost of $43,944,162.Scenario 2: Assume that the proportion of driver-gene-negative NSCLC patients (where the driver genes include those targeted by drugs approved in China: EGFR, ALK, ROS1, BRAF V600, RET, and MET exon 14 skipping) is 40%, for 10,000 driver-gene-negative NSCLC patients, the pan-TRK IHC+RNA-NGS testing strategy demonstrated an incremental benefit of 3.21 LYs and 2.78 QALYs, while reducing costs by $17,743,631. In both scenarios, the pan-TRK IHC+ RNA-NGS was dominant, offering higher LYs and QALYs and lower costs than NGS alone. Sensitivity analysis confirmed the robustness of the results. Moreover, the average wait time per patient for pan-TRK IHC+RNA-NGS was reduced by 11 days.

Table1: Cost-Effectiveness Analysis Results-Scenario1

	Testing	Total Cost(USD$)	Effectiveness (LYs)	Effectiveness (QALYs)	Incremental cost ($)	Incremental QALYs	ICER (Cost/QALY)
10,000 NSCLC patients	NGS	$61,811,372	5278.9	3750.6			
	pan-TRK IHC+RNA-NGS	$43,944,162	5280.2	3751.7	-$17,867,210	1.11	pan-TRK IHC +RNA-NGS was dominant

Table2: Cost-Effectiveness Analysis Results-Scenario2

	Testing	Total Cost (USD$)	Effectiveness (LYs)	Effectiveness (QALYs)	Incremental cost ($)	Incremental QALYs	ICER (Cost/QALY)
10,000 driver-gene-negative NSCLC patients	NGS	$62,541,935	5303.6	3772.0			
	pan-TRK IHC+RNA-NGS	$44,798,305	5306.8	3774.7	-$17,743,631	2.78	pan-TRK IHC +RNA-NGS was dominant

Conclusions: Initial pan-TRK IHC testing followed by RNA-NGS confirmation for positive results is the preferred strategy for detecting NTRK fusions in patients with NSCLC in China. This approach provides better economic value and clinical outcomes than NGS testing alone.

Keywords: NTRK, NSCLC, Cost-Effectiveness Analysis

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.26 Evaluation of Large Language Models for Clinical Decision Support in Lung Cancer Treatment: ChatGPT-4.5 Vs. Deepresearch Vs. AvoMD

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Introduction: Artificial intelligence (AI) can reduce the documentation burden in oncology by supporting diagnostics and clinical decision-making through electronic health record (EHR) data analysis. Among large language models (LLMs), ChatGPT-4.5 is widely adopted and recognized for high accuracy and versatility. DeepResearch, a new agentic LLM powered by the O3 reasoning model, aims to generate evidence-based academically rigorous responses. Treatment guidelines in oncology are typically based on expert consensus and evidence, raising questions about whether AI models like DeepResearch could effectively complement or replace traditional guidelines in clinical decision-making. This study compares ChatGPT-4.5, DeepResearch, and AvoMD using real-world lung cancer patient data, evaluating each model's strengths and limitations in evidence-based clinical decision support.

Methods: Electronic health record (EHR) data—including clinical notes, imaging, laboratory, and pathology results—were collected from 13 lung cancer patients at Northwestern Hospital. Three LLMs (ChatGPT-4.5, DeepResearch, and AvoMD) were evaluated based on their ability to recommend treatments given the prompt: "What is the recommended treatment for this patient?" Only AvoMD was pre-loaded with NCCN Guidelines for Non-Small Cell Lung Cancer, Version 3.2025. Outputs were assessed using two metrics: Accuracy (1 = correct, 2 = mixed, 3 = incorrect) based on NCCN, ASCO, and ESMO guidelines, and Clinical Usefulness (1 = usable without modification, 2 = usable with modification, 3 = unusable in clinic).

Results: Across patient data summarization, AvoMD performed best, achieving 76.9% correct responses, surpassing DeepResearch and ChatGPT-4.5 (each 61.5%). For accuracy of treatment recommendations, DeepResearch was in the lead (69.2%), followed by AvoMD (61.5%) and ChatGPT-4.5 (53.8%). However, incorrect recommendations (Grade 3) were most frequent in DeepResearch and ChatGPT-4.5 (23.1% each), compared to AvoMD (7.7%). In clinical usefulness, AvoMD again ranked highest with 46.2% Grade 1 (usable without modification), followed by DeepResearch (38.5%) and ChatGPT-4.5 (30.8%). Most responses required some clinical modification (Grade 2), while ChatGPT-4.5 had the highest rate of clinically unusable outputs (23.1%). Qualitative analysis highlighted DeepResearch's strengths in referencing guidelines and generating evidence-based content but also revealed challenges with accurate cancer staging and patient-specific recommendations. ChatGPT-4.5 provided broad and flexible recommendations but occasionally generated clinically inappropriate content or misprioritized treatment options. AvoMD consistently adhered to guidelines with structured reasoning but sometimes overlooked patient-specific contexts such as comorbidities or palliative goals.

Conclusions: Large language models (LLMs) hold significant potential for supporting oncologists, particularly in summarizing complex clinical information and providing guideline-informed treatment recommendations. While DeepResearch demonstrated the strongest performance in generating evidence-based recommendations, its practicality is limited by lengthy computation times—often exceeding 15 minutes. In real-world clinical settings, time and resource constraints are critical factors. In our study, LLM reasoning agents pre-configured with NCCN guidelines proved more effective than those relying on real-time external searches. AvoMD, for instance, operates more like a real-time query engine focused on trusted clinical guidelines, rather than retrieving individual research articles. In conclusion, leveraging a single, expert-curated source like the NCCN guidelines minimizes variability and enhances consistency in AI-assisted clinical decision-making.

Keywords: Clinical Decision Support, Large Language Models, Lung Cancer Treatment

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.27 Assessing Sarcopenia in Lung Cancer: Feasibility and Training Considerations of Using Quantitative Imaging Metrics From CT Scans

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Introduction: Sarcopenia, the loss of skeletal muscle mass and function, is an emerging prognostic factor in surgical resection of lung cancer. This study evaluates the feasibility of training thoracic surgeons to assess muscle mass on preoperative imaging.

Methods: Two thoracic surgeons were trained by a thoracic radiologist to review preoperative PET-CT/CT (Positron Emission Tomography-Computed Tomography) scans from patients who underwent lobectomy or segmentectomy. Muscle groups analyzed included pectoralis major, pectoralis minor, psoas, paraspinal, and total abdominal muscles bilaterally, at variable vertebral levels. For each muscle, maximum thickness, surface area, and average Hounsfield units (HU) were recorded. A root-cause analysis was conducted for the noted differences in measurements, and interobserver variability was assessed using Bland-Altman plots. A learning curve analysis was performed to track improvements in measurement efficiency.

Results: Twenty cases were randomly selected for this pilot cohort. Root-cause analysis indicated that knowledge of radiologic anatomy and a consensus on the vertebral level for measurement, significantly improved measurement accuracy and efficiency. The best four levels for measurements were middle of fourth thoracic vertebra for pectorals, twelfth thoracic vertebra at full emergence of ribs for paraspinals, and lower endplate of third lumbar vertebra for the psoas and total abdominal muscles. Surface area measurements showed significant improvement in agreement over time, whereas thickness measurements remained inconsistent. Pectoralis major and the psoas muscle related parameters achieved best consensus over time, while pectoralis minor had the most interobserver variability (Figure-1). Learning curves demonstrated progressive improvement, with the average time per scan stabilizing at 7.5 minutes (Figure-2).

Conclusions: This study suggests that non-radiologists can be trained to assess muscle mass measurements for sarcopenia using preoperative chest-CT/PET-CT scans, which are easily available and widely applicable, without requiring abdominal-CT and other three-dimensional reconstructions. Further research will explore correlations between these measurements and clinical outcomes to refine assessment methods.

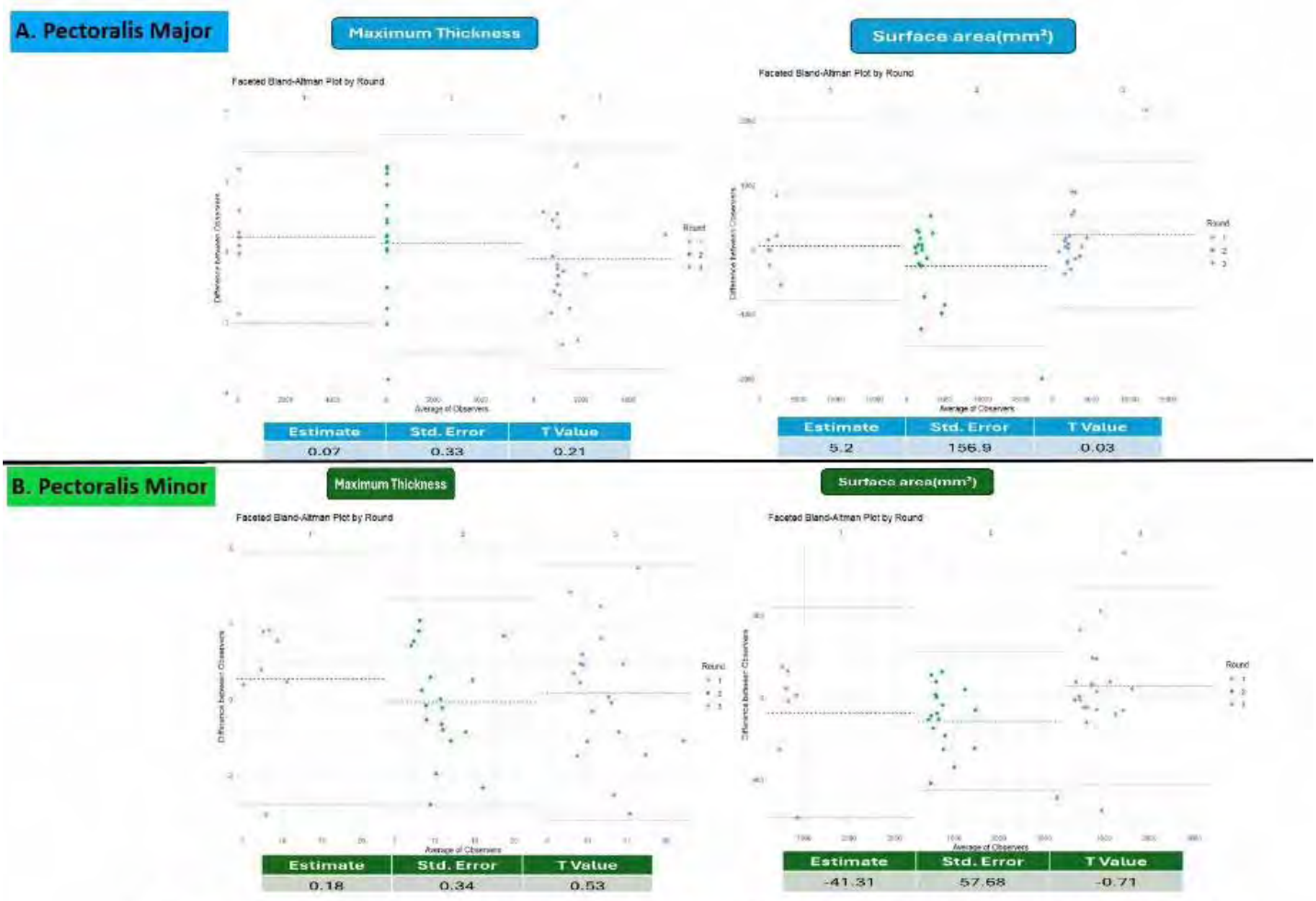

Figure-1: Trend in interobserver variability over time as noted in (A) Pectoralis Major versus (B) Pectoralis Minor

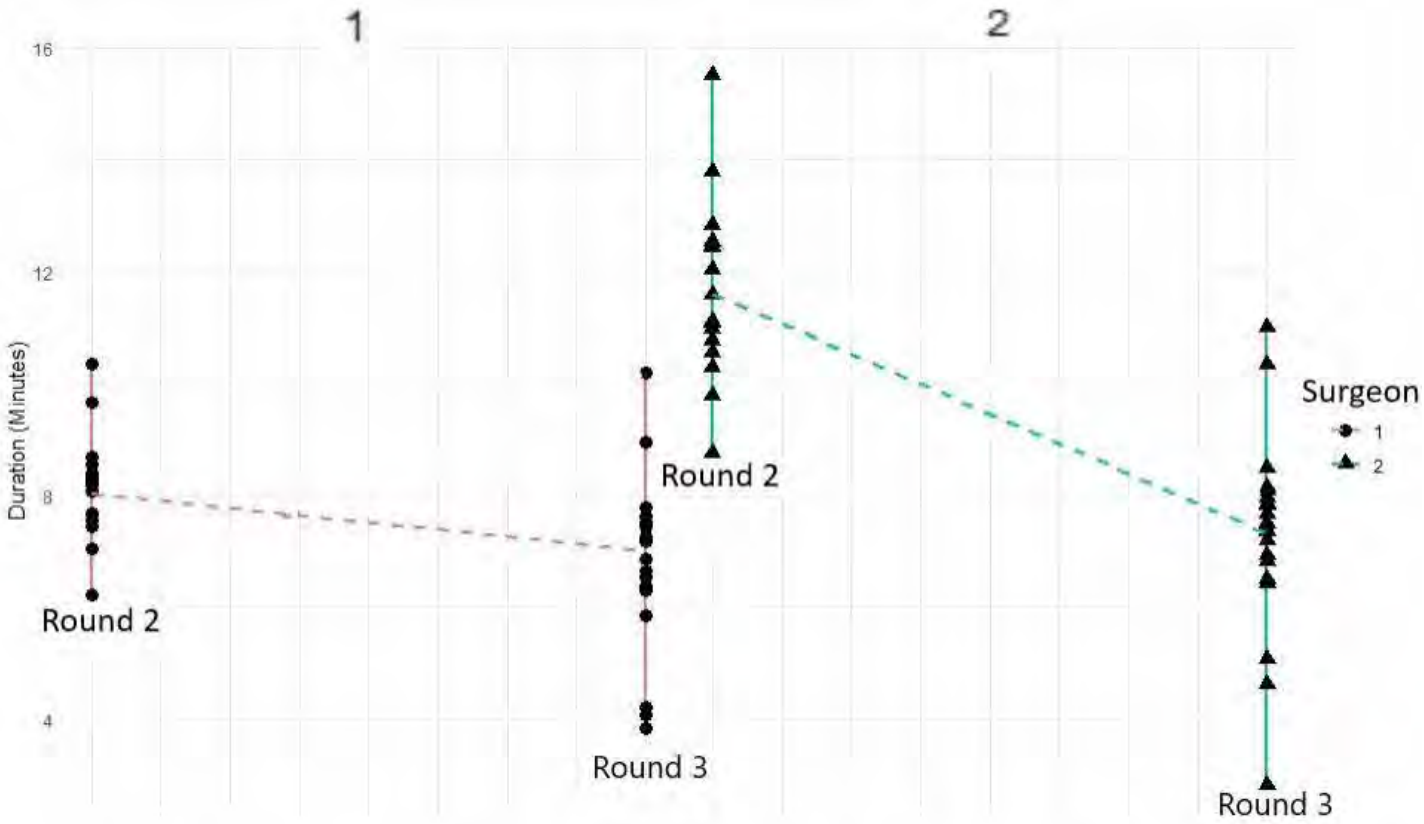

Figure 2: A comparison of learning curves of thoracic surgeons (1 vs. 2) trained in muscle mass measurements.

Keywords: sarcopenia, lung cancer, chest CT

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.28 Developing a Multifaceted Implementation Strategy to Increase Clinical Trial Accruals in Thoracic Oncology

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Introduction: Clinical trials are essential for advancing medical research and are a key priority at Mayo Clinic Comprehensive Cancer Center, yet enrollment of patients is suboptimal nationally. Barriers include a work culture that often prioritizes standard treatments, challenges in communicating risks and benefits, time-intensive accrual processes, and difficulties in trial matching. While tools such as trial matching systems, digital databases, and reporting tools are available, they have not been fully integrated to address these barriers effectively.

Methods: An integrated, system-driven process to develop solutions to barriers was completed including 1-1 feedback sessions with all physician and advance practice providers, observations, and a 7-question provider survey. The survey was completed at baseline and three-months post-intervention. A revised clinical trial accrual process was developed alongside frontline staff with frequent input from the provider team, designed to create closed-loop communication and leverage digital tools. Data was tracked on the number of clinical trial accruals pre- and post-intervention. The intervention was launched in Q4 2023, with the number of accruals tracked for the 12-month post-intervention in comparison with the prior period.

Results: Micro-interventions were implemented that correlated with an increase in clinical trial accruals and provider satisfaction, including (1) Trial summary sheets to synthesize trial information (2) A portfolio of active trials for the team on a digital screen (3) Workflow to integrate research nurses into the clinical practice. In the twelve months after the implementation, there was a 109% increase in accrual of patients to interventional thoracic oncology clinical trials. Before the implementation, 20% of providers felt they had enough support to easily enroll patients onto clinical trials, after implementation 80% of providers agreed with this statement (n = 5).

Conclusions: This project demonstrates that a systematic approach to identifying and addressing barriers to clinical trial participation can increase clinical trial accruals. Micro-interventions, such as integrating a research nurse, implementing trial summary sheets, and displaying active trial listings, optimized trial logistics, increased accruals and translated . Effective change management, including listening sessions and feedback, was pivotal in gaining stakeholder engagement and process buy-in. These strategies offer a scalable framework for other cancer care teams to enhance clinical trial participation and advance medical research.

Keywords: Clinical Trials, Research Nurse, Research

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.29 Access to Novel Therapies for the Treatment of NSCLC in 18 EU Member States

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Introduction: Swift advancement in anticancer drug development in the last two decades for the treatment of NSCLC (non-small cell lung cancer) patients poses challenges in availability of these therapies in European Union (EU) member states (MS). Although EU MS share the same regulatory status, access to anticancer treatments vary significantly.

Methods: Using a questionnaire sent to experts in EU MS, we analysed the availability and accessibility of NSCLC anticancer therapies incorporated in the European Society for Medical Oncology (ESMO) guidelines and graded by the ESMO MCBS (Magnitude of Clinical Benefit Scale) committee. The reimbursement status was retrieved for 18 EU MS: Austria, Bulgaria, Croatia, Cyprus, Estonia, Germany, Greece, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden. Reimbursement categories included fully reimbursed (paid by insurance in full), partially reimbursed (patients cover some expenses), per patient reimbursement (based on individual application, then covered in full), out-of-pocket (patients cover all expenses), compassionate use program or donation (available through various programs), clinical trial (any phase for that indication), and unavailable. Data cut-off: 01-Jan-2025.

Results: Thirty-three anticancer therapies for 59 indications were found in the ESMO NSCLC guidelines, which were approved by the EMA (European Medicines Agency) and another three without indication at data cut-off. Of them, 27 received a high ESMO MCBS score (4 or 5) and another six with score A, which indicate substantial clinical benefit. Overall, 3 therapies are fully reimbursed in all MS, and additional 8 are not fully covered in only one MS. Moreover, three MS have more than 90% of identified therapies fully reimbursed, while the median number of fully reimbursed therapies are 63%. On the other hand, one MS has less than 25% of therapies fully reimbursed; however, this MS covers 71% of therapies through per patient reimbursement scheme. In general, small number of indications are available for out-of-pocket payments, except in two MS with 56% and 68% of such payments, respectively. Another two MS have high number of unavailable treatments, 61% and 48%, respectively. A median number of fully reimbursed targeted therapies for either EGFR, ALK/ROS1 and all other molecularly positive patients across MS are 9, 14, and 6, respectively. Eighty percent of EGFR and 50% of ALK/ROS1 inhibitor indications with ESMO MCBS score of 4 are at least partially covered in every MS. More than half of the immune checkpoint inhibitors either as mono- or combination treatment with MCBS score of 4, 5 or A are fully reimbursed in almost all (16) MS. Similarly, at least three out of six treatment indications for early NSCLC with ESMO MCBS score A are available free of charge in 16 MS.

Conclusions: Although EU MS operate under a shared regulatory framework, reimbursement systems differ, yet still generally provide access to most clinically meaningful anticancer therapies for NSCLC patients. However, disparities are still evident and need to be adressed in the future to improve anticancer therapies availibilty.

Keywords: Access to anticancer therapies, EU member states, Non-small cell lung cancer

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.30 Deep Learning-Based Lung Tumor Segmentation for Survival Prediction in NSCLC Patients

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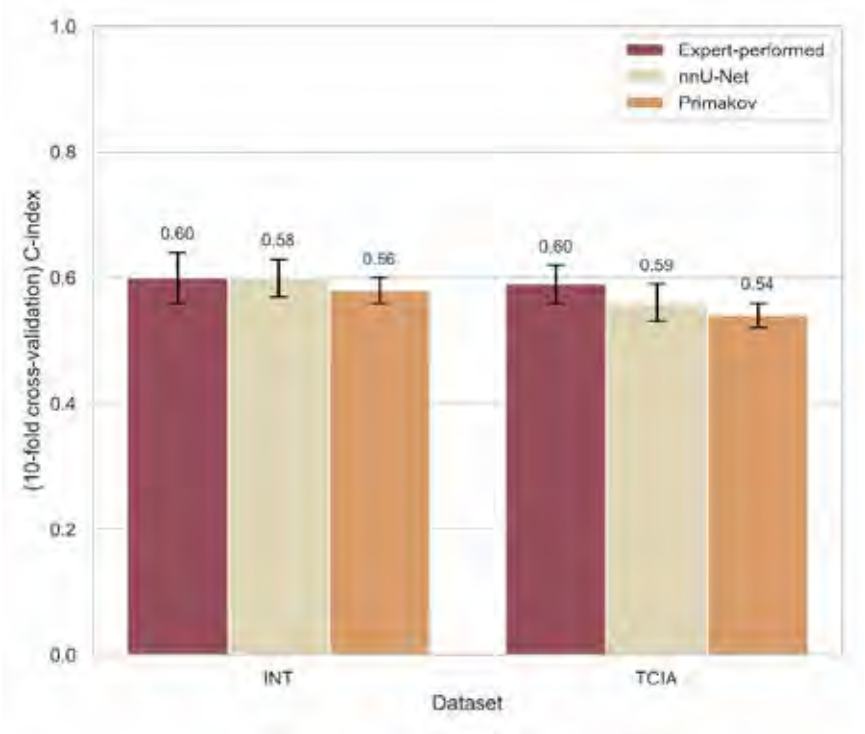
Introduction: Accurate prediction of treatment outcomes in Non-Small Cell Lung Cancer (NSCLC) remains a major clinical challenge. AI-based models hold significant potential for identifying novel imaging-based biomarkers to enhance treatment efficacy prediction. In this context, accurate gross tumor volume (GTV) segmentation is crucial for response assessment. However, manual segmentation is time-consuming and expert-dependent. Deep Learning provides a promising approach for automatic segmentation. This study evaluates the performance of nnU-Net automatic segmentation method in supporting AI-driven survival analysis using baseline CT scans. The objective was to compare expert-provided and automated segmentation methods, assessing their impact on survival models.

Methods: We used three NSCLC datasets composed of baseline lung CT scans with expert-delineated GTVs. We included two public datasets: 402 CT scans from NSCLC-Radiomics TCIA dataset and 63 from Medical Segmentation Decathlon (MSD). Additionally, we used an in-house dataset (NCT0550961) of 276 scans of NSCLC patients treated with immunotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori (INT). To allocate different patients for training automatic and survival analyses, we used 63 MSD CTs and 126 TCIA scans exclusively for training automatic segmentation. Two sets, consisting of the remaining 276 TCIA and 276 INT scans, were reserved for testing automatic segmentation and conducting survival analysis. We evaluated both nnU-Net and state-of-the-art Primakov method for automatic segmentation, assessing performance using Dice similarity coefficient. We extracted 107 radiomic features from nnU-Net, Primakov, and expert-provided GTVs using PyRadiomics. We performed feature selection by combining univariate Cox regression with correlation analysis (threshold=0.75). Four Machine Learning (ML) survival models were trained to predict Overall Survival using features derived from each segmentation method. We assessed models' performance using 10-fold cross-validation based on concordance index (C-index) and we used Friedman test to assess statistically significant differences in performance.

Results: The nnU-Net segmentation method outperformed the Primakov method in terms of Dice score. Figure 1 shows the C-index of survival predictions of the three analyzed methods, using the best-performing ML model for each. The Friedman test confirmed that the performance differences were not statistically significant, with all p-values > 0.05.

Conclusions: In this study, automatic segmentation methods demonstrated comparable performance to those performed by radiologists in survival models. While further validation on larger cohorts is needed to ensure generalizability, these findings highlight the potential of emerging technologies to automate the segmentation process, reducing human effort without compromising performance. In some cases, limited data manipulation may support more data-driven and unbiased image analysis.



Keywords: Non-Small Cell Lung Cancer, AI-based automatic segmentation, Radiomics for survival analysis

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.31 Feasibility of Integrating Ai-Assisted Lung Cancer Screening in High Tuberculosis Burden Settings

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Introduction: Lung cancer (LC) and tuberculosis (TB) share overlapping clinical and radiological features, often leading to misdiagnosis and delayed treatment. TB screening programs in low- and middle-income countries are increasingly using artificial intelligence (AI) to interpret chest X-ray (CXR) images for TB detection. This presents an opportunity for additional LC screening, which often goes undiagnosed and untreated, with minimal incremental resources. This project's aim was to observe the application of the AI software, qXR for lung cancer screening in high TB burden settings.

Methods: Community- and facility-based CXR screening for TB was conducted in Ethiopia, the Philippines, and Vietnam. CXR images from these programs/centers were processed using qXR AI software (Qure.ai, India) and those with potentially malignant lung nodules were referred for a CT scan as part of a lung cancer screening feasibility pilot. CT scans were analysed by a radiologist using the Lung RADS scoring system and post-CT scan care followed local clinical guidelines.

Results: A total of 198,271 CXRs screened for TB were also analyzed for the presence of lung nodules using AI as part of the feasibility pilot across the three countries. 3,518 (1.8%) potentially malignant lung nodules were detected by the qXR AI software, from which further information was available for 2,232 (63.4%). A total of 725 (32.5%) CT scans were performed, resulting in the detection of 497 (68.6%) with a Lung RADS score ≥4A.

Conclusions: These pilot findings show that integrating AI-assisted CT referrals for LC screening into CXR screening programs for TB is feasible approach for scaling up LC screening. Further studies assessing how AI-assisted LC screening can improve population-level LC treatment and patient outcomes, as well as the cost-effectiveness of this approach, are warranted.

Keywords: Chest X-Ray Artificial Intelligence, Tuberculosis, Lung Cancer

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.32 Comparing ChatGPT's and Google Gemini'S Responses to Lung Cancer Questions

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Introduction: People who are not experts in lung cancer often struggle to keep up with advances in the field. While ChatGPT and Gemini have the potential to provide quick and accessible medical information, their suitability and reliability remain unverified. We evaluated the appropriateness of these AI models for providing lung cancer information.

Methods: We selected 40 questions from the Korean Association for Lung Cancer, categorized them into five domains, and then presented these questions to ChatGPT and Gemini. The AIs generated 80 answers and cited 262 references. Twenty medical professionals including physicians (n=10) and nurses (n=10) assessed accuracy, relevance, and sufficiency using a 5-point Likert scale, while ten patients evaluated understandability using the same scale. Readability was assessed using the Flesch Reading Ease (FRE) and Flesch-Kincaid Grade Level scores. Additionally, references were analyzed for consistency, evidence level, region, and type.

Results: ChatGPT provided more consistent references than Gemini (Consistency: 91.16% vs. 48.79%, $P < 0.0001$), whereas Gemini generated more readable answers (FRE: 29.81 vs. 42.91, $P < 0.0001$). The proportion of references from Korean sources was lower in ChatGPT than in Gemini (ChatGPT: 10.88% vs. Gemini: 79.13%, $P < 0.0001$). While there was no significant difference in accuracy (Physician, $P = 0.9451$) (Nurse, $P = 0.5438$), relevance (Physician, $P = 0.9757$) (Nurse, $P = 1.0000$), understandability (Patient, $P = 0.9292$), evidence level ($P = 0.8488$), and type ($P = 0.9532$), Gemini exhibited hallucination effects in references (Hallucination, n = 7). In contrast, ChatGPT demonstrated a more reliable citation process (Hallucination, n = 0).

Conclusions: ChatGPT provided more reliable references than Gemini in answering lung cancer questions. Although ChatGPT's and Gemini's answers were comparable, ChatGPT appears more suitable for providing lung cancer information to people who are not experts in the field.

Keywords: ChatGPT, Gemini, Hallucination

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.33 Addressing Educational Gaps in Lung Cancer Care: Insights Based on Global Practice Setting and Experience

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Introduction: Practice setting and years of experience play critical roles in shaping oncologists' (oncs) approach to lung cancer care, especially given its rapidly evolving landscape. The objective was to assess how practice setting and years in practice influence oncs' understanding of key management concepts in lung cancer.

Methods: The analysis included 63 online, continuing medical education (CME)-certified activities. Educational impact was measured with pre-/post-education assessments including multiple-choice knowledge/competency questions and 5-point Likert scale confidence questions. Data from onc learners who completed pre- and/or post assessments were aggregated across activities and stratified by practice setting, experience, and learning themes. Relative changes in percentage of correct responses and level of confidence (value of 4 or 5) were used to measure impact, with significance measured via McNemar tests ($P < .05$). Data collected through March 2025.

Results: Statistically significant improvements ($P < .01$) were observed across learning themes, regardless of practice setting or years in practice. Outside the United States (OUS) oncs demonstrated higher relative changes compared to United States (US) oncs across all themes, with the exception of awareness of disparities and challenges in care. Confidence staying abreast of and applying evolving data remained one of the largest gaps across all groups (≥70%). Overall relative changes presented below (N=48 to 2252).

Conclusions: Findings suggest that recent education had a more pronounced impact on OUS oncs' understanding of lung cancer management, regardless of practice setting, suggesting a higher baseline need for education. US oncs' had a generally stronger baseline knowledge and confidence, but showed smaller relative improvements, indicating a need for more advanced or targeted education. Despite progress, persistent challenges remain, highlighting critical focus areas for future initiatives. The true effect of these activities on corresponding clinical practices requires further study.

Learning Theme	OUS Oncologist % Change		US Oncologist % Change	
	≤5 Years in Practice	>5 Years in Practice	≤5 Years in Practice	>5 Years in Practice
Ability completing comprehensive work-up	146	121	27	35
Awareness of disparities and/or challenges in care	8	8	10	13
Competence tailoring treatment decisions	97	123	10	30
Confidence communicating and collaborating with the MDT	131	128	16	33
Confidence prioritizing patient values and preferences in care	129	55	43	16
Confidence staying abreast of and applying evolving data to clinical practice	67	42	14	39
Knowledge of biomarkers	76	69	47	42
Understanding of clinical trial data	93	100	59	58

Keywords: CME, Experience, Gaps

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.34 Assessing the Outcome of 10-Year Lung Cancer Survivors and the Necessity of Long-Term Postoperative Surveillance

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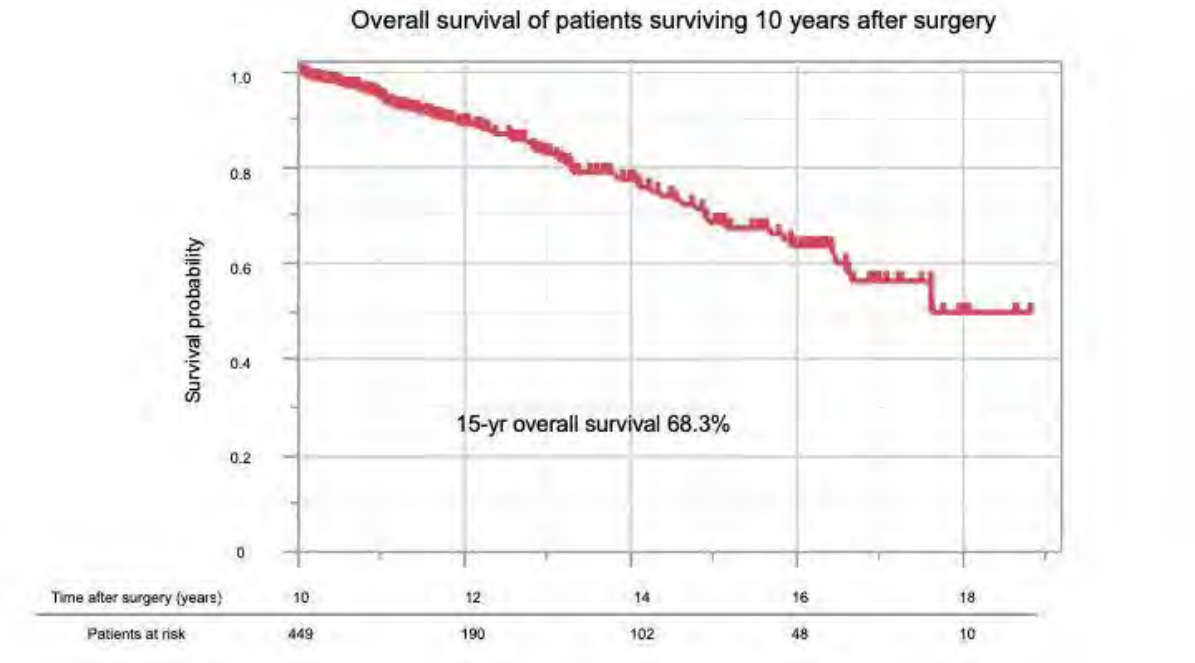
Introduction: Recurrence and second primary lung cancer may occur at 10 years after lung cancer surgery. However, few studies exist of lung cancer survivors at 10 years or more after surgery. In addition, the necessity and standard schedule of long-term postoperative surveillance has not been clarified. There is no consensus regarding the appropriate postoperative surveillance period. Here, we assessed the prognosis of 10-year lung cancer survivors who underwent lung cancer surgery.

Methods: Between May 2004 and December 2014, 1,154 patients underwent complete resection of lung cancer. After excluding patients who died after less than 10 years, who missed follow-up, or whose outcomes were unknown, 449 (39.0%) patients surviving 10 years after surgery were assessed.

Results: The median follow-up time and median age at surgery were 11.8 and 67 years, respectively. Median survival time after 10 years was 7.6 years. Two hundred ninety (64.6%) and 159 (35.4%) patients had stage 0-IA and stage IB-III disease, respectively. Forty-six (10.2%) patients had cancer recurrence at 10 years after surgery. Three (0.7%) patients developed recurrence and 11 (2.5%) patients developed second primary lung cancers 10 years after surgery. The 15-year overall survival rate was 68.3% (Figure). Univariable analyses revealed that age (≥70 years) ($p < 0.001$), male ($p < 0.001$), smoking ($p < 0.001$), carcinoembryonic antigen (>5 ng/ml) ($p = 0.007$), forced expiratory volume in the first second / forced vital capacity % (<70%) ($p = 0.002$), standardized max value (≥3.0) on positron emission tomography/computed tomography ($p = 0.020$), non-adenocarcinoma ($p = 0.001$), tumor size (>3cm) ($p = 0.020$), invasive focus size ($p = 0.021$), and histological grade 2 or 3 ($p = 0.017$) were prognostic factors. Multivariable analysis confirmed that age (≥70 years) ($p < 0.001$) was the only prognostic factor for 10-year lung cancer survival. Receiver operating curve analysis showed that 64 years was a cut-off value for better prognosis.

Conclusions: Age was the prognostic factor for 10-year lung cancer survival. Given that recurrence is very rare, and cancer-related factors were not prognostic factors in multivariable analysis, the prognosis of 10-year lung cancer survivors is promising and postoperative surveillance after 10 years may not be necessary. However, as there is a potential risk of second primary lung cancer, 10-years-or-more lung cancer survivors would need annual health check-ups.



Keywords: Lung cancer, Survivorship, Postoperative surveillance

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.35 Patient Navigation and the Opportunity to Improve Experiences and Outcomes of Lung Cancer Care

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Introduction: The Lung Cancer Policy Network is a global network of multidisciplinary experts from the lung cancer and oncology community. This year, the Network has developed a comprehensive report that makes the case for patient navigation as an essential component of lung cancer care and provides recommendations for its integration throughout the care pathway. The comprehensive and coordinated service delivery promised by patient navigation programmes could alleviate the strain on the world's health systems caused by lung cancer - the leading cause of cancer-related deaths. By guiding people through the health system, patient navigators can address barriers to timely care along the care pathway, decrease the impact of fragmented services, and promote holistic, person-centred care. For a variety of cancer types, there is compelling evidence supporting the role of patient navigators in treatment and care. But studies on patient navigation specifically for lung cancer are few, and there are limited strategies for implementation; patient navigator initiatives originated in the US and have only recently started to emerge in Europe, with varying levels of application.

Methods: The report was informed by a review of existing peer-reviewed and grey literature, interviews with 14 experts (including programme coordinators, clinicians, navigators, implementation researchers, patients and advocates) and insights from members of the Lung Cancer Policy Network. The report also incorporates practical case studies and examples from around the world.

Results: This report identifies tangible actions for implementing and optimising patient navigation for lung cancer; the recommendations have been developed to be adaptable depending on the needs of different health systems and countries/regions, and recognise that approaches to lung cancer care are evolving. Recommended actions include: to address barriers to sustainable funding and governance; to create patient navigation models and frameworks that can be flexible to individual needs; to accelerate research into the potential benefits of new technologies and dedicated digital navigator roles; and to engage communities and the health system in the development of tailored patient navigation programmes and training.

Conclusions: To our knowledge, this report presents the first series of recommendations to support the implementation of patient navigation programmes for lung cancer. Lung cancer care is multidisciplinary and complex, and there are many barriers to delivering equitable care. Effective patient navigation helps deliver a holistic and high-quality experience for all people with lung cancer, driving improvements in outcomes and optimising the use of infrastructure and resources. This in turn may help address inequities that persist along the lung cancer care pathway, with differences in incidence, mortality and outcomes observed for a variety of factors, including sex, age, race, ethnicity and socioeconomic status. To realise this opportunity to reduce inequalities in lung cancer care, health system leaders and decision-makers must assess and identify how patient navigation can improve current practice, develop navigation programmes where they do not exist, and optimise these programmes accordingly.

Keywords: Patient, Navigation

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.36 Perspectives on Health-Related Quality of Life Among Physicians and Patients With ALK-Positive NSCLC in China

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Introduction: The project aimed to explore the knowledge, perspectives, and practice regarding health-related quality of life (HRQoL) and patient-reported outcome measures (PROMs) among physicians and patients with ALK-positive NSCLC in China, focusing on similarities and differences in their perception and expectations.

Methods: This cross-sectional online survey, conducted from September to October 2024, included a representative sample of 200 physicians and 200 patients in China. Physicians experienced in treating ALK-positive NSCLC in tertiary or secondary hospitals and adult patients who received ALK-TKIs for first-line treatment were included. Descriptive statistics were used for data analysis.

Results: Respondents included physicians (median age: 45 years, 61.5% male) and patients (median age: 58 years, 44.0% male, median disease duration: 3 years). The majority of physicians (65.5%) and patients (60.0%) were familiar with HRQoL (rated as extremely or very, the same below). Most respondents acknowledged the importance of each HRQoL functional dimension in managing ALK-positive NSCLC (Figure A). Patients valued the impact of ALK-TKIs on HRQoL more than physicians, who prioritized efficacy, safety, and drug accessibility (Figure B). Regarding symptoms (Figure C), physicians considered coughing, hemoptysis, and shortness of breath as the top 3 symptoms influencing HRQoL, whereas patients identified cancer pain, peripheral neuropathy, and loss of appetite as most impactful. Moreover, 17.5% of patients regarded cognitive impairment and hallucinations as affecting their HRQoL, compared to 9.0% and 1.5% of physicians, respectively. Awareness varied among respondents who had heard of HRQoL PROMs: 69.1% (123/178) of physicians and 44.1% (45/102) of patients were familiar with them. Differences were also observed in HRQoL clinical practice: 76.0% of physicians spent <40% of their time discussing HRQoL with patients, while 45.0% of patients expected physicians to dedicate ≥40% of the consultation to this topic. About two-thirds of physicians (67.0%) reported using HRQoL PROMs, while less than one-third of patients (32.5%) did for disease management. Despite these differences, both groups expressed a desire of more HRQoL knowledge: 83.0% of physicians anticipated training on HRQoL PROMs application or easier results interpretation, while 78.5% of patients desired more HRQoL knowledge dissemination.

Conclusions: This national survey underscores a substantial awareness of HRQoL among physicians and patients with ALK-positive NSCLC, but discrepancies in awareness and use of HRQoL PROMs persist. Differences in perceptions of HRQoL discussions and PROMs application highlight the need for better integration into clinical practice. Targeted education and training may help harmonize understanding and enhance patient-centered care in the management of ALK-positive NSCLC.

Figure. A) Perception of importance on various dimensions of HRQoL by physicians and patients. B) Perception of importance on various dimensions related to ALK-TKIs by physicians and patients. C) Perception of influence of various symptoms on HRQoL by physicians and patients.
Abbreviations: HRQoL: Health-related quality of life; ALK-TKI: Anaplastic lymphoma kinase tyrosine kinase inhibitor; NSCLC: Non-small cell lung cancer
Note: Options selected by 0 respondent are not displayed with numbers in the figure.

Keywords: ALK-positive NSCLC, Health-related quality of life, Patient-reported outcome measure

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.37 Providing Equal Access to Lung Cancer MDT Consultation Through Digital Innovation

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Introduction: Cancer treatments vary due to care inequality across regions, and socioeconomic groups. In China, lung cancer has high mortality of 733K deaths annually, accounting for 40.3% of world total. Lower-tier hospitals, mainly in county-level areas, face challenges in lung cancer care due to limited resources and expertise. Inter-hospital remote multidisciplinary team (iMDT) consultations offer a promising approach to sharing medical resources and improving lung cancer diagnosis and treatment. An AI-based digital platform has been developed to facilitate this. This study aims to share best practices of the iMDT digital platform, evaluate its effectiveness, and extract replicable experiences for other MDT teams.

Methods: Focus groups of HCPs and tech experts determined key data inputs and outputs for the iMDT digital platform. This platform was used in 20 remote MDT sessions between lower-tier hospitals and Shanghai Chest Hospital to discuss 70 patient cases. Relevant data from MDT management were automatically generated and recorded. Semi-structured qualitative feedback surveys were collected from over 30 HCPs, along with their feedback on patient post-MDT performance for analysis.

Results: The iMDT digital platform systematically extracted and structured four key categories of patient information:

1. Anonymized demographic data (age and gender).
2. Pre-MDT diagnosis details and clinical staging from lower-tier hospitals.
3. Pre-MDT treatment history, including surgery, systemic therapy, and radiation therapy.
4. Final MDT diagnosis and treatment plan, signed off by the MDT chair.

The platform demonstrated five core benefits:

1. Enhanced efficiency in MDT preparation and case discussions.
2. Standardized review and auditing to assess guideline concordance.
3. Creation of a patient case library for physician training and education.
4. Establishment of a structured database for patient follow-up and monitoring.
5. Foundation for predictive analytics, enabling future patient outcome forecasting.

User feedback revealed a high satisfaction rate, with over 95% of HCPs advocating for its wider adoption, citing improvements in workflow efficiency and diagnostic accuracy. Additionally, more than 90% of patients expressed confidence in MDT decisions, suggesting a positive impact on shared decision-making and patient-centered care.

Conclusions: The iMDT digital platform facilitates more structured, efficient, and standardized MDT discussions, addressing regional disparities in lung cancer care, particularly in underdeveloped areas. By integrating AI-driven data extraction and decision support, the platform enhances diagnostic precision, treatment planning, and physician education. The observed high levels of HCP and patient satisfaction highlight its clinical utility and scalability. Future enhancements, including expanded data collection and AI-driven predictive modeling, could further personalize MDT recommendations and refine treatment strategies, ultimately improving patient outcomes.

Keywords: Remote MDT, Healthcare equity, Digital platform

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.38 A Two-Layer MDT Model as the Standard of Care for Lung Cancer - a Good MDT Example With High-Volume Patients in Central Western China

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Introduction: China reported 820,000 new lung cancer cases in 2020, representing 37% of global cases. Central-Western China is home to over 700 million people—comparable to Europe's population. Managing lung cancer in this vast, resource-limited region is a major public health challenge. As diagnosis and treatment involve multiple specialties, a well-structured MDT ensures accurate diagnosis, treatment coordination, and timely care. This study evaluates a model of Henan Cancer Hospital — one of Chinese biggest cancer centers with 3,000 beds and designated Lung Cancer Center for Henan province (population ~100 million). The hospital treats over 6,000 new lung cancer cases annually and has more than six years of MDT experience, providing a valuable best-practice case for high-volume MDT implementation in high-burden regions.

Methods: We conducted 10+ expert interviews and 2 workshops with MDT members across 10+ specialties from Henan Cancer Hospital, including thoracic surgery, medical oncology, radiology, pathology, and radiation oncology to gain insights around their specific two-layer lung cancer MDT implementation.

Results: Henan Cancer Hospital developed a two-layer MDT model (see Table 1) to efficiently manage high patient volumes by triaging cases based on disease stage and complexity. 1). The first layer—MDT Clinic focuses on early-stage pulmonary nodules, reducing unnecessary surgeries through multi-specialty input. 2). The second layer—Inpatient Lung Cancer MDT covers all newly diagnosed lung cancer cases, ensuring timely, standardized decisions. This model achieved improved resource allocation by reducing unnecessary surgeries (20-30%), shortening hospital stays, and increasing discharge rates. Optimized resource reduced the hospital's average treatment cost for lung cancer by over 50% compared to other provincial hospitals, demonstrating significant economic benefits. Through the MDT, every patient receives a standardized diagnosis and treatment plan aligned with clinical guidelines. Given the hospital's high patient volume, these benefits scale effectively, amplifying cost savings, efficiency gains, and improved treatment outcomes. Beyond hospital-level improvements, Henan Cancer Hospital extends its expertise through regular remote MDTs via the 'iMDT' platform, enabling lower-tier hospitals to manage more cases locally. This approach reduces unnecessary referrals and healthcare costs while enhancing regional medical resource allocation.

Conclusions: Henan Cancer Hospital's two-layer MDT model provides a scalable and effective framework for delivering high-quality, cost-effective lung cancer care in high-volume settings. Additionally, through remote MDTs, it enables lower-tier hospitals to improve MDT capacity. This approach could serve as a replicable best practice for hospitals in China and worldwide facing similar challenges, ultimately improving patient outcomes and increasing cost-effectiveness in public healthcare systems.

Table 1. Key Characteristics of the Two-Layer MDT Model

MDT type	First layer—MDT Clinic	Second layer—Inpatient Lung Cancer MDT
Scope	Early-stage pulmonary nodules	All newly diagnosed lung cancer cases
Specialties	Led by thoracic surgeons, with support from respiratory medicine, radiation oncology, interventional radiology, and imaging specialists	Rotating leadership among multiple departments
Frequency	Weekly	4 times/week
Volume	15 cases/session, 5-20 min/ case	~6,000 cases/year, 1-6 min/ case
Patient Involvement	Patients and families participate in discussions	Patients directly receive results the same day
Key Outcomes	- 20-30% reduction in unnecessary surgeries - Minimizes overtreatment - Enhances psychological support	- Improves staging accuracy - Strengthens medical education - Extends expertise via remote MDTs

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.39 Clinical Predictive for Early Mortality in Stage IV Lung Cancer Without Targetable Mutations From Country With High Smoking Prevalence

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Introduction: Lung cancer is the leading cause of cancer mortality worldwide; approximately 25%-30% of patients with stage IV non-small cell lung cancer (NSCLC) die within 3 months of diagnosis (early mortality). Identifying high-risk patients could influence treatment decisions and outcome. This study examines clinical characteristics and risk factors for early death.

Methods: Medical records of patients aged 18 years or older, initially diagnosed with stage IV NSCLC, tested for PD-L1 expression, and confirmed negative for EGFR, ALK, and ROS1 at King Hussein Cancer Center from 2017 to 2024 were retrospectively reviewed. They were divided into patients who died within 3 months of diagnosis (early mortality) and patients who died later. Clinical variables were compared using Pearson's chi-squared tests, likelihood ratio chi-square, Mann-Whitney U tests, and linear model ANOVA.

Results: A total of 721 patients were included; 243 (41.2%) died within 3 months of diagnosis; the majority were male (604, 83.8%); the median age was 60 years; adenocarcinoma was the most common subtype (525, 72.8%); and the performance status (PS) of 3-4 was reported in 128 patients (17.8%). The PD-L1 expression ≥50% was observed in 225 (31.2%). The most common comorbidities were hypertension (37%) and diabetes mellitus (30%), while hyponatremia was the most common electrolyte abnormality at diagnosis (161, 22.3%). Brain metastases were reported in 331 (45.9%) patients, and adrenal metastases in 207 (28.7%). A total of 280 patients (39%) received immunotherapy either as a single agent or in combination, while 162 (22.5%) did not receive any systemic therapy. The early mortality group was older, with a median age of 62 vs. 59 (P = 0.001), and it was associated with PD-L1 ≥50% (37% vs. 27.1%; OR = 1.6, 95% CI: 1.03-2.52, p = 0.037), ECOG PS 3-4 (34.6% vs. 10.7%; OR = 4.09, 95% CI: 2.61-6.50, p < 0.001), adrenal metastases (38.7% vs. 25.5%; OR = 1.79, 95% CI: 1.21-2.63, p = 0.003), and congestive heart failure (CHF) (5.3% vs. 1.7%; OR = 2.65, 95% CI: 0.97-7.96, p = 0.066). Palliative care consultation at the time of diagnosis was associated with less frequent deaths in the intensive care unit (39.9% vs. 72.5%, p < 0.001). Patients receiving palliative care were less likely to die from treatment side effects (5.4% vs. 10.9%) or co-morbidities (5.7% vs. 10.0%, p = 0.0051). However, it did not influence the site of death (home vs. hospital).

Conclusions: A substantial proportion of patients initially diagnosed with Stage IV NSCLC die early, before reaching their first disease assessment. Risk factors such as older age, high PD-L1 expression, poor ECOG PS, and adrenal metastases should guide treatment decisions and follow-ups. Early palliative care is essential, reducing ICU deaths, treatment-related mortality, and ensuring improved quality of life.

Keywords: lung cancer, Early Mortality, palliative care

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.40 Impact of Remote MDT Through a Digital Platform: Insights From 70 Patient Follow-Ups

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Introduction: Multidisciplinary Team (MDT) management is essential for lung cancer diagnosis and treatment. However, disparities between urban and rural areas in China limit access to standardized MDT care. Remote MDTs, facilitated via digital platforms, help bridge this gap by providing lower-tier hospitals with expert guidance, standardized treatment, and multidisciplinary decision-making. This study evaluates a digital remote MDT model using physician-assessed patient outcomes to measure its impact on patient care and quality of life.

Methods: An AI-based digital MDT platform, "iMDT," enabled remote MDT sessions between lower-tier hospitals and Centers of Excellence (CoE). Following these sessions, healthcare providers (HCPs) at lower-tier hospitals conducted patient follow-ups every 2-3 months (3-4 follow-ups total) and completed structured questionnaires (see Table 1) assessing quality of life, treatment effectiveness, physical, psychological & conscious status, social reintegration, and overall MDT satisfaction. For treatment effectiveness, a combination of Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and physician assessment was applied. By January 2025, data from 70 eligible patients across 40 lower-tier hospitals had been collected by treating physicians (including 55 responses for treatment effectiveness) and analyzed for insights.

Results: Among the 70 eligible patients, 71% reported an improvement in quality of life since their last follow-up, with 47% "significantly improved." In terms of treatment effectiveness, 43 patients were evaluated using RECIST 1.1 and 12 through HCP assessment. Among them, 51% showed a complete or partial response, while 13% remained stable, demonstrating the clinical efficacy of remote MDT interventions. Patient satisfaction levels were high across multiple dimensions, with 91% rating their MDT-based treatment plan as good or excellent. With regards to specific sub-dimensions, 84% reported good or excellent physical status, 80% reported good or excellent psychological status, and 92% reported good or excellent conscious status. Additionally, 83% stated that recovery allowed them to reintegrate into social life, highlighting both clinical and social benefits. These findings demonstrate that remote MDTs improve treatment decisions, patient experience, and multidisciplinary collaboration, reinforcing their value in expanding access to high-quality cancer care.

Conclusions: Remote MDTs via AI-based platforms improve patient outcomes, enhance treatment effectiveness, and ensure high satisfaction rates. The structured questionnaire provides a standardized method for evaluating MDT effectiveness, supporting continuous quality improvement in multidisciplinary cancer care. Expanding such standardized assessment processes will help optimize MDT models and enhance care delivery in lower-tier hospitals.

Table 1. Questionnaire of remote MDT follow up

Question	Answer Options
How would you assess the patient's overall quality of life?	Much improved / Somewhat improved / No significant change / Worse
Has the patient achieved an objective response according to ORR criteria?	Yes, through RECIST 1.1 / Yes, through physician's Assessment / No
What is the patient's RECIST 1.1 evaluation result?	Complete response / Partial response / Stable disease (Non-CR/Non-PD) / Disease progression
What is your clinical assessment of the patient's current condition?	Remission / Stable / Progression
What is the patient's current treatment outcome?	Maintained current treatment / Adjusted treatment plan / Further examination
How satisfied is the patient with their overall treatment experience?	Very satisfied / Fairly satisfied / Neutral / Not satisfied
Is the patient satisfied with their physical condition (e.g., physical strength)?	Very satisfied / Fairly satisfied / Neutral / Not satisfied
Is the patient satisfied with their psychological condition (e.g., anxiety levels)?	Very satisfied / Fairly satisfied / Neutral / Not satisfied
Is the patient satisfied with their cognitive function (e.g., memory and attention)?	Very satisfied / Fairly satisfied / Neutral / Not satisfied
Is the patient satisfied with their ability to reintegrate into social roles (e.g., work, social activities)?	Very satisfied / Fairly satisfied / Neutral / Not satisfied

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.41 Bridging Gaps in Lung Cancer Care: The Quantitative Impact of Inter-Hospital Remote MDT Consultations in China

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Introduction: China's vast geography, socioeconomic diversity, and uneven healthcare distribution create disparities in lung cancer treatment. While many Tier 3 hospitals have advanced expertise and well-established multidisciplinary team (MDT) models, most Tier 2 hospitals face resource and knowledge limitations, negatively impacting patient outcomes. Remote inter-hospital MDT consultations help bridge this gap by integrating resources, improving diagnostic and treatment capabilities, and expanding access to quality care, particularly for rural patients. This study evaluates the impact of remote MDTs, their educational benefits, and best practices for broader implementation.

Methods: In 2024, 80 hospitals (11 Centers of Excellence [COE] and 69 Tier 2 hospitals) participated in inter-hospital MDTs through the iMDT digital platform, an AI-facilitated MDT management tool. A total of 302 healthcare professionals (HCPs) discussed 200 qualified lung cancer cases through remote MDT based on the platform. A structured questionnaire was distributed to HCPs to evaluate changes in treatment plans, improvements in diagnostic accuracy, and the perceived educational value of remote MDT participation. As of January 10, 2025, responses from 39 HCPs in 5 COEs and 194 HCPs in 69 Tier 2 hospitals were analyzed for insights on clinical and professional impact.

Results: Remote MDT consultations significantly improved lung cancer diagnosis, treatment decisions, and professional development. Following discussions with Centers of Excellence (COEs), treatment plans changed in 43% of cases (16% incorporating radiotherapy and ~10% adding immunotherapy) and the CRT rate increased significantly from 46% to 62%, demonstrating better alignment with standard care guidelines and broader adoption of comprehensive treatment strategies. Beyond clinical impact, remote MDTs were highly valued for professional development. 100% of healthcare professionals (HCPs) expressed satisfaction and willingness to continue participation, while 99% of Tier 2 hospital HCPs reported enhanced expertise. Additionally, 98% observed improvements in their hospital's diagnostic and treatment capabilities, reinforcing the role of remote MDTs in elevating care standards in lower-tier hospitals. These findings highlight the effectiveness of remote MDTs in optimizing treatment decisions, enhancing clinical expertise, and improving healthcare capacity in resource-limited settings.

Conclusions: Inter-hospital remote MDTs are an effective strategy for bridging the gap between Tier 3 and Tier 2 hospitals, improving diagnostic precision, treatment adherence, and HCP expertise. By facilitating real-time multidisciplinary discussions, digital platforms enable broader access to specialized lung cancer care while strengthening regional hospital capacity. To further reduce disparities and maximize impact, remote MDTs should be expanded to more regions, especially those with limited access to oncology expertise. Encouraging wider adoption will require stronger policy support, investment in digital infrastructure, and greater inter-hospital collaboration. Additionally, Hospitals could strengthen knowledge-sharing networks by sharing MDT resources, providing in-hospital training, and leveraging digital tools to enhance accessibility, efficiency, and long-term capacity building.

Keywords: Inter-Hospital Remote MDT, Treatment optimization, Healthcare capacity building

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.42 Canadian Consensus Recommendations for Multi-Disciplinary Team Meetings in Lung Cancer Care

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Introduction: Multi-disciplinary team meetings (MDTMs) are a key piece in the lung cancer care pathway, where healthcare providers collaborate on patient cases and decide on treatment plans. MDTMs increase adherence to guidelines and positively impact survival. MDTM preparation and follow-up are organized differently across hospitals and countries. These variations may lead to sub-optimal decision-making and outcomes. The increasing complexity of the diagnostic and therapeutic landscapes, importance of perspectives from multiple disciplines, and evolution towards patient-centered care emphasize the importance of MDTMs. The objective of this study was to understand current MDTM structures and practices in Canada, as well as develop a series of recommendations to improve MDTMs.

Methods: We created an MDTM Network with 15 representatives of Canadian lung cancer MDTMs across the country, including medical oncology, radiation oncology, thoracic surgery, respirology, pathology, nuclear medicine, nursing, radiology, and a patient representative. To develop insights, our framework of analysis focused on MDTM structure, including key process steps. An electronic survey was distributed, followed by one-on-one semi-structured interviews with each representative. A level of agreement of greater than 80% was considered consensus. Representatives then engaged in a face-to-face meeting to validate preliminary findings and discuss areas of uncertainty or disagreement.

Results: Within MDTM structure, the network identified core skills and disciplines that should be represented at each MDTM. Representatives agreed that MDTMs should be held at regular predefined intervals determined by center case volume, with a patient list circulated ahead of the meeting to allow time for preparation. Consensus on categories of patients who should always be discussed included but was not limited to patients with complex presentations, cases that do not fit standard of care, and patients that meet specific local criteria. Organizations can consider discussing all patient cases if resources allow. Representatives agreed that MDTM recommendations should be clearly documented in patient charts to facilitate communication with the entire healthcare team. The network understands MDTMs as the reification of a distributed community of practice (CoP), which is the multidisciplinary team (MDT). The MDTM is the regular event where healthcare professionals of an unstructured MDT providing care to lung cancer patients come together, clarifying the relationship between MDT and MDTM. Accordingly, we propose that Wenger-Trayner's CoP maturity model be used to assess MDT developmental stage in seven dimensions.

Conclusions: MDTMs are an essential part of the lung cancer patient journey. Any patient or healthcare professional involved in lung cancer management should have access to an MDTM. As MDTs and MDTMs are a standard part of patient care, recommendations focused on the details of how MDTMs operate are important to maximize the benefits of these collaborative efforts. Framing MDTs appropriately as communities of practice and fostering their growth can justify institutional resource allocation, enhance essential multidisciplinary representation, and could optimize both throughput of cases and patient outcomes. These recommendations support continuous improvement of MDTMs, ensuring they remain a cornerstone in patient management. Optimization of MDTMs should constitute a key part of the continuous improvement of the communities of practice they represent.

Keywords: Multidisciplinary, Consensus, Community of Practice

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.43 Association Between Pretreatment Emotional Distress and EGFR-TKI Therapeutic Response in EGFR-Mutant Non-Small Cell Cancer

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Introduction: Association between pretreatment emotional distress and EGFR-TKI therapeutic response in EGFR-mutant non-small-cell lung cancer. Cancer patients frequently experience emotional distress (ED), typically presenting as anxiety and/or depressive symptoms. Experimental studies have indicated that ED may negatively influence the effectiveness of antitumor therapies. However, there is a lack of clinical research examining how ED may affect responses to EGFR-TKIs treatment.

Methods: Here we report results from a multicenter retrospective study,which investigated the association between ED and clinical efficacy of first-line treatment of EGFR-TKIs in patients with advanced EGFR-mutant lung cancer. ED was assessed by Patient Health Questionnaire-9 and Generalized Anxiety Disorder7-item scale.

Results: The study included 573 patients with 246(42.9%) exhibiting ED who presented depression(Patient Health Questionnaire-9≥5) and/or anxiety(Generalized Anxiety Disorder 7-item score≥5) symptoms at baseline. On the primary endpoint analysis, patients with baseline ED exhibited a significantly shorter median progression-free survival compared with those without ED(14.2 months versus 19.7 months, hazard ratio 1.70, 95% confidence interval 1.20 to 2.51, P=0.003). On the secondary endpoint analysis, ED was associated with lower objective response rate (75.1% versus 88.3%, odd ratio 0.37, P=0.031) and detriments in quality of life.

Conclusions: This study demonstrates that ED is associated with poorer clinical outcomes in advanced EGFR-mutation positive NSCLC patients receiving EGFR-TKI therapy, underscoring the importance of evaluating and managing ED as part of comprehensive cancer care.

Keywords: Emotional distress, EGFR-TKI, Therapeutic response

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.44 Multiomic Interaction Among Host and Tumor Immunity for Chemo De-Escalation. People Phase II Trial, First Line Pembrolizumab in Low PD-L1 NSCLCy

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Introduction: Multi-omics data represent a valuable source of biological insights to drive cancer research. While analyzing each omic layer independently remains effective, integrating multiple omic layers provides the greatest potential to characterize underlying biological processes. The PEOPLE (NCT03447678) trial is a multi-omic investigation designed to identify novel immune biomarkers in advanced non-small-cell lung cancer (aNSCLC) patients with negative or low PD-L1 expression, treated with first-line pembrolizumab.

Methods: Data were collected through multiparametric flow cytometry (FACS) in peripheral blood, transcriptomic profiling of tissue samples using the nCounter PanCancer IO 360 Panel (Nanostring), and gut microbiome taxonomic abundances via shotgun sequencing of stool samples. Transcriptomic counts were normalized using EdgeR package, converted into counts per million (CPM), and log2-tranformed. FACS counts and microbial relative abundances were log2-normalized to stabilize variance. The multi-omic integration was performed using MOFA2 package, generating 25 latent clusters. Survival analyses based on individual clusters were conducted. Gut microbiome data were further analyzed through network analysis using WGCNA package. Cluster loadings were analyzed to interpret their biological significance.

Results: Among 87 patients NSCLC patients screened, 65 patients were enrolled in the analysis with at least 1 available omic. 57, 48, and 54 patients had FACS, Nanostring, and microbiome data at baseline. Two clusters significantly stratified patient overall survival (OS). In cluster 5 all omics have a significant contribution to stratify OS (p = 00027). In particular, gene expression of CD79A, BLK, LTB, CD45RA, neutrophil CD15 high and leukocyte CD45+, Senegalimassilia anaerobia and Prevotella stercorea bacterias positively correlate with OS while gene expression of COL6A3, JAG1, Monocyte CD14+/HLADR+, Granulocyte CD16+ and Neutrophils 15+CD16+, Romboutsia timonensis, Clostridium saudiense) negatively correlates with OS. Cluster 6 two omics (FACS and gene expression) have significant contributions to stratify OS (0 = 0.0035). In particular gene expression of EIF2AK2 and different monocytes populations (intermediate $CD14^{+}CD16^{+}$, with or without high HLA-DR expression, non-classical $CD14dimCD16^{+}$, with or without HLA-DR expression) negatively correlate with OS. Network analysis of the gut microbiome revealed a more interconnected microbial network in patients with longer survival, consistent with findings in existing literature.

Conclusions: The present multiomics data integration methodology highlights the critical role of the interaction between host immunity specifically the microbiome and circulating immune profiles and tumor gene expression in predicting response to immunotherapy. Importantly, the approach also proved technically feasible in the presence of missing data, maintaining robustness across analyses. Notably, two distinct patient clusters were identified, indicating that pembrolizumab monotherapy may be effective in a subset of patients with low PD-L1 expression. This finding is particularly relevant for treatment de-escalation strategies, offering the potential to spare selected patients from chemotherapy and reduce treatment-related toxicity without compromising efficacy. The PEOPLE trial serves as a strong example of how prospective, biomarker-driven academic interventional studies should be designed to enable chemotherapy de-escalation.

Keywords: Multi-omic, Immunotherapy

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.45 Multidisciplinary Digital Platform for Independent Adjudication of ILD/Pneumonitis Related to T-DXd Treatment

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Introduction: Misdiagnosis or delayed diagnosis of T-DXd-associated ILD/p is common, contributing to increased morbidity and mortality. Access to pulmonologists and radiologists specialized in ILD/p remains limited in Brazil and globally. Our study aimed to evaluate the feasibility of a digital platform for independent adjudication and real-time management of suspected ILD/p cases through remote, asynchronous, multidisciplinary discussions.

Methods: Our platform consists of a secure phone/web-based app enabling referring physicians to upload anonymized clinical data and digital imaging. Pulmonologists, radiologists, and medical oncologists asynchronously discuss each case through a confidential, HIPAA-compliant chat. We analyzed data from the first 37 cases of suspected ILD/p submitted through the platform, assessing the ILD/p adjudication rate, time from submission to adjudication (TSTA), and time from submission to therapeutic plan formulation (TSTFT).

Results: Among the 37 submitted cases, 22 (59.5%) had clinical, radiological, and laboratory features consistent with ILD/p. Compared to pooled data from independent adjudication committees across nine phase I and II T-DXd studies (84.8% concordance), our observed concordance rate was 59.5%. Confirmed ILD/p cases were predominantly grade ≤2, with fewer grade 3 events. Median TSTA was 8.88 hours (range 0.05-86.53 hours), and median TSTFT was 11.65 hours (range 0.33-86.58 hours).

Conclusions: Implementing a digital platform for adjudication and management of suspected T-DXd-associated ILD/p was feasible and effective, with diagnostic rates consistent with those reported in clinical trials and timely adjudication and treatment decision-making. Approximately 40.5% of suspected ILD/p patients had alternative diagnoses, potentially allowing them to safely continue treatment. This approach could mitigate clinical challenges in regions lacking specialized ILD/p expertise.

Keywords: Interstitial Lung Disease, Trastuzumab-Deruxtecan, Telemedicine

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.46 The Best Care One-Lung Program; a Pathway for Lung Cancer Screening in Primary Care

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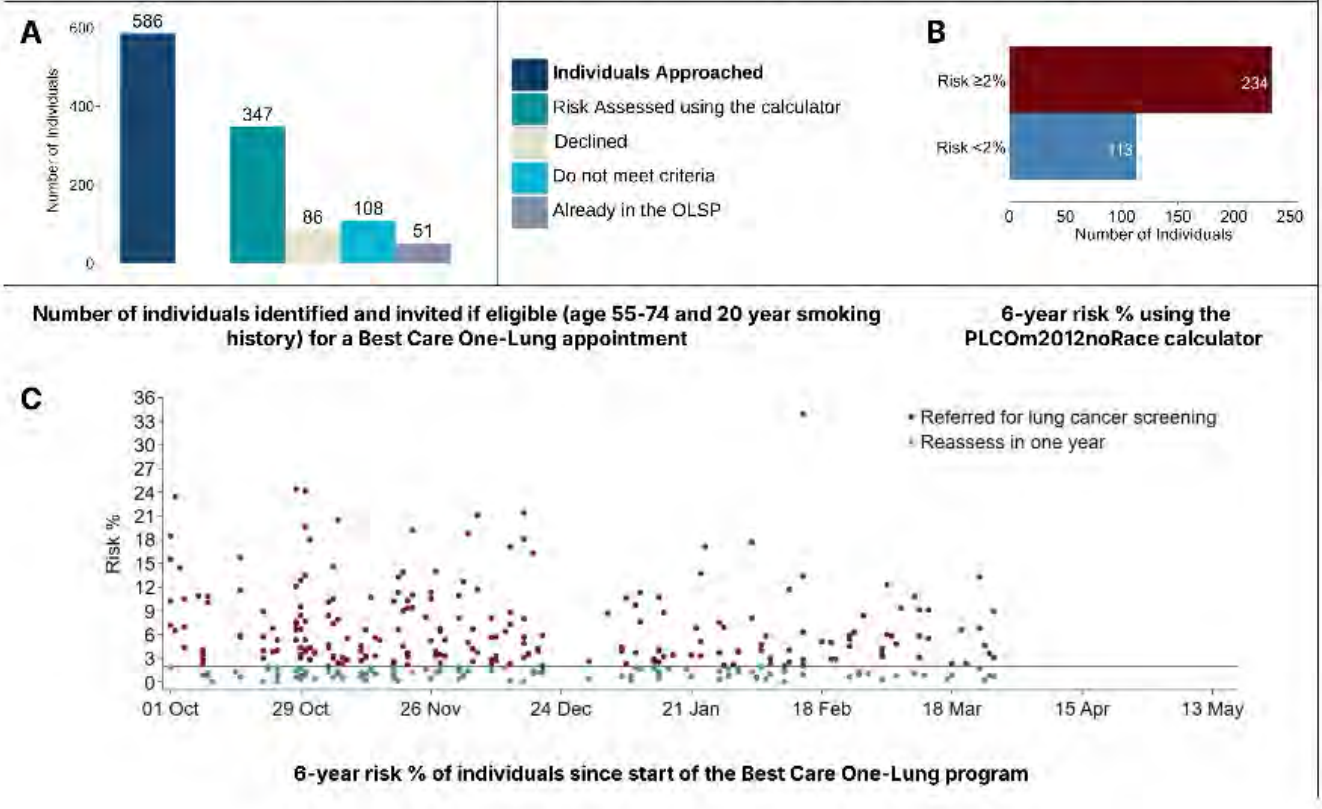
Introduction: Lung cancer screening of at-risk individuals by annual low-dose CT (LDCT) scanning reduces mortality, however, low rates of patient identification and referral limit access. In Ontario, Canada, primary care physicians (PCPs) are requested to identify and refer eligible patients, aged 55 to 74 with a 20-year smoking history, to the lung screening program. After referral, a regional cancer program navigator completes a risk assessment tool (PLCOm2012noRace) with the patient by telephone. Individuals with a ≥2%, 6-year, risk of developing lung cancer receive annual LDCT screening. Best Care is an established integrated chronic disease management program that embeds certified respiratory educator-case managers (CRE-CM) within primary care practices, to support PCPs to deliver guideline-concordant care. Chronic obstructive pulmonary disease (COPD) is one of the diseases that Best Care provisions. Exposure to tobacco smoke is a common risk factor for COPD and lung cancer, and COPD elevates lung cancer risk. We describe preliminary results from the Best Care One-Lung program, a new pathway in primary care that leverages the unique position of Best Care COPD, supporting PCPs in the identification, shared decision-making, and referral of high-risk individuals.

Methods: The Best Care One-Lung program was implemented in a pilot region (Hamilton, Ontario) in October 2024. Five CRE-CMs from 21 primary care practices identified patients aged 55 to 74 and with a 20-year smoking history from Best Care COPD (≈850 patients enrolled), primary care EMR searches, and PCP referrals. Eligible patients were invited to a Best Care One-Lung appointment led by CRE-CMs. Appointments included spirometry (if there was no existing COPD diagnosis), completion of the PLCOm2012noRace calculator, and for individuals with a lung cancer risk ≥2% shared decision-making and coordination of PCP referral to the screening program.

Results: Identified patients were predominantly from Best Care COPD with a confirmed COPD diagnosis. To date 586 individuals have been approached and 347 (59%) attended a One-Lung risk assessment (Figure1A). 234 (67%) were determined eligible for lung cancer screening (Figure 1B,1C) with a median risk of 5.4% equating to the potential detection of 13 lung cancers with 6 years of annual screenings (mean risk 7.1% SD(5.1)). LDCT scan results for 57 of the screened individuals included 5 scans reporting Lung-RADS assessment categories 4A,4B,or 4X (suspicious nodules).

Conclusions: The Best Care One-lung pathway to lung cancer screening is critically positioned to support primary care, identifying high-risk populations and improving access to life-saving screening.

Figure 1: Preliminary results from the Best Care One-Lung pathway to lung cancer screening in primary care



Keywords: primary care, lung cancer, screening

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.47 Safety and Efficiencies of Specialist Lung Cancer Nurse-Enabled Pulmonary Nodule Management: An Australian Demonstration

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Introduction: In July 2025, Australia will introduce a National Lung Cancer Screening Program (NLCSP). Specialist assessment and management of pulmonary nodules is a NLCSP aspect anticipated to have major implications on health workforce, resource utilisation and service delivery. April 2023, clinical redesign of a regional, public outpatients respiratory medicine specialist service in New South Wales, Australia, implemented a lung cancer nurse consultant to triage, undertake malignancy risk categorisation and subsequent clinical pathway management of patients referred for investigation of pulmonary nodules. This multipronged project aimed to understand the safety and efficiencies of nurse-enabled pulmonary nodule management. In project A, safety is defined as congruence between nurse and physician malignancy risk category and clinical pathway recommendation. In project B, efficiencies are defined as alignment of service delivery with Optimal Care Pathway for people with lung cancer critical time intervals.

Methods: Project A: Retrospective audit of a random sample of 33 nurse triaged referrals (post April 2023) were examined for congruence between nurse and physician nodule risk scoring and pathway recommendation. Descriptive statistics of e.g., clinical characteristics and comorbidities, proportion of incidental to screen detected nodules, informed the sensitivity analyses, which explored the accuracy of nurse risk categorisation (i.e., high/very high risk or non-urgent) by comparing nurse and physician risk scores and pathway recommendations (e.g., rapid access or surveillance), including patient outcomes over time. Instances of non-congruence between nurse and physician were examined. Project B: A retrospective audit of 30 high/very high-risk referrals (15 referrals pre-15 referrals post April 2023) with critical time intervals across patient clinical pathways (e.g., referral received by outpatients department to first specialist appointment, and more) examined between the two referred cohorts. The mean time in days for time intervals was calculated.

Results: Project A: In the high/very high-risk patient cohort, 12/18 (67%) had screen detected nodules; 9/15 (60%) of the non-urgent cohort were referred due to incidental nodules. In the non-urgent cohort, nurse malignancy risk categorisation was 100% congruent with physician risk scoring, yet congruence between subsequent clinical pathway recommendation was 53% (8/15 times congruent). Differences centred around patient complexities (e.g., pregnancy). In the high/very high-risk cohort, nurse malignancy risk categorisation was 83% (15/18) congruent with physician risk scoring and pathway recommendation. Despite a nurse guideline concordant approach to the assessment and recommendation of three patients, these were assessed by physicians as non-urgent. Project B: Post April 2023, the cumulative effect of time saved in the front-end steps of the clinical pathway represented a mean saving of 20 days (SD 9) from 'referral received to time to diagnosis'. Like the pre April 2023 data, post April 2023 patients who undergo bronchoscopy represented a longer time to diagnosis. The data suggest the nurse model increases the likelihood of high/very high-risk patients receiving curative intent treatment.

Conclusions: Specialist lung cancer nurse-enabled pulmonary nodule management is safe and offers patients a quality experience regarding the critical timeliness of their case management. The findings reinforce the need for an effective, multidisciplinary clinical governance framework in this advanced nursing practice context.

Keywords: Advanced practice nursing, Pulmonary nodules, Model of care

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.48 Characteristics and Associated Survival of Patients Diagnosed With Non-Small Cell Lung Cancer in Western Kenya

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Introduction: Advances in lung cancer treatment in high-income countries have significantly improved lung cancer patients' survival rates. Identification and treatment of driver mutations in lung cancer, such as EGFR, ALK, ROS-1, and others, have resulted in high response rates and notably extended survival in patients who harbor these mutations and receive molecular therapies. However, many of these treatment options have remained infrequently or entirely unavailable in Kenya and other low—and middle-income countries, significantly limiting survival in these patients. Improved data across the lung cancer care continuum including diagnostics and treatment are urgently needed to inform interventions that can improve lung cancer-related mortality in these regions. While lung cancer is a significant cause of mortality worldwide, studies in sub-Saharan Africa are scarce. Here we characterize outputs from a designated lung cancer program, part of the in western Kenya, part of the Multi-National Lung Cancer Control Program, which is focused on case finding, diagnosis, and treatment.

Methods: We retrospectively reviewed patients with pathologically confirmed non-small cell lung cancer (NSCLC) who enrolled in this program at Moi Teaching and Referral Hospital from January 2018 to December 2022. We analyzed clinical data using descriptive statistics, Kaplan-Meier methods, and a proportional hazards regression model.

Results: Two hundred forty-nine patients diagnosed with NSCLC were included with median age at diagnosis of 61(IQR 52-70) years. Most patients were married (177;73%) and non-smokers (177; 71) with 58 (23%) having received tuberculosis treatment and 93 (37%) having ECOG performance status of 2. At diagnosis, adenocarcinoma was the prominent histology (187;75%) along with clinical stage IV (195; 78% stage IV) or un-staged (40; 16%) disease. Most patients received chemotherapy and radiotherapy (176; 71%) with few palliative care referrals (2; 0.8%). Median overall survival (OS) was only 3.7 months (IQR 2.7-5.4). ECOG performance status (3 or 4) and being un-staged were predictors of poor 1-year OS.

Conclusions: Patients with NSCLC enrolled in this program presented with advanced disease and poor survival. Despite a designated case-finding effort, late diagnosis remained common and highlights a need for locally relevant interventions targeting community and provider education as well as timely and innovative diagnosis that can improve early recognition of lung cancer in Kenya. These interventions must also be paired with access to diagnostics and associated treatments including molecular therapies and palliative care which can extend lung cancer survival.

Keywords: Non-small cell Lung Cancer (NSCL), Retrospective review, Lung cancer survival

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.49 Real-World Outcomes With IO and Chemo-IO Demonstrate Unmet Need for 1L KRAS G12C-Mutant Advanced NSCLC in the US

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Introduction: While KRAS G12C mutations are fairly common amongst US patients with NSCLC, there are no approved 1L treatments directed at KRAS mutations. Current 1L options are commonly immunotherapy (IO) alone or with platinum-based chemotherapy (PBC). We evaluated clinicopathologic characteristics, treatment patterns, and outcomes among patients with KRAS G12C-mutant advanced NSCLC.

Methods: This retrospective study included patients with advanced NSCLC who initiated 1L treatment from 8/1/2018-12/31/2022 and had KRAS test results. The US-based deidentified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic database (CGDB) and Flatiron Health Research database were queried. These are longitudinal, comprising patient-level structured and unstructured data. Patients were evaluated by KRAS mutation status: KRAS G12C-mutant, other KRAS-mutant, KRAS wild-type (with driver alteration and without driver alteration). Progression-free survival (PFS), time-to-treatment discontinuation (TTD), and overall survival (OS) were estimated using Kaplan-Meier methods and Cox proportional hazards models.

Results: In the CGDB, 447(11.9%) patients had KRAS G12C-mutant, 657(17.4%) had other KRAS-mutant, and 2,664(70.7%) had KRAS wild-type NSCLC. Most patients with KRAS G12C-mutant NSCLC had non-squamous carcinoma (92.0%), were treated in community practice (88.1%), and had a history of smoking (98.7%). The prevalence of brain metastasis at diagnosis of advanced disease was higher among patients with KRAS G12C-mutant (25.1%) and other KRAS-mutant (25.7%) than KRAS wild-type NSCLC (20.9%; p=0.008). In the KRAS G12C-mutant cohort, PBC+pembrolizumab was the most common regimen (46.1%) regardless of PD-L1 status. Pembrolizumab monotherapy was most common (36.8%) in the PD-L1 ≥50% subgroup. Among patients who received 1L treatment, 37.4% received 2L therapy. Median PFS and OS for patients with KRAS G12C-mutant NSCLC treated with PBC+pembrolizumab were 5.3 and 12.8 months, respectively. In adjusted Cox proportional hazards models for patients treated with PBC+pembrolizumab, patients with other driver mutations had significantly longer PFS and OS compared to patients with KRAS G12C mutations. No significant differences were observed among patients treated with pembrolizumab monotherapy. In the Research database, 1,227(10.0%) patients had KRAS G12C-mutant, 1,821(14.8%) had other KRAS-mutant, and 8,830(71.9%) had KRAS wild-type NSCLC. Median TTD and OS for patients with KRAS G12C-mutant NSCLC treated with PBC+pembrolizumab were 5.5 and 15.6 months, respectively, and with pembrolizumab monotherapy were 5.0 and 22.1 months, respectively.

Conclusions: Real-world evidence suggests patients with KRAS G12C-mutant NSCLC have shorter PFS and OS compared to those with KRAS wild-type, when treated with PBC+pembrolizumab. Additionally, most patients with KRAS G12C-mutant NSCLC never received 2L therapy. These data highlight the need for more effective 1L therapies for KRAS G12C-mutant patients.

CGDB	N	Median PFS (months) Adjusted HR, p-value	Median OS (months) Adjusted HR, p-value
PBC+pembrolizumab PD-L1 all comers			
KRAS G12Cm	206	5.28 mo. (Reference)	12.82 mo (Reference)
Other KRASm	304	6.43 mo. HR=0.94, p=0.53	13.54 mo. HR=1.01, p=0.93
Other driver	164	7.11 mo. HR=0.78, p<0.05	21.18 mo HR=0.70, p=0.01
No driver	804	6.33 mo. HR=0.86, p=0.10	14.46 mo. HR=0.83, p=0.07
Pembrolizumab in PD-L1 ≥50%			
KRAS G12Cm	46	4.56 mo. (Reference)	20.43 mo. (Reference)
Other KRASm	75	4.33 mo. HR=0.95, p=0.83	14.33 mo HR=0.96, p=0.88
Other driver	27	5.36 mo. HR=0.92, p=0.77	30.26 mo. HR=0.75, p=0.40
No driver	110	6.66 mo. HR=1.03, p=0.90	12.85 mo. HR=1.26, p=0.36

Keywords: KRAS, Immunotherapy, Real-world outcomes

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.50 Correlation Between Clinical and Pathological Stage in Resected NSCLC

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Introduction: Accurate clinical staging is critical for guiding treatment decisions in patients (pts) with resectable non-small cell lung cancer (NSCLC), particularly as neoadjuvant therapy becomes more widely utilized. While adjuvant therapy is based on the pathological staging, neoadjuvant therapies rely on the clinical staging. This study assessed the correlation between clinical (c) and pathological (p) staging in surgically resected NSCLC.

Methods: We queried the National Cancer Database (NCDB) for patients diagnosed with NSCLC between 2004 to 2020 who underwent upfront surgical resection with documented cTNM and pTNM staging. Pts with stage IV, missing data, or who received neoadjuvant therapy were excluded.

Results: Among the 325,794 eligible pts, clinical stages I, II, and III accounted for 78.3%, 14.9%, and 6.8% of pts, respectively. Pathological staging was 67.1% stage I, 19,9% stage II, 12.3% stage III, and 0.6% stage IV. Overall clinical to pathological TNM were downstaged in 4.0%, upstaged in 17.4%, and concordant in 78.6% of the cases. T stage was concordant in 76% of cases, downstaged in 4% and upstaged in 19% while N stage was concordant in 84% of cases, downstaged in 3% and upstaged in 13%. Patients with cN0, cN1 and cN2 had concordant pathological stages in 86.6%, 63.6% and 63.5% respectively. pN2 was seen in 4.7% of cN0 and 15.3% of cN1. Among pts with cN2, 24.4% had pN0, 11.7% pN1 and 0.4% pN3. While cN2 is downstaged to pN0 in 24.4% and to pN1 in 11.7% of cases, there are more pN2 cases overall than cN2 due to upstaging from cN0 and cN1 to pN2 (Table). Factors associated with staging discordance included female gender, Black race, squamous cell carcinoma histology, ≥ 5 lymph nodes sampled intraoperatively, pneumonectomy, treatment at non-academic centers, and a delay of > 30 days from diagnosis to surgery.

Conclusions: Significant discrepancies exist between clinical and pathological stages in real-world practice. Optimizing staging is critical to decrease the clinical and pathological staging discordance, and allow better treatment selection in resectable pts.

Table. Frequency of clinical and pathological staging

	Clinical	Pathological	Concordant	Upstage	Downstage
Stage I	255,018 (78.3%)	218,776 (67.1%)	81.9%	18.1%	-
Stage II	48,520 (14.9%)	64,859 (19.9%)	64.6%	20.9%	14.5%
Stage III	22,256 (6.8%)	40,232 (12.3%)	71.0%	1.8%	27.3%
Stage IV	0	1,927 (0.6%)	-	-	-
T1	207,503 (63.7%)	167,275 (51.3%)	75.8%	24.2%	-
T2	90,894 (27.9%)	115,965 (35.6%)	78.1%	12.7%	9.2%
T3	20,367 (6.3%)	31,910 (9.8%)	73.1%	7.5%	19.4%
T4	7,030 (2.2%)	10,644 (3.3%)	72.4%	-	27.6%
N0	289,537 (88.9%)	258,854 (79.5%)	86.6%	13.4%	-
N1	23,478 (7.2%)	41,390 (12.7%)	63.6%	15.4%	21.0%
N2	12,779 (3.9%)	25,385 (7.8%)	63.5%	0.4%	36.1%
N3	0	165 (0.1%)	-	-	-

Keywords: Non–Small Cell Lung Cancer (NSCLC), Staging concordance, Clinical-Pathological Correlation

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.51 Real World Outcomes of Metastatic Mucinous Adenocarcinoma of Lung

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Introduction: Mucinous adenocarcinoma is a distinct entity among patients with lung cancer, with the diagnosis made both pathologically and radiologically. It is a rare disease with varying treatment patterns and outcomes globally. The aim of our multi-site single center retrospective study was to describe the unique clinicopathologic and genetic features of metastatic invasive mucinous adenocarcinoma (MIMA) of lung origin, also describe the treatment patterns and survival outcomes.

Methods: We analyzed data from 160 patients with MIMA, treated at Mayo Clinic Comprehensive Cancer Center (MCCCC) from Jan 2010 until Dec 2023. The clinical and radiologic findings were confirmed by 2 independent reviewers prior to inclusion of patients in our cohort. Data analysis was performed with Blue sky statistics (v 10.4).

Results: The median age at diagnosis was 68.5 years and our cohort included 56 patients with a confirmed diagnosis of Stage IIIC or IV MIMA. About 77% of patients had a smoking history. Pathology of mucinous adenocarcinoma was was made by features of abnormal glandular cells with presence of abundant intracelllular or extracellular mucin. Commonly analyzed pathologic markers included CK-7 (33%), CK-20 (15%), napsin (5%) and mucicarmine (3%). Less frequently analyzed pathologic markers were MUC 2, MUC 6, CDH1 and 2, PAX 8 and CDX 2. Targetable genetic alterations seen included KRAS [39%, KRAS G12D (20%), KRAS G12V (17%)], ALK, EGFR, ROS1, MET (2.5%), and RET, TP53, STK11, BRAF, IDH2, CHEK2, CDKN 1A/B, ERBB2, ARID1 oncogenic alterations (1%). NRG1 mutations were not observed in our cohort. 54% patients were treated with chemoimmunotherapy (Table 1). Median progression Free Survival for patients treated with chemoimmunotherapy Vs other therapy was 8.15 months Vs 8.18 months respectively (p=0.8). There was no difference in median overall Survival for patients who received first line chemoimmunotherapy vs other therapy 19.2 Vs 19 months (p=0.8). OS was lowest in current smokers at 12.5 months, followed by past-smokers at 13.8 months and was higher in non-smokers at 33.3 months (p=0.1).

Conclusions: This is the first real-world study assessing the outcomes in patients diagnosed with metastatic MIMA in the precision medicine era. It is interesting to note that survival outcomes do not differ much in patients who received chemoimmunotherapy vs other therapies highlighting the aggressive nature of this disease. The unique and distinct nature of this disease highlights the need for further research to identify pathways for precision medicine for MIMA.

Table 1: First line regimens used to treat MIMA of lung origin:

Name of Regimen	Genetic alteration targetted for therapy	Percentage of patients (N=56)
Carboplatin Pemetrexed Pembrolizumab	NA	54%
Carboplatin Paclitaxel Atezolizumab	NA	2%
Carboplatin Pemetrexed Cemiplimab	NA	2%
Pembrolizumab Datopotamab Deruxtecan	NA	2%
Pembrolizumab	NA	2%
Carboplatin Pemetrexed	NA	6%
Carboplatin Gemcitabine	NA	2%
Carboplatin Paclitaxel	NA	2%
Docetaxel	NA	2%
Carboplatin Pemetrexed Bevacizumab	NA	7%
Sotorasib	KRAS G12C	2%
Capmatinib	MET exon 14	5%
Crizotinib	EML4:ALK	5%
Dabrafenib Tremitinib	BRAF V600E	2%
Pralsetinib	ERC1:RET	2%

Key words: Lung cancer, mucinous adenocarcinoma, cancer genetics, metastatic cancer, immunotherapy, targetted therapy

Keywords: metastatic lung cancer, mucinous adenocarcinoma, cancer genetics

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.52 Real-World Treatment and Survival in KRASG12C-Mutated Locally Advanced/Metastatic Non-Small Cell Lung Cancer in England

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Introduction: With the advent of immunotherapies and novel targeted therapies, the treatment landscape for locally advanced/metastatic (LAM) non-small cell lung cancer (NSCLC) has evolved rapidly, necessitating real-world evaluations of treatment patterns and effectiveness to guide therapeutic decision-making. As a part of the international I-O Optimise initiative, this study aimed to characterize treatment patterns and survival in patients with KRASG12C-mutated LAM NSCLC in England using the Cancer Analysis System database.

Methods: This historical study included adult patients (≥18 years) with de novo or recurrent LAM NSCLC. Two cohorts were established: (1) patients receiving sotorasib who were assumed to harbor the KRASG12C mutation due to the drug indication (sotorasib cohort) and (2) patients with confirmed KRASG12C mutation, receiving a second or later lines of treatment (2L+ cohort). The overall study period spanned from January 2014 to October 2023, encompassing NSCLC diagnoses from 2014-2021, KRASG12C mutation testing from 2016-2021, and treatment data collection through 2023. Treatment sequences were identified algorithmically and will be presented using Sankey diagrams. The kaplan-Meier method was used to estimate overall survival (OS) from the start of sotorasib or a second-line treatment for the sotorasib and 2L+ cohorts, respectively.

Results: The sotorasib and 2L+ cohorts included 240 and 141 patients, respectively. In the sotorasib cohort, 67.1% were female, median age was 69 years at inclusion date, and 92.5% had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1. In the 2L+ cohort, 59.6% were female, median age was 69 years at inclusion date, and 87.9% had an ECOG PS ≤1. In the sotorasib cohort, the most common treatments were anti-programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) plus platinum-based chemotherapy in first line and tyrosine kinase inhibitors (TKIs) alone (predominantly sotorasib) in second and third line (Table). In the 2L+ cohort, the most common treatments were platinum-based chemotherapy in first line, anti-PD-1/PD-L1 ICI monotherapy in second line, and docetaxel ± nintedanib in third line (Table). Median OS in the sotorasib and 2L+ cohorts were 13.1 and 12.4 months, respectively. Median OS in the 2L+ cohort by type of second-line treatment received ranged from 9.2 months with anti-PD-1/PD-L1 ICI monotherapy to 15.1 months with TKIs.

Conclusions: These real-world results from England provide insights on the adoption of KRASG12C inhibitors into routine clinical practice as second or later lines of therapy for patients with KRASG12C-mutated LAM NSCLC and the associated survival outcomes.

Type of systemic anticancer treatment, n (%)	Sotorasib cohort (n = 240)	2L+ cohort (n = 141)
First line		
Anti-PD-1/PD-L1 ICI + platinum-based chemotherapy	98 (40.8)	**
Platinum-based chemotherapy	59 (24.6)	75 (53.2)
Anti-PD-1/PD-L1 ICI monotherapy	57 (23.8)	33 (23.4)
TKIs	18 (7.5)	*
Non-platinum-based chemotherapy	*	*
Other treatments	*	*
Second line		
TKIs	157 (65.4)	36 (25.6)
Platinum-based chemotherapy	21 (8.8)	30 (21.3)
Anti-PD-1/PD-L1 ICI monotherapy	20 (8.3)	51 (36.2)
Docetaxel ± nintedanib	20 (8.3)	17 (12.1)
Anti-PD-1/PD-L1 ICI + platinum-based chemotherapy	*	*
Other treatments	*	*
Non-platinum-based chemotherapy	0	*
Third line		
TKIs	47 (19.6)	*
Docetaxel ± nintedanib	21 (8.8)	23 (16.3)
Platinum-based chemotherapy	13 (5.4)	*
Anti-PD-1/PD-L1 ICI monotherapy	11 (4.6)	7 (5.0)
Non-platinum-based chemotherapy	*	*
Other treatments	*	*

*Indicates primary data masking of patient counts between 1 and 5. **Indicates secondary data masking to prevent calculation of primary masked data.

Keywords: KRASG12C mutation, Advanced NSCLC, Targeted therapy

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.53 Real-World Experience With EGFR-Positive NSCLC in Resource-Limited Settings: A Decade-Long Single Center Study From Jordan

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Introduction: Real-world evidence for EGFR TKI outcomes in Jordan and the Middle East is limited. While the use of third-generation TKIs first-line has become the standard, first-generation TKIs use is common here. This study evaluate the outcomes of EGFR-positive NSCLC over the last 10 years at King Hussein Cancer Center

Methods: This retrospective study analyzed data from 200 patients diagnosed with EGFR-positive NSCLC at King Hussein Cancer Center (KHCC) between 2014 and 2024. Data were extracted from electronic medical records, including demographics, clinical characteristics, molecular testing results, treatment regimens, responses, and survival outcomes. Descriptive statistics summarized baseline characteristics. Kaplan-Meier analysis estimated overall survival (OS) and progression-free survival (PFS). Cox regression analysis identified predictive factors for treatment response and survival outcomes.

Results: The study included 200 patients with median follow up of 26.8 (21-33.6)months, Clinical characteristics included median age 61.2 (29-91.6) years, female 103/200 (51.5%), never-smoking 129/200(61,4%), Exon 19/L858R 114/200 (57%) 71/200 (35.5%) , brain metastasis at diagnosis in 90/200 (45.0%) patients , Gefitinib was most common first line in 150 (75%) , followed by chemotherapy 33 (16.5%), Osimertinib used in 9 (4.5%). the most common second line was Osimertinib in 52 (43.0%), followed by chemotherapy in 31 (25.6%).Median PFS for Gefitinib in the first line was 10 [95%CI:8-13]months, median PFS for Gefitinib and Osimertinib at any line was 10 [95% CI:8 - 12] months and 14 [95% CI:7 - 21] months respectively ,the median overall survival was 25 [95% CL:19 - 31] months for all patients who received TKI in any line .Factors contributing to worse OS in the multivariate model were liver metastasis and PD-L1 >50% , HR 1.78 (1.08-2.91, p=0.022) and HR 1.74 (1.01-3.00, p=0.045) respectively .

Conclusions: Jordanian patients with EGFR mutated lung cancer treated with any TKI have long survival consistent with published literature. Liver metastasis at diagnosis and high PD-L1 expression were associated with worse survival. Access to third and newer generation TKI is critical

Keywords: Real world, low middle income countries, EGFR

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.54 Long-Term Outcomes From Pembrolizumab in Patients With Advanced PD-L1 =50% NSCLC and Poor PS: A Transformer-Based AI Approach

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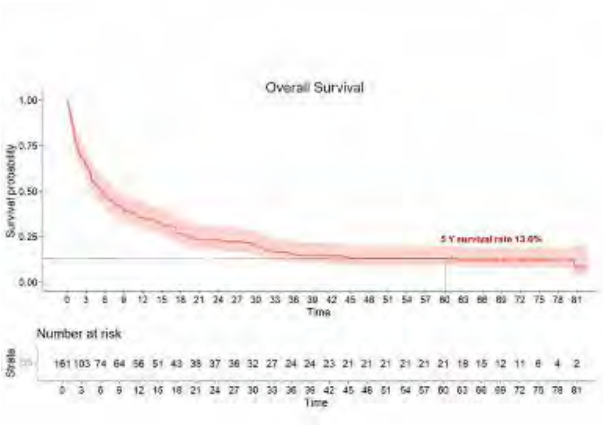
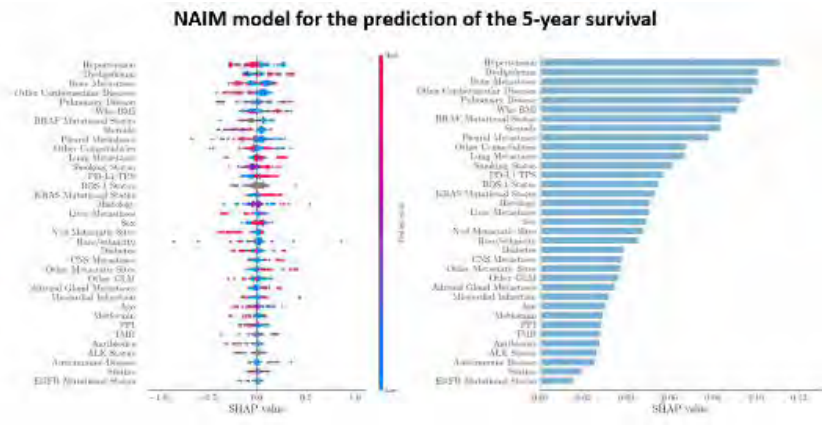
Introduction: The use of first-line single agent immunotherapy in patients with advanced NSCLC and ECOG PS ≥2 remains controversial, as this frail population has been largely excluded from pivotal clinical trials. Real-world evidence suggests that although median survival is poor, a subset of these patients may achieve long-term benefit.

Methods: We analyzed data from the Pembro-Real 5Y registry, a global real-world dataset with >5 years follow-up. The cohort included patients with advanced NSCLC, PD-L1 TPS ≥50%, treated with first line pembrolizumab outside of clinical trials. Univariable analyses were conducted to identify descriptive characteristics associated with survival. To address the complexity of long-term outcome prediction, we integrated Elastic Net regression and a transformer-based AI model (NAIM). The Elastic Net model was employed to mitigate collinearity and select relevant prognostic factors, while NAIM was used to explore non-linear, time-dependent interactions between variables. Endpoints included overall survival (OS) and 5-year survival rates.

Results: Out of 1050 patients, 161 patients with ECOG PS ≥2 were included, showing a median OS of 5.4 months (95% CI: 3.8-7.8), and a 5-year survival rate of 13.0% (95% CI: 8.1-19.9) (Figure). Univariable analysis indicated that no single baseline variable was associated with the 5-year survival, except for TMB (p=0.01), KRAS (p=0.01), and BRAF status (p=0.02), which were significantly limited by missingness. Elastic Net identified only two significant predictors of 5-year survival: high TMB (with unstable confidence intervals, OR 7.09×10^{8}, 95% CI: 0.00-∞ and KRAS mutation (OR 3.04, 95% CI: 1.08-8.27). NAIM provided a dynamic perspective, confirming that bone metastases and baseline corticosteroid use were strong predictors of early mortality, whereas BMI increase and systemic health markers/host factors (e.g., hypertension and dyslipidemia) gained importance in long-term survivors (Figure). However, NAIM exhibited a notable performance drop from training to validation suggesting overfitting and the challenge of modeling long-term outcomes using baseline static variables.

Conclusions: Despite the overall poor prognosis, a subset of patients with ECOG PS ≥2 achieves long-term survival with pembrolizumab monotherapy, indicating that performance status alone should not preclude treatment in all cases. Our analysis highlights the limitations of traditional statistical approaches and AI-driven models in predicting long-term benefit in this heterogeneous population. Future efforts should focus on refining hybrid modeling strategies and incorporating prospective validation to better identify those who may benefit from immunotherapy beyond short-term expectations.





Keywords: artificial intelligence (AI), Immunotherapy, Real world

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.55 Transforming Prognostication: A 5-Year Follow-Up Study to Unravel Prognostic Predictors Across Age Groups in NSCLC Using Transformer-Based AI

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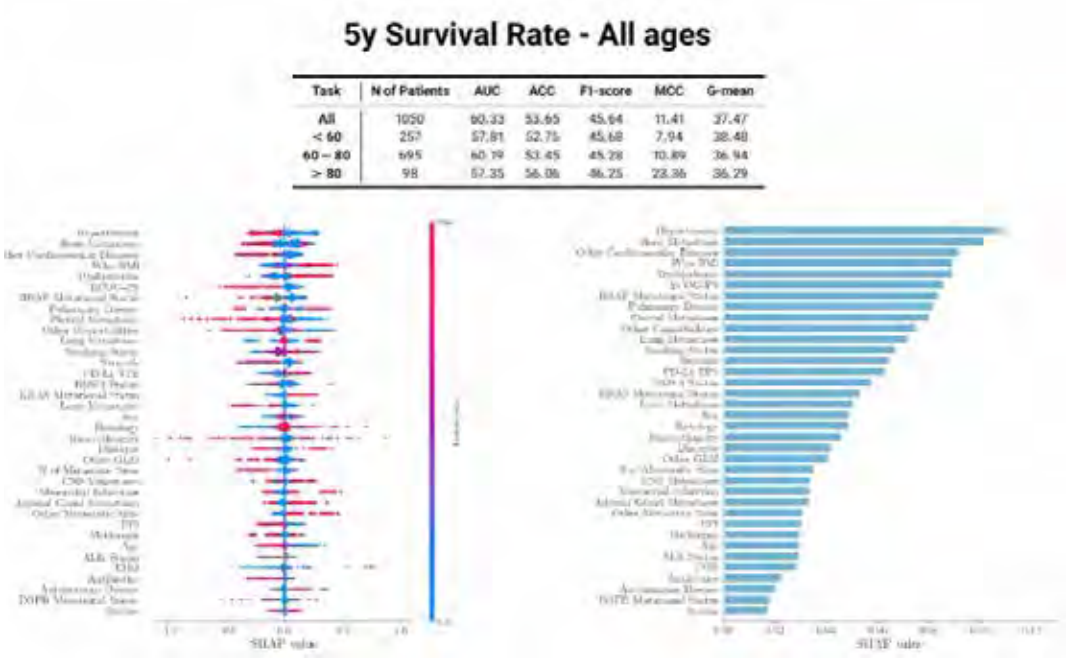
Introduction: Older adults patients represent a growing proportion of individuals with advanced NSCLC. Long-term survival in this population is particularly challenging to assess due to the complex interplay of aging, comorbidities, and immunotherapy outcomes. Traditional statistical approaches may fail to capture the granular effects of age and systemic health factors, underscoring the need for more advanced methodologies.

Methods: We analyzed data from the Pembro-Real 5Y registry, a global real-world dataset of 1,050 patients with advanced PD-L1 ≥50% NSCLC treated with first-line pembrolizumab across 61 institutions in 14 countries. The dataset features over 5 years of follow-up and includes 36 baseline variables. To identify predictors of overall survival (OS) and 5-year survival, we applied Elastic Net regressions with multiple imputation by chained equations (MICE) to account for missing data and collinearity. To enhance interpretability and better capture the nuanced role of age, we employed the NAIM approach, a novel transformer-based AI model capable of handling missing data without imputation. Model explainability was provided via SHAP values.

Results: Increasing age was significantly associated with a higher risk of death (HR 1.01, 95% CI: 1.00-1.02) and lower 5-year survival rate (OR 0.98, 95% CI: 0.97-0.99) in the Elastic Net regression model. In the NAIM analysis, which achieved an AUC of 60.5 ± 3.7 for 5-year survival and a C-index of 62.9 ± 2.1 for OS, SHAP values ranked age as the 7th most important variable for 5-year survival and the least important for OS among the 36 variables. When stratified by age groups (<60 years [n=249, 23.7%], 60-80 years [n=703, 67.0%], >80 years [n=98, 9.3%]), the prioritization of variables influencing OS was consistent across groups. Predictors such as poor ECOG-PS (≥2), exposure to steroids, bone metastases, male sex, higher BMI, and smoking status emerged as key factors. For 5-year survival, systemic health markers (e.g., absence of hypertension or cardiovascular comorbidities), dysmetabolic factors (e.g., dyslipidaemia, increasing BMI), and the absence of bone metastases dominated across all age groups. Notably, good ECOG-PS was the strongest predictor in patients aged >80 years.

Conclusions: This study emphasizes the importance of a multidimensional approach to long-term prognostication also in older adults with advanced NSCLC undergoing immunotherapy. The NAIM analysis underscored the diminishing standalone importance of age and highlighted the critical role of systemic health factors across all age groups. These findings advocate for comprehensive assessments that integrate functional status and comorbidities irrespective of chronological age.



Keywords: Artificial Intelligence (AI), NSCLC, Immunotherapy

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.56 Clinical Features and Outcomes of Lung Cancer in Young Patients

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Introduction: Lung cancer is the leading cause of cancer-related death worldwide and shows a tangible trend of rejuvenation. Nevertheless, data focusing on young patients with lung cancer is rare. This study aimed to present clinicopathologic characteristics and treatment outcomes of young patients with lung cancer.

Methods: Lung cancer patients less than 40 years old at the time of diagnosis were retrospectively collected between October 2021 to April 2024. Demographic data, clinical efficacy, gene profiles and survival outcome were collected during the treatment.

Results: 230 eligible patients were retrospectively collected, 111 males and 119 females, median age 37years old (range: 14-40years), and 83% of them were non-smoker. Most of the population were found stage IV disease (76.5%) or stage III disease (16.5%) at baseline, 15.7% of them were diagnosed during health examination, the others usually presented with nonspecific respiratory symptoms such as cough (41.3%), chest tightness (17.0%) and polypnea (12.2%). As for the histology, 80.9% were adenocarcinoma, 4.8% were squamous carcinoma, 5.2% were lymphoepithelioma, 2.2% were small cell carcinoma and 5.2% were other rare types. Most of the population were driver gene positive (74.8%), with 33.5% EGFR mutation, 25.2% ALK fusion, 5.7% ROS1 fusion, 3.9% RET fusion and 6.5% others. For EGFR sensitive mutant patients, the objective response rate (ORR) for first line EGFR-TKI was 61.67%, the median progression free survival (PFS) was 14.4months (95%CI: 10.1-18.7months), with 15.4months for 19del and 9.8months for L858R. For ALK fusion patients, the ORR for first line ALK-TKI was 73.10%, the median PFS was 22.0months (95%CI: 14.7-29.2months). For patients who received chemotherapy or chemotherapy plus immunotherapy as first line, the ORR was 31.40%, the median PFS was 10.1months (95%CI: 7.5-12.8months), with 9.7months for adenocarcinoma, 16.5 months for squamous carcinoma and 7.6months for other types of histology.

Conclusions: Young patients with lung cancer were presented with atypical symptoms and often diagnosed at advanced stage. Adenocarcinoma accounted for higher proportion and rare driver gene mutations were more common in young patients. The treatment outcome for young patients were similar with the overall population, but the PFS was obviously shorter for ALK fusion young patients.

Keywords: lung cancer, young patients, clinical features

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.57 Estimates of Clinical Endpoints in Matched Patients Between the French Cancer Cohort (FCC) and Durvalumab Stage III NSCLC Eap

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Introduction: Early Access Program (EAP) are an opportunity to document first use of innovative treatments in real-world settings. Since 2021, French HTA body has recommended a linkage of EAP with National Health Data System (NHDS), the French health claims database.

Objective: to investigate if FCC, an NHDS extract of patients (pts) with cancer, can substitute a follow-up EAP study to estimate Overall Survival (OS) and treatment duration; and to evaluate if time to first subsequent therapy or death (TFST) can be used as a Progression Free Survival (PFS) proxy.

Methods: Indirect deterministic linkage was performed between :1/ French EAP follow up study of locally advanced unresectable NSCLC pts who initiated durvalumab between Oct.1 2017 and Dec. 31 2018, and treated up to 12 months (n=342); 2/ pts from FCC who received durvalumab at time of EAP (n=666).

In FCC, clinical outcomes such as disease progression can only be approximated by reported healthcare consumptions. All endpoints were calculated from first durvalumab administration date and up to last pt contact for EAP, Nov.30 2020 for FCC. First and last administration dates were reported in EAP vs each injection in FCC.

Results: 278 matched pts were included in analyses (linkage rate=81.4%). Median [IQR] EAP follow up was 747.5 [550;822] days vs. 812.5 [545;895] days in FCC. Discordances were limited in first and last durvalumab administration dates between EAP and FCC: in 51 pts (18.3%) for first date and in 35 pts (12.6%) for last date (median difference FCC-EAP: 47 [28;83] days and -1 [-28;14] day respectively).

81/82 deaths in EAP were reported in FCC with death date equal +/- 1 day in 75 (91.5%). OS 1- year (87.1% in both sources) and 2-years (71% and 70.8%) rates in EAP and FCC fully overlap (Table 1).

Treatment duration was longer in EAP (median 328.5 [274;346] days vs 295 [242;323] days in FCC).

Although TFST in FCC is close to PFS in EAP at 2 years (Table 1), TFST rates are not consistent between the 2 sources (+21 events in FCC).

Conclusions: Estimates of OS are aligned between the 2 sources and confirm the interest to use NHDS to document OS in a real-world setting. EAP treatment duration can be underestimated in FCC since free-of-charge treatment like compassionate use are not recorded. No evidence was found to use TFST in NHDS as a PFS proxy. Studies with longer follow up will be needed for this evaluation.

Table 1

	OS		PFS	TFST	
	EAP	FCC	EAP	EAP	FCC
N° events / N° pts	82 / 278	87* / 278	140 / 278	122 / 278	143 / 278
Rate 1 year (%) [95% CI] $	87.1 [85.0-89.1]	87.1 [85.0-89.1]	63.2 [60.3-66.1]	70.5 [67.8-73.2]	68.7 [65.9-71.5]
Rate 2 years (%) [95% CI] $	71.0 [68.3-73.8]	70.8 [68.0-73.5]	51.5 [48.4-54.6]	56.9 [53.9-59.9]	52.8 [49.8-55.8]

*5 additional deaths in FCC due to longer follow up $: +/- survival standard error

Keywords: Early Access Program, NHDS, Stage III NSCLC

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.58 Real-World (RW) Study of Biomarker Testing Patterns Among Patients With Early-Stage Resected NSCLC in the United States

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Introduction: Molecular diagnostics are increasingly important for patients with resected early-stage NSCLC as trials have demonstrated improved survival with biomarker-targeted adjuvant treatments and neoadjuvant/perioperative chemoimmunotherapy. We evaluated biomarker testing patterns in the US setting using Flatiron Health data.

Methods: Patients with stage IB-IIIB (T3N2) NSCLC diagnosed during 2021-2023 who had surgical resection were included. Biomarker testing rates (EGFR, ALK, and PD-L1), time from diagnosis to test date, turnaround time (time from test date to results) and time from biomarker test results to adjuvant treatment were evaluated overall and by stage and sociodemographic characteristics (age, gender, region, socioeconomic quintile [Q], and race).

Results: In this cohort (N=885), we observed increased molecular biomarker testing over time (1H2021: EGFR 62% ALK 54% vs. 2H2023: EGFR 77% ALK 69%) (p<.05). However, only 26.7% were tested prior to surgery. Neoadjuvant testing rates were stable during the study period (1H2021: EGFR 21% ALK 21% PD-L1 26% vs. 2H2023: EGFR 20% ALK 17% PD-L1 26%). Patients in the West were more likely to receive neoadjuvant PD-L1 (40.0%) tests versus the South (PD-L1: 22.8%), Midwest (PD-L1: 17.6%), and Northeast regions (PD-L1: 21.3%) (p<.05). Higher proportions of patients in the highest socioeconomic quintiles received PD-L1 tests (Q4/Q5: 78.9%) versus the lowest quintiles (Q1/Q2: 66.7%) (p<.05). Stage IIIB patients were more likely to receive EGFR (79.3% vs. 64.4%), ALK (75.9% vs. 48.3%), and PD-L1 (89.7% vs. 73.8%) tests following diagnosis versus Stage IB (p<.05). We saw numerically shorter times from diagnosis to biomarker testing for Black (11.4 days) versus White (20.5 days) and Hispanic/Latino (21.8 days) patients and those in the top 2 socioeconomic quintiles (Q4/Q5: 16.2 days) versus the lowest quintiles (Q1/Q2: 24.8 days). Among patients receiving adjuvant treatment (539/885), 90.5% received at least one test prior to treatment. Testing was highest for PD-L1 testing (82.2%), followed by EGFR (79.8%), and ALK (67.9%). Most EGFR tests were conducted using next generation sequencing (NGS) (85.9%) while ALK relied on NGS (59.4%) and FISH (30.5%). Turnaround times for EGFR tests administered before adjuvant treatment were shorter for PCR (28.6 days) versus NGS (45.3 days) (p<.05) and shorter for FISH (32.1 days) versus NGS (50.6 days) for ALK (p<.05). However, NGS tests for EGFR and ALK had shorter times from results to adjuvant treatment compared to other testing methods. Turnaround times for any biomarker were numerically shorter for Stage IIIB (31.9 days) vs. IB (43.6 days).

Conclusions: We found lower rates of PD-L1 testing and longer times from NSCLC diagnosis to biomarker test dates in patients in the lowest two SES quintiles. Biomarker testing was more prevalent and with shorter turnaround times in stage IIIB versus stage IB, and shorter for PCR/FISH testing versus NGS. We observed low rates of biomarker testing in the neoadjuvant setting. Significant regional differences were observed with the West having higher neoadjuvant PD-L1 testing rates. Improving turnaround times in NGS testing and understanding reasons behind socioeconomic disparities are keys to better biomarker testing outcomes in early stage NSCLC.

Keywords: Neoadjuvant biomarker testing, Adjuvant treatment, EGFR-mutated resected NSCLC

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.59 Real-World Uptake of Immunotherapy for Stage III-IV Non-Small Cell Lung

Cancer: Insights From the National Cancer Database (2016–2021)
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Introduction: The introduction of immune checkpoint inhibitors (ICIs) has transformed treatment for Stage III-IV lung cancer, yet real-world adoption and access remain unclear. Landmark trials, e.g., KEYNOTE-024 (2016), PACIFIC (2017), and CheckMate 227 (2019), established ICIs as standard of care in various non-small cell lung cancer (NSCLC) settings. We examined trends and variations of immunotherapy utilization using the National Cancer Database (NCDB), a hospital-based registry capturing >70% of new U.S. cancer cases.

Methods: This retrospective study included patients diagnosed with Stage III-IV NSCLC between 2016 and 2021. The primary outcome was receipt of immunotherapy. Trends were evaluated by diagnosis year. We fit multivariable logistic regression models to assess demographic, socioeconomic, and facility-level factors associated with immunotherapy use.

Results: Of 130,328 NSCLC patients, immunotherapy use rose from 10% in 2016 to 41% in 2021. The largest increase occurred between 2016 and 2019, aligning with major clinical trial results and guideline changes. However, only 41% of patients received immunotherapy in 2021, raising concerns about adoption barriers extending beyond clinical contraindications or biomarker exclusions. In multivariable analysis, patients treated at academic centers had higher odds of immunotherapy receipt (OR: 1.07, 95% CI: 1.06-1.09). Compared to non-Hispanic White patients, the odds of immunotherapy receipt were lower among Black (OR: 0.92, 95% CI: 0.90-0.94), Hispanic (OR: 0.76, 95% CI: 0.73-0.79), and Asian/Pacific Islander (OR: 0.67, 95% CI: 0.65-0.70) patients. Privately insured patients had greater odds of immunotherapy receipt than Medicaid enrollees (OR: 1.16, 95% CI: 1.13-1.20), while the odds were lower for Medicare enrollees (OR: 0.86, 95% CI: 0.84-0.88) or those uninsured (OR: 0.76, 95% CI: 0.72-0.80). Higher-income quartiles were associated with greater odds of immunotherapy use (OR: 1.03, 95% CI: 1.00-1.06); areas with higher high school non-completion rates had reduced odds (OR: 0.82, 95% CI: 0.79-0.84). Compared to metro residence, rural (OR: 1.10, 95% CI: 1.05-1.16) or urban (OR: 1.04, 95% CI: 1.02-1.06) residence was associated with greater odds of immunotherapy use. Female patients had lower odds of receiving immunotherapy than males (OR: 0.95, 95% CI: 0.94-0.97).

Conclusions: In this large national cohort of Stage III-IV NSCLC patients, immunotherapy utilization increased substantially between 2016 and 2021. However, real-world delivery continues to lag behind clinical expectations, with fewer than half of patients receiving recommended ICIs in recent years. Uptake varied across socioeconomic and demographic factors, underscoring the need for targeted efforts to close treatment gaps and ensure equitable access to immunotherapy in lung cancer care.

Table. Rates of Immunotherapy Use and Associated Characteristics in Patients with Stage III-IV NSCLC

Year	Immunotherapy Use, N (%)	OR (95% CI), p	Characteristic	Comparison	OR (95% CI), p
2016	7,647 (10%)	Reference year	**Facility Type**	Academic vs. Non-Academic (ref.)	1.07 (1.06–1.09), p<0.001
2017	15,697 (21%)	2.32 (2.25–2.39), p<0.001	**Race/Ethnicity**	Black vs. White (ref.)	0.92 (0.90–0.94), p<0.001
				Hispanic vs. White	0.76 (0.73–0.79), p<0.001
				Asian/Pacific Islander vs. White	0.67 (0.65–0.70), p<0.001
2018	24,163 (34%)	4.59 (4.46–4.72), p<0.001	**Insurance Type**	Private vs. Medicaid (ref.)	1.16 (1.13–1.20), p<0.001
				Medicare vs. Medicaid	0.86 (0.84–0.88), p<0.001
				Not Insured vs. Medicaid	0.76 (0.72–0.80), p<0.001
				Other Government vs. Medicaid	0.82 (0.78–0.87), p<0.001
2019	28,854 (40%)	6.08 (5.91–6.25), p<0.001	**Median Household Income Quartiles**	≥$74,063 vs. ≤$46,277 (ref.)	1.03 (1.00–1.06), p=0.046
2020	26,465 (41%)	6.34 (6.16–6.52), p<0.001	**Percent High School Non-Completion**	≥15.3% vs. <5% non-completion (ref.)	0.82 (0.79–0.84), p<0.001
2021	27,502 (41%)	6.53 (6.34–6.71), p<0.001	**Location**	Rural vs. Metro (ref.)	1.10 (1.05–1.16), p<0.001
				Urban vs. Metro	1.04 (1.02–1.06), p<0.001
			Sex	Female vs. Male (ref.)	0.95 (0.94–0.97), p<0.001

Keywords: Immunotherapy, NSCLC, Real-world outcomes

P1.17.60 Characterizing Multi-Timepoint Lung Cancer Progression With Dynamic Bayesian Network, Structural Equation Modeling and Random Forest Model

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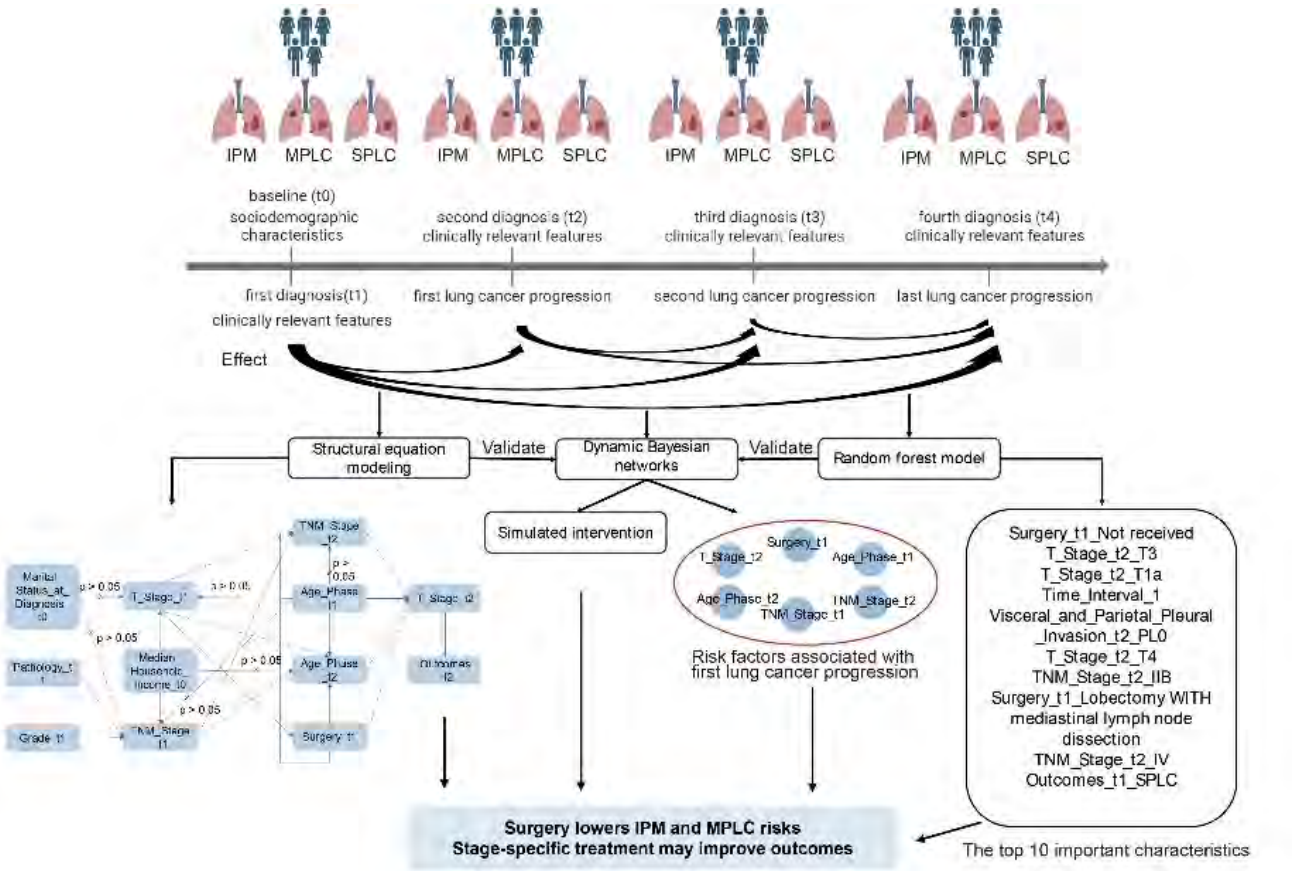
Introduction: Although significant advances have been made in lung cancer treatment, post-treatment disease progression including intrapulmonary metastasis (IPM), multiple primary lung cancer (MPLC), and single primary lung cancer (SPLC), remains common. This study aims to investigate how clinical and sociodemographic factors influence lung cancer progression and to evaluate the effects of different surgical and systemic treatment approaches on subsequent disease outcomes.

Methods: Lung cancer patients with at least two recorded visits in SEER (2000-2019) were included. Dynamic Bayesian networks (DBNs) identified key temporal relationships among baseline (t0), first (t1), second (t2), and third (t3) diagnoses. A simulated intervention (SI) was performed by fixing the DBN structure and modifying surgical/systemic therapy scenarios to calculate hazard ratios (HRs) for IPM, MPLC, and SPLC. Structural equation modeling (SEM) and random forest were used to validate the DBN findings.

Results: Of the 3,450 patients, 337 experienced IPM, 24 had MPLC, and 3,089 had SPLC as their first lung cancer progression. Baseline analysis revealed significant group differences in TNM stage, treatment details, grade, and pathology. The DBN highlighted T_Stage_t2, Surgery_t1, Age_Phase_t1/t2, and TNM_Stage_t1/t2 as key factors for first disease progression. Segmentectomy did not significantly alter progression risk relative to lobectomy with mediastinal lymph node dissection (MLND) or wedge resection ($p > 0.05$). Compared to wedge resection, lobectomy with MLND lowered IPM risk while increasing SPLC risk in disease progression [HR of IPM: 0.7513 (95% CI: 0.6176-0.8988); HR of SPLC: 1.0299 (95% CI: 1.0101-1.0530)]. In stage I patients, lobectomy reduced MPLC risk compared to no surgery in disease progression [Stage IA+IB: 0.4781 (95% CI: 0.2257-0.8098)], though this was not observed in stage II or later ($p > 0.05$). Chemotherapy and radiotherapy also influenced progression, increasing the risk of IPM compared with none-chemotherapy and none-radiotherapy group [Chemotherapy: 1.2681 (95% CI: 1.1908-1.3503); beam radiation: 1.3850 (95% CI: 1.2440-1.5480)] and MPLC [Chemotherapy: 1.1741 (95% CI: 1.0676-1.3029); beam radiation: 1.2617 (95% CI: 1.1026-1.4550)] while decreasing SPLC risk [Chemotherapy: 0.9692 (95% CI: 0.9602-0.9773); beam radiation: 0.9582 (95% CI: 0.9408-0.9728)]. SEM validated core pathways, and random forest identified Surgery_t1_Not received and T_Stage_t2 as key predictors for first disease progression.

Conclusions: This study emphasizes the role of surgery, tumor staging, systemic therapy, and their timing in lung cancer progression. By leveraging multi-timepoint data and advanced modeling, we can explore strategies to mitigate high-risk progression events, such as IPM and MPLC, thereby supporting stage-specific personalized treatment approaches to optimize patient outcomes.



Keywords: Lung cancer progression, Dynamic Bayesian network, Simulated intervention

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.61 Rebiopsy in Oncogene-Driven Lung Cancer: Real-World Practices in ALK, EGFR, and ROS1 Cohorts in the Australian AURORA Longitudinal Cohort Study

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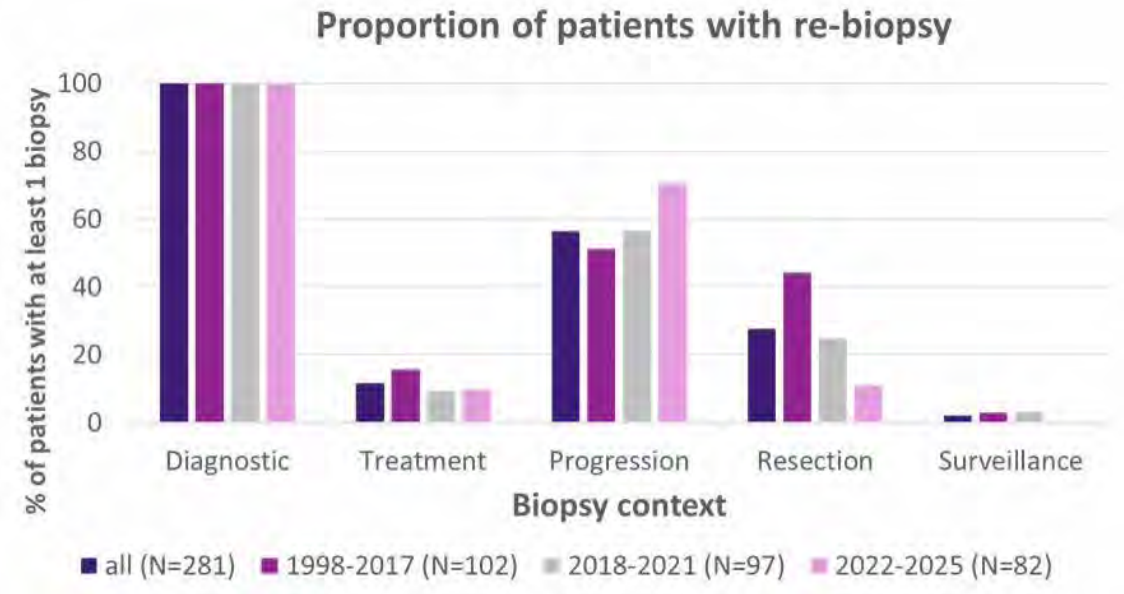
Introduction: Targetable mutations including EGFR, ALK, and ROS1 have expanded advanced NSCLC treatment options. However, identifying genomic drivers of progression remains challenging, with re-biopsies crucial for detecting resistance mechanisms and guiding therapy. Real-world practice is unclear. We examined re-biopsy patterns in EGFR, ALK, and ROS1 NSCLC at an Australian cancer centre using data from the AUstralasian thoRacic cancers lOngitudinal cohoRt study and biobAnk (AURORA, ACTRN12625000038493).

Methods: This retrospective real-world study used AURORA data from Peter MacCallum Cancer Centre. Eligible patients were enrolled before 14Feb2025, with diagnosis of EGFR, ALK, or ROS1 NSCLC. Focussed on current treatments within a manageable cohort size, EGFR was limited to patients receiving first-line osimertinib. No treatment-based eligibility was applied to ALK/ROS1 cohorts. All biopsy types were included, noting liquid biopsies were unfunded and accessed through trials. Biopsy characteristics (sample type, frequency, and context—diagnostic, resection, on-treatment, progression, or surveillance) were analysed over time. Treatment lines and local therapies were reported to contextualise re-biopsy patterns. Data were extracted from AURORA, updated via medical record review, and analysed using descriptive statistics and visualised by Swimmer plot.

Results: This analysis included 622 biopsies from 281 patients: 141 ALK+, 105 EGFR+, and 35 ROS1+. The median biopsies per patient was 2 (range 1-9). All had a diagnostic biopsy (326 total), with 28% at resection (95 biopsies), 12% on-treatment (47 biopsies), 56% at progression (144 biopsies), and 2% for surveillance (10 biopsies). Most were tissue biopsies (N=388, 62%), with fewer cytology samples (N=224, 36%) and limited liquid biopsies (N=10, 2%). Re-biopsy at progression increased over time from 51% to 70%, p=0.04 (Figure 1). Among EGFR+ first-line osimertinib patients, 16% (17/105) had prior early-stage treatment. In subsequent lines, 23% (24/105) received EGFR-targeted therapies, including 19% (20/105) rechallenged with osimertinib, 22% (24/105) received chemotherapy, and 56% (59/105) radiotherapy. Among ALK+ patients, the most common first-line treatments were alectinib (26%, 37/141), crizotinib (24%, 34/141), chemotherapy (20%, 29/141), and lorlatinib (12%, 17/141). Across all lines, 38% (54/141) received ALK-targeted therapies, and 60% (84/141) radiotherapy. Among ROS1+ patients, first-line treatments included entrectinib (23%, 8/35), crizotinib (23%, 8/35), and chemotherapy (20%, 7/35). Across all lines, 80% (28/35) received ROS1-targeted therapies, and 51% (18/35) radiotherapy.

Conclusions: Treatment selection and sequences reflect new evidence and drug availability over the reporting period. Re-biopsy at progression increased over time with evolving evidence of benefit, increasing opportunities for personalised treatment selection. Improved access to funded liquid re-biopsy may further improve rates.



Keywords: rebiopsy, real-world, oncogene

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.62 Real-World Insights on Treatment Patterns and Outcomes in ROS1 NSCLC: An Australian Multicenter Study (AURORA)

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Introduction: ROS1-rearranged non-small cell lung cancer (ROS1 NSCLC) is a rare, yet clinically significant subset driven by oncogenic ROS1 fusions. While targeted therapies have transformed outcomes, real-world data on treatment patterns and survival remain limited. This consumer-informed analysis leverages the AUstralasian thoRacic cancers lOngitudinal cohoRt study and biobAnk (AURORA) to present one of the largest real-world ROS1 NSCLC cohorts, providing a comprehensive evaluation of patient characteristics, treatment approaches, and survival across multiple Australian hospitals.

Methods: Patients with ROS1 NSCLC diagnosed by fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS) enrolled in AURORA (ACTRN12625000038493) were included. Key outcomes included demographics, diagnostics, treatment patterns, and overall survival (OS). OS was estimated using Kaplan-Meier analysis and measured from ROS1 NSCLC diagnosis. The cohort continues to enrol as part of ongoing AURORA enrolment, with a final data cut on this analysis in June 2025 to enable multivariate modelling on clinical and molecular markers of treatment performance. This study is supported by the Kha Kiang Khoo Memorial Award, Lung Foundation Australia.

Results: Among 104 patients enrolled across 15 hospitals with ROS1 NSCLC diagnosed 2009-2024, median age was 56 years (range: 24-79), and 66% (69/104) were female. At diagnosis, 24% (24/104) had early-stage disease treated with curative intent, while 76% (80/104) presented with advanced/metastatic disease, including 14% (11/80) with brain metastases. Among early-stage patients, 54% (13/24) subsequently relapsed and received treatment for advanced disease. In the advanced treatment setting (93/104, 89%), the median number of treatment lines was 2 (range: 1-8). Most received one (32/93, 34%) or two (29/93, 31%) therapy lines, while 34% (32/93) underwent three-lines or more, including one patient with eight lines. ROS1-directed therapy was given first-line in 72% (67/93) and at any line in 96% (89/93), accounting for total 239 lines of ROS-1 therapies. Entrectinib (31/93, 33%) and crizotinib (23/93, 25%) were the most common first-line targeted agents. Across all lines, entrectinib (35/93, 38%) and crizotinib (33/93, 35%) were frequently used, followed by lorlatinib (26/93, 28%), NVL-520 (24/93, 26%), repotrectinib (17/93, 18%). Clinical trial enrolment was 17% (16/93) at first line and 59% (55/93) overall. Median OS was 92 months (95%CI: 54-NR) in early-stage patients treated with curative intent (N=24). For those diagnosed with de-novo advanced/metastatic disease (N=80), median OS was 56 months (95%CI: 49-82). In the subgroup receiving first-line ROS1-directed therapy in the advanced disease setting (N=67), median OS was 56 months (95%CI: 49-92).

Conclusions: In this large real-world ROS1 NSCLC cohort, 72% received ROS1-directed therapy in the first line, and 96% at any line, with 59% enrolled in trials. First-line ROS1 therapy demonstrated a median survival of 56 months, comparable to PROFILE 1001 (51 months) and exceeding other real-world cohorts (24 months), likely due to reflex molecular testing, targeted therapy access, and trial prioritisation. This real-world data provides valuable insights into the longitudinal patient journey, outcomes with serial therapies, and the potential impact of treatment sequencing.

Keywords: ROS1, real-world, survival

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.63 Docetaxel and Docetaxel Plus Ramucirumab Demonstrate Similar Real-World Overall Survival: A Contemporary Analysis

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Introduction: In the US, docetaxel as a monotherapy or in combination with ramucirumab are standard treatment options for patients with NSCLC following disease progression on or after immunotherapy (IO) with or without platinum-based chemotherapy (PBC). In clinical trials, median overall survival (OS) was 9.1-12.5 months with docetaxel and 10.5 months with docetaxel plus ramucirumab. This study describes real-world clinical outcomes in patients with NSCLC who received docetaxel monotherapy or combined with ramucirumab following PBC and IO.

Methods: This retrospective study included patients from the nationwide Flatiron Health electronic health record-derived deidentified database who had advanced NSCLC and were treated with PBC and IO separately or in combination, followed by second-line or later docetaxel or docetaxel plus ramucirumab between January 1, 2011, and August 31, 2022. Real-world OS (rwOS) and real-world progression-free survival (rwPFS) were examined from docetaxel-containing therapy initiation to end of follow-up (February 28, 2023).

Results: Of the 1696 patients who received docetaxel or docetaxel plus ramucirumab, 1295 (76%) had nonsquamous histology, and 484 (29%) had an actionable genomic alteration (AGA). Median rwOS was 6.7 months (95% CI, 6.2-7.2) in the overall population; rwOS was similar with docetaxel (6.3 months [95% CI, 5.8-7.4]) and docetaxel plus ramucirumab (6.9 months [95% CI, 6.2-7.4]), regardless of histology or AGA status (Table). In the subgroup of patients with nonsquamous NSCLC and no prior taxane use, median rwOS was 7.3 months (95% CI, 6.6-7.8) and similar with docetaxel and docetaxel plus ramucirumab regimens. Median rwPFS was 3.5 months (95% CI, 3.2-3.7) in the overall population but shorter with docetaxel (2.8 months) vs docetaxel plus ramucirumab (3.9 months); median rwPFS outcomes were similar across histological subtypes and in the nonsquamous and no prior taxane subgroup.

Conclusions: For patients with advanced NSCLC receiving docetaxel or docetaxel plus ramucirumab in the second-line setting or later, rwOS is poor at approximately 6.7 months and similar with either regimen. Current treatment options are inadequate and there is a pressing need for novel therapies to improve patient outcomes.

	rwOS (95% CI), months; n			rwPFS (95% CI), months; n		
Population	Overall	Docetaxel	Docetaxel + ramucirumab	Overall	Docetaxel	Docetaxel + ramucirumab
All	6.7 (6.2–7.2); 1691	6.3 (5.8–7.4); 635	6.9 (6.2–7.4); 1056	3.5 (3.2–3.7); 1626	2.8 (2.7–3.2); 605	3.9 (3.5–4.1); 1021
Histology						
Squamous	5.6 (5.0–6.4); 400	5.6 (4.8–6.3); 146	5.8 (4.9–7.2); 254	3.2 (2.9–3.7); 385	2.7 (2.4–3.3); 136	3.7 (3.0–4.3); 249
Nonsquamous	7.1 (6.5–7.6); 1291	6.9 (6.2–8.0); 489	7.1 (6.5–7.7); 802	3.5 (3.2–3.9); 1241	3.0 (2.7–3.4); 469	4.0 (3.6–4.2); 772
Nonsquamous + no prior taxane use	7.3 (6.6–7.8); 1089	7.4 (6.2–8.2); 416	7.3 (6.5–7.9); 673	3.5 (3.3–3.9); 1048	3.1 (2.7–3.5); 398	4.0 (3.5–4.2); 650
AGA positive	7.6 (6.8–9.5); 482	7.4 (5.9–10.0); 176	7.6 (6.8–9.8); 306	3.8 (3.2–4.2); 460	2.8 (2.4–3.4); 165	4.2 (3.8–4.8); 295

Keywords: non-small cell lung cancer, real-world, docetaxel

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.64 Acinar Cell Lung Carcinoma: A Unique Subtype of NSCLC Adenocarcinoma,Insights From the AACR Project Genie Database

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Introduction: Acinar cell lung carcinoma (ACLC) is a rare subtype of non-small cell lung cancer (NSCLC), accounting for approximately 6.0% of cases. ACLC exhibits unique clinical and genetic characteristics compared to other NSCLC adenocarcinoma subtypes. This study utilizes data from cBioPortal and GENIE to evaluate and compare the molecular, clinical, and survival profiles of ACLC and adenocarcinoma lung cancer Not Otherwise Specified(NOS)

Methods: This retrospective cohort study analyzed 798 patients, including 109 with ACLC and 689 with adenocarcinoma not otherwise specified (NOS). Genetic mutation profiles, clinical characteristics (age, gender, stage, race, and organ involvement in stage IV disease), and overall survival (OS) in stage IV were compared. Statistical tests included chi-square for categorical variables and Kaplan-Meier survival curves with Cox proportional hazards modeling for OS analysis.

Results: The median age at diagnosis was significantly higher in ACLC (69.2 years) than in adenocarcinoma NOS (65.4 years; p = 0.002). Both groups were predominantly White (ACLC: 86.2%, adenocarcinoma NOS 79.6%) with no significant racial differences (p = 0.18). Females were more frequently diagnosed with ACLC (79.1%) compared to adenocarcinoma NOS (57.4%; p < 0.0002). ACLC was more often diagnosed at earlier stages (Stage I: 50% vs. 13%) and less frequently at Stage IV (28% vs. 72%; p < 0.0001). In stage IV, the organ involvement was similar between the groups. Median OS in Stage IV ACLC was 23.1 months (95% CI: 14.8-NA) versus 27.6 months in adenocarcinoma NOS (95% CI: 23.6-29.7; p = 0.5) Genetic analysis showed TP53 mutations were significantly less frequent in ACLC (43.33%) compared to adenocarcinoma NOS (56.5%; p = 0.007), while KRAS mutations were more common in ACLC (36.67% vs. 31.8%; p = 0.2). Among targetable mutations, EGFR (25.83% vs. 29.8%; p = 0.39), ALK (8.33% vs. 9.5%; p = 0.8), and ROS1 mutations were absent in ACLC but present in 5.51% of adenocarcinoma NOS (p = 0.006); RET (7.50% vs. 4.5%; p = 0.1), MET (10.83% vs. 7%; p = 0.19), NTRK1 (0.88% vs. 3.90%; p = 0.18), and BRAF (4.17% vs. 5.9%; p = 0.53) mutations were less common in ACLC.

Conclusions: Acinar cell lung cancer differs from lung adenocarcinoma NOS in several important aspects. Patients with ACLC are typically older, more often female, and diagnosed in earlier stages with similar survival in stage IV. It also has a distinct genetic pattern since ACLC has a lower incidence of TP53 and ROS1 with a comparable rate of other targetable mutations, so this suggests a unique subtype that needs further precise treatment.

Keywords: lung cancer, Acinar cell, lung cancer genetic

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.65 Age-Associated Incidence of Somatic Mutations and Survival Outcomes in Non-Small Cell Lung Cancer

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Introduction: In NSCLC, the incidence of driver mutations and their prognostic role related to age are poorly described, especially for young and longevous adults. This study aims to describe the molecular landscape and survival of patients of different ages with NSCLC.

Methods: 40,510 NSCLC specimens underwent DNA/RNA sequencing at Caris Life Sciences. Patients were stratified based on age at specimen collection into adolescent/young adults (AYA, <40 years, 0.6%), older adults (OA, 40-65 years, 37%), geriatric adults (GA, 66-79 years, 49%), and longevous adults (LA, 80+ years, 14%). Survival was calculated from claims data using Kaplan-Meier estimates with overall survival (OS) from sample collection to last contact. Multiple hypothesis corrections were made where applicable with q<.05 denoting significance.

Results: Sex did not differ between groups. Fewer AYA smoked or were Caucasian; Black race was less common with advancing age (q<.05; Table 1). Mutations in many tumor suppressor genes (TSG) were least common in AYA, peaked in OA, then declined in GA/LA (for example, TP53 mutation incidence was 52% in AYA, 71% OA, 66% GA, 60% LA; q<.05). The incidence of individual TSG mutations did not differ between AYA and LA except GNAS and NF1. GNAS was the only TSG that had highest incidence in AYA (3.1% vs 0.49% - 0.68% OA/GA/LA, q<.05). While the overall incidence of driver mutation was highest among AYA (67% vs 49-54%, q<0.05), specific alterations such as METex14 skipping and KRAS mutations (mimicking smoking history) were more prevalent among older age groups (q<.05; Table 1). EGFR mutations were equally incident across age; however, AYA had less frequent L858R (0% vs 17-33%) and more frequent Del19 (67% vs 33-41%, q<.05) mutations. OS declined with advancing age for driver-negative, BRAF+, and KRAS+ tumors. However, AYA OS was heterogeneous between driver groups, with longer OS (compared to LA) in ALK+ and driver-negative tumors but no differences in ERBB2 and EGFR mutations (Table 1). Interestingly, OA with Del19 had longer OS compared to OA with L858R (p<.05); this was not noted in other age groups.

Conclusions: AYA patients with NSCLC had more driver mutations and fewer TSG and RAS-pathway mutations than older patients. GNAS mutations have not previously been known to be associated with younger age. While increasing age is generally associated with shorter OS, there were substantial deviations from this trend, most notable in EGFR mutations.

Table 1: Demographics, driver mutation incidence, and overall survival by age cohort

		AYA (18-39 years)	OA (40-65 years)	GA (66-79 years)	LA (80+ years)
N		259	15014	19361	5606
Female sex		52.1%	49.6%	49.6%	49.5%
Never smoker		24.1%	5.4%*	7%*	7.9%*
Race	Black	18.9%	14.5%	12.2%*	8.6%*
	White	34.4%	51.0%*	74.5%*	79.3%*
	Asian	5.4%	3.3%	3.2%	3.6%
	Hispanic	11.6%	6.6%*	7.2%*	7.3%*
Driver mutation incidence	*EGFR*	14.3%	11.3%	11.0%	13.7%
	KRAS	13.1%	27.9%*	27.5%*	27.5%*
	ALK fusion	26.0%	3.0%*	1.2%*	1.0%
	BRAF	1.2%	3.8%	4.4%	4.3%
	RET fusion	3.0%	0.9%	0.6%	0.7%
	MET ex14 skipping	0%	0.7%	2.60%	6.4%*
	ROS1 fusion	3.9%	0.4%*	0.2%*	0.1%*
	ERBB2	5.4%*	1.7%*	1.4%*	1.6%*
Overall survival (months)	Driver-negative	21.1	18.4	15.1	10.4*
	Any EGFR	20.2	33.2*	34.1	22.1
	EGFR ex19del	20.1	35.5+	35.1+	23.2+
	EGFR L858R	--	31.3+	34.6+	20.7+
	KRAS	27.8	18.1	18.7	11.4
	ALK fusion	not reached	42.8*	68.1	40.0*
	BRAF	--	26.9	18.9	10.3
	RET fusion	--	39.4	43.7	19.5
	MET ex14 skipping	--	23.9	28.1	20.9
	ROS1 fusion	not reached	30.1	35.2	--
	ERBB2	--	21.9	29.6	15.0

-- = not reported if n<10.
* = p<.05 compared to AYA.
+= Cross-age comparisons not performed

Keywords: Age, Molecular, NSCLC

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.66 Impact of Concurrent Tissue and Liquid Comprehensive Genomic Profiling (CGP) on Receipt of First-Line (1L) Therapy in a NSCLC

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Introduction: With the growing array of targeted treatments for patients with advanced NSCLC (aNSCLC), molecular testing to inform 1L therapy selection has become a guideline-recommended practice. Liquid biopsy offers a pragmatic, non-invasive alternative with a faster turnaround time. We sought to examine the effect of concurrent tissue-liquid testing on 1L therapy selection and outcomes.

Methods: The US-based de-identified Flatiron Health-Foundation Medicine (FMI) clinico-genomic database (CGDB) was queried to assess the patterns of 1L biomarker testing (FMI and abstracted non-FMI central lab CGP providers) for NCCN-defined drivers for 3,005 patients diagnosed with denovo aNSCLC between 9/2020-9/2024 with ≥1 CGP test reported before 1L treatment. Tissue and liquid tests were classified as concurrent when both were ordered before the report date of either test, sequential if the first test was ordered before 1L and the second was ordered 1-60 days after the first report, and single testing if one test result reported before 1L and no second test was ordered within 60 days. Outcomes were summarized by real-world overall survival [rwOS], progression-free survival [rwPFS)], and time-to-next-treatment [rwTTNT] for the EGFR+ subset, a longstanding and well-defined actionable driver.

Results: Of 3,005 aNSCLC patients with a tissue or liquid CGP test reported before 1L therapy initiation, 565 (19%) had concurrently ordered tissue-liquid tests, 289 (10%) had sequentially ordered tests (73% liquid-first), 1,274 (42%) had tissue-only, and 877 (29%) had liquid-only testing. There were no significant differences in age, sex, practice type, socioeconomic status, or ECOG PS between cohorts. Concurrent testing was more likely to result in a driver+ report than sequential, tissue-only, and liquid-only testing (65% vs. 59% vs. 53% vs. 48%, p<0.01) and had the highest rate of 1L targeted therapy receipt (24% vs. 16-21%, p<0.01). Concurrent testing was also associated with a shorter time from the first CGP order to 1L treatment than sequential (24 vs. 28 days, p=0.009) and tissue-only testing (24 vs. 30 days, p<0.001) but was not significantly different from patients with liquid-only testing (24 vs. 23 days, p=0.20). Among driver+ patients, 76% of patients with concurrent testing started 1L therapy after receipt of both tissue and liquid reports vs. 37% of liquid-first sequential testing patients (p<0.01). Among EGFR+ patients, 1L-matched targeted therapy was initiated for 80% of concurrent (median 23 days post-first order) and 74% of liquid-first sequential (27 days post-first order) testing patients. In these patients, we observed longer rwOS (26 vs. 18 mos; HR 0.52; 95% CI 0.31-0.90; p=0.02), rwPFS (11 vs. 6.7 mos; HR 0.75; 95% CI 0.48-1.19; p=0.23), and rwTTNT (13 vs. 8.0 mos; HR 0.64; 95% CI 0.41-1.01; p=0.06) in patients with concurrent vs. liquid-first sequential testing.

Conclusions: In this large CGDB, patients with tissue and liquid CGP ordered concurrently or sequentially, higher rates of driver detection than those with a single test were observed. Patients with tissue and liquid CGP ordered concurrently also had a faster time to 1L start than sequential testing. Among EGFR+ patients, those with concurrent testing had superior outcomes than those with liquid followed by tissue CGP.

Keywords: Concurrent tissue liquid testing, Sequential testing, Outcomes

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.67 A Large-Scale Network Study on Impact of Immune Checkpoint Therapy in Metastatic Non-Small Cell Lung Cancer: The iCan mNSCLC Study-A-Thon

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Introduction: Immune checkpoint inhibitors (ICIs) have improved outcomes in clinical trials for metastatic non-small cell lung cancer (mNSCLC). However, evidence of the uptake, treatment, and effectiveness patterns of ICIs in real-world settings, particularly across diverse healthcare systems and populations, remains scarce. Real-world data (RWD) is vital to complement clinical trial findings. Yet, barriers such as data standardization, lack of networks, especially across borders, and privacy concerns hinder comprehensive global assessments.

Data harmonization to the OMOP common data model (CDM) and federated data analysis frameworks address these challenges by enabling standardized, large-scale analyses while maintaining patient privacy.In March 2025, a mNSCLC study-a-thon held in Helsinki brought together a multidisciplinary team from 21 sites and nine countries, from academic and industry data partners, with the primary objective to characterize patients with mNSCLC and evaluate shifts in treatment patterns and outcomes after introduction of ICIs.

Methods: This study-a-thon introduced an iterative, standardized data readiness and quality workflow for oncology studies. Each participating Data Partner executed a comprehensive lung cancer-specific Data Quality Assessment, followed by a corrective patching script executed individually on the OMOP database at each site, to ensure data interoperability and quality. The study cohorts included adult patients with NSCLC and no other cancer, diagnosed after January 1st 2015. Specific cohorts included patients with NSCLC and mNSCLC, as well as the subset that initiated standard-of-care systemic therapies for metastatic disease. mNSCLC regimens in each database were inferred from individual drug prescriptions using the open-source OHDSI ARTEMIS package. Key outcomes were overall survival, time to subsequent treatment, time to treatment discontinuation, and treatment-free interval.

Results: Fifty data partners completed the oncology data readiness assessment and 22 qualified for inclusion in a mNSCLC study-a-thon. Currently, 17 data partners are actively running the study package and results from 11 are available now. So far, 25,352 patients with NSCLC from Australia, Belgium, Finland, Germany, Spain, the UK, and the US are included in the study. Median age ranges from 65 years in the Roche WAYFIND-R (Basel) database to 72 years in Tampere University Hospital (Finland). The proportion of men ranges from 43% in DFCI (Boston) to 69% in IIS La Fe (Valencia). Median follow-up time in the NSCLC cohort is between 306 days in Wayfind-R and 642 days in Emory University (Atlanta). Detailed analysis for the different cohorts is ongoing and will be presented at the Conference.

Conclusions: Our experience from the iCAN mNSCLC study-a-thon demonstrates that high-quality, secure, reproducible, and scalable lung cancer RWE research is achievable and essential, setting the stage for future efforts.Given the complexity, specificity, and granularity required in oncology data, such as detailed histology and treatment episode abstraction, individual data sources rarely suffice to achieve robust sample sizes for meaningful inference. Standardized community-developed and -maintained methods, tools, and systematic quality assurance practices are critical to managing this complexity. Furthermore, intensive and structured collaborations, exemplified by the study-a-thon model, enable rapid iterative improvements and sustained engagement across multiple data partners.

Keywords: OMOP, Metastatic disease, Immune checkpoint inhibitors

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.68 Real-World Validation of Other Disease Morbidity After Lung Cancer Surgery Using a Japanese Database in Reference to JCOG0802/WJOG4607L

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Introduction: The JCOG0802/WJOG4607L phase III trial demonstrated that segmentectomy was superior to lobectomy in terms of overall survival (OS) for peripheral small non-small cell lung cancer. The difference in OS was attributed not to lung cancer-related deaths but rather to other causes, such as other cancers, respiratory diseases, and cerebrovascular diseases. The direct impact of surgery on morbidity of other diseases remains unclear. Postoperative morbidity from other diseases and subsequent hospitalizations may contribute to reduced activities of daily living (ADL) and shortened OS. Since studies comprehensively assessing the risk of non-cancer-related mortality and morbidity after lung cancer surgery are scarce, we utilized the JMDC database to analyze OS based on readmission rates due to other diseases after pneumonectomy.

Methods: JMDC, Inc. has created a database using data collected from health insurance societies in Japan, consisting of claims (including hospitalization, outpatient treatment and drug prescriptions), and health checkup results. Using the JMDC Receipt Database, We analyzed 3,349 cases of thoracoscopic lobectomy (lobectomy group) and 744 cases of thoracoscopic lung segmentectomy (segmentectomy group) for lung cancer between 2011 and 2021. Postoperative readmissions were classified based on ICD-10 criteria for the following conditions: pneumonia, congestive heart failure, ischemic heart disease, cerebral infarction, cerebral hemorrhage, arrhythmia, aortic dissection, valvular heart disease, and sudden death. Pneumonia-related readmissions were identified based on antibiotic use. Health checkup data, number of readmissions, and disease-specific overall survival (OS) were analyzed by surgical procedure.

Results: The patient cohort (n=4093) had a median age of 57 years, with approximately 60% being male. The median observation period was approximately two years. Pneumonia was the most frequent cause of rehospitalization (6.8%), followed by heart failure (3.5%), ischemic heart disease (3.2%), and stroke (1.6%). Although significant differences were observed in age, gender, observation period, and smoking history between the lobectomy and segmentectomy groups, no significant differences were found in health checkup data. Postoperative readmissions varied significantly by procedure: pneumonia (lobectomy: 7.4% vs. segmentectomy: 4.6%, $p<0.005$), heart failure (lobectomy: 4.0% vs. segmentectomy: 2.4%, $p=0.039$), and cerebral infarction (lobectomy: 1.9% vs. segmentectomy: 0.5%, $p=0.007$). The cumulative readmission rate was higher in the lobectomy group for pneumonia ($p=0.012$) and cerebral infarction ($p=0.0112$). The five-year OS analysis showed that rehospitalization for pneumonia, cerebral infarction, cerebral hemorrhage, aortic dissection, and sudden death was associated with worse OS regardless of the procedure ($p<0.001$ for all these conditions). Additionally, OS was significantly worse in the lobectomy group for heart failure ($p<0.001$), ischemic heart disease ($p=0.022$), and arrhythmia ($p=0.04$).

Conclusions: This study revealed that specific diseases had higher rehospitalization rates depending on the surgical procedure. Lung preservation through segmentectomy may have contributed to maintaining cardiopulmonary function, potentially preventing the progression of pneumonia and heart failure to a severity requiring hospitalization. Maintaining performance status (PS) after surgery is fundamental in cancer treatment. Our findings suggest that non-cancer disease-related hospitalizations may contribute to PS decline, ultimately impacting OS. Given that our study population was relatively young, the effect of hospitalizations on OS might be less pronounced than in an older population.

Keywords: Real-world data, Lung cancer surgery, Other disease morbidity

P1.17.69 A Real-World Study of Advanced ALK-Fusion NSCLC Patients Receiving First-Line ALK-TKI Therapy with Telehealth Care

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Introduction: To evaluate the impact of telehealth care on the efficacy and safety of patients with advanced ALK-fusion NSCLC undergoing first line ALK-TKI therapy.

Methods: Treatment-naïve ALK fusion-positive advanced NSCLC patients receiving first-line ALK-TKI therapy were enrolled in the WeDoc telehealth care system. Patient-physician communication regarding treatment and adverse events was facilitated via the WeDoc online platform. Progression-free survival (PFS) and adverse events (AEs) were compared among patients treated with different ALK-TKIs, including alectinib, brigatinib, and lorlatinib. Multivariate regression analysis was performed to identify factors influencing PFS and AE, including clinical and molecular characteristics, communication frequency, and adherence to telehealth care protocols.

Results: From June 2021 to September 2024, 174 advanced NSCLC patients treated with ALK-TKIs were enrolled in the WeDoc telehealth system across 15 Chinese hospitals. The cohort comprised 102 patients in the alectinib group, 40 in the brigatinib group, and 32 in the lorlatinib group. The objective response rates (ORRs) were 80.3%, 80%, and 78.9%, respectively. Median progression-free survival (PFS) was 31 months (30.9-NR) for alectinib, while PFS for brigatinib (14.4-NR) and lorlatinib (10.0-NR) remained unreached due to insufficient follow-up time. No significant differences in ORR or PFS were observed among the three groups. Multivariate regression analysis in the alectinib group identified adherence to WeDoc telehealth protocols and close doctor-patient communication as independent factors associated with prolonged PFS, without significant impact on side effects or patient-reported outcomes.

Conclusions: The use of WeDoc, a telehealth system, for managing advanced NSCLC patients on long-term ALK-TKI therapy in real-world practice is linked to prolonged PFS, warranting validation through future randomized controlled trials.

Variable	N	Multivariate analysis
		HR
Age (>57, ≤57)	51, 51	NA
Sex (M, F)	45, 57	
Pathology (Ad, Non-Ad)	73, 29	
TNM (III, IV)	11, 91	
Brain Meta (Yes, No)	14, 88	7.521'
Frequency of communication (High, low)	50, 52	0.297'
Execution of telehealth protocol (No, Yes)	42, 60	NA

Keywords: Real-World Study, Lung Cancer, Internet

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.70 Clinicomolecular Characteristics and Treatment Patterns in Stage IV NSCLC: A Retrospective Study From Southwestern Ontario

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Introduction: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality in Canada, with over half of patients diagnosed with advanced disease. Outcomes for Stage IV disease remain poor, with a 5-year survival rate of <10%. Recent advancements in treatment, particularly immunotherapies, hold promise for improving clinical outcomes. However, the real-world implementation and impact of these treatments remain uncertain. This is especially true for Southwestern Ontario, Canada, a region with a large, demographically diverse population and varying levels of healthcare access. Our study aims to evaluate emerging clinico-pathologic characteristics, treatment patterns, and clinical outcomes of this population in a real-world setting.

Methods: We conducted a retrospective chart review of serially registered adult patients diagnosed with Stage IV NSCLC at the London Health Sciences Centre, Ontario, Canada, between January 1, 2017, and December 31, 2020. Data on demographics, clinico-pathologic features, treatment characteristics, toxicity, progression, and survival were collected. Descriptive statistics were applied to demographic, treatment and clinico-pathologic characteristics. The data cutoff was May 4, 2024. The research protocol was approved by the local research ethics board.

Results: A total of 523 patients were included in the analysis. Median age was 69 years, approximately 50% male, and >85% current or former smokers. Adenocarcinoma was the most common histologic subtype (~70%). Autoimmune comorbidities present in <5% of patients. ALK mutations were identified in <3% of patients, while EGFR mutations in approximately 11%. Of those with known PD-L1 status, PD-L1 expression was negative in 30.4%, weakly positive in 31.2%, and strongly positive in 38.4%. PD-L1 status was unknown in 23.9% of patients. Of patients who received first-line systemic treatment, 31.2% received single-agent immunotherapy, 17.2% chemoimmunotherapy, 33.2% chemotherapy, and 18.4% molecularly targeted therapies. Of the entire cohort, 31.7% patients received palliative radiation alone, and 11.3% received no treatment. PD-L1 status was associated with treatment selection (Figure 1).

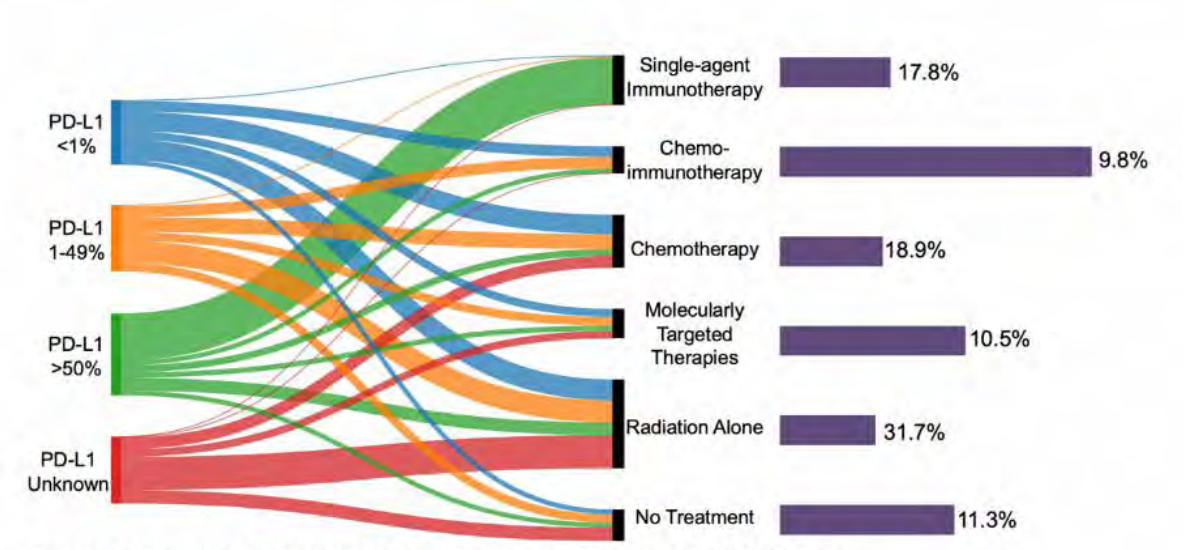

Figure 1: First-line treatment by PD-L1 status in Stage IV NSCLC

Conclusions: Lung cancer patients in Southwestern Ontario represent a distinct population. The prevalence of EGFR and ALK mutations mirrors rates seen in early-stage NSCLC in this region. Despite a high smoking rate (>85%), squamous cell carcinoma accounted for a small minority of patients. First-line treatment was influenced by PD-L1 status, reflecting knowledge translation efforts. Notably, about 40% of patients received palliative radiotherapy or no treatment, highlighting a significant segment of patients not being able to access available systemic therapy. Limitations include missing data and potential regional bias. Future research will assess clinical outcomes in this cohort.

Keywords: Lung cancer, Real-world data, Treatment patterns

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.71 Treatment Changes Over 12 Months of Observation for ALK and EGFR-Positive NSCLC - Results From an Real-World Study

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Introduction: It is important to understand patterns of and impact of treatment changes in patients outside of the clinical trial setting. While most patients with ALK or EGFR-positive NSCLC may derive substantial benefit from their first-line treatment, a group of patients require treatment switch within one year of starting treatment. Here, we sought to investigate participant-reported treatment change and its impact on physical functioning (PF) and quality of life (QoL) at the time of treatment change in a longitudinal real-world study.

Methods: We analyzed data from LUNGevity Foundation's longitudinal study on the experiences of people living with lung cancer (Project PEER). In this analysis, we focus on people who reported stage IV ALK (n=63) or EGFR-positive (n=92) NSCLC with at least one follow-up assessment (n=152). We compare those who also reported a treatment change (n=56) (defined as change in medication or change in dose) at any time during the 12-month follow-up period to those who did not (n=96). Patient-reported outcomes (PROs) included EORTC QLQ-C30 domains of PF and general health (GH)/QoL, a patient-reported performance status (PS) and overall side effect bother single items.

Results: • More participants with EGFR-positive lung cancer (42%) reported a treatment change than ALK (29%). • For the 56 participants who reported change, there were a total of 121 changes as more than one change could be reported. The most common reason for a change was disease progression (45% of changes) followed by side effects (21%). 27% of changes involved a dose change prior to a treatment switch. • No difference was noted on baseline performance status, PF and GH/QoL between participants with a treatment change and those without. • Among those with EGFR-positive lung cancer and reporting a treatment change (n=34): o 14% rated their overall side effect bother as "severe"/"very severe", however, 32% self-reported their performance status to be equivalent of ECOG PS 2/3.o Median PF and GH/QoL were 6.6 and 17 points lower (worse) respectively at time of a change of treatment than their scores at baseline. Variability throughout was observed (PF Figure 1).

Conclusions: Understanding how treatments are tolerated in patients outside of clinical trials is critical. These data provide a snapshot of how people experience 12 months of their treatment, with regularly collected PROs. It is important to use real-world data such as these, alongside clinical trial data, to better understand people's ability and desire to tolerate their treatment.

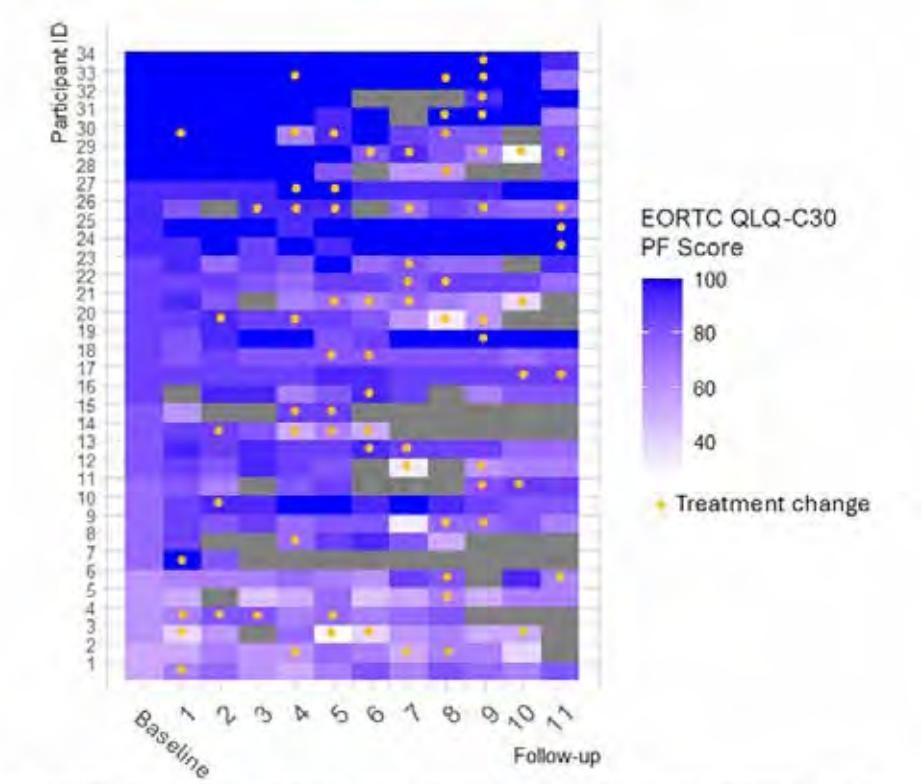

Figure 1. Heatmap of Physical Function (PF) reported monthly for 12 months for each participant with EGFR-positive NSCLC with a treatment change

Keywords: longitudinal data, physicial functioning, patient-reported outcomes (PROs

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.72 Clinical and Dosimetric Predictors for Post-Radiotherapy Lung Cancer Recurrence: A Model for Resource-Limited Settings

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Introduction: Optimizing post-radiotherapy surveillance for lung cancer recurrence is crucial, especially in developing countries where healthcare resources andup-to-date technology are limited. This study aims to create a predictive model integrating clinical and dosimetric factors to accurately enhance personalizedsurveillance and recurrence control in resource-constrained settings.

Methods: We retrospectively analyzed lung cancer patients treated with radiotherapy between 2018 and 2023. Clinical variables, tumor staging, and dosimetric parameters were evaluated to explore factors associated with survival, recurrence, and pulmonary toxicity and recurrence data were collected from clinical records. Logistic regression and AUC curve analysis were used to assess predictive factors and model performance.

Results: A total of 207 lung cancer patients were analyzed, with a median age of 66 years (range 29-92) and a balanced gender distribution. Smoking history was reported in 81,16 % of patients, and 56.04% were diagnosed at stage IV. The cohort included 191 NSCLC (92.3%) and 16 SCLC (7.7%) patients. Overall mortality was 24.6% (51 deaths), and recurrence occurred in 65,22% (133 of 207) of patients. SCLC patients showed unexpectedly higher survival rates (75.4%, 12 patients) and minimal recurrence (37,5%, 6 patients) compared to NSCLC patients (74,87% survival, 143 patients; 67,54% recurrence, 129 patients). This finding contrasts with existing literature, where SCLC typically demonstrates rapid recurrence and poor 5-year survival (<10%). Dosimetric analysis revealed a mean V5% of 9.01%, a mean V20% of 16.78%, a mean lung dose (MLD) of 1764 cGy, and a mean maximum dose (Dmax) of 4195 cGy." Patients with V20% >35% and MLD >2000 cGy had a significantly higher recurrence risk. Advanced cancer stage (III and IV) was significantly associated with recurrence (p=0.002). Patients with a history of smoking had a 3.2-fold higher recurrence rate compared to nonsmokers. Furthermore, higher Dmax values correlated with increased recurrence, highlighting the impact of radiation exposure on local tumor control. The predictive model achieved strong discriminative performance with an AUC of 0.83.

Conclusions: Integrating clinical and dosimetric parameters provides an effective and clinically relevant model for predicting recurrence following radiotherapy in lung cancer patients. In resource-constrained healthcare environments, such a model is instrumental in tailoring surveillance protocols, prioritizing high-risk individuals, and facilitating timely intervention. Implementation of this predictive strategy can substantially enhance recurrence detection, optimize healthcare resource utilization, and ultimately improve patient outcomes.

Keywords: Recurrence, Third World Countries, SCLC NSCLC

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.73 Misperception of Unintentional Weight Loss and Anorexia More Prevalent in Lung Cancer Among Other Solid Tumors in a Mexican Cohort

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Introduction: Cancer is a catabolic inflammatory disease that causes patients to often experience weight loss, or even cachexia in severe cases. Undernourishment in patients with cancer impairs the quality of life and therapeutic response, further leading to poor prognosis. Anorexia is seen in 30% of cancer patients, leading to reduced food intake or reduced nutrient absorption and, consequently, to a worsening of quality of life, as well as to increased morbidity and mortality. Unintentional pre-treatment weight loss, which can be a consequence of anorexia, is also associated with a worsening of functional capacity and tolerance to prognosis. Objective: To evaluate the prevalence of anorexia and weight loss at diagnosis (pre-treatment) in different solid tumors, and identify the frequency and factors associated with pre-treatment weight loss, and to determine the malnutrition risk in patients with advanced solid tumor diagnosis.

Methods: This was a prospective observational cohort study. Patients over 18 years old from the State Oncology Center of ISSEMyM, diagnosed with solid tumor, from April 1st 2019 to July 31st 2019, Once the informed consent was signed by the patient, the Malnutrition Screening Tool (MST) and NUTRISCORE nutritional screenings were applied. The patients were stratified by the presence/absence of anorexia and of pre-treatment weight loss, which generated a measure composed of four categories, which were the independent variables. Data analysis was performed with the statistical program SPSS 22. For descriptive analysis of qualitative variables, frequency and percentage distributions were used, while quantitative variables were described by measurements of central tendency and dispersion analyzed and compared using the two-way ANOVA test with a confidence level of 95%.

Results: The total sample consisted of 312 patients including cases of lung, breast, cervical, colorectal, ovarian and prostate cancer, which were the most prevalent diagnoses during the study period. The average age of the total sample was 57.94 ± 12.92 year old, Among the 312 patients included in the study, anorexia and pre-treatment weight loss were present in 37% and 38.5%, respectively. Most cases with involuntary weight loss are reported in the breast, cervical and colorectal cancer groups, however, 29% of patients with lung cancer report no know about lost while patients with other diagnoses have lower or no percentages of ignorance. However, although fewer lung cancer patients report not having lost weight involuntarily, 11.7% who lost weight were considered moderate to severe (11 or > 15 kg).Lung cancer was the tumor group with highest nutritional risk, followed by ovarian, cervical, colorectal, prostate and breast cancer, with significant differences p 0.000

Conclusions: Anorexia and pre-treatment weight loss appear to be relevant problems in patients with solid tumor but mainly in lung cancer with more severe grade even lung cancer patients misperceive them. Specific interventions are of crucial importance in individualized treatment plans, even within the context of palliative care.

Keywords: Lung cancer, weight loss, anorexia

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.74 Bridging Data Gaps in Brazilian Lung Cancer Surgery Care: The Evolution of the Brazilian Lung Cancer Registry (RBCP)

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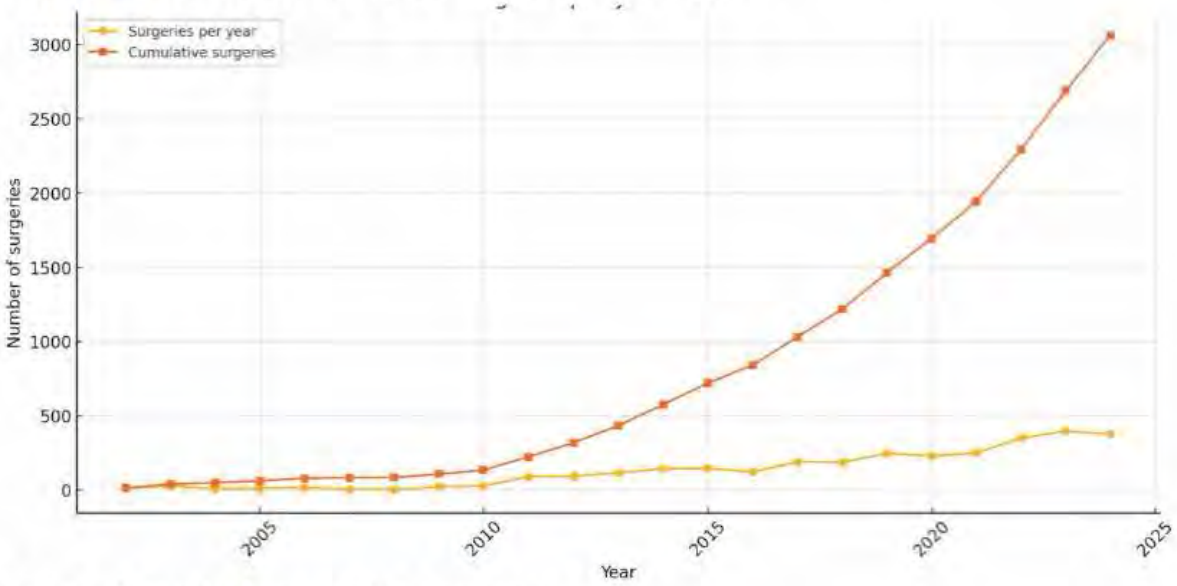
Introduction: Reliable data on lung cancer in Brazil are scarce. Existing sources offer basic epidemiology but lack detail on surgical quality and outcomes. To address this, the RBCP was created in 2014. Initially a state-level effort, it expanded into a national, multicenter clinical registry aimed at monitoring surgical practice and improving care. RBCP data also supported Brazil's contribution to the 3rd IASLC Lung Cancer Staging Project.

Methods: The RBCP collects standardized data on demographics, risk factors, procedures, complications, staging, treatment, molecular profile, survival, and recurrence. Hosted on REDCap, it relies on voluntary participation and trained local teams. Quality control includes real-time validation and periodic audits assessing completeness, consistency, and accuracy. As of 2024, data from 20 institutions were analyzed.

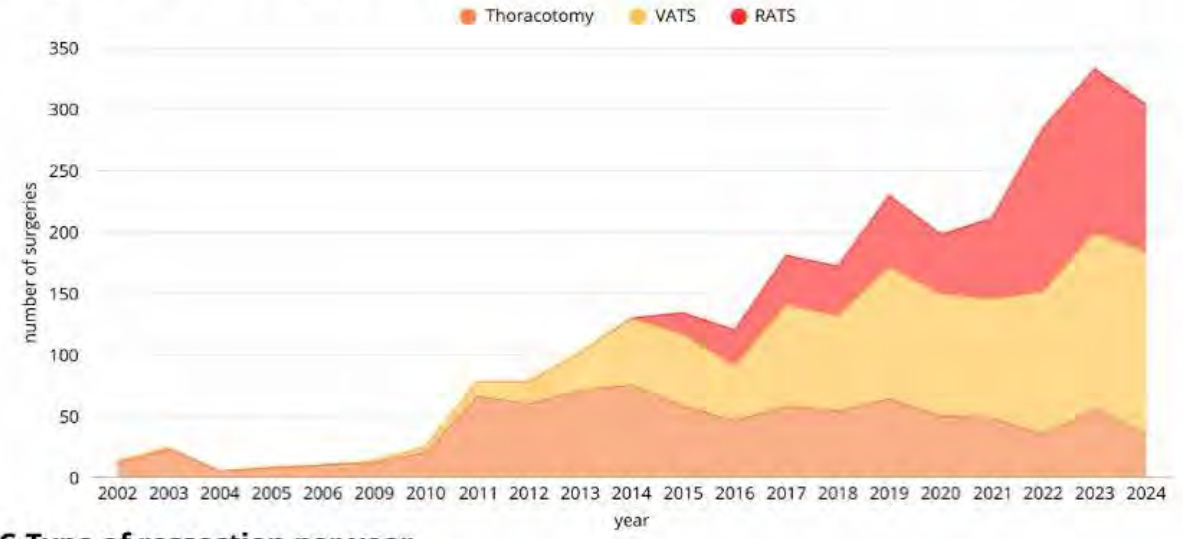
Results: By the end of 2024, 3,109 surgeries were recorded, with numbers rising steadily post-2015 (Figure 1A). Most patients were women (57.32%), with median ages of 62.8 (women) and 66.6 (men). Racial distribution: 80.95% White, 12.04% Mixed, 4.21% Black, 2.8% Asian. A smoking history was present in 60.2%. Comorbidities included hypertension (49.7%), coronary disease (9.3%), and COPD (33%). Surgeries were conducted via the public health system (43%) and private insurance (55%). Diagnosis was incidental in 47.4%, symptom-driven in 29.2%, during follow-up of other cancers in 15.7%, and via screening in 7.7%. Figure 1B illustrates a shift from thoracotomy to minimally invasive approaches—mainly RATS and VATS—reaching 88.8% in 2024. Figure 1C shows lobectomy as the main procedure, with a consistent rise in segmentectomies and wedge resections, indicating broader use of parenchyma-sparing techniques. Early-stage tumors predominated: IA1 (14.8%), IA2 (21.0%), IA3 (11.7%), IB (14.6%), and IIA (4.4%). Advanced stages included IIB (12.5%), IIIA (12.3%), and IIIB (2.3%). Molecular testing was available in 15.8%, with EGFR mutation most frequent (23%). Data quality analysis showed 83% completeness and 7% inconsistency.

Conclusions: The RBCP is an emerging source of oncologic thoracic surgery data in Brazil. It enables detailed evaluation of patient demographics, treatment trends, and clinical outcomes. The widespread adoption of minimally invasive and robotic techniques reflects modernization in surgical care. Ongoing quality assessment strengthens the reliability of the registry for research and policy. Despite being a non-funded, researcher-led initiative, the RBCP demonstrates the potential of structured databases to drive improvements in lung cancer care. However, the registry is still expanding and does not yet encompass all Brazilian states, reflecting both the country's vast geography and the need for broader institutional engagement.

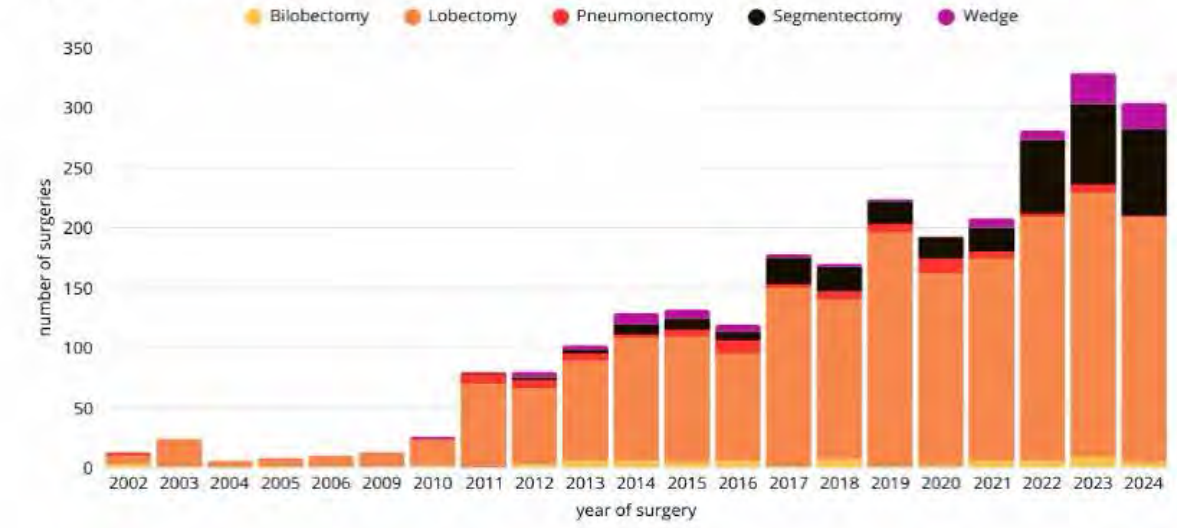
A- Number of surgeries per year and cumulative total



B- Type of surgical approache per year



C-Type of ressection per year



Keywords: Lung Cancer Registry, Real-World Data, data quality

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.75 Realizing Digital Transformation in Health: Findings From the TRANSITION Project

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Introduction: Technology has rapidly infiltrated many aspects of healthcare changing the landscape of cancer care in numerous ways across the disease continuum. Despite the potential of technology to impact cancer care it is pivotal that the drivers of such digital transformation, namely healthcare professionals (HCPs) and health managers need to achieve and maintain adequate levels of digital health literacy. This requires a specific set of digital skills of various levels of expertise that will allow them to assume roles in designing, developing, and utilising digital solutions as a means of high-quality and efficient services. The European Commission funded TRANSiTION Project was developed to support the EU Beating Cancer Plan through fostering up-skilling and reskilling in the context of digital health solutions for the oncology workforce.

Methods: The TRANSiTION training has been made primarily available to 14-European Member States. The project allowed recruitment through participating cancer centers and from eligible individuals. Eligible participants to the program met specific pre-defined requirements. Following the introduction of the training in the EU, the project has been globally released allowing participants to sign up for the training. The program has been comprehensively evaluated through the adoption of the CIPP Evaluation Model (Context, Input, Process, and Product) that included measurements before and after the training on the following: o Learning Objective Review Instrument (LORI). o Online Readiness Questionnaire for learners (provides feedback and readiness score). o Technology Acceptance Model (TAM v1) questionnaire to assess acceptability. o Post-Study System Usability Questionnaire (PSSUQ v3) for usability

Results: Over 1000 participants from over 53 countries have been recruited to the program, undertaking different learning pathways according to their specialty/profession. The analyses demonstrated statistically significant ($P < 0.05$) results of the training across all the assessment domains. Statistically highly significant results ($P < 0.001$) were recorded in terms of the impact of the training on the trainees' ability to introduce and utilized digital solutions in diverse clinical pathways across the cancer continuum.

Conclusions: There is a pressing need for comprehensive digital skill training for oncology healthcare professionals across diverse backgrounds and healthcare systems. Healthcare systems around the world undergo a digital transformation to facilitate the use of technology for innovative solutions to improve healthcare delivery and efficiency, to achieve improvement in medical problems and overcome consistent challenges posed by a growing need for healthcare services, a shrinking and burdened workforce and reduced funding. A smooth digital transformation requires an adequately prepared workforce that acts as the driver of implementation and sustainability. The findings provide evidence that designing digital skills training programs that support a holistic approach can significantly impact cancer care delivery across the disease continuum. Commitments on the policy, clinical practice, research and education fields are needed to increase the digital transformation preparedness of the oncology workforce. The overall work of the TRANSiTION Project serves as an innovative training programme in oncology that reflects the needs and preferences of HCPs and health managers.

Keywords: Digital skills training, technology, healthcare digital transformation

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.76 Facilities and Workforce Available for Thoracic Oncologic Care and Research in Nigeria, a Low-Middle Income Country (LMIC)

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Introduction: Advances in lung cancer diagnostics, staging and treatment have markedly improved outcomes, but also increase the complexity of care delivery, potentially worsening geographic disparities. Improved care and outcomes requires facilities, equipment and a skilled workforce. This can be particularly challenging in LMICs. We took a national inventory of material and human resources available for lung cancer care in Nigeria, a Sub-Saharan African country.

Methods: In February and March 2025, we surveyed tertiary care institutions categorized as Federal University Teaching Hospitals (FUTH), Federal Medical Centers (FMCs), State University Teaching Hospitals (SUTH) and Specialty Hospitals (SH). We inventoried available care delivery facilities, services and workforce at respondents' institutions, summarized data with standard statistical methods.

Results: We received responses from 38 institutions, including 21 of 33 (64%) FUTH, 7 of 24 (29%) FMCs, 4 SUTH and 6 SH, from 26 of 36 States (72%) and all 6 geopolitical regions (100%). Institutions had a median of 500 (IQR 300-670; range 10 - 1350) beds; 3 of 38 institutions (8%) were privately owned. A summary of the available facilities, services and workforce is summarized in Table 1. Strikingly, only 1 facility had a PET-CT scanner, EBUS was available at only 1 facility and no facility had genomic testing. Only 9 facilities had a linear accelerator. Nevertheless, most institutions had available specialists for care delivery. 31 of 41 respondents (76%) provided 67 responses detailing challenges to care delivery (Table 2); 39 (95%) respondents indicated interest in contributing patient-level data to an observational registry.

Conclusions: Despite nominally available facilities and a workforce, services for contemporary lung cancer care were limited. Affordability, lack of equipment, workforce inadequacies and delayed patient presentation were the most frequently reported challenges. Existing resources provide opportunity for partnerships to test corrective interventions.

Facilities Available	N (%)	Services Available	N (%)	Workforce Available	Median (IQR; Range)
Diagnostic radiology		Image-guided biopsy	26 (68)	Radiologists	6 (4-8; 0 – 20)
CT	29 (76)	Genomic testing	0 (0)		
MRI	18 (47)	Immunohistochemistry	12 (32)	Pathologists	2 (1-4; 1 – 8)
PET-CT	1 (3)	Bronchoscopy	26 (64)		
		EBUS	1 (3)		
		Fiberoptic	14 (37)		
		Rigid	18 (47)		
		Endobronchial therapy	2 (5)		
Treatment facilities					
Cardiothoracic surgery	33 (87)	Mediastinoscopy	3 (8)	Pulmonologists	2 (1-3; 0 – 9)
		Minimally invasive surgery	10 (26)	Thoracic surgeons	2 (1-3; 0 – 6)
				Medical oncologists	1 (0-4; 0 – 10)
				Radiation oncologists	1 (0-3; 0 – 10)
Chemotherapy infusion	34 (89)	Chemotherapy	34 (89)	Nurses	3 (0-8; 0 – 20)
Linear accelerator	9 (24)	Radiation therapy	11 (29)		
Cancer Registry	25 (66)			Onco-Pharmacists	2 (1-2; 1 – 4)
Hospital-based	21 (84)			Tumor registrars	0 (0-2; 0 – 8)
Population-based	5 (20)			Clinical trials staff	0 (0-0; 0 – 5)
Clinical trials infrastructure	12 (32)	Clinical trials	3 (8)		

Challenges to quality lung cancer care	N (% of 31 respondents)	# (% of 67 responses)
Lack of facilities/equipment	15 (48)	17 (25)
Workforce deficiency/manpower	11 (35)	12 (18)
Late presentation (patient)	11 (35)	12 (18)
Delayed/mis-diagnosis (clinician)	4 (13)	5 (7)
Cost (patient)	18 (58)	18 (27)
Funding (institution)	3 (10)	3 (4)
Poor record keeping/registry	3 (10)	2 (3)
Pathology services	6 (19)	6 (9)
Sociocultural problems/poverty/ignorance	2 (6)	2 (3)

Table 2. Challenges in lung cancer care delivery in Nigerian tertiary hospitals

Keywords: Geographic disparities, Lung cancer care, Global health services

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.77 Lung Cancer Consensus: Uniting for a Healthier World

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Introduction: As health professionals, ratify Bridging the Gap in the Diagnosis & Management of Lung Cancer, presented at International Lung Cancer Network (2023), Emirates Oncology Society Conference (2024), & Pan-African Conference on Lung Cancer (2025). This Consensus Statement outlines 5 core principles to guide health professionals, policy-makers, patient organizations, and stakeholders in improving global lung cancer outcomes:

1. Improve & expand prevention; 2. Focus on early detection; 3. Ensure equitable & sustainable access to treatment; 4. Build partnerships & promote investment; 5. Combat stigma, recognizing it as a social determinant of public health

Methods: Practices analyzed across Africa, Asia-Pacific, Gulf States, & Latin America using a benchmarking framework informed by WHO, OECD, and published literature. Findings discussed in regional expert panels and meetings. Our approach highlights barriers in knowledge, service delivery, access, & governance, underscoring the need for global ratification of the Consensus Statement to drive awareness, policy, & action.

Results: While good practices exist, no country excels across all principles:

1. Prevention: 24 of 29 countries studied are FCTC signatories, yet none have fully implemented its commitments. Only 4 have national agencies for tobacco control.

2. Early detection: National screening programs exist in Korea (2019), Croatia (2020), Taiwan (2022), and Australia (2025). Outreach gaps persist in 18 countries, particularly among marginalized groups, while 17 countries fail to address never-smokers' risks. In sub-Saharan Africa and Asia-Pacific lung cancer results more from solid fuel use than tobacco.

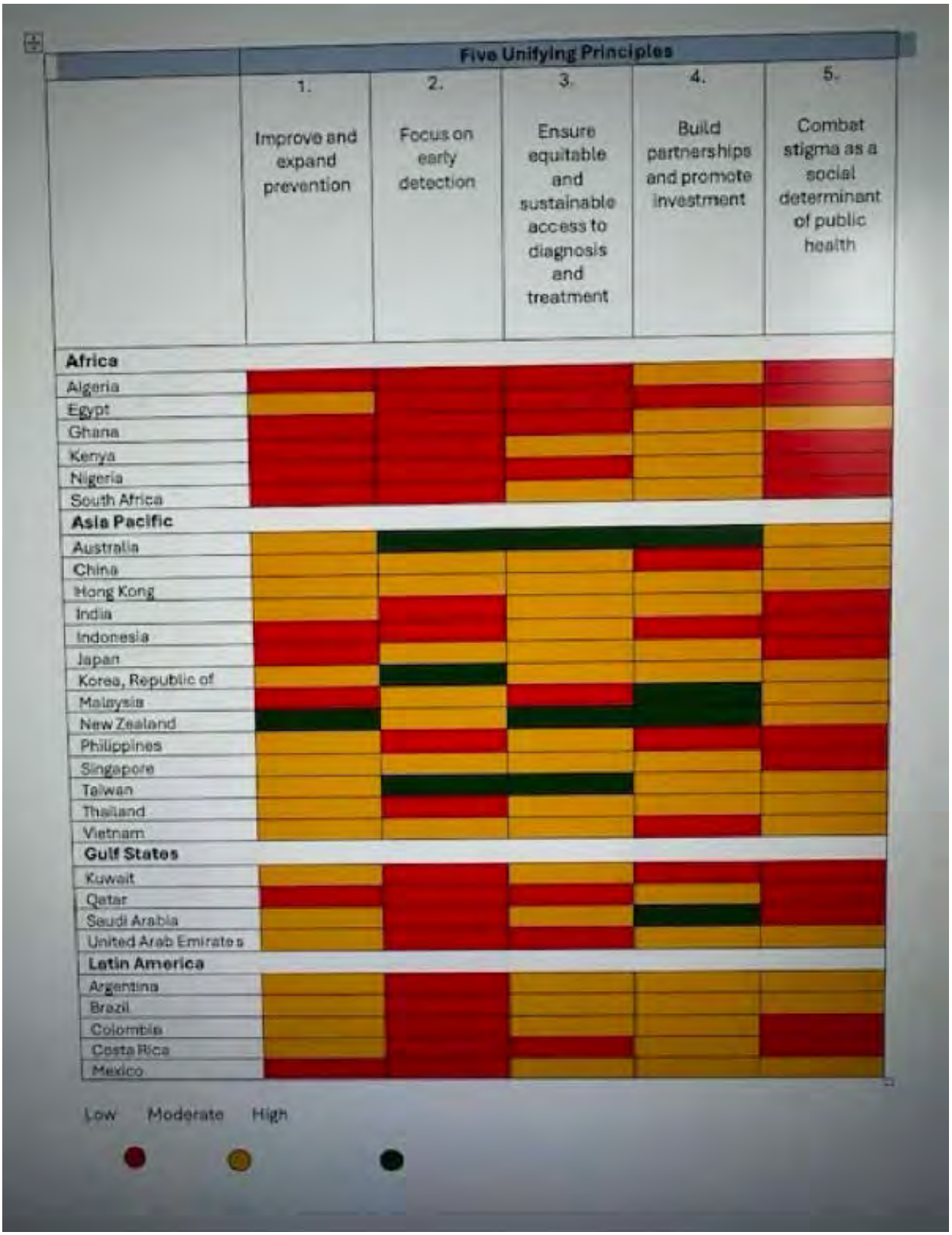
3. Equitable Access to Treatment: Of 17 countries with clinical guidelines, only 8 have updated them in the past 5 years, missing opportunities to fully align with best practices.

4. Partnerships: 14 countries have lung cancer-specific patient organizations. General cancer organizations exist in 25 countries, but they often lack a specific focus on lung cancer.

5. Stigma: Stigma remains pervasive, largely due to smoking's association with lung cancer. 14 countries have published literature recognizing this challenge. Destigmatization efforts help address unconscious bias across society & within healthcare settings.

These findings emphasize the urgent need for coordinated global action to close gaps in prevention, detection, treatment, investment, and stigma.

Conclusions: Despite progress, access remains inequitable. Disadvantaged populations, particularly in low-income countries, face disproportionately poor outcomes. Unifying global efforts through the Lung Cancer Consensus Statement can drive meaningful change, highlight opportunities for improvement & ensure those at-risk for and living with lung cancer receive the care they need. There is neither time nor room for complacency.



Keywords: global lung cancer consensus, lung cancer policies, improving lung cancer outcomes

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.78 Living Systematic Review Linked to Guidelines and Regulatory Approvals as a Treatment Decision Support Tool in NSCLCy

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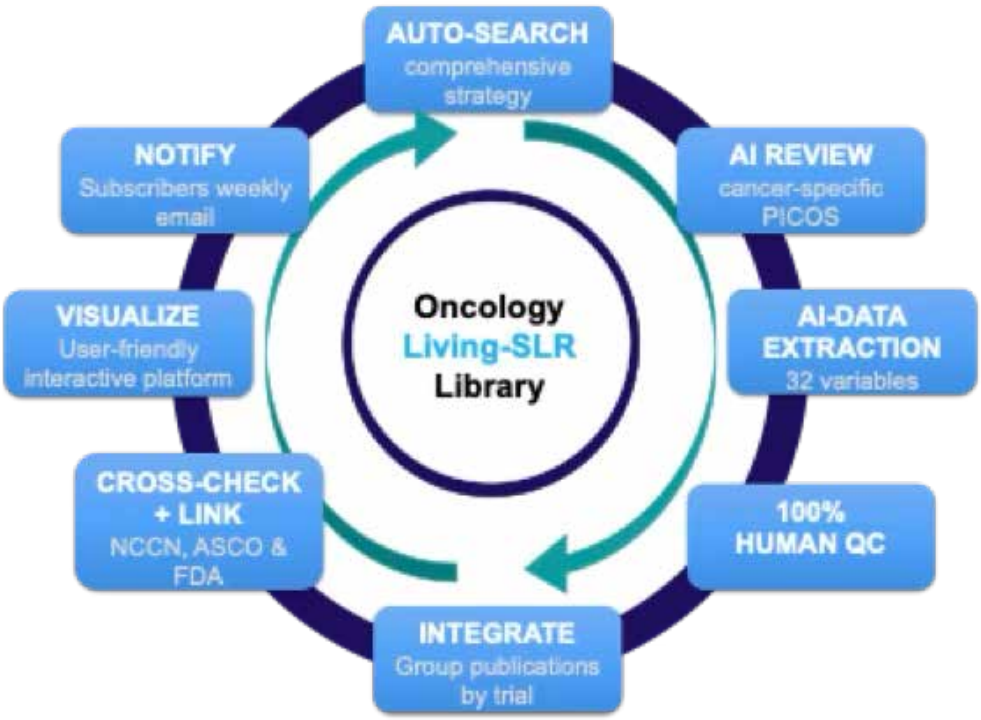
Introduction: A Systematic Literature Review (SLR) of interventional clinical trials in Non-Small Cell Lung Cancer (NSCLC) projects > 2,500 publications in 2025, alongside > 6 NCCN updates and numerous regulatory approvals. For oncologists with demanding schedules, staying updated is a challenge. A clinical data system integrating automated NCCN treatment paradigm with a real-time SLR, regulatory approvals, and ongoing trials can support evidence-based decisions. This study leveraged Artificial Intelligent (AI) and automation to create a comprehensive Decision Support Tool (DST) for NSCLC.

Methods: A Cochrane-compliant SLR protocol was automated for daily updates. A Large Language Model trained on > 20,000 annotated clinical trial records (across six cancer types, including NSCLC) extracted 32 variables per publication (e.g., TNM staging, histology, biomarker, risk factors, treatment line, interventions, interventions; randomization, study phase and sample size; analysis type, follow-up period; reported outcomes (median and landmark overall survival (OS), progression-free survival (PFS) and other progression measures, response data, quality of life); subgroup analyses, safety/toxicity). Extracted data were standardized and integrated with established guidelines treatment paradigm. A software tool was built to filter this database, linking treatment pathways to real-time SLR, FDA approvals, and ongoing clinical trials.

Results: The real-time SLR identified 110 interventional NSCLC trial publications, of which 356 were since January 2024. In a test-case query for treatments in NSCLC patients with EGFR alterations, 114 studies were identified in < 1 minute. Of these, 62 focused on post-TKI progression with 39 reporting on Phase 2 or 3 studies. Fourteen randomized controlled studies investigated nine Immune checkpoint inhibitors, two antibody drug conjugates, and three targeted therapies. Two studies showed significant OS, and 5 studies showed significant PFS improvement vs. comparators, of which only one study was included in NCCN guidelines. Traditional SLR would require 3 weeks and multiple researchers to achieve similar results.

Conclusions: By selecting key patient criteria (e.g., biomarkers, metastatic stage, treatment path), our Decision Support System links real-time clinical data to established guidelines. Implementation in clinical practice could enable oncologists to make timely, informed decisions, potentially improving patient outcomes.



Keywords: Living Systematic Review, Decision Support Tool, NSCLC

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.79 Assessing Radiotherapy Access and Patient Experience in Lung Cancer Treatment:A Survey on Financial and Logistical Challenges

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Introduction: Lung cancer treatment is complex and typically involves multiple modalities. Radiotherapy, uniquely applicable across all disease stages, plays a crucial role in the treatment spectrum. While the medical efficacy of radiotherapy is well-documented, there is a lack of comprehensive assessment regarding patient perspectives and overall treatment experiences. This audit seeks to evaluate patient-related factors comprehensively, focusing on understanding patient satisfaction, and access to radiotherapy, and identifying areas for potential improvement.

Methods: A cross-sectional survey was conducted involving 252 lung cancer patients receiving radiation treatment at PGIMER, Chandigarh, India. Data were collected through structured questionnaires capturing various aspects of their journey including demographics, facility accessibility, waiting times, travel and accommodation issues, financial burden, and satisfaction levels.

Results: The majority of patients reported significant financial strain due to travel and accommodation costs. About 72% of patients indicated a significant or moderate financial burden, with unexpected expenses contributing to the overall cost. Family members reported significant economic strain, with 45% indicating a moderate to significant financial impact. About 85% of family members had to reduce their work hours or leave their jobs to support the patient, while 31% of patients themselves had to stop working or take extended leave due to treatment. Despite the high patient workload, 65% of patients were started radiation treatment within two weeks. Waiting times for appointments and treatment varied, with 42% of patients experiencing occasional delays and 30% reporting never having to wait. Patients faced considerable travel challenges, with 48% travelling daily and 37% covering distances of over 200 km. Travel time was often more than 2 hours for 62% of patients. Accommodation was a concern for 53% of patients, with a significant percentage reporting high costs. Access to radiotherapy facilities near home was limited, with 50.79% reporting no nearby facility, leading to significant travel burdens—36.51% of patients travelled over 200 km, and 62% had travel times exceeding two hours. Financial support was available for 63% of patients, mainly through government programs. While 63% received financial aid through government programs, 38.5% incurred unexpected costs due to machine breakouts, extended stays, or additional travel. Out-of-pocket expenses persisted, with 40.08% of patients reporting a significant impact on their financial stability. Patient satisfaction with treatment was high, with 92% rating their overall experience as good or excellent.

Conclusions: The audit highlights the substantial financial burden and logistical challenges faced by lung cancer patients during treatment. While government programs and financial support have alleviated some costs, there remains a significant impact on patients' finances and daily lives. The availability of cancer care facilities in India is markedly uneven, with a concentration of advanced care in specific centres leading to overburdening and strain on resources. This disparity adversely affects the quality of care and patient outcomes, highlighting the need for a more equitable distribution of cancer care resources.

Keywords: Radiotherapy, cancer care access, patient experience

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.80 Economic Burden of Disease Management and Recurrences After Complete Resection of Early-Stage ALK+ Non-Small Cell Lung Cancer (NSCLC) in Spain

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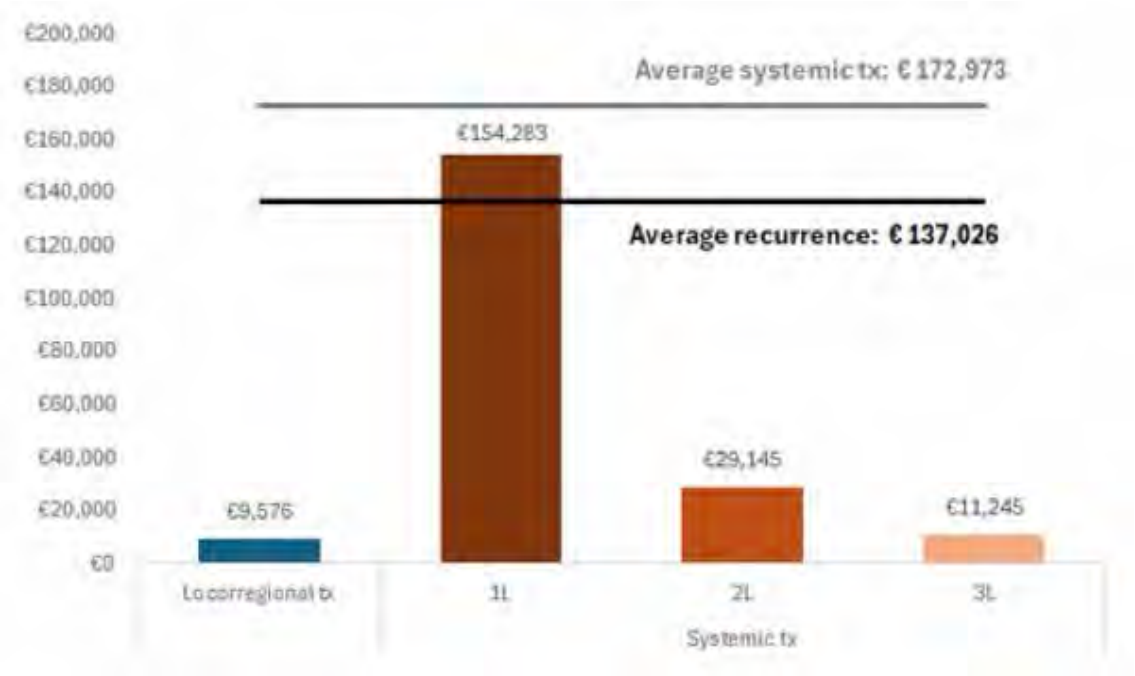
Introduction: Adjuvant alectinib has shown a significant benefit with respect to disease-free survival as compared with adjuvant platinum-based chemotherapy (PbCH) in early-stage ALK rearranged non-small cell lung cancer (NSCLC) patients, as well as a mainly low-grade safety profile. The aim of this analysis was to estimate the economic burden of disease management with current adjuvant PbCH after complete resection of ALK+ NSCLC in Spain, focusing on the costs of patients with recurrent disease.

Methods: A two-round consensus panel was conducted with six Spanish experts. First, the experts completed a questionnaire designed to capture expert opinion on the epidemiology, treatment pathways and healthcare resource use associated with disease management in patients with ALK+ NSCLC. The responses were then shared in a second round to reduce variability and reach a common consensus. Afterward, a 3-states Markov model was built to estimate the 5-years costs after complete resection of ALK+ NSCLC (IB ≥4cm - IIIA), from the Spanish National Health System (NHS) perspective. The efficacy data used to model transitions between health states were obtained from the ALINA study and other published articles on NSCLC. Unit costs were obtained from national databases and expressed in euros of 2025. To account for uncertainty in the model parameters, a one-way sensitivity analysis was performed, generating a range of possible outcomes around the mean cost estimates.

Results: A target population of 98 hypothetical patients with resected ALK+ NSCLC was estimated, of which 62 would experience recurrence after 5 years from treatment with adjuvant PbCH. In Spain, the total cost in absolute terms of managing these 62 relapses would amount €8,519,175 and the total cost of 35 disease-free patients would be €707,500. Therefore, the total cost for the target population of the analysis was 9,2 million €. The average cost of ALK+ NSCLC recurrences in Spain over a 5-year period would be €137,026 (€9,576 and €172,973 for recurrences managed with local or systemic treatment, respectively). Figure 1 summarises the average cost of recurrences by type. Sensitivity analyses reinforced the robustness of the results obtained.

Conclusions: Although the number of patients with ALK+ early-stage NSCLC is low, the cost of recurrences (particularly those requiring systemic therapies) represents a substantial burden for the National Health System. Early intervention and the incorporation of more efficacious adjuvant therapies to mitigate recurrence risk are critical to optimize disease management.



Keywords: Early-stage NSCLC, Recurrence, Economic burden

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.81 Unveiling the Natural History of Lung Cancer by Sex, Histology, and Nodule Type Using Mathematical Modeling

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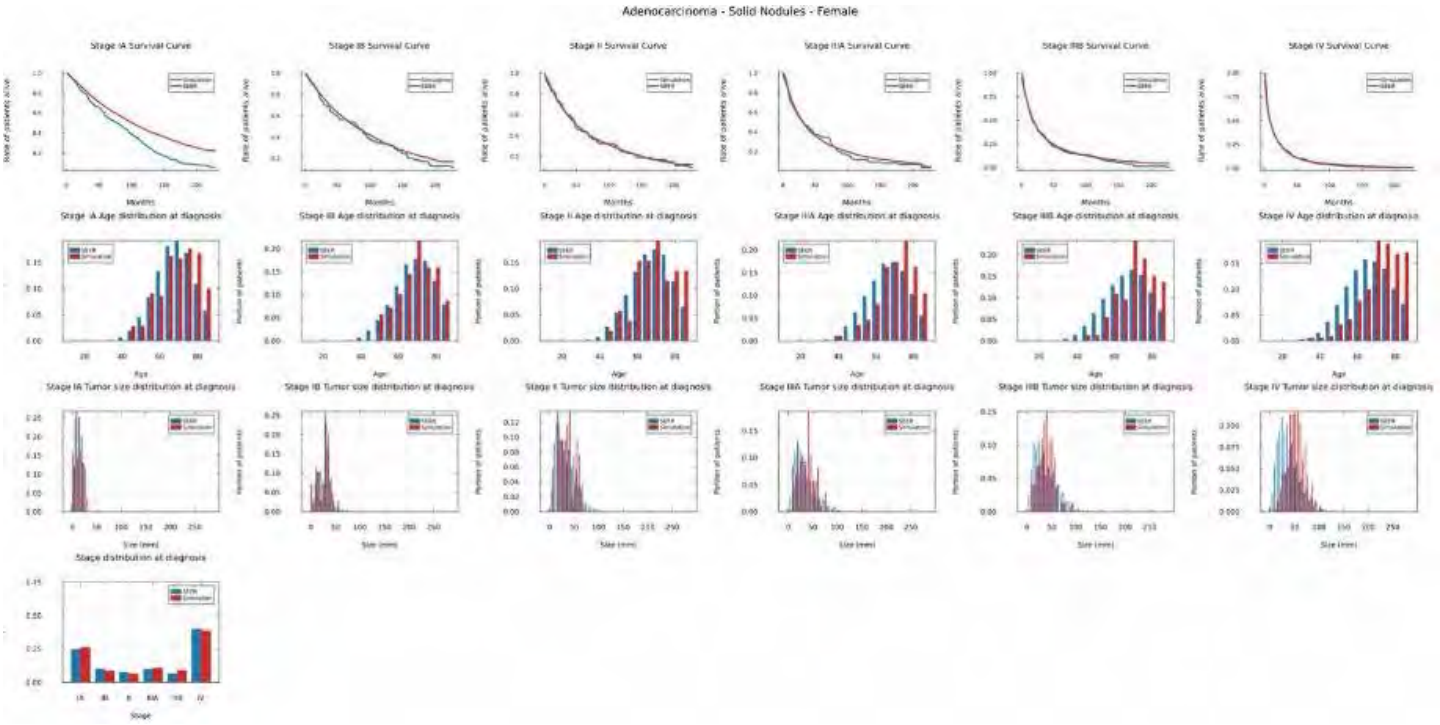
Introduction: Lung cancer is the leading cause of cancer-related death globally. Mathematical models that simulate the natural course of the disease, commonly referred to as natural history models (NHMs), have been developed and used to provide insights into the effectiveness of interventions. In a recent scoping review of the literature focusing on existing NHMs, we found that no existing lung cancer NHM accounts for the differences in the disease progression by nodule type, and very few explicitly model tumor growth. We thus developed and validated a sex-, histology-, and nodule type-specific NHM for lung cancer that explicitly models tumor growth.

Methods: We developed sex-specific state-transition lung cancer NHMs for the most common histological subtypes (small cell, squamous cell, adenocarcinoma, and other non-small cell) using the AJCC staging system. Adenocarcinomas were further stratified by nodule type into solid, part-solid, and non-solid. We assumed that tumors grow according to Gompertz models, which were calibrated to observed data from the Surveillance, Epidemiology, and End Results (SEER) 17 registry from 2000-2021. Because SEER does not provide information on nodule type, we assumed all adenocarcinomas in SEER are solid nodules and adjusted the progression rates for part-solid and non-solid nodules based on estimates of tumor volume doubling time from the literature. Each of the NHMs had a similar structure. We used the observed stage-specific survival after diagnosis, stage distribution at diagnosis, stage-specific tumor size distribution at diagnosis, and stage-specific age distribution at diagnosis as calibration targets. We assessed the goodness of fit of each model using the weighted sum of root mean squared error (RMSE) and validated the NHMs on the control arms of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) and the National Lung Screening Trial (NLST) trials.

Results: The number of parameters for each model ranged between 27-33 parameters estimated through calibration. The calibrated NHMs successfully reproduced the observed data from SEER in terms of all calibration targets by sex and histological subtype (Figure 1). The RMSE for all models was less than 3%. The NHMs reproduced the observed outcomes of the PLCO and NLST control arms.

Conclusions: The NHMs accurately simulate the sex-, histology-, and nodule type-specific progression of lung cancer while explicitly modeling tumor growth. The resulting NHMs will inform future microsimulation studies to evaluate the effectiveness of alternative lung cancer screening strategies by nodule type.



Keywords: natural history, tumor growth, nodule type

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.82 Lung Cancer's Price Tag: Escalating Hospitalization Costs in Brazil Over the Past Two Decades

J.H. Maselli Schoueri[1], A.C. Viana[1], M. Magalhães Filho[2], J. Favoretto Neto[3], L.V. de Alcantara Sousa[1], L. da Silva Paiva[1], J.J. Namura[1], C. Vaz de Melo Sette[1], A. del Giglio[1], P. Nazareth Aguiar Jr[4]
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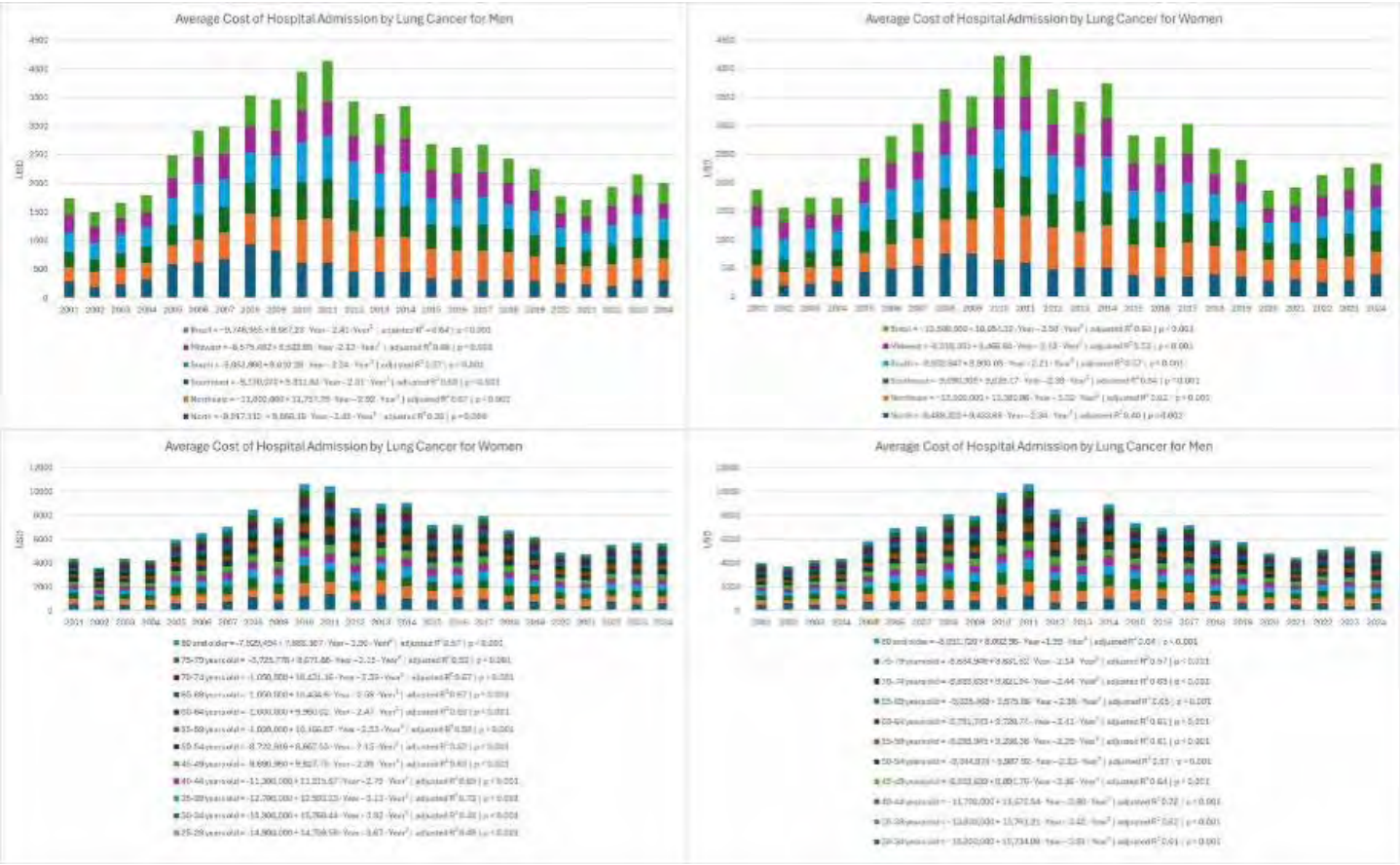
Introduction: Lung cancer (LC) is the leading cause of cancer-related death worldwide. In Brazil, despite the universal healthcare system (SUS), regional and demographic disparities may influence both access to care and treatment outcomes. Economic analyses focusing on hospitalization costs are essential to understanding the burden of LC on the public healthcare system. This study aimed to analyze trends in average hospitalization costs for LC in Brazil.

Methods: Ecological study in which LC was classified according to ICD-10. Average In-Hospital Admission costs were collected from the Hospital Information System for each administrative region of Brazil, and stratified by year, sex and age group of involvement. Values were first adjusted for inflation, using the Broad Consumer Price Index (IPCA), obtained from the Accumulated Variation in the year during the Real Plan by the Brazilian Institute of Geography and Statistics (IBGE). Then, the values were adjusted by the annual exchange rate for US dollars, obtained from the Institute of Applied Economic Research (IPEA), allowing for international comparison. The period studied was defined between the years 2001 and 2024, taking 2020 as the basis for starting inflation calculations. Since the data did not follow a linear distribution, quadratic regression was used to evaluate its behavior over time. The program used was Stata 15.0. The confidence level was 95%.

Results: From 2001 to 2024, average hospitalization costs (in USD, not adjusted for inflation) were consistently higher among women compared to men. This difference may reflect sex-based variations in clinical presentation, resource utilization, or treatment strategies. Quadratic regression demonstrated nonlinear patterns in in-hospital costs for LC in Brazil between 2001 and 2024. Increasing trends were observed until the mid-2010s, followed by a subsequent decline in both sexes (especially women), regions, and age groups ($p < 0.001$). The highest cost curves occurred in the 20-34 age group, and the lowest among the elderly. The North region presented a lower adjusted R^2, which may suggest greater local variability.

Conclusions: There was a parabolic behavior in hospital costs for lung cancer in Brazil, with growth until approximately 2011, followed by a decline. The analysis by subgroups reinforces regional, age and gender inequalities, with a potential impact on public policies.



Keywords: Non-Small Cell Lung Cancer, Public Health, Costs

P1.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS
SUNDAY, SEPTEMBER 7, 2025 - 10:30 - 12:00

P1.17.83 Implementation of Lung Cancer Screening by Family Physicians in the U.S.: Results of a National Survey

R. Volk[1], J. Eberth[2], M.P.B. Brietzke[1], J. Lettieri[1], K. Maki[3], N. Tan[4], M. Monroe[5], K.N. Reid[5], L. Rosenthal[6], E.A. Kazerooni[7], R.A. Smith[6]
[1]The University of Texas MD Anderson Cancer Center, Houston/TX/USA ,[2]Drexel University, Philadelphia/PA/USA ,[3]Wayne State University, Detroit/MI/USA ,[4]Rutgers University, New Brunswick/NJ/USA ,[5]American Academy of Family Physicians, Leawood/KS/USA ,[6]American Cancer Society, Atlanta/GA/USA ,[7]University of Michigan Medical School, Ann Arbor/MI/USA

Introduction: Lung cancer screening (LCS) rates in the U.S. remain low despite endorsements from professional organizations and broad insurance coverage with no co-pay. Family physicians play an essential role in LCS, in having long-term relationships with their patients that emphasize preventive care, established screening protocols for other cancers, routinely screening for tobacco use, and providing cessation resources to their patients who smoke. Understanding what family physicians know about LCS, how they are implementing it their practices and their preferences for doing so, is critical to increasing the uptake of this life saving screening test.

Methods: An online, self-administered survey (Alchemer©) of active members of the American Academy of Family Physicians (AAFP) was conducted between February and August 2024. Sampling involved stratification of members by the nine geographic Census Divisions in the U.S., and then taking random samples until the target sample size per division was achieved. Recruitment was conducted in two waves, with four reminders sent to AAFP members with valid email addresses. Survey items captured participants' practice and demographic characteristics; lung cancer screening attitudes, practices, and resources; and attitudes and practices around smoking cessation and new screening technologies. Data are reported descriptively with sample weight adjustments for gender, years since residency, urban/rural status, and Census Division.

Results: The sample included 1,183 family physicians, with balanced participation across the nine Census Divisions. Participants' practice and demographic characteristics mirrored the overall AAFP membership. Among survey participants, 22.7% completed residency training within the past seven years, while 37.1% completed training more than 21 years ago. Nearly all (95.9%) used an electronic health record (EHR), with Epic® (43.7%) being the most common. Familiarity with the 2021 United States Preventive Services Task Force recommendation and current American Cancer Society guideline was high. Participants "agreed/strongly agreed" that the benefits of lung cancer screening (LCS) outweighed the risks (85.2%). The majority (89.6%) had ordered LCS for their patients, with 53.6% referring at least 11 patients for LCS over the past year. Nearly two-thirds (63.5%) indicated their center/clinic had a decentralized approach to LCS, where family physicians were responsible for ordering LCS, tracking results, and coordinating follow-up care, while 11.1% were supported by a centralized LCS program that coordinates care after the order was placed, and 15.8% relied on a hybrid approach (i.e. some centralized support was available). Most (71.3%) had clinical protocols for collecting smoking histories from patients, and 50.1% used EHR alerts to prompt them about a patient's LCS eligibility. Use of standardized protocols for follow-up of abnormal findings (38.7%) and incidental findings (35.5%) were less common. Only 26.4% had access to care navigators to facilitate the screening process.

Conclusions: Nearly all U.S. family physicians agreed that LCS was beneficial for patients and refer eligible patients for LCS. Approximately 2 in 3 physicians coordinate LCS themselves, without resources such as a navigator or provided in a centralized screening program. This lack of support is a major barrier to implementing high quality LCS uptake.

Keywords: screening, primary care, cancer care delivery

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.01 Characterizing UPP1 Expression in Non-Tumor Cells of Lung Cancer and Its Clinical Implications

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Introduction: Uridine phosphorylase 1 (UPP1) is a key enzyme in uridine metabolism, recently reported to promote tumor cell proliferation through metabolic reprogramming (Nature, 2023). Our previous study demonstrated its tumor-promoting role in lung adenocarcinoma and its potential as a prognostic biomarker (Nature Communications, 2024). However, the functional role of UPP1 in non-malignant cells within the tumor microenvironment (TME) and its impact on immune regulation in lung cancer remain largely unknown.

Methods: We conducted an integrative analysis using single-cell RNA sequencing data from nearly 200 lung cancer patients, combined with clinical and transcriptomic data from over 500 patients. Multiplex immunofluorescence and spatial transcriptomics were applied to validate spatial distribution and cellular localization of UPP1. Functional roles were assessed through conditional knockout mouse models targeting macrophages and neutrophils. A tumor organoid-UPP1+TAM-CD8+T cell co-culture system was developed to examine immune interactions. Additionally, high-throughput drug screening was performed using organoids and immune cells to identify potential UPP1-targeting agents.

Results: UPP1 was significantly upregulated in several non-malignant cell populations, particularly tumor-associated macrophages (TAMs), neutrophils (TANs), and endothelial cells within the TME. High UPP1 expression in these populations was associated with poor overall survival, increased tumor progression, and reduced response to immune checkpoint blockade (ICB). Mechanistically, UPP1 expression was induced under hypoxic conditions and by cytokines such as GM-CSF and IL-6. Functionally, UPP1 upregulation in TAMs contributed to the establishment of an immunosuppressive TME by promoting secretion of inhibitory mediators such as G-CSF and CCL9, leading to impaired CD8+T cell cytotoxicity. Conditional deletion of UPP1 in myeloid populations inhibited tumor growth, enhanced CD8+T cell activation, and sensitized tumors to anti-PD-L1 therapy in vivo. In ex vivo organoid co-culture systems, UPP1+TAMs suppressed CD8+T cell-mediated cytotoxicity, a phenotype reversible by targeting UPP1.

Conclusions: This study uncovers a previously underappreciated role of UPP1 in shaping the immunosuppressive microenvironment of lung cancer through its expression in non-malignant stromal and immune cells. UPP1 serves as a critical metabolic-immune regulator and a promising therapeutic target to enhance anti-tumor immunity and improve immunotherapy outcomes. Our findings provide novel insights into metabolic regulation within the TME and offer translational strategies for targeting non-malignant components of lung tumors.

Keywords: Lung Cancer, Tumor microenvironment, UPP1

P2.02.02 R-Loop-Associated DNA Damage Facilitates Chemosensitivity of NSCLC

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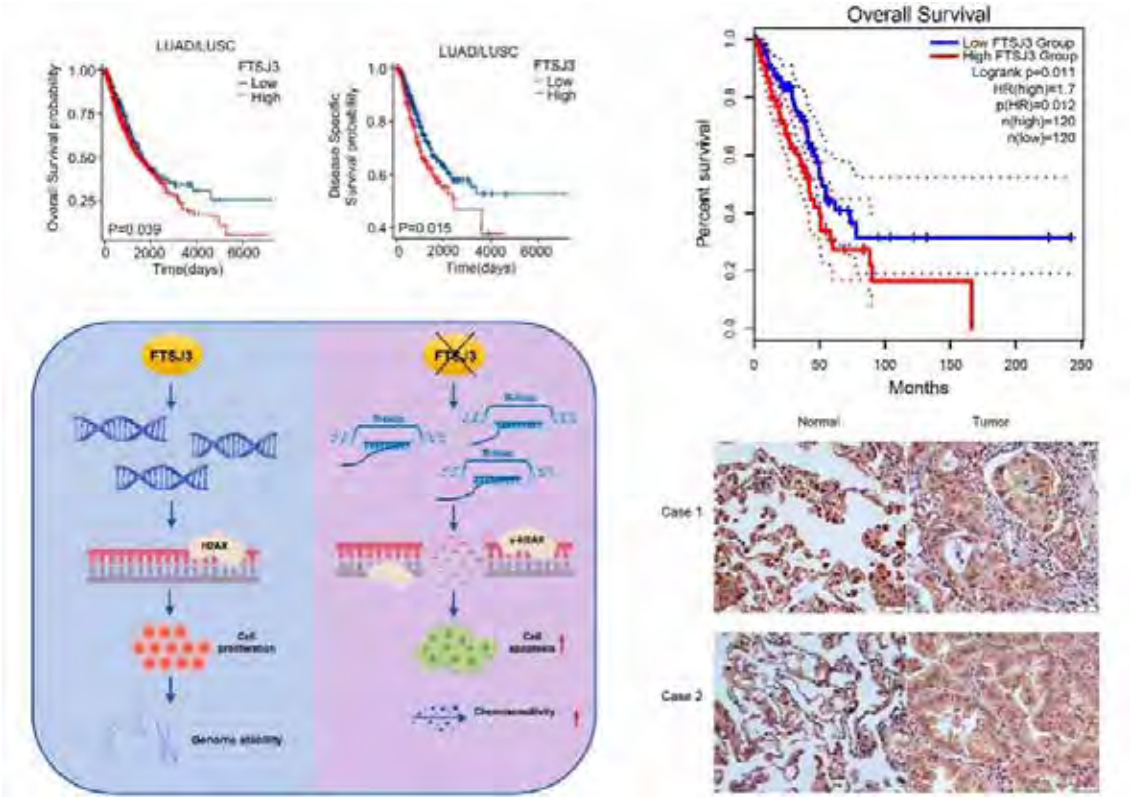
Introduction: Aberrant accumulation or impaired resolution of R-loops compromise genome stability, leading to DNA damage and contributing to tumorigenesis, including NSCLC(non-small cell lung cancer). Notably, Several R-loop-associated proteins serve as critical regulators of R-loop structures across the genome, which are essential for mRNA metabolism and genome stability. In this study, we aimed to identify novel regulators of R-loops associated to NSCLC and to underscore their potential roles in modulating chemotherapeutic response.

Methods: RNA/DNA hybrids were immunoprecipitated from HeLa cells using the S9.6 antibody and subjected to mass spectrometry to identify R-loop-associated proteins. FTSJ3 function was evaluated via siRNA knockdown, overexpression, and rescue with RNase H1 overexpression. R-loop accumulation and DNA damage were assessed by immunofluorescence, comet assay, and proximity ligation assay. Cell viability and chemosensitivity to CPT or cisplatin were measured in lung cancer cell lines. TCGA and IHC analyses were used to evaluate FTSJ3 expression and its association with prognosis in NSCLC patients.

Results: FTSJ3 was identified as a novel R-loop-binding protein. Its depletion led to R-loop accumulation, increased DNA damage, and reduced cell viability. These phenotypes were reversed by RNase H1 overexpression, confirming their R-loop dependence. Loss of FTSJ3 enhanced sensitivity to CPT and cisplatin in vitro. Clinical analysis including TCGA and IHC showed FTSJ3 was upregulated in multiple cancers and correlates with poor prognosis in NSCLC, suggesting its potential as a predictive biomarker for NSCLC chemotherapy response.

Conclusions: Our study identifies FTSJ3 as a critical regulator of R-loop homeostasis, given its role in modulating DNA damage and chemotherapy sensitivity, FTSJ3 represents a potential therapeutic target and prognostic biomarker for improving treatment outcomes in NSCLC.



Keywords: R-loop, DNA damage, Chemosensitivity of NSCLC

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.03 Ferroptosis-Induced SUMO2 Lactylation Counteracts Ferroptosis by Enhancing ACSL4 Degradation in Lung Adenocarcinoma

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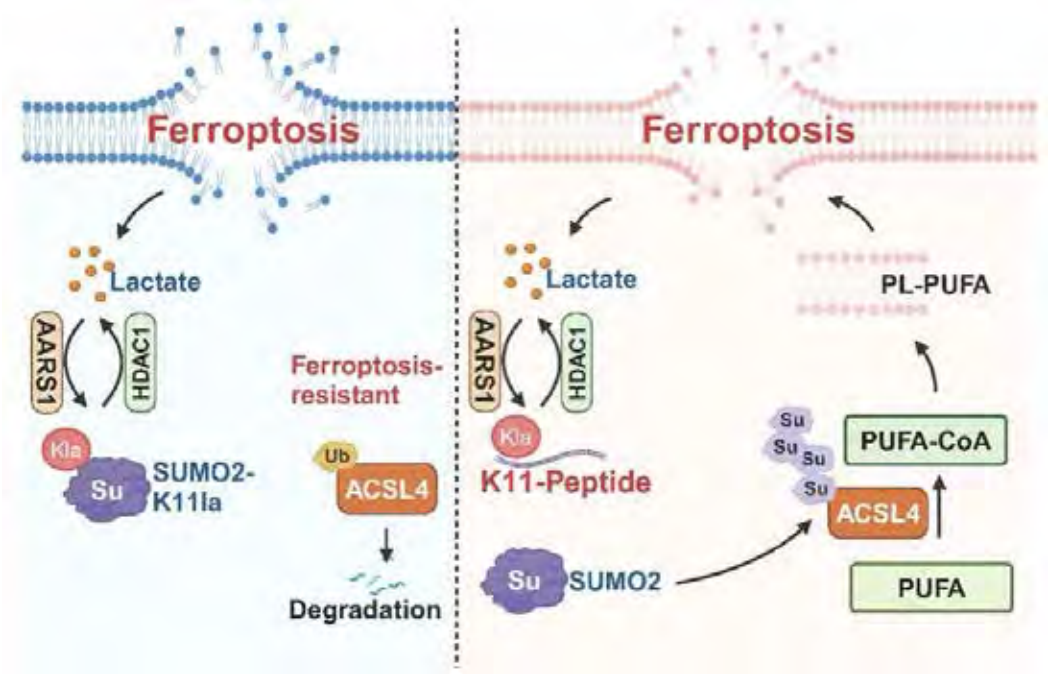
Introduction: Lactylation, a lactate-mediated post-translational modification, has garnered significant attention for its pivotal role in epigenetic modulation. However, the intricate interplay between lactylation and ferroptosis in lung adenocarcinoma (LUAD) remains to be fully elucidated.

Methods: In this study, we employed metabolomic profiling and metabolic library screening to identify metabolites related to ferroptosis. Lactylation proteomics analysis was conducted to determine the proteins and residue sites that undergo lactylation during ferroptosis. Furthermore, we utilized immunofluorescence, cycloheximide chase assays, and sumoylation proteomics to assess the effects of lactylation on SUMO2. Cell viability assays, lipid peroxidation quantification, transmission electron microscopy of mitochondrial damage, malondialdehyde, and glutathione measurements were employed to evaluate the influence of SUMO2 lactylation on ferroptosis. Additionally, we designed a cell-penetrating peptide targeting SUMO2 lactylation and validated its efficacy in promoting ferroptosis in cellular, patient-derived organoid, and xenograft models.

Results: Utilizing metabolomic profiling and metabolic library screening, our study uncovered that ferroptotic stress markedly enhances glycolysis and lactate accumulation, which in turn confers resistance to ferroptosis in LUAD cells. Subsequently, we demonstrated that ferroptosis induction elevates protein lactylation levels within LUAD, especially SUMO2 at the K11 residue. Cell viability, lipid peroxidation detection, malondialdehyde, and glutathione measurements, collectively revealed that SUMO2-K11 lactylation contributes to ferroptosis resistance. The sumoylation proteomics and co-immunoprecipitation assays indicated that SUMO2-K11 lactylation hinders the interaction between SUMO2 and ACSL4. This disruption facilitates ACSL4 degradation, thereby mitigating ferroptosis. Furthermore, we identified AARS1 as the lactyltransferase and HDAC1 as the delactyltransferase for SUMO2. Based on these findings, we developed a cell-penetrating peptide capable of entering cells independently of cell membrane receptors or transfection reagents. By selectively inhibiting SUMO2-K11 lactylation, this peptide promotes ferroptosis and sensitizes LUAD to cisplatin treatment in vitro and in vivo.

Conclusions: This study suggests a promising therapeutic approach of targeting SUMO2-K11 lactylation to potentiate ferroptosis-based cancer therapies.



Keywords: Lactylation, Ferroptosis, Cell-penetrating peptides

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.05 CXCL12/CXCR4 Axis Mediates M2 Monocyte Polarization-Induced Immune Resistance in NSCLC Liver Metastasis

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Introduction: The low response rate to PD-1/PD-L1 inhibitors in patients with NSCLC liver metastasis limits the benefit of immunotherapy in this population. The patients may have their own unique immune escape mechanism, and the analysis of this mechanism will help to explain the reasons for the poor efficacy of immunotherapy in these patients.

Methods: The differences of gene expression, cytokines, number of immune cell infiltration and function of immune cell subsets in lung primary disease in patients without liver metastasis, lung primary disease in patients with liver metastasis and lung primary disease in patients with liver metastasis were compared based on clinical samples. Luminex multifactor assay to validate differences in cytokine and immune cell function. OLINK technique was used to detect proteomic expression difference and related function in serum of patients with liver metastasis. Difference of intestinal flora and serum metabolome in 16S. The mechanism hypothesis of poor efficacy of immunotherapy was proposed. To establish a mouse model of liver metastasis of non-small cell lung cancer. Bioinformatics analysis, flow cytometry, in vitro co-culture, key target RNA interference, PCR and other techniques were used to further analyze the key targets related to liver metastasis and immunotherapy efficacy of NSCLC and their regulatory mechanisms.

Results: At the transcriptome level, gene expression profile and protein-protein interaction network analysis showed that CD36 and CXCR4 were the core proteins responsible for differences in the expression of liver metastasis genes in NSCLC. The results of enrichment analysis suggest the activation of lipid metabolism-related pathways in patients with liver metastasis. It was found that the immune cell diversity of liver metastases was lower than that of the primary lesions, and the T cell subtype analysis showed that CD8+T cell infiltration was significantly reduced. The expression of M2-TAM was mainly increased in the myeloid cell population. By establishing a mouse model of lung adenocarcinoma liver metastasis, M2-TAM has been preliminarily confirmed to mediate tumor immune escape by inhibiting CD8+T cell function in NSCLC liver metastasis TME. The secretion of CXCL12 increased in patients with NSCLC liver metastasis, and the expression of CXCR4 increased on the surface of TAM in liver metastasis, which participated in and promoted the recruitment of monocytes into M2 liver metastasis. The number of intestinal microbial species in patients with NSCLC liver metastasis was more abundant. Lipid deposition and increased fatty acid uptake of TAM were found in liver metastatic specimens. CD36 can promote lipid accumulation in TAM, activate PI3K/AKT pathway by regulating fatty acid metabolism reprogramming, and enable macrophages to have a tumor-promoting phenotype.

Conclusions: CXCL12/CXCR4 axis participated in and promoted the recruitment of monocytes to M2 in liver metastases. Increased lipid deposition and fatty acid uptake in TAM were detected in liver metastasis specimens, which was consistent with previous studies on the M2-polarization characteristics of TAM with high lipid levels. CD36 is the core protein of differences in liver metastases, which can promote lipid accumulation in TAM, activate PI3K/AKT pathway and promote M2 polarization by regulating fatty acid metabolic reprogramming.

Keywords: Non-small cell lung cancer, CXCL12/CXCR4, Lipid metabolism

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.06 Functional Impact of Missense Mutations Affecting Immune Response Genes in Human Cancer

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Introduction: In recent years, immunotherapy has emerged as a promising therapeutic approach to stimulate the immune response against cancer cells. Immune Checkpoint Blockade (ICB) therapies, based on the use of monoclonal antibodies targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1), have demonstrated durable antitumor effects, particularly in non-small cell lung cancer (NSCLC). However, these therapies can fail in patients who are expected to benefit from them, underlining the need of identifying reliable biomarkers to select those patients who will truly benefit from ICBs. Our research group has pioneered the discovery of tumor-specific mutations in genes involved in tumor immune evasion, which is the ability of the tumor cell to evade the action of the immune system. These alterations may predict resistance to ICB therapies. Our study aims to characterize the landscape and functional impact of previously uncharacterized amino acid changes in genes involved in immune response.

Methods: We characterized the mutational landscape and assessed the functional impact of amino acid substitutions in key immune response genes (B2M, CALR, IFNGR1, IFNGR2, JAK1 and JAK2), in more than 12,000 tumors. Missense mutations with potential functional impact in genes involved in immune response were identified using public databases (cBioPortal, UniProt, ClinVar, Cosmic, PolyPhen2, SIFT and Alphamissense). Wild-type IFNGR1, IFNGR2, JAK2 cDNAs were cloned and targeted mutagenesis was performed to assess the effect of selected missense mutations on protein functionality. Lentiviral vectors were used to ectopically express the generated constructs in cell lines. We tested the response to IFNγ using western blot, RT-qPCR and toxicity assays and the positioning of the HLA-I complex in the cell surface uisng immunofluorescence.

Results: We detected mutations in the aforementioned genes in 11% of the tumors, of which 58% were classified as missense, with B2M having the highest mutation frequency per base pair, predominantly truncating variants. We also identified colorectal and endometrial cancers with the highest mutation rates, followed by melanoma and lung cancer. We predicted the pathogenicity of a curated list of 226 amino acid substitutions at B2M, IFNGR1, IFNGR2, and JAK2, evaluated by SIFT, PolyPhen2, and AlphaMissense, from which we performed the functional characterization of 18 mutations with potential impact on the functionality and assembly of IFNGR1 (n=3), IFNGR2 (n=3), JAK2 (n=7), and B2M (n=5). This revealed that 43% and 33.3% of selected JAK2 and IFNGR1 mutations impaired transcriptional activation and did not suppress cell growth by IFNγ, while 80% of B2M mutations disrupted HLA-I complex, indicating pathogenicity. When computational predictions were compared to experimental data, AlphaMissense aligned best.

Conclusions: We provide a comprehensive mutational profile of HLA-I complex and IFNγ response components in human cancer, along with functional insights into selected missense mutations that may aid in patient stratification for ICB.

Keywords: Immune evasion, Immunotherapy, Biomarkers

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.07 Targeting SLC4A7 Reprograms the Acidic Tumor Microenvironment to Overcome Immunotherapy Resistance in NSCLC

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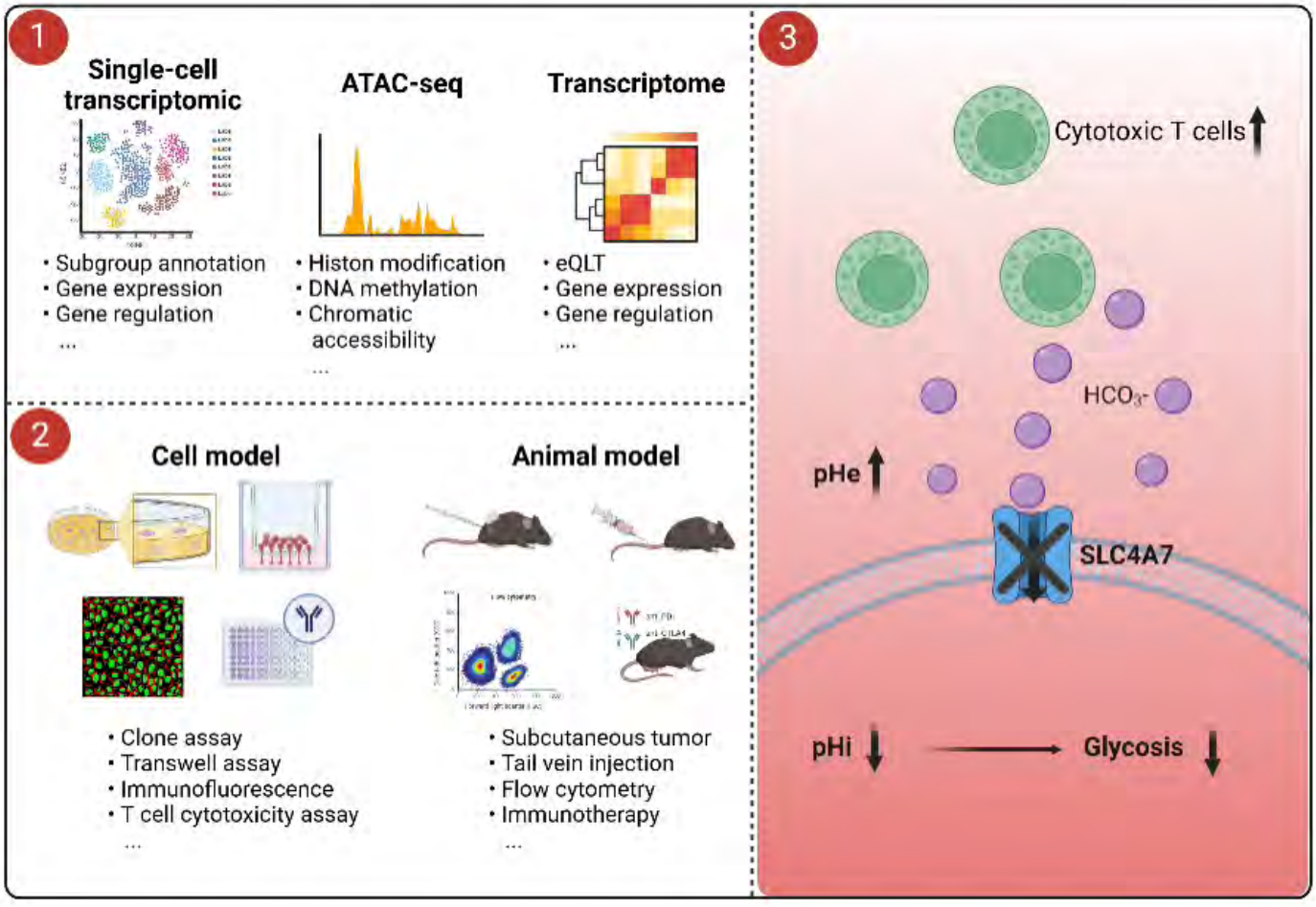
Introduction: Solid tumors maintain an acidic tumor microenvironment (TME) that drives cancer progression, therapy resistance, and immune evasion. However, the molecular mechanisms linking TME acidosis to metabolic-immune crosstalk in non-small cell lung cancer (NSCLC) remain incompletely understood. Here, we investigated the role of bicarbonate transporters in regulating TME pH dynamics and its functional consequences.

Methods: Through single-cell transcriptomic profiling of NSCLC specimens, we identified solute carrier family 4 member 7 (SLC4A7) as the predominant bicarbonate transporter. Functional studies combined genetic ablation and pharmacological inhibition of SLC4A7 in preclinical NSCLC models. Immune landscape remodeling was assessed via flow cytometry and functional T cell assays. Mechanistic insights into SLC4A7 regulation were derived from integrated RNA-seq and ATAC-seq analyses.

Results: SLC4A7 was broadly expressed across malignant and stromal cells. Its suppression attenuated extracellular bicarbonate accumulation, ameliorating TME acidosis, while promoting intracellular acidification to suppress glycolytic metabolism. In vivo, SLC4A7 inhibition enhanced cytotoxic T cell infiltration and function, suppressing tumor growth and metastasis. Combinatorial therapy targeting Slc4a7 with PD-1/CTLA-4 checkpoint blockade synergistically improved therapeutic efficacy and survival. Mechanistically, BACH1 was identified as the transcriptional regulator of SLC4A7 expression.

Conclusions: Our study establishes SLC4A7 as a dual metabolic-immune regulator in NSCLC, orchestrating TME pH homeostasis and immune evasion. The synergistic effect of Slc4a7 targeting with immune checkpoint blockade provides a novel strategy to overcome immunotherapy resistance. These findings highlight pH modulation as a promising therapeutic axis for precision oncology in NSCLC.



Keywords: non-small cell lung cancer, tumor microenvironment, immunotherapy

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.08 A Unique VEGFA-Expressing CAF Subpopulation Emerges in TKI-Resistant Lung Cancer to Mediate Immunotherapy Sensitization and Adverse Outcomes

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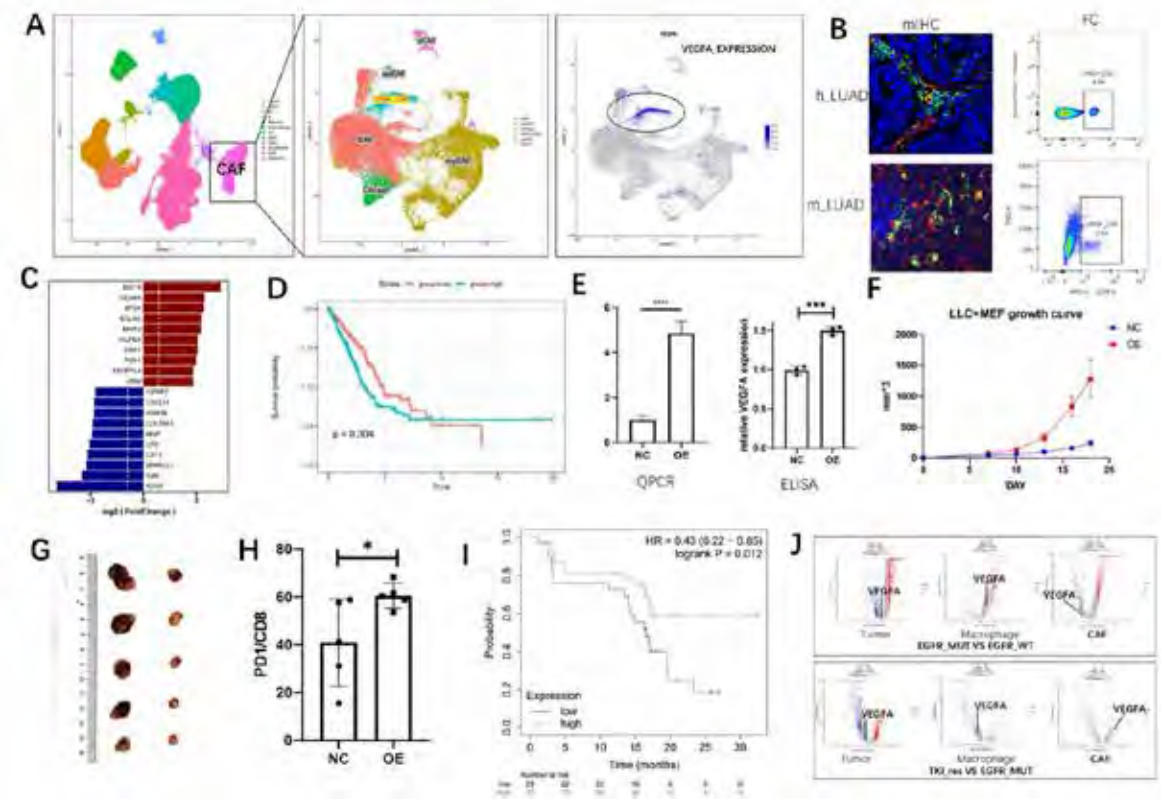
Introduction: Resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs) represents a major challenge in targeted treatment for lung cancer patients harboring EGFR mutations. While emerging evidence suggests that immunotherapy yields superior efficacy in TKI-resistant patients compared to those with EGFR-mutant tumors, the underlying mechanisms remain elusive. Elucidating the mechanisms driving immunotherapy responsiveness in TKI-resistant patients is critical for designing post-resistance therapeutic strategies.

Methods: We collected lung cancer biopsy samples from EGFR wild-type, EGFR-mutant, and TKI-resistant patients for single-cell sequencing to analyze compositional alterations in the tumor microenvironment (TME). Comparative analysis of TME components before and after TKI resistance was performed to identify potential target cell populations. Multicolor immunofluorescence and flow cytometry were employed to validate the presence of these cells in human and murine tumors. An in vitro cell line model was established to mimic the identified cells, followed by co-implantation with tumor cells to investigate their effects on tumor progression and immunotherapy response.

Results: Single-cell sequencing analysis of cancer-associated fibroblasts (CAFs) revealed a distinct subpopulation characterized by high VEGFA expression, designated as VEGF_CAFs. Their existence was confirmed in both human and murine TMEs using multicolor immunofluorescence and flow cytometry. Differential gene expression analysis between VEGF_CAFs and other CAFs identified key variable genes, which were used to infer VEGF_CAF abundance in the TCGA lung adenocarcinoma cohort. Elevated VEGF_CAF levels correlated with poor patient prognosis. We established a murine fibroblast cell line stably overexpressing VEGFA (validated by qPCR and ELISA) to model VEGF_CAFs. Co-implantation of VEGF_CAFs with LLC cells in mice demonstrated their tumor-promoting effects. Flow cytometry revealed increased PD1 expression on CD8+ T cells in VEGF_CAF-bearing tumors, suggesting potential immunotherapy sensitization. Notably, high expression of VEGF_CAF-specific variable genes was associated with improved immunotherapy outcomes in patients. Among major VEGFA-expressing cell types in the TME (tumor cells, myeloid cells, CAFs), only CAF-derived VEGFA was significantly reduced in EGFR-mutant patients and further diminished post-TKI resistance, implicating VEGF_CAFs in patients with enhanced immunotherapy responsiveness.

Conclusions: Our study identifies a unique CAF subpopulation within the TME that exhibits high VEGFA expression, associates with unfavorable prognosis, emerges in TKI-resistant patients, and potentially sensitizes tumors to immunotherapy. These findings provide mechanistic insights into the superior efficacy of immunotherapy in TKI-resistant populations and inform therapeutic strategies for overcoming EGFR-TKI resistance.



Keywords: EGFR-TKI resistance, Immunotherapy, Tumor microenvironment

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.09 Early-Stage Lung Adenocarcinoma: PLVAP-Driven Regulation of the Tumor Microenvironment

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Introduction: Early-stage neovascular infiltration emerges as a critical determinant of tumor advancement. Anti-angiogenic therapy induces a dynamic reduction in the prevalence of tip-like endothelial cells (TECs), a specialized tumor-associated endothelial subpopulation. However, mechanistic investigations into TEC phenotypic plasticity and their gene regulatory networks during incipient vascular co-option remain sparse, particularly regarding how TEC-specific molecular signatures functionally orchestrate microvascular remodeling and metastatic priming.

Methods: Surgical specimens from patients with CT-confirmed pulmonary nodules, alongside lung tissues from KrasG12D (K) and KrasG12DTgfbr2-/- (KT) murine models, were subjected to integrated single-cell RNA sequencing (scRNA-seq) and 10x Visium spatial transcriptomic profiling. PLVAP's functional relevance was systematically validated through multi-modal approaches: prognostic meta-analysis of clinical databases, immunofluorescence-based spatial mapping, transwell invasion/migration assays, endothelial tubulogenesis models, and tumor-endothelial co-culture systems.

Results: Integrated analysis of single-cell RNA sequencing (scRNA-seq) and 10x Visium spatial transcriptomics in both human and murine models revealed elevated proportions of tip cells in human tumor tissues and KT mice, potentially originating from type I capillaries. PLVAP, a molecular marker characteristic of tip cells, demonstrated a significant inverse association with clinical outcomes in lung adenocarcinoma patients. In vitro investigations further identified heightened PLVAP expression in tumor-associated endothelial cells, with its activation regulated by TGFβ1 signaling. Functional studies implicated PLVAP in modulating endothelial cell behaviors, including invasion, migration, and angiogenic tube formation, while also influencing tumor cell metastatic activity. Cell-cell communication analysis uncovered a mechanistic role for TGFβ1-expressing tip cells during early tumorigenesis, wherein paracrine TGFβ1 signaling enhances tumor cell invasiveness.

Conclusions: During early-stage lung adenocarcinoma progression, a marked elevation in tip cell populations originating from type I capillaries was observed, with their molecular signature gene PLVAP demonstrating an inverse correlation with survival outcomes. Mechanistically, tumor-derived TGFβ1 secretion upregulated PLVAP expression in endothelial cells, driving pro-angiogenic endothelial invasion/migration and vascular remodeling. Notably, scRNA-seq trajectory analysis suggested that a limited subset of tip cells in incipient tumors autonomously produce TGFβ1, which paracrinely amplifies tumor cell invasiveness through epithelial-mesenchymal transition pathways, thereby accelerating malignant progression.

Keywords: tumor endothelial cells, tip cells, PLVAP

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.10 Emotional Distress Following Lung Cancer Surgery and Tandospirones Dual Benefits for Chemotherapy

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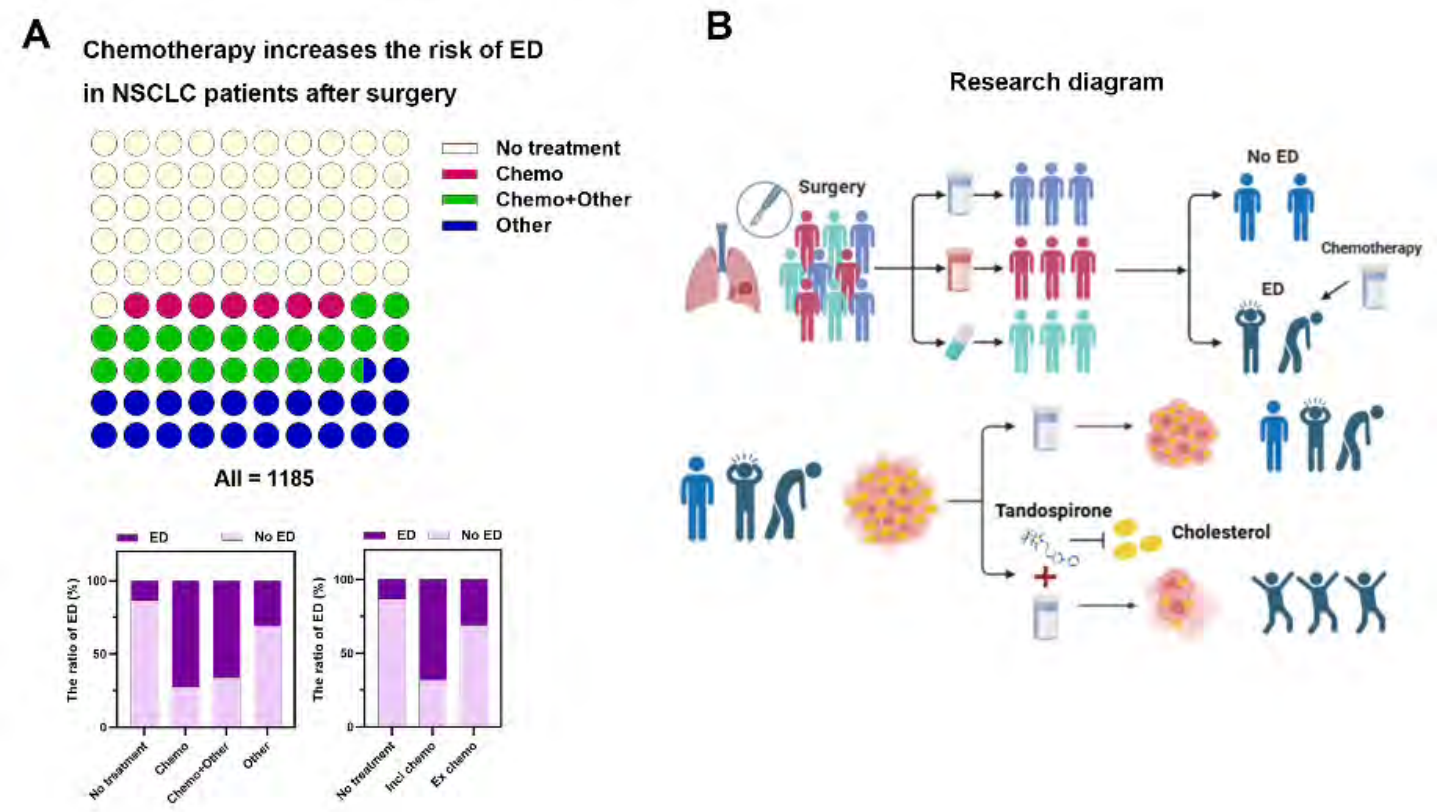
Introduction: Patients undergoing lung cancer surgery face a significantly heightened risk of emotional distress (ED), including anxiety and depression, which severely impacts their quality of life and may compromise treatment outcomes. Effective management of ED is crucial in postoperative care, yet the interaction between anti-ED medications and cancer therapy remains poorly understood.

Methods: This study systematically evaluated the mental health status of 1,185 non-small cell lung cancer (NSCLC) patients post-surgery, identifying chemotherapy as an independent risk factor for ED. Additionally, we investigated the safety and therapeutic effects of six commonly prescribed anti-ED drugs in NSCLC cell lines (A549 and H1299) and animal models. Cell viability, apoptosis, and cholesterol metabolism were assessed using CCK-8 assays, flow cytometry, RNA sequencing, and functional enrichment analyses.

Results: The prevalence of ED was significantly higher in postoperative NSCLC patients (32.2%) compared to healthy controls (8.9%). Chemotherapy was strongly associated with increased ED incidence. Among the tested anti-ED drugs, tandospirone exhibited no tumor-promoting effects and unexpectedly enhanced cisplatin's cytotoxicity. Mechanistically, tandospirone reduced cholesterol levels in tumor cells, activating feedback pathways involving SREBP2 and HMGCR, thereby promoting apoptosis and chemosensitivity. In vivo experiments confirmed that tandospirone synergized with cisplatin to inhibit tumor growth and metastasis.

Conclusions: Our findings highlight the dual role of tandospirone in alleviating ED and enhancing chemotherapy efficacy through cholesterol metabolism modulation. Furthermore, our study provides a scientific basis for integrating psychological support with metabolic interventions in lung cancer treatment, offering a novel strategy to improve patient outcomes.



Keywords: Emotional distress, Chemotherapy sensitization, Cholesterol metabolism

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.11 SRC Activation Drives Acquired Pemetrexed Resistance in Non-Small Cell Lung Cancer and Is Targetable by Dasatinib

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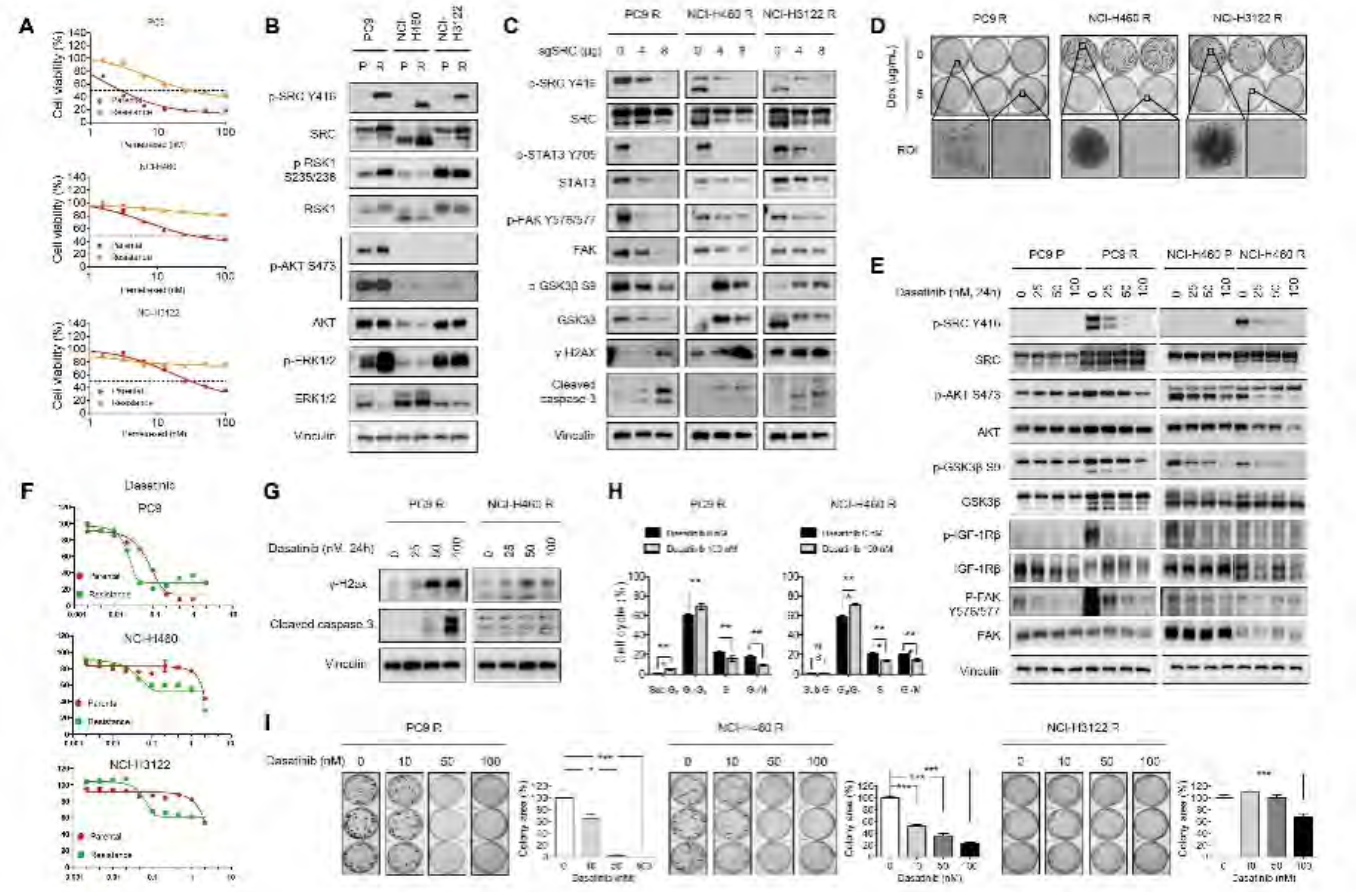
Introduction: Pemetrexed, a standard antifolate chemotherapy for non-squamous non-small cell lung cancer (NSCLC), is often limited by acquired resistance. This study investigated the role of SRC kinase in mediating pemetrexed resistance and evaluated whether SRC inhibition impairs the viability of pemetrexed-resistant NSCLC cells.

Methods: Pemetrexed-resistant cell lines (PC9 R, NCI-H460 R, and NCI-H3122 R) were generated through continuous exposure to pemetrexed for 12 months. Protein phosphorylation profiling and Western blot analyses were conducted to identify key signaling alterations. SRC was abrogated using both transient and doxycycline-inducible CRISPR/Cas9 systems to evaluate its role in cell viability and survival signaling. We assessed the efficacy of three SRC inhibitors—dasatinib, bosutinib, and saracatinib—using cell viability assays, colony formation assays, apoptosis detection, and cell cycle analyses.

Results: All pemetrexed-resistant cell lines demonstrated significant upregulation of phosphorylated SRC (p-SRC Y416) accompanied by enhanced activation of downstream effectors. SRC knockout significantly reduced p-SRC Y416 and downstream signaling (including p-STAT3 and p-FAK), while increasing markers of DNA damage (γ-H2AX) and apoptosis (cleaved caspase-3), resulting in reducing cell viability and clonogenic capacity. Among the SRC inhibitors tested, dasatinib showed the most potent, dose-dependent suppression of SRC activation and downstream signaling, including p-AKT, p-GSK3β, and p-FAK. Furthermore, dasatinib treatment promoted cell cycle arrest predominantly at sub-G1 and G0/G1 phases, accompanied by increased DNA damage and apoptosis, ultimately reducing colony formation. These findings indicate that SRC inhibition disrupts pro-survival pathways and triggers DNA damage-mediated cell death in pemetrexed-resistant cells.

Conclusions: Our findings identify SRC activation as a critical mechanism that drives acquired pemetrexed resistance in NSCLC. Targeting SRC, particularly with dasatinib, effectively impairs the survival of pemetrexed-resistant cells by promoting DNA damage, apoptosis, and cell cycle arrest. These findings provide a strong rationale for further preclinical and clinical investigation of SRC inhibitors, either as monotherapy or in combination with pemetrexed, as a therapeutic strategy to overcome resistance in NSCLC patients.



Keywords: Pemetrexed resistance, SRC kinase, Dasatinib

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.12 hUC-MSC-Derived Exosomes Mitigates Immune Checkpoint Inhibitor-Associated Lung Injury by Suppressing GSDME-Mediated Pyroptosis

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Introduction: Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 and CTLA-4 enhance anti-tumor immunity but can cause immune-related lung injury (ICI-LI) in 3-18.5% of patients, with glucocorticoids often ineffective in 10% of cases. Our previous research suggests pyroptosis via CASPASE/GSDME contributes to ICI-LI, and mesenchymal stem cell-derived exosomes (MSC-exos)—known to inhibit pyroptosis and treat lung injuries—may offer a novel therapy.

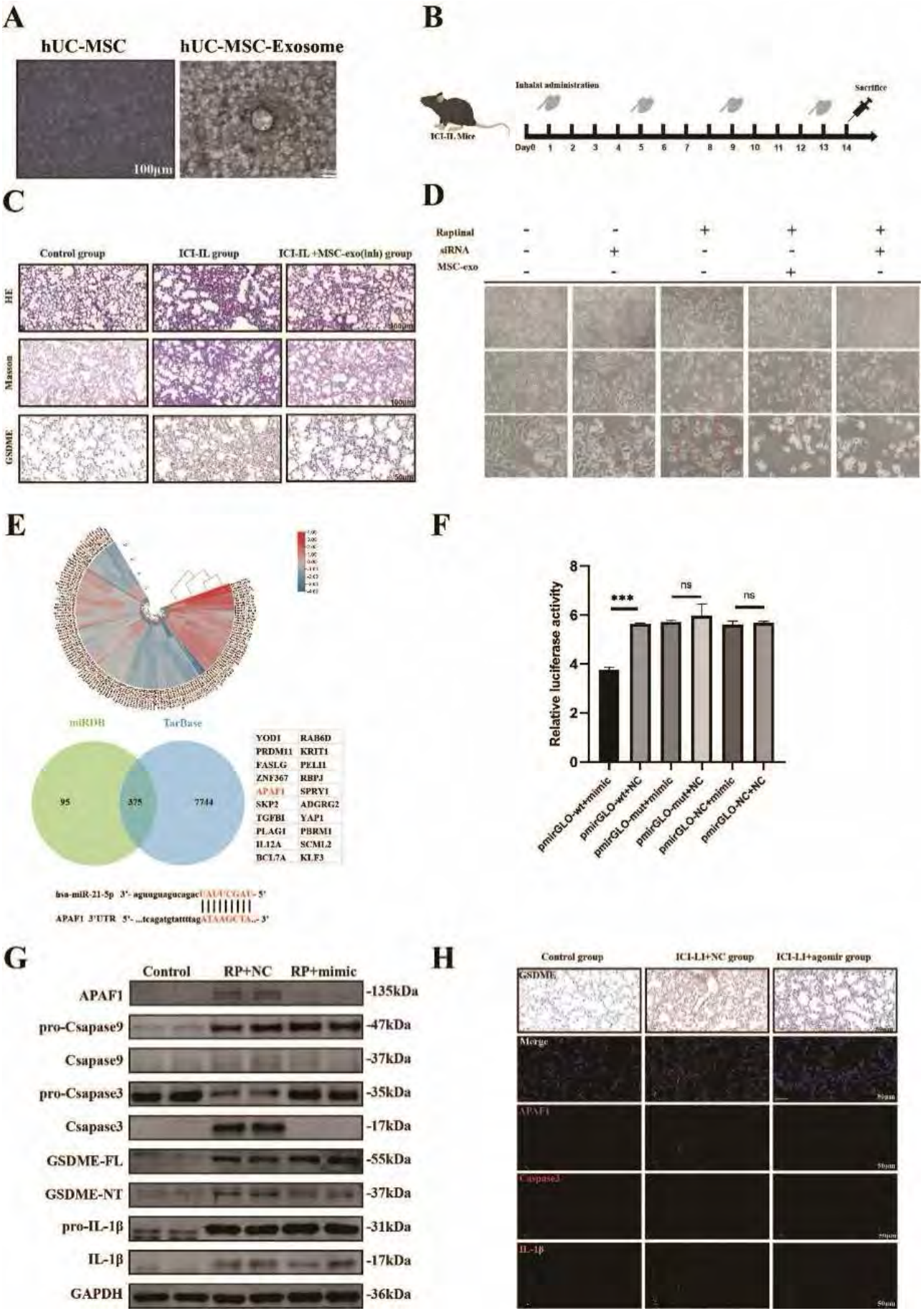
Methods: We isolated and characterized human umbilical cord-derived mesenchymal stem cell exosomes (hUC-MSC-exos), then administered them to ICI-LI mouse models and pyroptosis-induced alveolar epithelial cells (HBE). Through small RNA sequencing of exosomes, we identified candidate miRNAs, predicted and validated their target genes. Finally, we verified the inhibitory effect on pyroptosis using miRNA mimics/agomir in both in vivo and in vitro experiments.

Results: 1. Exosomes purified from hUC-MSC through ultracentrifugation were rigorously characterized and validated to meet established quality criteria(FIG.A).

2. hUC-MSC-exos alleviate lung injury in ICI-LI mouse models and suppress pyroptosis in HBE cells in vitro by inhibiting GSDME-mediated pyroptosis(FIG.B-D).3. MiR-21-5p is highly expressed in hUC-MSC-exos and targets the APAF1 gene(FIG.E-F).

4. MiR-21-5p in hUC-MSC-exos mitigates lung injury in ICI-LI mice and reduces damage in the HBE cell pyroptosis model by suppressing the APAF1/CASPASE3/GSDME/IL1β pathway(FIG.G-H).

Conclusions: hUC-MSC-derived exosomal miR-21-5p suppresses APAF1 expression, inhibiting CASPASE3/GSDME activation both in vivo and in vitro, demonstrating the therapeutic potential of hUC-MSC-Exos for ICI-LI treatment.



Keywords: immune checkpoint inhibitor-associated lung injury, mesenchymal stem cell-derived exosomes, pyroptosis

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.13 Macrophages Exhibit Enhanced Cholesterol Efflux in Early-Stage Lung Adenocarcinoma

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Introduction: Macrophages have been proved an important part in the microenvironment of many cancer types including lung adenocarcinoma (LUAD) and play a major regulatory role in promoting malignant development. However, most attempts to block their infiltration and function failed to bring clinical benefits. Notably, the majority of these studies focus on advanced tumor, in which stage the immune microenvironment has been reshaped to favor the progress of tumor. How macrophages exert their role in early-stage tumor, a question associated with improvement of macrophage-targeted therapy, remains less well studied.

Methods: We profile cells from 6 treatment-naïve patients with stage IA LUAD by single-cell RNA sequencing (scRNA-seq). After unsupervised graph-based clustering, monocyte / macrophage (MM) clusters based on canonical marker genes were identified. Then all these MM clusters were turned into re-clustering and we performed further analysis including KEGG enrichment analysis on them. To validate our results from local database, we also obtained scRNA-seq data released previously and characterized the MM clusters. Also, in vitro cell co-cultures were used to evaluate the effects of lung tumor cells on macrophages.

Results: Followed quality control, we collected approximately 100,000 high-quality cells from 6 paired samples, of which around 6,000 cells were from tumor and 4,000 were from adjacent normal tissue. In MMs, while the fraction of alveolar macrophages was strongly reduced in tumor, a cluster expressed SEPP1 and LGMN (SEPP1+ macrophages) demonstrated a significant increase. The differential expression analysis of SEPP1+ macrophages from tumor compared to para-tumor showed upregulation of genes involved in cholesterol metabolism, lysosome and complement and coagulation cascades. Of note, up-regulated genes related to cholesterol were responsible for cholesterol efflux (such as APOC1, APOE and ABCA1) instead of synthesis. Analysis of database from prior studies on of early-stage LUAD also showed an enrichment of macrophages associated with cholesterol-efflux in early-stage LUAD. Furthermore, in vitro experiment showed that ABCA1 expression was significantly increased in THP-1-derived macrophages upon co-culture with A549.

Conclusions: Our results reveal a cluster of macrophages with enhanced cholesterol efflux in early-stage lung adenocarcinoma.

Keywords: macrophages, cholesterol efflux, lung adenocarcinoma

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.14 Urolithin a Alleviates Radiation Pneumonitis by Activating PINK1-PRKN-Mediated Mitophagy

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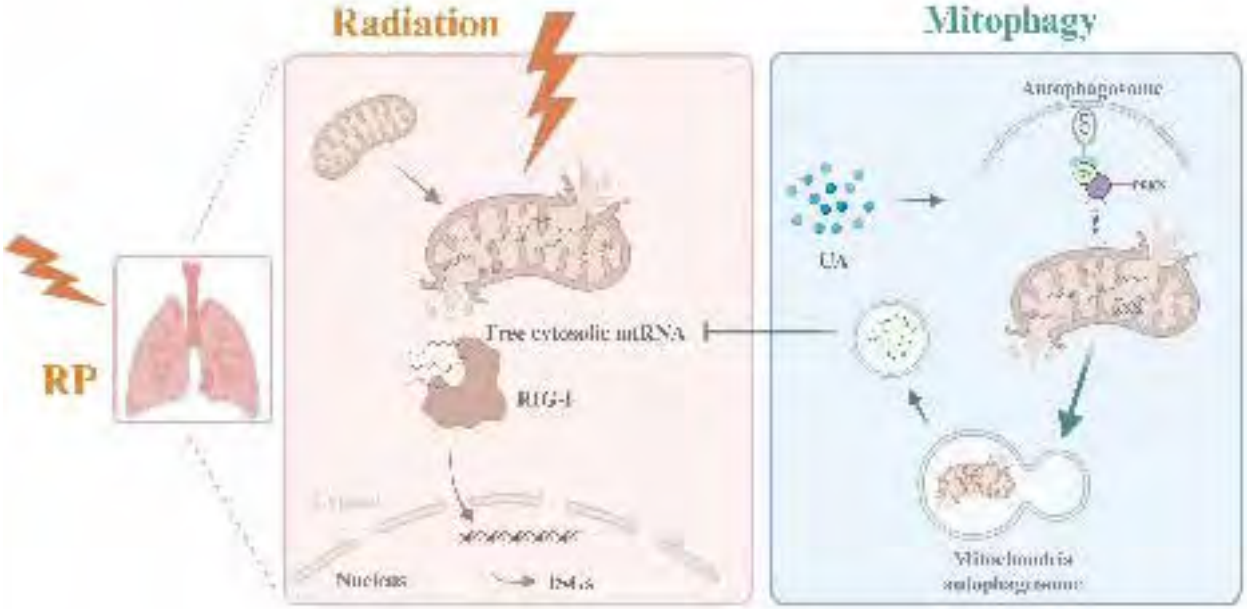
Introduction: Radiation pneumonitis (RP) is a common and severe complication of radiotherapy. Currently, effective treatments for RP are lacking. This study aims to investigate the role of radiation-induced PINK1/PRKN-mediated mitophagy and type I interferon responses in RP, and to evaluate the pharmacological effects of Urolithin A (UA) in regulating inflammation through mitophagy activation.

Methods: We established RP mouse models (20 Gy thoracic irradiation) and radiation-induced BEAS-2B cell models (6 Gy). Histopathological analysis, transcriptomic analysis, immunofluorescence, Micro-CT, Western blot, confocal microscopy, and RT-qPCR were used to systematically investigate mitochondrial damage, mtRNA release, RIG-I/MDA5-MAVS pathway activation, and changes in PINK1/PRKN-mediated mitophagy. Moreover, the effects of mitophagy inducers (UA) on inflammation regulation were analyzed.

Results: Radiation significantly caused mitochondrial damage in lung tissues, inducing mtRNA release and RIG-I/MDA5-MAVS-mediated type I interferon response. PINK1/PRKN-mediated mitophagy was significantly enhanced, clearing damaged mitochondria and reducing cytosolic mtRNA release, thereby suppressing inflammation. UA activation of mitophagy significantly alleviated pathological damage, reduced inflammatory cytokine levels, and inhibited excessive activation of the RIG-I/MDA5-MAVS pathway. Knockdown of PINK1 or PRKN weakened the protective effects of UA. Both in vitro and in vivo, UA reduced radiation-induced inflammation and improved lung tissue structure and function through mitophagy.

Conclusions: Radiation-induced mtRNA release activates the RIG-I/MDA5-MAVS pathway and triggers a type I interferon response, leading to inflammation. PINK1/PRKN-mediated mitophagy significantly alleviates inflammation by reducing cytosolic mtRNA release. As a mitophagy inducer, UA demonstrates therapeutic potential for RP, providing a new direction for the development of anti-inflammatory strategies.



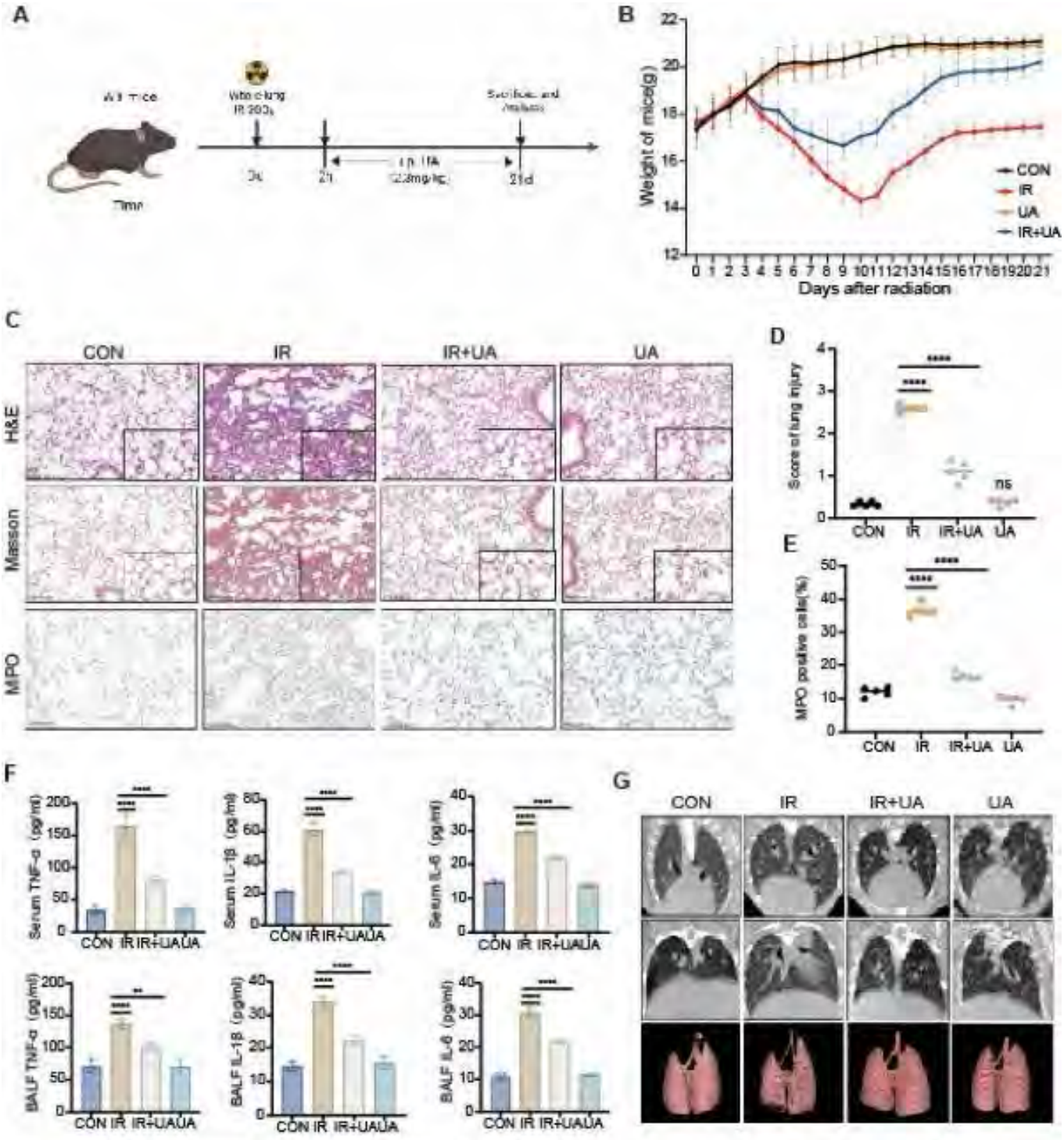


Fig. UA induces PINK1/PRKN-dependent mitochondrial autophagy to alleviate radiation-induced pneumonia in RP mice. (A) Urolithin A (UA, 2.3 mg/kg/day during 8 weeks i.p.) treatment of control and irradiated C57BL/6J mice. Created with BioRender.com.(B) Changes in grams of body weight of mice in different treatment groups during 21 days, n=10.(C) H&E and Masson's staining images. (Up). Representative images of IHC for MPO in the lung tissues. (Down).Scale bar=100μm, magnifying scale bar=25 μm,n=3. (D) The score of lung injury at day 21, n=5. (E)The MPO activity in lung tissues, n=5. (F) TNF-α、IL-1β、IL-6 in Serum and BALF, n=3. (G) Representative micro-CT images of lungs of irradiated and control mice. Horizontal (top row), trans-axial (middle row), and 3D micro-CT (bottom row) images were acquired two weeks after irradiation.

Keywords: mitophagy, radiation pneumonitis, Urolithin A

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.15 Drug Tolerance and Persistence to EGFR Inhibitor Treatment Are Mediated by an ILK-SFK-YAP Signaling Axis in Lung Adenocarcinoma

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Introduction: Lung cancer is the leading cause of cancer-related deaths world-wide. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have extensively improved patients outcomes. However, patients inevitably develop resistance against EGFR-TKIs. Epithelial-mesenchymal transition (EMT) in tumour cells is a known non-genetic resistance mechanism to EGFR tyrosine kinase inhibitors (TKI) that is also associated with worse outcome in patients. The progression towards EMT-mediated resistance exist a key transitory state of drug-tolerant-persistence (DTP), in which permits cancer cells to survival during drug treatment. Integrin-linked kinase (ILK) has been implicated in the pathogenesis of other cancers through the promotion of EMT and has recently been shown to be associated worse outcomes in patients treated with EGFR-TKIs. Therefore, we hypothesize that ILK may be an important mediator of DTP survival to EGFR-TKI treatment of lung adenocarcinoma (LUAD).

Methods: Gene Set Enrichment Analysis was performed on LUAD patient databases. Genetic and pharmacological manipulation of ILK were used to regulate ILK's function in lung cancer cells. Cell viability and clonogenic assays were used to evaluate osimertinib (Osi) sensitivity. Osi-resistant (OsiR) cells were made by dose-escalation. RNAseq, qPCR, and western blots were performed to assess expression levels. Confocal microscopy was used to evaluate YAP activity. Subcutaneous tumour were implanted in NRG mice to assess response to Osi in vivo. Immunohistochemistry and MSK-IMPACT sequencing were used correlate ILK staining with resistance mechanisms in patient samples.

Results: High ILK expression was found to be significantly correlated with an EMT expression signature in patients. Genetic suppression of ILK in LUAD cells reduced the viability of DTP cells by impairing SFK-YAP activation, ultimately improving Osi response. In addition, we found that LUAD cells in extracellular-matrix rich microenvironments have increased dependences on ILK-mediated cytoprotective effects during Osi treatment. These LUAD cells with high ILK expression are able to persist during EGFR-TKI treatment, progressing through EMT to develop EGFR-TKI resistance. To improve the translatability of our findings, we showed that pharmacological inhibition of ILK suppressed EMT, improved Osi response, and delayed the onset of Osi resistance in LUAD cells. Lastly, we found that high ILK expression in patient biopsies was associated with receptor tyrosine kinase-independent mechanisms of resistance to EGFR-TKIs and may be exploited as a biomarker for acquired resistance in LUAD.

Conclusions: Our results suggest that ILK is an important regulator of EGFR-TKI response and may be exploited as a predictor for acquired resistance, providing evidence for co-targeting ILK with EGFR to better control minimal residual disease and EGFR-TKI resistance in lung cancer.

Keywords: Targeted therapy, Drug resistance, Drug tolerant persisters

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.16 Identification of Deruxtecan-Induced Methylome Signature in NSCLC Cell Lines

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Introduction: Antibody drug conjugates (ADCs) with topoisomerase I (Topo-I) inhibitor payloads represent a promising therapeutic approach for lung cancer. However, predictive biomarkers of response to this new class of therapeutics remain undefined. In this study, we evaluated non-small cell lung cancer (NSCLC) cell lines treated with deruxtecan, a Topo-I inhibitor, using a validated cell-free DNA Methylome Sequencing (cfMethyl-Seq) assay to identify a unique methylome signature associated with response to deruxtecan.

Methods: Ten NSCLC cell lines were treated with deruxtecan (D), cisplatin (P), or control (C) at their IC50 concentrations. Methylation profiling was conducted using an improved cf-MethylSeq, covering 144,400 analyzable genomic regions (Stackpole et al, Nature Communications, 2022). The average methylation levels were calculated for every profiled genomic region, and Wilcoxon signed-rank tests (W) were utilized to identify differentially methylated regions (DMRs), focusing on relative changes in the sample pairs (comparing D vs. C and D vs. P). We used two replicates for each sample, and to avoid duplicated samples in the statistical testing, we performed analysis on the first replicate (r1) and second replicate (r2) independently. To confirm the signature is specific to deruxtecan, rather than being a marker of chemotherapeutic effect in general, we selected DMRs based on the following criteria: 1) P-value < 0.01 in the one-sided W of r1 or r2 between D and C. 2) P-value < 0.05 in the one-sided W of r1 or r2 between D and P. 3) In replicate, P-value < 0.05 in the one-sided (same directionality) W between D and C. 4) In replicate, P-value < 0.1 in the one-sided (same directionality) W between D and P. Identified DMRs were mapped to gene promotor regions annotated using the GeneHancer database to determine associated genes within the DMRs.

Results: Whole methylome sequencing identified 30 hypermethylated DMRs specific to deruxtecan-treated NSCLC cell lines. These regions were linked to 64 genes. Cross-validating these genes with genecards.org, 25 genes (39%) encode recognized proteins (Table 1).

Conclusions: In vitro analysis of NSCLC cell lines treated with deruxtecan revealed a unique methylation signature characterized by 30 DMRs and 25 associated genes encoding recognized proteins. This represents the first methylome signature associated with deruxtecan response, offering guidance for treatment strategies, including potential ex vivo assays or a theranostic approach using small doses of ADC. We aim to validate this signature in patient plasma samples to evaluate its potential as a predictive biomarker for response to deruxtecan-based ADCs.

Chromosome	Gene symbol	Protein (Genecards.org)
1	DPYD	Dihydrouracil Dehydrogenase
1	LRRC8B	Leucine Rich Repeat Containing 8 VRAC Subunit B
1	TPRG1L	Tumor protein P63-Regulated Gene 1-Like Protein
2	NRXN1	Neurexin 1
2	SPRED2	Sprouty related EVH1 Domain Containing 2
3	GATA2	GATA Binding Protein 2
3	LRCH3	Leucine Rich Repeats and Calponin Homology Domain Containing 3
4	SLC30A9	Solute Carrier Family 30 Member 9
6	TFAP2A	Transcription Factor AP-2 Alpha
7	MRPS33	Mitochondrial Ribosomal Protein S33
10	GBF1	Golgi-Specific Brefeldin A Resistance Factor 1
11	GPR137	G Protein-Coupled Receptor 137
11	PAFAH1B2	Platelet Activating Factor Acetylhydrolase 1b Catalytic Subunit 2
14	SAMD4A	Sterile Alpha Motif Domain Containing 4A
16	KATNB1	Katanin Regulatory Subunit B1
16	ZKSCAN2	Zinc Finger with KRAB and SCAN Domains 2
17	CPD	Carboxypeptidase D
17	CHRNE	Cholinergic Receptor Nicotinic Epsilon Subunit
17	C17orf107	Chromosome 17 Open Reading Frame 107
17	NEK8	NIMA Related Kinase 8
17	RAB34	RAB34, Member RAS Oncogene Family
17	RPL23A	Ribosomal Protein L23a
17	TLCD1	TLC Domain Containing 1
17	TBCD	Tubulin Folding Cofactor D
19	IL11	Interleukin 11

Keywords: whole methylome sequencing, deruxtecan, NSCLC cell lines

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.17 GNAZ as a Tumor Suppressor Marker Inhibits Tumor Development Through Interaction With the KIF11 Protein

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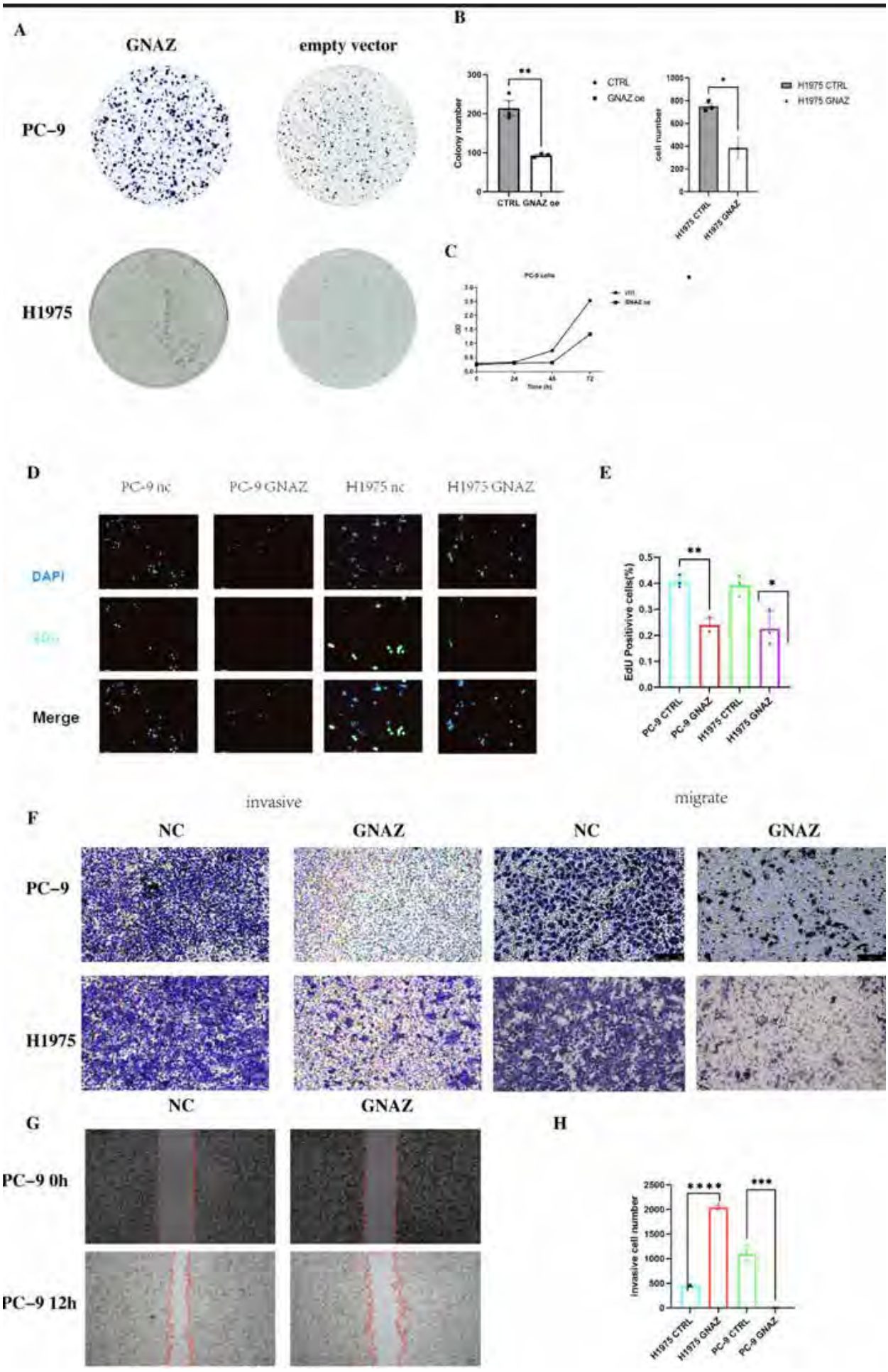
Introduction: Current research on lung cancer primarily focuses on immunotherapy and targeted therapy, while studies on small molecule inhibitors remain limited. GNAZ is a subunit of the G protein involved in the MAPK pathway mediated by EGFR and plays a role in vesicular transport within the body. Clinical data analysis reveals that lung adenocarcinoma patients with high GNAZ expression have a higher five-year survival rate. In the EGFR-resistant cell lines PC-9 and H1975, overexpression of GNAZ significantly reduces cell proliferation, invasion, and migration. Immunofluorescence analysis indicates that GNAZ overexpression is associated with vesicular transport and may be involved in autophagy. We performed mass spectrometry and transcriptome sequencing, which revealed that GNAZ interacts with the KIF11 gene and plays a regulatory role in the WNT signaling pathway, potentially involving the WNT-Ca2+ pathway.

Methods: Mass spectrometry was used to detect protein interactions, while transcriptome sequencing was conducted to identify upstream genes. Cell proliferation, migration, and invasion abilities were assessed using scratch assays, colony formation assays, CCK-8 assays, EdU proliferation assays, and Transwell assays. Western blot (WB) was employed to validate protein expression, and quantitative PCR (Q-PCR) was used to verify RNA-level expression.

Results: Our findings suggest that GNAZ functions as a tumor suppressor gene by interacting with KIF11 and regulating the WNT signaling pathway. KIF11 plays a role in endoplasmic reticulum stress regulation and contributes to tumor progression by promoting invasion and metastasis. Therefore, KIF11 inhibitors hold significant potential as small molecule inhibitors for cancer treatment.

Conclusions: In summary, our study identifies GNAZ as a potential tumor suppressor gene that inhibits lung cancer progression by interacting with KIF11 and regulating the WNT signaling pathway. Functional experiments demonstrate that GNAZ overexpression significantly suppresses tumor cell proliferation, migration, and invasion, while KIF11 is implicated in endoplasmic reticulum stress and tumor metastasis.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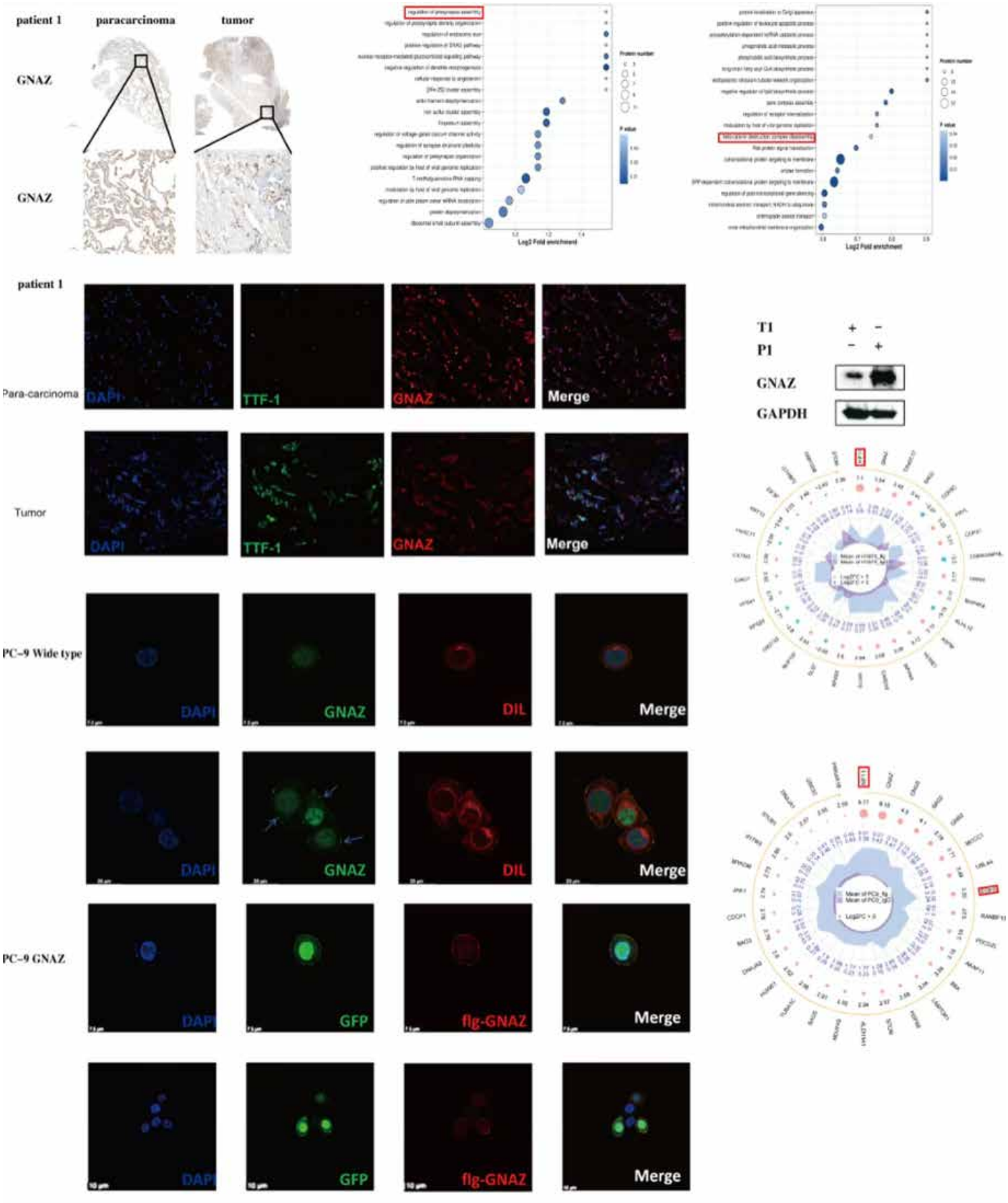

Keywords: lung cancer, EGFR mutation, vesicular transport

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.18 Crosstalk Between Oncogenic Signaling Pathways and Immune Checkpoint Proteins in Pleural Mesothelioma

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Introduction: Pleural mesothelioma (PM) is an aggressive malignancy primarily associated with asbestos exposure. It is characterized by an inflammatory tumor microenvironment, poor prognosis, and resistance to conventional therapies. Chronic inflammation-induced reactive oxygen species (ROS) are believed to play a key role in PM development. However, very little is known about the mechanism of PM development and immune checkpoint protein (ICP) expression. Understanding the molecular mechanisms underlying PM development and ICP expression is crucial for developing more effective strategies for PM prevention and management. This study aims to elucidate mechanisms that link ROS exposure to oncogenic signaling pathways and immune checkpoint protein (ICP) expression.

Methods: Mesothelial (Met5a and NP2-hTERT) and PM (SPC212 and MSTO-211H) cells were treated with xanthine (X) and xanthine oxidase (XO) to produce ROS. Dichlorodihydrofluorescein Diacetate (DCDFA) assay was performed to assess ROS generation using the X/XO system. Hoechst-33342 and PI staining were done to check ROS-induced cytotoxicity. Oxidative stress-mediated changes in cell migration and behavior were evaluated using live cell imaging microscopy. Protein expression levels and phosphorylation of MAPK, AKT, and YB-1 were determined by immunoblotting. Expression of the ICPs PDL1, PDL2, PVR, PVRL1, and VISTA was investigated by qRT-PCR. Furthermore, pharmacological inhibitors for AKT, MEK, and RSK were used to check for pathway dependencies of ROS-induced changes.

Results: X/XO treatment resulted in dose-dependent ROS induction in all four cell models. ROS mediated an increase in cell migration and changes in cell morphology at concentrations that resulted in only minimal toxicity in the investigated models. Moreover, it increased the phosphorylation of ERK, AKT, and YB-1, indicating the activation of key oncogenic signaling pathways. With respect to ICPs, the expression of PDL1 and PDL2 was increased after ROS treatment in PM as well as in mesothelial cells. The MEK and RSK inhibitors not only abolished the effect of ROS but also restored the expressions of PDL1 and PDL2.

Conclusions: This study demonstrates that ROS activates MAPK, AKT, and YB-1 signaling and also increases cell migration and immune evasion in PM cells. Importantly, these effects are also present in mesothelial cells, from which PM development ensues. Furthermore, the study also observed a notable crosstalk between YB-1 phosphorylation and PDL1/2 expression, suggesting YB-1 as a new potential target to interfere with immune evasion in PM.

Keywords: Reactive Oxygen Species, Pleural Mesothelioma, Immune Checkpoint Proteins

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.19 SIN3A/MIR22HG/Beclin1 Axis Regulates Both Autophagy and Ferroptosis in Lung Adenocarcinoma

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Introduction: Long non-coding RNAs (lncRNAs) have been implicated in tumourigenesis. Our previous study found that the lncRNA MIR22HG was significantly underexpressed in lung adenocarcinoma by RNA-seq analysis and was associated with poor prognosis. MIR22HG is located on chromosome 17p13.3, and MIR22HG is susceptible to loss and methylation during tumourigenesis, and its dysfunction has been implicated in a variety of human diseases. However, how dysregulation of MIR22HG expression and activity affects the progression of lung adenocarcinoma (LUAD) remains unknown.

Methods: Lentiviral-mediated gene overexpression and in vivo experiments were carried out to confirm the tumor-suppressive effect of MIR22HG. LC3-GFP-RFP adenovirus was transfected into LUAD cells, followed by siRNA-mediated gene silencing, and formation of autophagic vesicles was observed through confocal microscopy. Western blotting was used to analyze the levels of key autophagy proteins after gene overexpression and silencing. ROS levels were measured using siRNA-mediated flow cytometry. The levels of autophagy and ferroptosis key proteins were analysed by Western blotting after overexpression or silencing of genes. The direct binding of SIN3A to MIR22HG was confirmed through a RIP assay. Response experiments confirmed the upstream position of SIN3A with respect to MIR22HG and its inhibitory effect on MIR22HG expression.

Results: In vivo experiments showed that overexpression of MIR22HG significantly inhibited lung adenocarcinoma proliferation. Mechanistic analysis showed that overexpression of MIR22HG increased the expression of autophagy-associated proteins LC3B and Beclin1, and decreased the expression of p62 protein and iron oxidation-regulated proteins GPX4 and SLC7A11. Knocking down MIR22HG had the opposite effect. What's more, the MIR22HG and Beclin1 replication assay showed that MIR22HG exerts oncogenic effects by mediating the combined effects of autophagy and ferroptosis activation of Beclin1. In addition, the combination of RIP and reversion experiments indicated that the low expression of MIR22HG in lung adenocarcinoma was due to the inhibition of the binding protein SIN3A, which binds to MIR22HG and inhibits its expression.

Conclusions: The findings suggest that MIR22HG has a synergistic oncostatic impact by inducing autophagy and ferroptosis through Beclin1. Additionally, The reduced expression of MIR22HG in lung adenocarcinoma arises from the binding of SIN3A to it and subsequent inhibition of expression.

Keywords: autophagy, ferroptosis, lung adenocarcinoma

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.20 Targeting BTN1A1 in Pd=D-L1-Negative NSCLC: A Clinically Actionable Immune Checkpoint for Docetaxel-Based Combination Therapy

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Introduction: Non-small cell lung cancer (NSCLC) remains challenging to treat due to its high heterogeneity, intrinsic resistance, and refractoriness to current immunotherapies. BTN1A1 has recently been identified as a novel immune checkpoint predominantly expressed in dormant or chemoresistant cancer cells, with expression patterns mutually exclusive to PD-L1. This study aimed to evaluate the therapeutic efficacy of anti-BTN1A1 and anti-PD-L1 antibodies, combined with docetaxel, in relation to BTN1A1 and PD-L1 expression in NSCLC patient-derived organoids (PDOs).

Methods: Patient-derived organoids (PDOs) were generated from NSCLC patient samples to investigate the differential expression of BTN1A1 and PD-L1. The therapeutic efficacy of monoclonal antibodies targeting BTN1A1 and/or PD-L1, administered alone or in combination with docetaxel, was evaluated by measuring organoid viability and apoptosis induction. Docetaxel, a microtubule-stabilizing chemotherapeutic agent known to disrupt tumor cell proliferation and enhance immunogenic cell death, was tested to determine potential synergistic effects when used alongside checkpoint inhibitors.

Results: Combination therapy involving docetaxel significantly reduced PDO viability and robustly induced apoptosis compared to antibody monotherapy alone. The mutually exclusive expression of BTN1A1 and PD-L1 was confirmed in PDOs, resulting in differential responses to either anti-BTN1A1 or anti-PD-L1 antibodies. Notably, docetaxel treatment increased BTN1A1 expression, enhancing the response to anti-BTN1A1 antibody treatment relative to anti-PD-L1 therapy, indicating a potential mechanism for synergistic effects.

Conclusions: Combining anti-BTN1A1 or anti-PD-L1 antibodies with docetaxel markedly enhanced therapeutic outcomes in NSCLC PDO models. The elevated BTN1A1 expression observed post-docetaxel treatment highlights anti-BTN1A1 therapy as a promising strategy for PD-L1-negative NSCLC patients refractory or resistant to current PD1/PD-L1 treatments. These findings suggest significant clinical potential for combination strategies targeting diverse immune evasion pathways in treatment-resistant NSCLC.

Keywords: Nelmastobart, BTN1A1, NSCLC

P2.02.21 CTNNB1 Activates LINC01426 to Promote Metabolic Reprogramming in Lung Adenocarcinoma Cells by Regulating NFAT5 Nuclear Translocation

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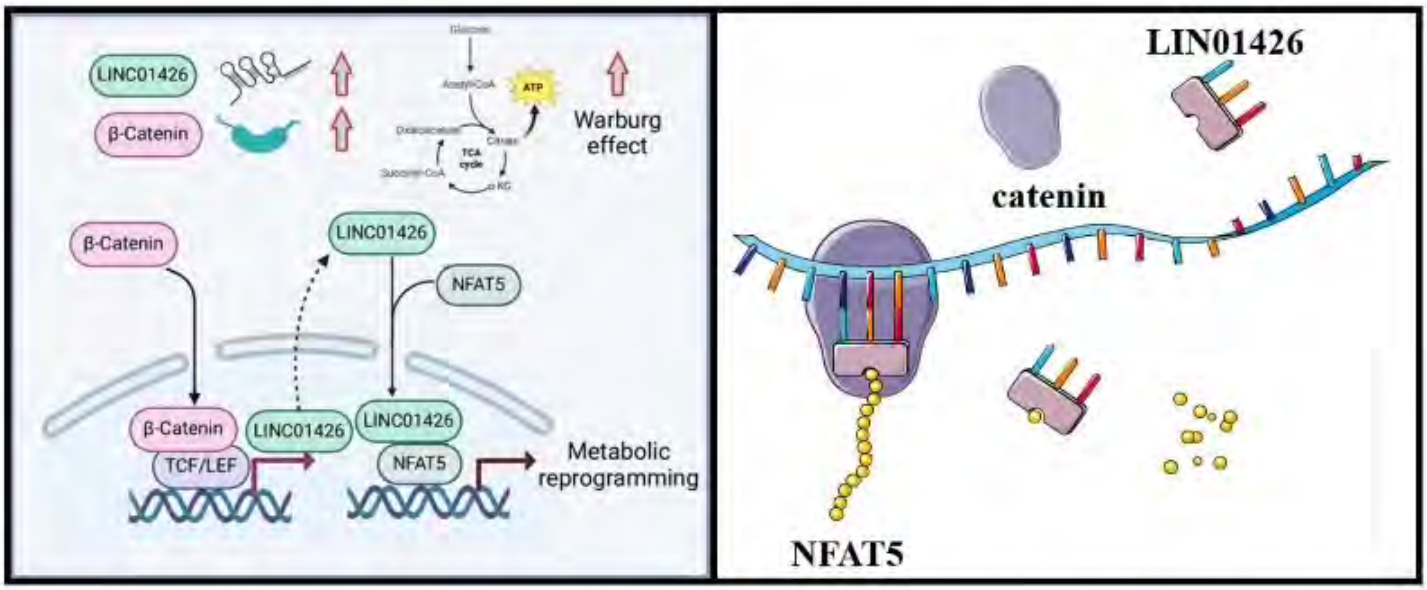
Introduction: Lung adenocarcinoma (LUAD) is mainly detected at advanced stages, with poor prognosis. This paper elucidated the mechanism of LINC01426 in regulating LUAD cells.

Methods: LncRNAs with differential expression in LUAD tissues were analyzed from the GEO database and the TCGA-LUAD database, and the upstream elements of LINC01426 were predicted by the TFBS R package and the JASPAR website. Subsequently, we screened the genes similar to LINC01426 in the TCGA-LUAD database by R Corr package and used KEGG enrichment analysis to derive the pathways that these genes were enriched on. Finally, we analyzed the screened genes by functional validation experiments to verify their effects on malignant behaviors and glycolysis.

Results: LINC01426 was raised in LUAD, and Tissue microarray analysis uncovered that the staining intensity of LINC01426 was notably higher in LUAD tissues. Patients with high LINC01426 expression had lower survival cycles. LINC01426 was regulated by CTNNB1, and CTNNB1 could bind to the LINC01426 promoter and transcriptionally activate LINC01426 expression. Moreover, LINC01426 could regulate the glycolysis of LUAD cells through NFAT5. Knockdown of LINC01426 or NFAT5 substantially inhibited the metabolic reprogramming, which in turn hindered LUAD cell growth.

Conclusions: CTNNB1 transcriptionally activates LINC01426, which binds to NFAT5 in the cytoplasm and thus promotes NFAT5 nuclear translocation, leading to metabolic reprogramming and accelerating LUAD progression.



Mechanism diagram of CTNNB1/LINC01426/NFAT5 regulating malignant behavior of Lung Adenocarcinoma

Keywords: Lung adenocarcinoma, Metabolic reprogramming, LINC01426

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.22 Analysis of FGF19 in Lung Squamous Cell Cancer Tissue and Cell Models

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Introduction: Fibroblast growth factor 19 (FGF19) is a member of the FGF family of growth factors and signals via binding to the cell surface receptor tyrosine kinase fibroblast growth factor receptor 4 (FGFR4). Overexpression of FGF19 caused by gene amplification has been identified as an oncogenic driver in several types of malignancies including lung squamous cell carcinoma (SCC). However, the link between FGF19 gene amplification, transcript expression, protein expression, protein secretion and sensitivity of SCC cells to FGFR inhibitors has not been well established. The aim of the current study was to identify possible gene dose alterations of FGF19 in a panel of SCC cell lines and in surgical specimens of SCC patients from Central Europe. Gene dose data were compared to gene and protein expression data. Additionally, the sensitivity of SCC cell lines against a specific FGFR4 inhibitor and a pan-FGFR inhibitor was evaluated in 2D and 3D cell culture.

Methods: FGF19 gene dose levels were evaluated by fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH) and qPCR. FGF19 transcripts were analyzed by qRT-PCR. Protein levels of FGF19 were analyzed by immunohistochemistry and ELISA. Testing of SCC cell lines for their sensitivity against a selective FGFR4 inhibitor (BLU9931) and a pan-FGFR inhibitor (Erdafitinib) was done in 2D monolayer and in 3D spheroid culture. Selected cell lines with high and low FGF19 levels were additionally tested for their stemness, sprout formation and migratory ability.

Results: Gene dose data analyzed by FISH, aCGH and qPCR showed a good overall agreement. Two of 14 SCC cell lines displayed gene amplifications with all three detection methods. In contrast, none of the 23 tissue specimens showed FGF19 gene amplification. Several SCC cell lines showed very high FGF19 transcript and protein expression in absence of gene amplification. FGF19 cellular protein levels, secreted protein levels and mRNA levels showed significant correlations but neither value correlated with gene dose. IC50 values of SCC cell lines varied between 1.5 µm - 12.8 µm and between 1.0 µm - 14.7 µm for BLU9931 and Erdafitinib, respectively, in 2D cultures and were generally higher in 3D spheroid growth assays. All cell lines were able to form spheroids and treatment with both inhibitors at concentrations above the IC50 values did not block the formation of spheroids. No significant correlations between inhibitors and FGF19 mRNA expression, protein expression and gene dose values were observed except for the correlation between BLU9931 sensitivity and FGF19 amplification assessed by FISH.

Conclusions: Taken together, our results suggest that FGF19 amplification is not as common in SCC of Central European patients as the 37% previously found in Chinese SCC patients. High FGF19 mRNA and protein expression in SCC cell lines is independent of FGF19 gene amplification but may not be a good predictor of FGFR inhibitor sensitivity.

Keywords: Squamous cell carcinoma, FGF19, Gene Amplification

P2.02.23 Screening of Autophagy Related Genes in Lung Squamous Cell Carcinoma and Study of Their Mechanisms of Action

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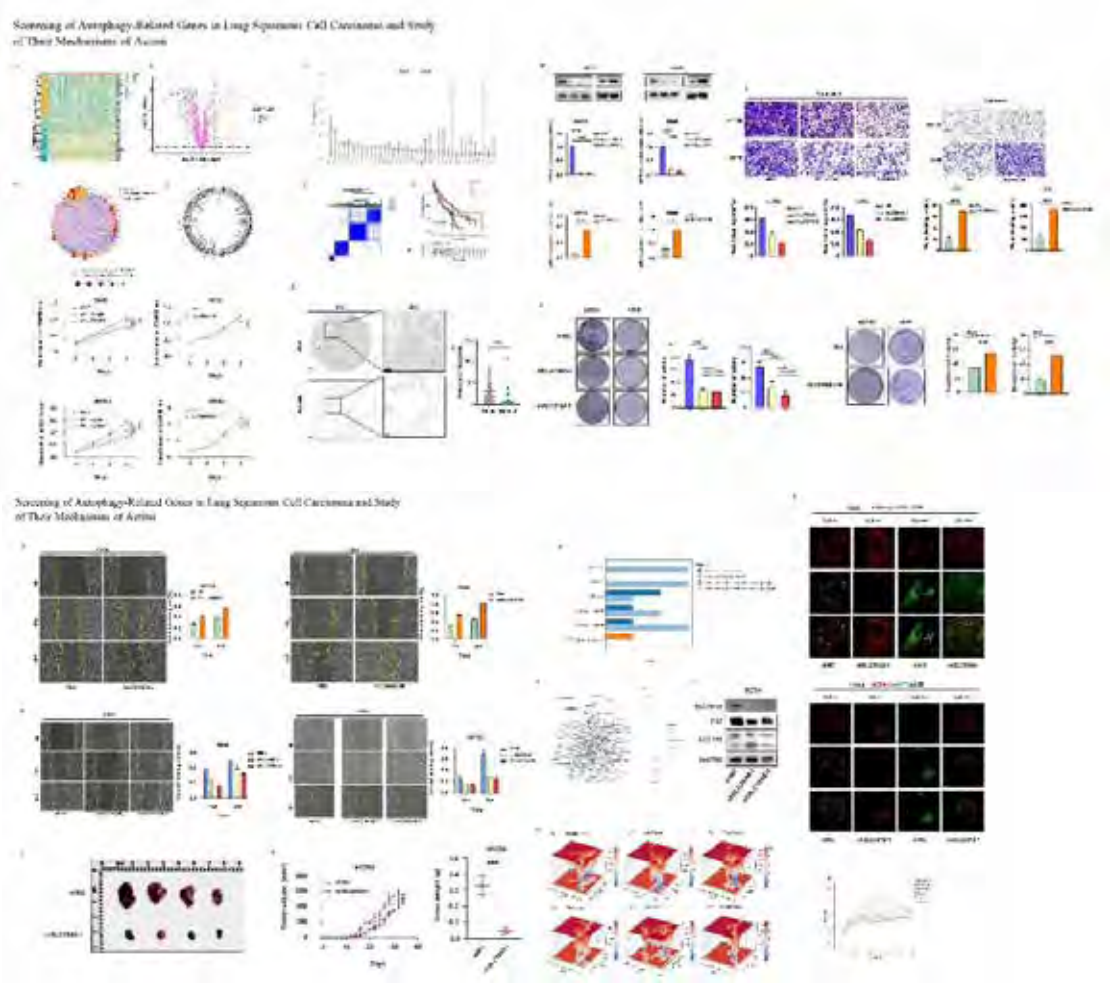
Introduction: Lung squamous cell carcinoma (LUSC) is a common, aggressive lung cancer subtype with high recurrence and metastasis rates, despite treatment advances. Autophagy-related genes are crucial in cancer progression and treatment response, but their roles in LUSC prognosis are unclear. This study explores these genes' impact on LUSC prognosis, focusing on the key gene SLC39A8, and seeks potential targeted drugs. The goal is to offer new insights and therapeutic targets for precise LUSC treatment.

Methods: The study analyzed transcriptomic data from LUSC patients using TCGA and GEO datasets (GSE12472, GSE157010, GSE157009) to identify autophagy-related genes. Consensus clustering divided patients into four subgroups, with subgroup A having the worst prognosis. Immunohistochemistry confirmed high SLC39A8 expression in subgroup A. LUSC cell models with altered SLC39A8 expression were created to study its impact on the transcriptome through RNA sequencing. SLC39A8's biological effects were further examined using Western blotting, dual fluorescence reporter systems, migration and proliferation assays, and tumorigenesis experiments in mice. Finally, AutoDock Vina was used for virtual screening.

Results: This study highlighted SLC39A8's key role in LUSC development, showing its high expression linked to poor prognosis. Silencing SLC39A8 increased autophagy and reduced cell growth and movement. Six potential small-molecule inhibitors were identified for targeted LUSC treatment.

Conclusions: This study highlights the crucial role of SLC39A8 in LUSC and suggests potential small-molecule inhibitors for targeted therapy. The findings offer important theoretical insights and propose new directions for drug development and precision therapy in LUSC.



Keywords: Lung Squamous Cell Carcinoma, SLC39A8, Autophagy

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.24 Zongertinib Has Activity Against NRG1 Fusion Positive Tumor Cells

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Introduction: Neuregulin 1 (NRG1) gene fusions are clinically actionable oncogenic driver mutations in non-small cell lung cancer (NSCLC) and other tumors, promoting tumor growth by binding to HER3 and inducing HER2-HER3 heterodimerization, which enhances downstream signaling. Therapeutic strategies targeting HER2-HER3 signaling have so far shown only modest activity in patients with NSCLC bearing NRG1 fusions. A better understanding of the signaling networks in cancer cells expressing NRG1 fusions is essential for developing effective therapeutic strategies for this patient population. Zongertinib, a HER2-specific tyrosine kinase inhibitor (TKI), has demonstrated notable clinical activity against HER2 mutant tumors. However, it is unclear whether blockade of HER family signaling with zongertinib is effective against NRG1 fusion-positive cancer cells.

Methods: We investigated the efficacy of zongertinib and other TKIs in NRG1 fusion-positive cancer cells using a panel of 16 Ba/F3 models engineered to express various HER family members in combination with NRG1 fusions as well as human cell line models of NRG1 fusion-positive cancer, LUAD0061AS3 (SLC3A2-NRG1) and MDA-MB-175-VII (DOC4-NRG1).

Results: We observed that zongertinib inhibited downstream signaling and tumor cell growth in NRG1 fusion-positive cells, most notably in those expressing HER2 and HER3, while sparing wild-type EGFR. EGFR signaling can also be activated in cells expressing NRG1 fusions, and we observed that dependency on EGFR and HER2 signaling varied among NRG1 fusion-positive cancer cell lines. Likewise, pan-HER family TKIs, poziotinib and afatinib, showed activity against NRG1 fusion-positive cells that expressed EGFR. This preclinical activity is consistent with the clinical responses in NRG1 fusions previously reported in the phase 1A of zongertinib.

Conclusions: Our findings indicate that zongertinib is a promising therapeutic approach for patients with NRG1 fusion-positive malignancies, particularly those expressing HER2 and HER3.

Keywords: NSCLC, NRG1, zongertinib

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.25 Elevated SGO2 Expression in Lung Adenocarcinoma Promotes Migration and Invasion by Regulating MAD2, Correlating With Poor Prognosis

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Introduction: Lung adenocarcinoma represents a globally prevalent malignant tumor characterized by its high mortality rate, primarily attributed to its aggressive invasive and metastatic potential. SGO2, a critical protein involved in the regulation of cell division, has been implicated in the progression of multiple malignancies. Despite its recognized role in various cancers, the biological functions of SGO2 in the context of Lung adenocarcinoma remain underexplored, necessitating further investigation to elucidate its potential mechanisms and therapeutic implications.

Methods: The Cancer Genome Atlas (TCGA) database was utilized to analyze the expression levels of SGO2 in a cohort of 206 lung adenocarcinoma patients compared to 200 non-neoplastic control samples. Subsequently, immunohistochemical staining was performed on a subset of 21 LUAD tissue samples obtained from Nanjing Second Hospital to validate the findings from the TCGA database. The functional role of SGO2 in the H1299 cell line was assessed through a series of in vitro experiments, including Western blotting to evaluate protein expression, CCK-8 assays to measure cell proliferation, Transwell assays to assess cell invasion, wound healing assays to analyze cell migration, and flow cytometry to examine cell cycle distribution. Additionally, the influence of SGO2 on the regulation of MAD2 expression was explored to further investigate the molecular mechanisms underlying SGO2's role in LUAD progression.

Results: The enhancement of SGO2 expression in Lung adenocarcinoma tissues is significantly associated with a poor prognosis in patients. A reduction in SGO2 expression markedly decreases the proliferative, migratory, and invasive capabilities of H1299 cells, a phenomenon that may be attributed to the regulation of MAD2 expression by SGO2.

Conclusions: SGO2 plays a critical role in regulating the malignant behaviors of lung adenocarcinoma cells, including proliferation, migration, and invasion, by modulating the expression of MAD2, thereby significantly contributing to the molecular pathogenesis of lung adenocarcinoma.

Keywords: lung adenocarcinoma, SGO2, MAD2

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.26 Establishment of a HER2 Overexpressing Lung Squamous Cell Carcinoma Cell Line Sensitive to Targeted and Cytotoxic Therapies

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Introduction: Lung squamous cell carcinoma (LSCC) accounts for approximately 30% of non-small cell lung cancer (NSCLC) cases and is often characterized by distinct genomic alterations compared to lung adenocarcinoma. While HER2 mutations, amplifications, and overexpression are well-documented in lung adenocarcinoma, their presence and therapeutic implications in LSCC remain poorly understood. Targeted therapies against HER2 have primarily shown efficacy in HER2-driven lung adenocarcinomas; however, their role in LSCC has not been clearly established. Here, we report the development and characterization of a novel LSCC cell line derived from resected patient specimens, which exhibits HER2 overexpression and sensitivity to HER2-targeted therapies, including trastuzumab deruxtecan and afatinib. This study aims to provide insights into the therapeutic potential of HER2 inhibition in LSCC and explore the feasibility of HER2-directed treatment strategies for this histological subtype.

Methods: A primary LSCC cell line was successfully established from surgically resected tumor specimens of a previously untreated 47-year-old Japanese male patient with a heavy smoking history. The cells were cultured and characterized for HER2 expression levels using quantitative PCR (qPCR). Whole genome sequencing (WGS) were conducted to evaluate additional genomic alterations and transcriptomic profiles. To evaluate drug sensitivity, an MTT assay was performed to assess the efficacy of trastuzumab deruxtecan and afatinib, along with standard chemotherapy agents, including carboplatin and paclitaxel, which are commonly used in LSCC treatment. The half-maximal inhibitory concentration (IC50) values for each drug were calculated to determine the degree of drug responsiveness. Furthermore, the clinical course of the parental patient, who later experienced recurrence post-surgery, was reviewed to correlate in vitro findings with actual treatment outcomes.

Results: The established LSCC cell line exhibited strong HER2 overexpression and amplification as confirmed by qPCR and WGS, but HER2 exon 20 mutations were not detected. Drug sensitivity assays demonstrated a significant reduction in cell viability upon exposure to trastuzumab deruxtecan and afatinib, with IC50 values of 65 nM and 57 nM, respectively, indicating strong HER2 dependency in this LSCC model. In addition, the cytotoxic agents carboplatin and paclitaxel significantly inhibited cell proliferation, with IC50 values of 8 μM and 10 nM, respectively. Notably, the patient from whom the LSCC cell line was derived later experienced disease recurrence and demonstrated a good clinical response to the combination of carboplatin and paclitaxel, supporting the translational relevance of our in vitro findings.

Conclusions: This study reports the first HER2-overexpressing LSCC cell line with confirmed sensitivity to HER2-targeted therapies and cytotoxic agents. The correlation between HER2 overexpression and therapeutic response suggests that a subset of LSCC patients may benefit from HER2-directed treatment strategies. These findings underscore the need for biomarker-driven therapeutic approaches in LSCC and advocate for HER2 testing as part of the molecular characterization of LSCC. Our newly established model provides a valuable platform for future research on HER2-driven oncogenesis in LSCC and potential clinical trials exploring HER2-targeted interventions in this histological subtype.

Keywords: cell line, lung squamous cell carcionma, HER2

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.27 Osimertinib Increases Expression of HER2 and Combination With T-DXd, a HER2-Directed ADC, Enhances Its Efficacy in PDX Models of EGFR Mutant NSCLC

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Introduction: Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that has demonstrated efficacy in the first-line treatment of advanced or metastatic EGFR-mutant non-small cell lung cancer. Despite clinical benefit, most patients become refractory to osimertinib, highlighting the need for combination strategies to maximize the duration of response or address osimertinib resistance. Trastuzumab deruxtecan (T-DXd; DS-8201) is a human epithelial growth factor receptor 2 (HER2)-directed antibody drug conjugate (ADC) with demonstrated antitumor activity against a range of tumor types.

Methods: Using multiomic studies, including proteomics and scRNAseq, we identified a cell surface marker whose levels are increased upon acute and chronic osimertinib treatment, both in vitro and in vivo. We then assessed the effect of an ADC against the cell surface marker identified in combination with osimertinib across 18 patient-derived xenografts (PDX) in vivo.

Results: Our research revealed that both acute and prolonged exposure to osimertinib leads to a significant upregulation of HER2. Furthermore, osimertinib treatment promotes increased EGFR-HER2 heterodimerization and enhances HER2 internalization. Single-cell RNA sequencing analysis of tumors treated with osimertinib identified a specific cell subpopulation with upregulated HER2 expression, which was eradicated when xenograft-bearing animals received a combination treatment of osimertinib and T-DXd. Importantly, the combination of T-DXd and osimertinib demonstrated superior in vivo efficacy compared to osimertinib alone in one of three Ex19del, three of six L858R, and four of five Ex20Ins EGFR TKI naïve mutant PDX models. Furthermore, in four PDX models derived from osimertinib-resistant patients, T-DXd treatment resulted in regression in all the models tested.

Conclusions: Our preclinical data emphasizes that prolonged osimertinib treatment can increase HER2 expression, showcasing the potential of a new combination treatment strategy with T-DXd. This approach could strengthen osimertinib's effectiveness as first-line treatment or address resistance to osimertinib.

Keywords: NSCLC, Osimertinib, T-DXd

P2.02.28 Proteasome Inhibitor Causes Proteotoxic Death and Reshapes TME in LKB1-Deficient NSCLC by Blocking Er-Stress Repair Addiction

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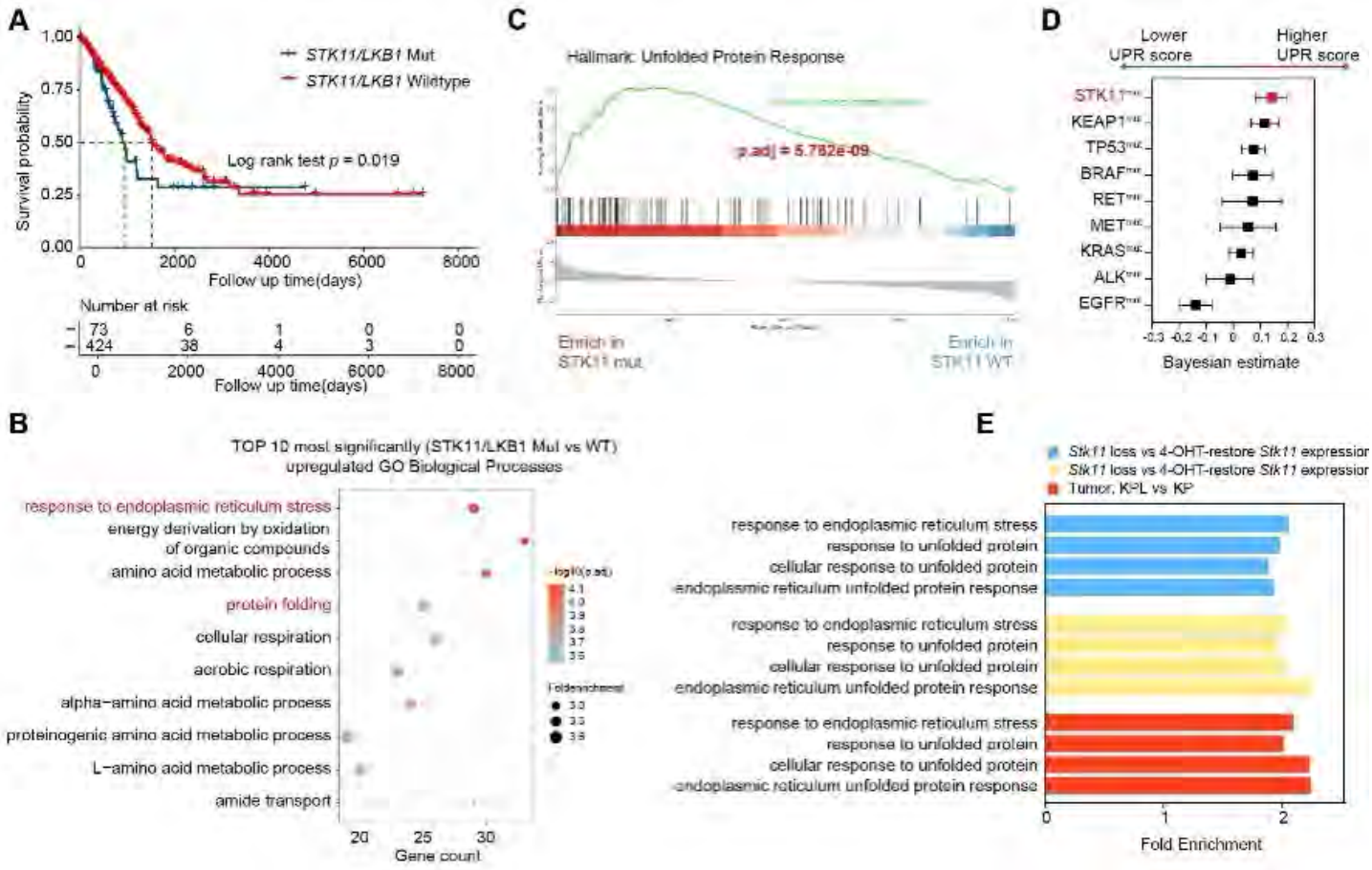
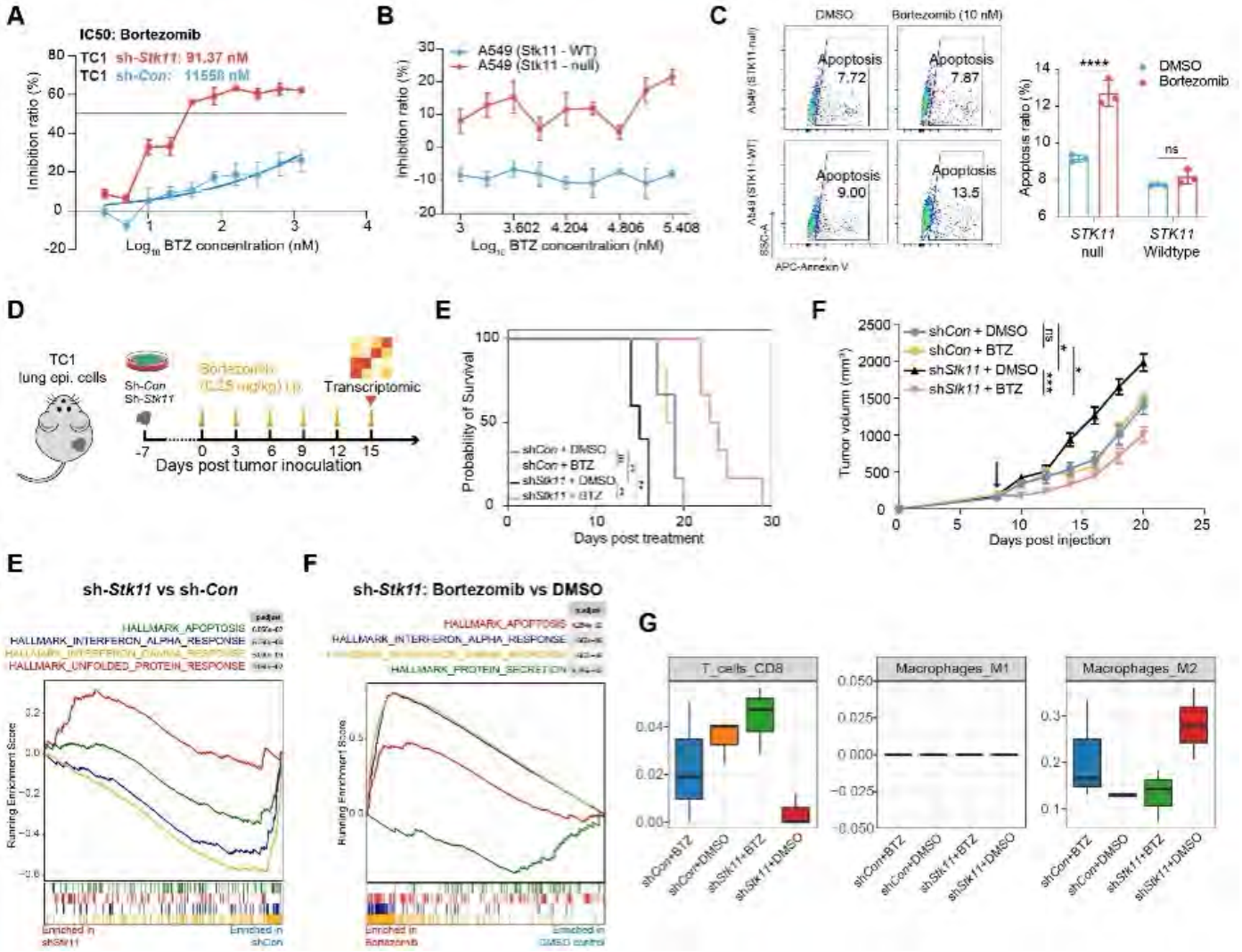
Introduction: STK11/LKB1 loss-of-function mutation is associated with extremely poor prognosis and multi-therapy resistance in non-small cell lung cancer (NSCLC), yet effective treatments remain elusive.

Methods: Integrated transcriptomic analyses were performed on human lung adenocarcinoma (LUAD) cohorts, Lkb1-knockout/rescue murine cell lines, and KrasLSL-G12D/+ Trp53flox/flox GEMMs with lentiviral Cre-induced Lkb1 deletion. The efficacy of proteasome inhibitor was assessed in vitro through proliferation assays and flow cytometry, and in vivo using syngeneic tumor models. Mechanistic insights were derived from bulk mRNA sequencing and immune deconvolution analyses.

Results: LKB1-deficient LUAD patients exhibited significantly reduced survival. Transcriptomic profiling revealed heightened reliance on endoplasmic reticulum (ER) stress resolution via unfolded protein response (UPR) in LKB1-deficient tumors, validated across murine models and human systems. The proteasome inhibitor bortezomib demonstrated selective cytotoxicity against murine TC1-shLkb1 and LKB1-null human A549 cells. In syngeneic in vivo models, bortezomib specifically inhibited Lkb1-deficient tumor growth and extended survival without affecting Lkb1-proficient tumors. Molecular analyses revealed bortezomib-mediated apoptosis restoration in Lkb1-deficient tumors, concomitant with rescued interferon-α/γ signaling. Immune profiling showed enhanced CD8+ T cell infiltration and reduced M2-polarized macrophages in treated tumors, indicating tumor immune microenvironment (TIME) reprogramming.

Conclusions: LKB1-deficient lung adenocarcinoma exhibits UPR pathway addiction to mitigate lethal ER stress. Proteasome inhibitor selectively targets this vulnerability through dual mechanisms: direct induction of proteotoxic crisis and TIME remodeling toward anti-tumor immunity. These findings position proteasome inhibition, either as monotherapy or in rational combinations, as a promising strategy for this aggressive NSCLC subset.





Keywords: LKB1, Endoplasmic Reticulum Stress, Proteotoxic Death

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.29 CXCR2 Inhibitor Plus KRAS G12C Inhibitor Remodels Immunosuppressive Tumor Microenvironment in KRAS G12C-Mutant NSCLC?

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Introduction: Sotorasib (AMG510), a first-in-class KRAS G12C inhibitor, demonstrates constrained clinical efficacy as monotherapy, with intrinsic/acquired resistance emerging as a critical barrier in patients with KRAS G12C-mutant non-small cell lung cancer (NSCLC). KRAS oncogenic activation triggers profound remodeling of the tumor immune microenvironment (TIME), establishing immunosuppressive networks that potentiate immune evasion. These mechanistic insights underscore the imperative to develop rationally designed combination therapies that co-target KRAS-driven signaling and reverse TIME dysregulation, thereby overcoming the therapeutic limitations of current KRAS G12C inhibitors.

Methods: The study systematically analyzed immune suppression-related pathways in KRAS G12C mutant lung adenocarcinoma samples from the TCGA database, with comparative profiling of KRAS wild-type tumors and normal lung tissues. Basing on these findings, a novel combination therapy strategy leveraging AMG510 to simultaneously reduce tumor burden and remodel the TIME in KRAS G12C-driven Lewis lung carcinoma (LLC) models in C57BL/6N mice we explored. The potential mechanisms underlying the combination strategy were further investigated. Complementary in vitro studies extend these observations to human KRAS G12C- mutant NSCLC cell lines, rigorously evaluating combination efficacy across multiple AMG510 resistance lung cancer cells.

Results: We observed that pathways associated with polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) were enriched in KRAS G12C-mutant lung adenocarcinomas (LUAD). Hence, co-administration of SB225002, a C-X-C motif chemokine receptor 2 (CXCR2) antagonist targeting PMN-MDSCs, significantly enhanced the inhibitory effect of AMG510 on tumor burden in LLC-bearing mice. However, the same combination strategy did not exert a synergistic therapeutic effect in LLC model in severely immunodeficient NCG mice, suggesting that the combination strategy depends on the TIME. Further analysis revealed that the combination of SB225002 and AMG510 markedly reduced the infiltration of PMN-MDSC and enhanced the activity of CD4+ T cells within the TIME. Depleting CD4+ T cells using an anti-CD4 antibody significantly reversed the anti-tumor effects of the combination strategy. Consistently, depletion of PMN-MDSCs with an anti-Ly6G antibody, in combination with AMG510, resulted in antitumor effects and TIME remodeling similar to those observed with SB225002. Mechanistic studies revealed that AMG510 inhibited the MAPK pathway, the expression of the transcription factor myelocytomatosis oncogene (MYC) and its downstream targets, C-X-C motif chemokine ligands (CXCL) 1/2 in tumor cells, thereby reducing their chemotactic attraction to PMN-MDSCs. This mechanism synergized with SB225002, which targets PMN-MDSCs via the ligand-receptor axis. Surprisingly, increasing the dosage of SB225002 showed a trend toward reduced tumor burden in NCG mice compared to the monotherapy group, implying that the combination strategy also exerts effects on tumor cells. In vitro experiments demonstrated that the combination regimen exhibited synergistic inhibition of clonal formation, apoptosis resistance, and proliferation in multiple human lung cancer cells resistant to AMG510. Further investigations revealed that the combination strategy synergistically suppressed the MAPK signaling pathway.

Conclusions: The combination therapy demonstrates dual efficacy by potently remodeling the immunosuppressive tumor microenvironment and directly inhibiting tumor cells proliferation. These findings establish a robust experimental foundation for advancing this therapeutic approach into clinical trials.

Keywords: KRAS G12C, non-small cell lung cancer, CXCR2

P2.02.30 Targeting MTA2 Lactylation as a Therapeutic Strategy to Overcome Chemoresistance in Lung Adenocarcinoma

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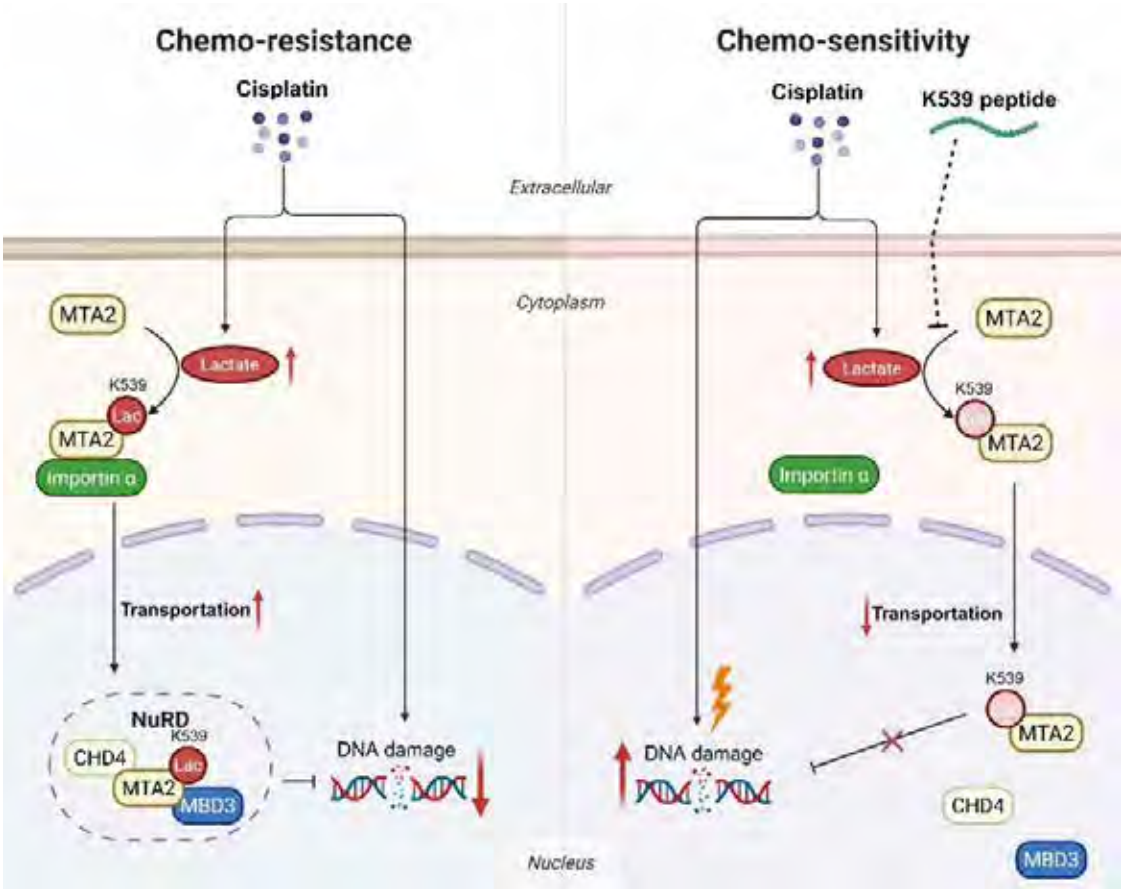
Introduction: The primary objective of conventional chemotherapeutic agents is to directly or indirectly induce DNA damage, leading to tumor cell death. To evade this, cancer cells must rapidly mobilize mechanisms to counteract genotoxic stress. This process is central to the development of chemoresistance in cancer. Chemoresistance in lung adenocarcinoma (LUAD) remains a critical barrier to effective treatment, requiring elucidation of molecular drivers. The Warburg effect is a hallmark of cancer that refers to the preference of cancer cells to metabolize glucose anaerobically rather than aerobically. This results in substantial accumulation of lactate. Lactylation is a lactate-induced post-translational modification. While lactylation is increasingly implicated in epigenetic regulation, its functional relevance to therapeutic resistance remains incompletely defined. Matastasis-associated protein 2 (MTA2) is the core component of the Nucleosome Remodeling and Deacetylase (NuRD) complex, which plays a critical role in mitigating DNA damage, yet its regulatory interplay with metabolic stress signaling is still unexplored.

Methods: Metabolomics and transcriptomics quantified lactate flux in LUAD. Proteomics and retrospective analysis pinpointed MTA2-K539la as a chemotherapy response mediator. Electrostatic modeling and immunofluorescence mapped MTA2-K539la-importin α interactions. Co-immunoprecipitation and comet assays dissected the NuRD complex dynamics and DNA damage. RNA-seq and molecular docking screen out the writer of MTA2 lactylation. An engineered cell penetrating peptide targeting MTA2-K539la was developed and functionally validated in cells, patient-derived organoids, and spontaneous lung cancer models under cisplatin and immunotherapy regimens.

Results: Cisplatin treatment exacerbated lactate accumulation, driving widespread protein lactylation and fostering chemoresistance. Mechanistically, MTA2 lactylation at K539 strengthened its binding affinity to importin α, enhancing nuclear translocation and subsequent stabilization of the NuRD complex. This mechanism suppressed cisplatin-induced DNA damage. KAT2A was identified as the writer catalyzing MTA2 lactylation. Pharmacological disruption of MTA2-K539la via a rationally designed peptide restored cisplatin sensitivity across preclinical models and synergized with immune checkpoint blockade to augment tumor regression.

Conclusions: This study establishes MTA2 lactylation as a metabolic checkpoint that safeguards genomic stability under genotoxic stress, thereby promoting chemoresistance in LUAD. By demonstrating the therapeutic efficacy of targeting this pathway, our findings position lactylation inhibition as a translatable strategy to resensitize refractory tumors to conventional and immunotherapeutic agents.



Keywords: Chemoresistance, Lactylation, Lung adenocarcinoma

P2.02.31 The Changes of Macrophage in EGFR Mutant TKI-Resistant Patients With Lung Cancer

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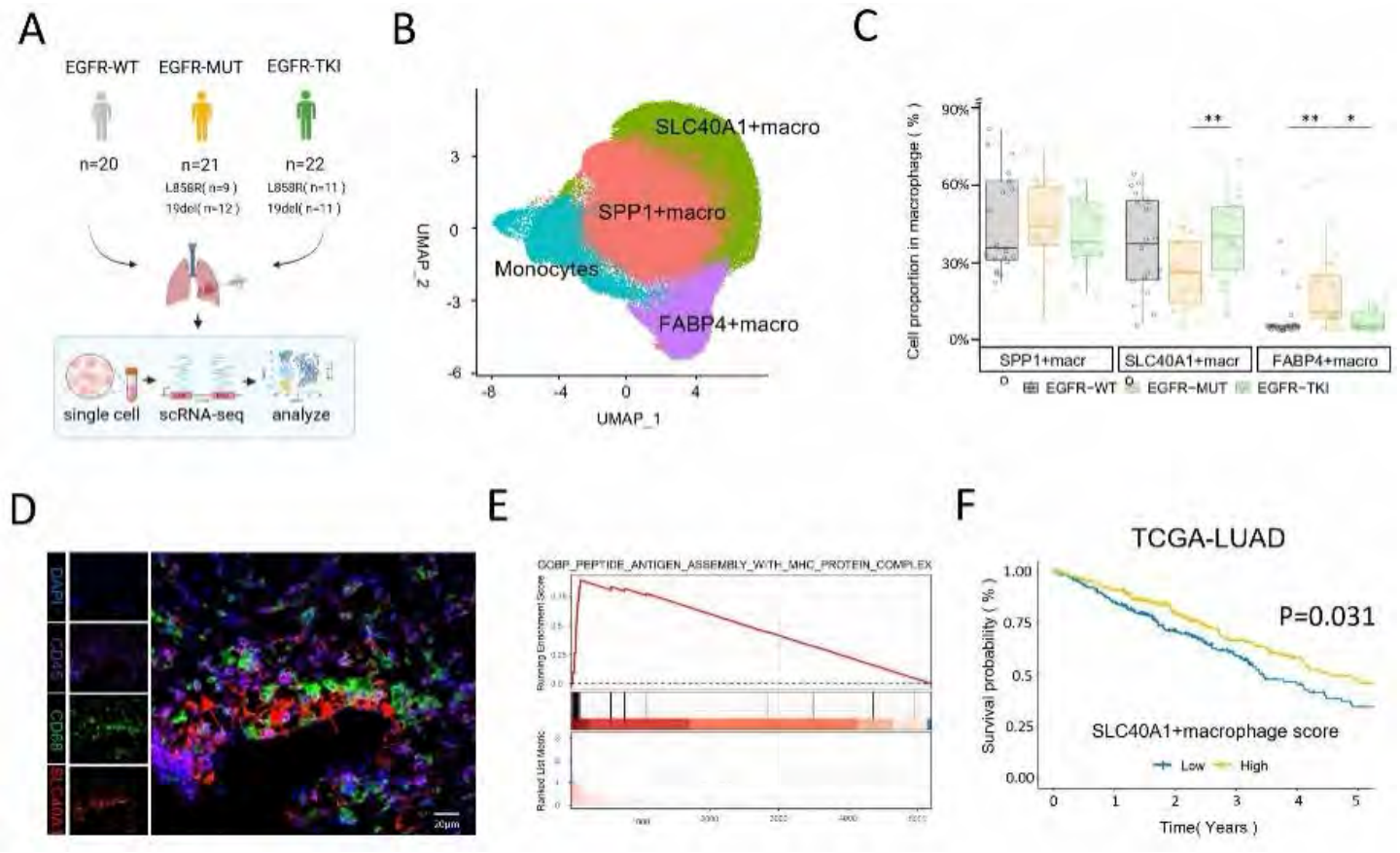
Introduction: Lung cancer patients harboring epidermal growth factor receptor (EGFR) mutations typically exhibit limited sensitivity to immune checkpoint inhibitors (ICIs) and are prone to developing resistance to first-line tyrosine kinase inhibitors (TKIs). However, effective therapeutic options for patients with TKI resistance remain limited. Notably, our team's ORIENT31 clinical trial demonstrated that ICI-based combination therapy can significantly improve progression-free survival in TKI-resistant patients. The underlying immune mechanisms contributing to the enhanced response to immunotherapy after TKI resistance require further investigation.

Methods: We performed single-cell RNA sequencing on lung cancer biopsy samples from three groups: EGFR wild-type, EGFR-mutated, and TKI-resistant. Comparative analyses were conducted to characterize the differences in immune cell subsets and molecular features of the tumor immune microenvironment among these groups.

Results: Our analysis revealed that macrophages comprise over 20% of the tumor microenvironment. Notably, TKI-resistant tumors exhibited a reduction in SPP1^{+} macrophages, a subset frequently associated with immunosuppression in previous single-cell studies. Conversely, we observed an increased proportion of SLC40A1^{+} macrophages in TKI-resistant patients. These macrophages exhibited elevated expression of MHC class II molecules, indicating enhanced antigen-presenting capacity. Importantly, high infiltration of SLC40A1^{+} macrophages was associated with improved overall survival in lung adenocarcinoma (P=0.031), highlighting their potential role in antitumor immunity.

Conclusions: Our study underscores the pivotal role of macrophages in shaping the immune microenvironment of TKI-resistant lung cancer. Notably, SLC40A1^{+} macrophages may serve as a key biomarker for predicting immunotherapy efficacy in this patient population. These findings offer valuable insights that could guide the future clinical application of ICIs in TKI-resistant lung cancer.



Keywords: Macrophage, TKI resistance, Immunotherapy

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.32 Homeostatic Dysregulation of Systemic CD8+ T Cell Compartment in Lung Cancer Patients

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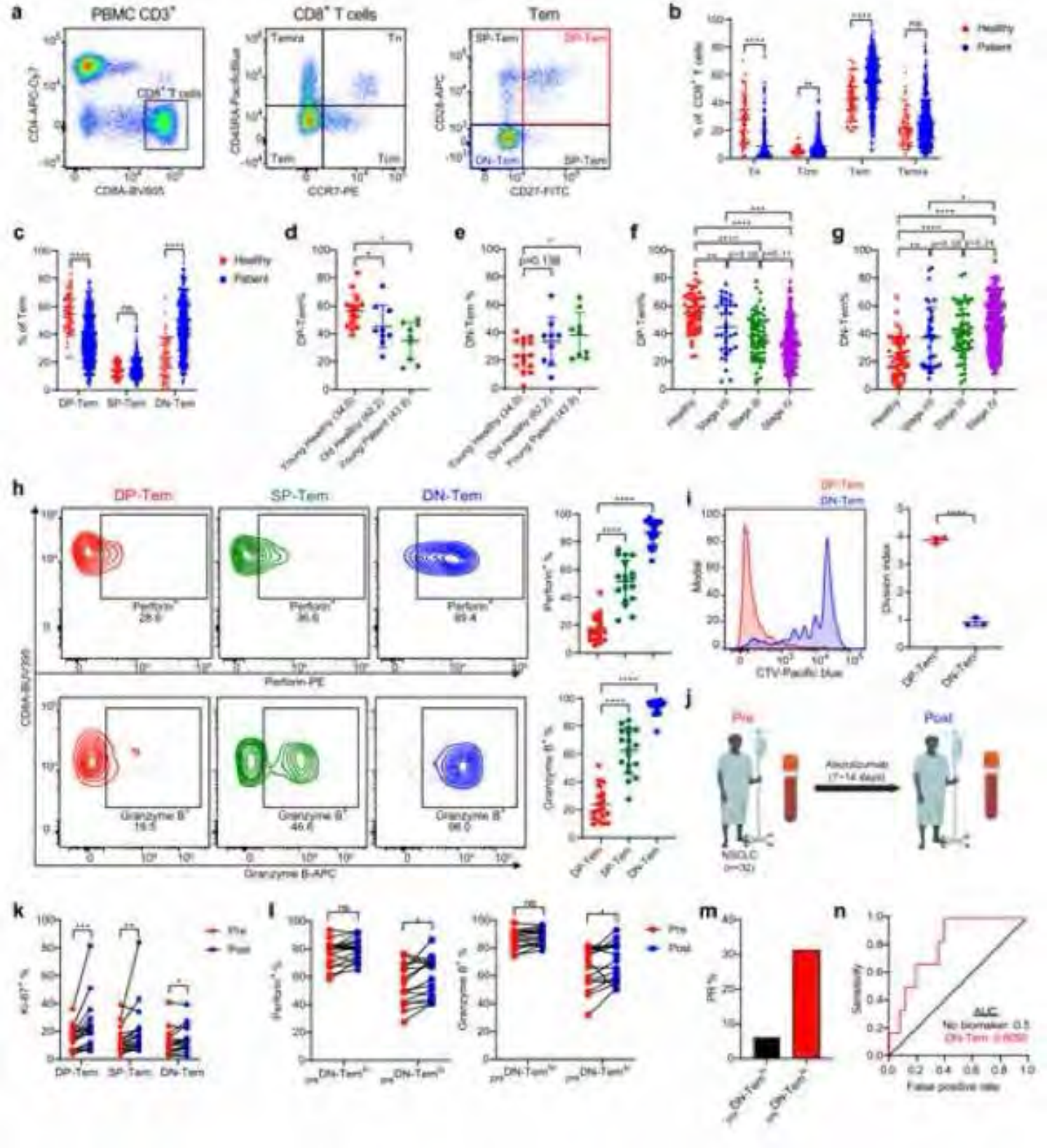
Introduction: Suppression of tumor-reactive CD8+ T cells is a well-known feature of the tumor microenvironment. However, the extent to which tumors exert systemic effects on the overall CD8+ T cell compartment remains unclear. This study investigates the systemic homeostatic dysregulation of CD8+ T cells in lung cancer patients and its implications for immune responses and therapy outcomes.

Methods: Peripheral blood samples from 349 lung cancer patients and 53 healthy donors were analyzed using flow cytometry, single-cell RNA sequencing, and T cell receptor (TCR) sequencing. We examined the composition and functional characteristics of CD8+ T cell subsets, focusing on differentiation states, proliferation capacity, and gene expression signatures associated with immune homeostasis. Clinical outcomes of immune checkpoint inhibitor (ICI) therapy were assessed in four independent patient cohorts.

Results: Lung cancer patients exhibited a progressive alteration in CD8+ T cell composition, characterized by an increased frequency of more differentiated effector memory T cells (DN-Tem) with diminished proliferative capacity. Single-cell RNA sequencing revealed reduced quiescence and increased spontaneous activation, indicative of systemic homeostatic dysregulation. Furthermore, a higher proportion of DN-Tem was associated with poor response to ICI therapy, suggesting that systemic CD8+ T cell dysregulation impairs effective antitumor immunity.

Conclusions: Our findings reveal that lung cancer induces widespread homeostatic dysregulation of the systemic CD8+ T cell compartment, leading to an accumulation of dysfunctional effector memory subsets. This phenomenon correlates with poor clinical response to ICI therapy, highlighting a novel immune evasion mechanism. Understanding this systemic alteration could inform the development of improved immunotherapeutic strategies for lung cancer patients.



Keywords: T cell, Lung cancer

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.33 Radiotherapy Induces Ferroptosis and Activates STING Pathway to Reverse Immunotherapy Resistance in LKB1-Mutant Lung Cancer

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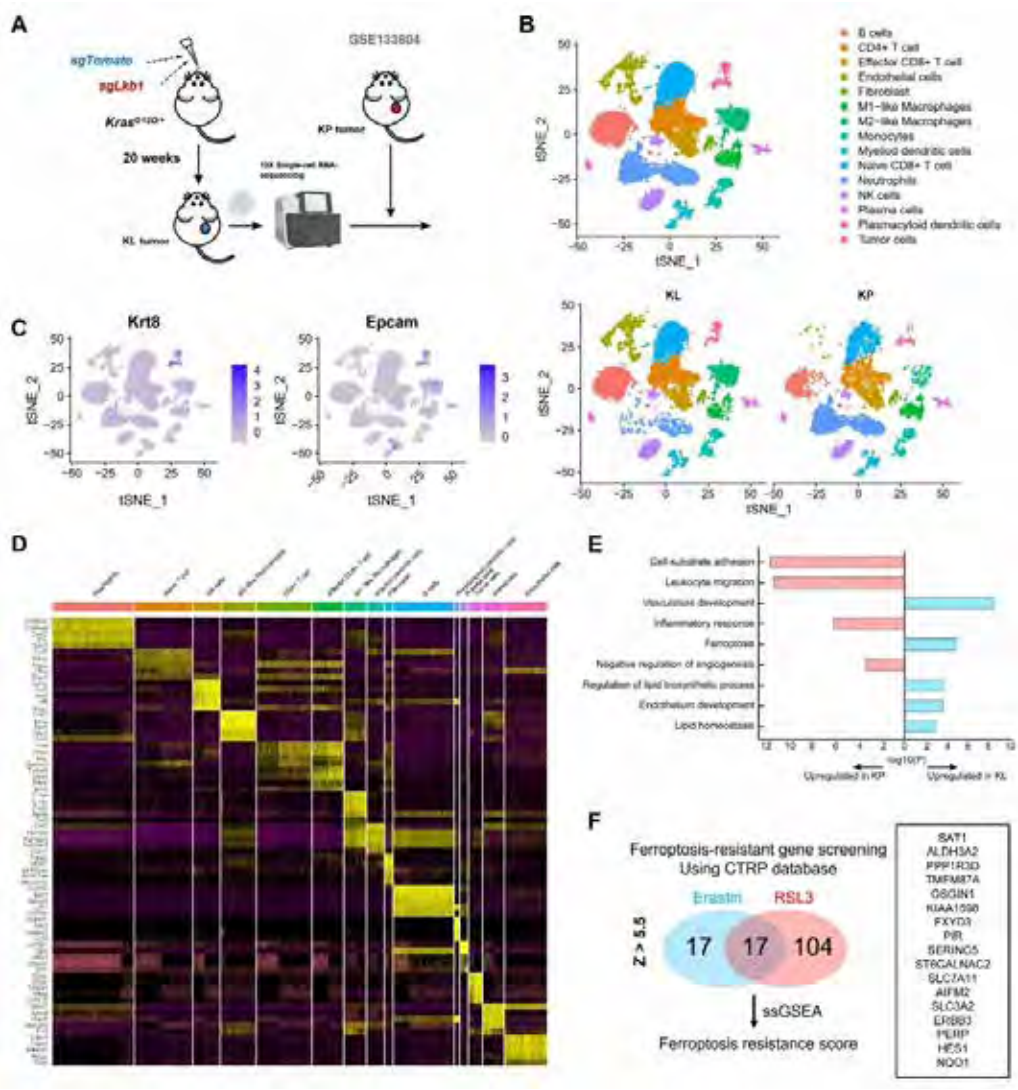
Shunde Hospital, Foshan/CN

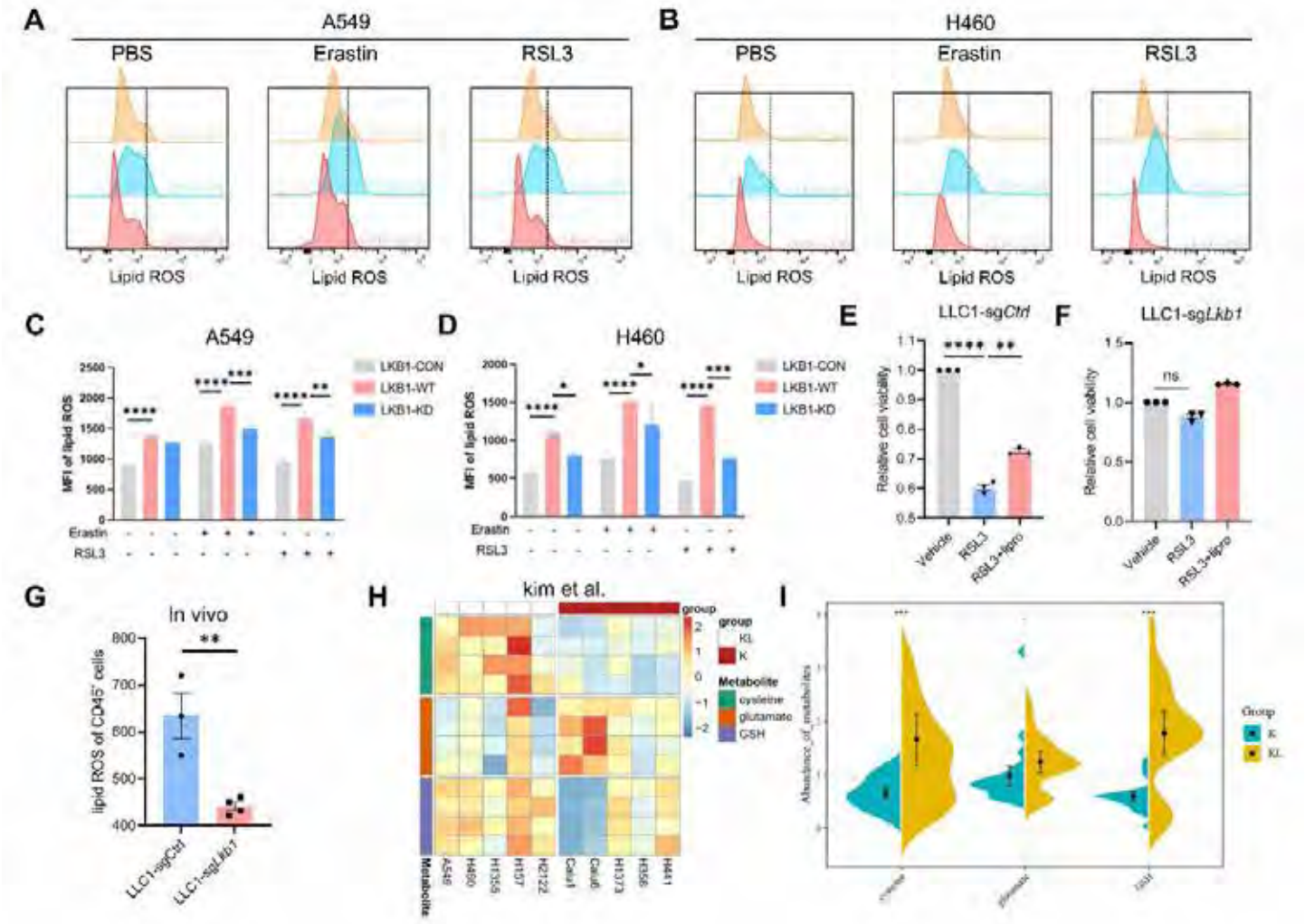
Introduction: LKB1 mutations are associated with primary resistance to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer, but the underlying mechanism remains unclear.

Methods: KrasG12D/+-sgLkb1 (KL) driven lung adenocarcinoma mouse model was established and analyzed by single-cell RNA sequencing (scRNA-seq) to decode the characteristics of LKB1-mutant lung cancer cells. The ferroptosis resistance score of lung cancer cells was constructed and validated in transcriptomic, cellular, and vivo levels. Relevant inducers and inhibitors were utilized to verify the ferroptosis resistance phenotype in LKB1-mutant lung cancer. TCGA database and multiple immunotherapy cohorts were leveraged to explore the relationship between ferroptosis resistance and immune-related pathways and the efficacy of immunotherapy. The impact of radiotherapy on ferroptosis resistance, the activation of the STING pathway and immunotherapy in LKB1-mutant lung cancer were explored in vitro and vivo experiments.

Results: The integrated analysis of single-cell data of KL and KrasG12D/+ TP53fl/fl (KP) driven lung adenocarcinoma mouse model revealed that the ferroptosis-related pathways were significantly enriched in KL tumors compared with the KP tumors. LKB1-mutant lung cancer cells owned higher ferroptosis resistance score and were resistant to ferroptosis in vitro and in vivo. Ferroptosis resistance was negatively correlated with immune-activating pathways and the efficacy of immunotherapy. LKB1 mutation might induced ferroptosis resistance via upregulating NRF2 signaling pathway. Radiotherapy could reverse ferroptosis resistance, activate the STING pathway and ignite the tumor immune microenvironment in LKB1-mutant lung cancer. The LKB1-mutant tumor was significantly shrunk in the combination of ICIs and radiotherapy group, which could be restored by a ferroptosis inhibitor.

Conclusions: Radiotherapy could reverse the immunotherapy resistance of LKB1-mutant lung cancer by inducing ferroptosis in tumor cells and activating the STING signaling pathway.





Keywords: LKB1 mutation, Radiotherapy, Ferroptosis

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.34 Synergistic Antitumor Effect of an XPO1 Inhibitor And/Or Sotorasib With V-ATPase Inhibitors Pretreatment in KRAS G12C NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) bearing KRAS G12C mutation has demonstrated limited clinical efficacy to KRAS G12C selective inhibitors, such as the covalent inhibitor sotorasib, due to primary and acquired resistance mechanisms. A major focus has been placed on developing combined therapies to avoid resistance. Selinexor, a selective inhibitor of Exportin-1 (XPO1), has shown promising efficacy in KRAS-mutant lung cancer cell lines. Additionally, the V-ATPase inhibitor omeprazole, has been demonstrated to increase cytoplasmic retention of cytotoxic drugs when pretreated, increasing the sensitivity of cells to chemotherapy and some targeted therapies. This study aims to evaluate the efficacy of combining selinexor or sotorasib with omeprazole pretreatment in KRAS G12C NSCLC cell lines and to identify the mechanism of action of these drug combinations.

Methods: Four KRAS G12C-mutated NSCLC cell lines (H358, H23, H358R [sotorasib-resistant], and H2030) were used in this study, ranging from more sotorasib-sensitive to resistant phenotypes, respectively. All experiments were performed administering omeprazole to cells 24 hours before treatment with selinexor or sotorasib for 72 hours. Cell viability was assessed by MTT assays using varying doses of omeprazole pretreatment. Synergy was studied using Loewe, Bliss and HSA models with Combenefit and SynergyFinder programs. Cell viability in H358 spheroids (3D conditions) was evaluated using CellTiter-Glo 3D Assays. Colony Formation Assays (CFA) were performed by treating cells for 15 days. Western blot analyses were conducted to analyze the protein levels of XPO1, the KRAS signaling pathway, the MRAS-PP1C-SHOC2 complex, and markers such as pEphA2, RanGAP1, IRE1α, DLC1, and AURKA.

Results: Combined therapy of selinexor with omeprazole pretreatment and sotorasib with omeprazole pretreatment increases sensitivity to both drugs across the four cell lines used in the study. Furthermore, omeprazole pretreatment can overcome resistance to selinexor or sotorasib in the resistant cell lines, as observed in the cell viability assays. Evidence suggests synergistic effects of selinexor/sotorasib with omeprazole pretreatment. Likewise, synergy of these drug combinations was also observed in 3D conditions using H358 spheroids and in the CFA. The CFA highlighted the effectiveness of the triple combination of selinexor and sotorasib pretreated with omeprazole, as it was able to almost eliminate all colonies. Regarding the mechanism of action of these drug combinations, selinexor significantly reduced the protein levels of XPO1, and sotorasib markedly reduced pEphA2 in all lines. The combination of selinexor/sotorasib with omeprazole reduced the levels of RanGAP1 and AURKA across all cell lines, as well as IRE1α in the two most sotorasib-sensitive cell lines, H358 and H23. Combination treatments increased DLC1 levels in the H23 and H2030 cell lines but were not detected in H358 or H358R.

Conclusions: This study highlights the synergistic antitumor effect of selinexor or sotorasib with omeprazole pretreatment in KRAS G12C NSCLC cell lines. It should be noted that pretreatment with omeprazole has demonstrated to potentially overcome resistance to both treatments. Future in vivo studies are necessary along with unveiling the role of XPO1 since XPO1 expression was present in cell lines and was not decreased by sotorasib, only by selinexor.

Keywords: XPO1 inhibitor, sotorasib, V-ATPase inhibitors

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.35 Association of Intratumoral Microbiota Composition With Tertiary Lymphatic Structure of Lung Adenocarcinoma

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Introduction: Emerging evidence implicates intratumoral microbiota in lung adenocarcinoma pathogenesis, though its functional consequences remain poorly characterized. Tertiary lymphoid structures (TLS) demonstrate clinical associations with survival outcomes and therapeutic responses across malignancies. This study employs sequencing-based microbial profiling to investigate potential crosstalk between intratumoral microbiota and TLS in lung adenocarcinoma.

Methods: We analyzed transcriptome profiles from The Cancer Genome Atlas (TCGA)-LUAD project and matched intratumoral microbiota abundance data from TCMbio. Our study employed stringent selection criteria: treatment-naive primary tumors with multi-omics data, excluding multiple samples per patient. Patients were stratified into TLS-high and TLS-low groups using a predefined threshold based on TLS-50 signature scores. Microbiota composition was systematically characterized across TLS subgroups. Differentially abundant genera between TLS groups underwent correlation analysis with tumor immune infiltration scores. External validation cohorts from GEO databases assessed reproducibility of TLS-associated microbial features.

Results: The analysis included 510 patients from the TCGA-LUAD cohort, with 109 (21.4%) stratified as TLS-high. Notably, TLS-high prevalence progressively decreased with advancing TNM stage (I: 26.7%, II: 22.0%, III: 9.8%, IV: 4.0%). TLS-high patients demonstrated significantly improved overall survival (Log-rank p=0.006). Comparative immune profiling revealed elevated tumor infiltration scores for B cells, T cells, Th1 cells, and NK cells in TLS-high patients, contrasted by reduced macrophage and neutrophil infiltration scores. Comparative analysis of microbiota diversity revealed distinct patterns between TLS-high and TLS-low groups. In alpha diversity indices, while Shannon and Simpson indices showed no significant differences (Wilcoxon rank test $p > 0.05$), Richness indices demonstrated marked variation (p=0.02). Beta diversity assessed through PCoA exhibited significant group separation (PERMANOVA test p=0.006). Differential abundance analysis using LEfSe (Wilcoxon rank test $P < 0.05$, LDA ≥ 2) identified Staphylococcus as significantly enriched in TLS-low specimens, whereas Priestia showed preferential abundance in TLS-high specimens. Notably, Priestia abundance displayed significant negative correlations with tumor-infiltrating immune cells through Pearson correlation analysis: macrophages (r=-0.12, p=0.006) and neutrophils (r=-0.12, p=0.007). Analysis of two independent validation cohorts reinforced the clinical relevance of Priestia-TLS associations. In Cohort 1 (n = 44), TLS-high specimens exhibited median Priestia abundance of 0.119 compared to 0.066 in TLS-low specimens. While between-group comparisons only disclosed marginally significant difference (Wilcoxon rank test p=0.066),Priestia abundance demonstrated significant positive correlation with TLS scores (Pearson's r=0.38, p=0.01). Cohort 2 (n=27) mirrored this pattern, showing median abundances of 0.026 (TLS-high) versus 0.007 (TLS-low) with borderline statistical separation (p=0.055), yet revealing stronger correlation coefficients with TLS scores (r=0.41, p=0.03).

Conclusions: This study establishes a significant association between intratumoral microbiota composition and TLS in lung adenocarcinoma. The elevated microbial richness and Priestia enrichment observed in TLS-high tumors may modulate TLS formation through immune microenvironment regulation. Notably, the identified negative correlations of Priestia with macrophages and neutrophils suggest a potential association with reduced immunosuppressive cell infiltration, which may create favorable conditions for TLS development. Importantly, the consistent positive correlations between Priestia abundance and TLS scores across independent validation cohorts highlight its promise as an emerging biomarker candidate for TLS-related immune activation.

Keywords: Intratumoral Microbiome, Lung adenocarcinoma, Priestia

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.36 Canakinumab Interception Trial and Preclinical Studies Reveal Stage-Dependent Biology in Lung Cancer and Precancers

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Introduction: Multiple clinical trials testing canakinumab, an interleukin-1β (IL-1B) antibody in lung cancers have yielded negative results. However, our work has highlighted the critical role of innate immunity in lung adenocarcinoma (LUAD) precancers, and demonstrated that IL-1B inhibition can delay the progression of precancers into invasive LUAD. These findings have led to the development of Can-Prevent-Lung (NCT04789681), a single-arm phase II trial evaluating whether canakinumab can enhance regression rates of persistent high-risk (presumably precancerous) pulmonary nodules to prevent invasive LUAD.

Methods: In the Can-Prevent-Lung trial, patients with persistent high-risk pulmonary nodules (nodules showing no regression on at least two CT scans three months apart, with a predicted malignancy risk >10% based on the Brock model) were enrolled to receive canakinumab subcutaneously. The initial dosing regimen was 200 mg every 3 weeks for up to eight doses, which was modified to 300 mg every three months for up to four doses following a planned interim analysis. CT scans were performed to evaluate response using modified RECIST (mRECIST) criteria, assessing both solid and ground-glass opacity components. A propensity-matched non-treatment control group was analyzed in parallel. Peripheral blood samples were collected for T cell receptor sequencing, cytokine profiling, and plasma cell-free DNA (cfDNA) analysis at multiple time points during the treatment. Additionally, in vivo IL-1B blockade experiments were conducted in LUAD mouse models, and single-cell and spatial transcriptomics profiling were utilized to investigate mechanisms of action and the impact of IL-1B inhibition on the tumor microenvironment.

Results: At the planned interim analysis, 15 patients had completed treatment and safety follow-up. No Grade 3 or higher drug-related toxicities were observed, with Grade 2 neutropenia without active infections (n=4) being the most common toxicity. According to mRECIST criteria, 11 patients exhibited pulmonary nodule shrinkage, with the best response being a 27% reduction, while 13 patients showed a slower growth trajectory post-canakinumab treatment compared to pre-treatment. In 3D volumetric analysis, the treatment group demonstrated a median annual growth rate of -6.7%, in contrast to a +14.8% annual growth rate in the control group. Pulmonary nodules in the IL-1B group exhibited fewer cells (P=0.024), lower intra-lesion spatial heterogeneity (P=0.049), and reduced density (P<0.001). Notably, abnormal cfDNA signals detected before treatment became negative following canakinumab therapy. An additional 10 patients received the revised 300 mg every three months regimen, with no Grade 2 or higher toxicities observed. In both genetically engineered and carcinogen-induced LUAD mouse models, IL-1B blockade significantly reduced tumor burden when administered at the precancerous stage, but not at the advanced cancer stage. Correlative analyses from the Can-Prevent-Lung trial, and single cell and spatial transcriptomics profiling from mouse models treated with anti-IL-1B or IgG controls—are ongoing.

Conclusions: Cancer biology, including immune response and evasion patterns, as well as therapeutic efficacy, is stage-dependent. Canakinumab has demonstrated a favorable safety profile and promising efficacy in patients with high-risk pulmonary nodules, despite previous negative trials in invasive lung cancer. These findings support the IL-1B pathway as a promising target for immune interception of high-risk (precancerous) pulmonary nodules.

Keywords: Prevention, Precancer, interleukin-1beta

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.37 ERBB3-BCAR4 Is a Recurrent and Oncogenic Fusion in Lung Adenocarcinoma Cases That Lack Other Driver Alterations

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Introduction: There has been great progress recently for patients with metastatic lung adenocarcinoma whose tumors harbor common driver alterations. However, there remains a subset of patients with rare variants of unknown significance, for which the treatment options are severely lacking. There have been two previous case reports of patients with lung adenocarcinoma for which an ERBB3-BCAR4 fusion was identified, including one in TCGA. Importantly both cases had WGS and were negative for known driver alterations. In addition, the TCGA case had elevated RNA expression of the fusion transcript, including the full extracellular and kinase domains of the ERBB3 gene, which encodes for the EGFR family member HER3. The objective of the study is to better understand the function and clinical relevance of the ERBB3-BCAR4 fusion. We hypothesize that ERBB3-BCAR4 is a driver fusion that can be targeted with drugs that bind to the HER3 extracellular domain.

Methods: UW-Oncoplex is a next-generation sequencing assay used at the University of Washington / Fred Hutch. The current assay has > 400 genes and includes ERBB3 in the panel. For in vitro work, overexpression of the fusion was performed in NCI-H3122 cells, an ALK-fusion positive lung adenocarcinoma cell line. The cells were then treated with lorlatinib to suppress growth of the parental cells, thereby testing if the ERBB3-BCAR4 fusion could function as a driver in a lung adenocarcinoma context. For RNA-Sequencing of the fusion case, RNA was extracted from FFPE, library prep performed using Illumina's TruSeq RNA Exome hybrid capture technique, and sequencing completed on a NovaSeq.

Results: Via UW-Oncoplex sequencing, we report the identification of the third case of an ERBB3-BCAR4 fusion. This patient is a young woman who lacks a significant smoking history, and like the two previous cases, had a tumor negative for other driver alterations. The breakpoint identified is nearly identical to the TCGA case, with RNA-Sequencing confirming high expression of an in-frame transcript that includes the extracellular and kinase domains of ERBB3 and exon 4 of BCAR4. Preliminary in vitro work shows that overexpression of this fusion in lung adenocarcinoma cells rescues cell growth when the endogenous driver is inhibited. Use of patritumab deruxtecan in vitro, a HER3 antibody drug conjugate, reverses the growth advantage of ERBB3-BCAR4, suggestive of a potential treatment option for patients with this rare fusion. Ongoing work includes assessing the signaling mechanisms of the fusion via in vitro studies and IHC of the patient tumor, testing other EGFR-family kinase inhibitors in vitro, and querying a large clinical database to better define the fusion frequency.

Conclusions: Here, we report the identification of ERBB3-BCAR4 as a recurrent fusion in lung adenocarcinoma cases. Data suggestive that this fusion is functional include the lack of other driver alterations, the elevated RNA expression, and in vitro studies showing a growth advantage. Ongoing research includes additional work to define the signaling mechanisms of the fusion and potential therapeutic options to aid in the care of this rare patient population.

Keywords: ERBB3, BCAR4, HER3

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.38 Single-Cell RNA-Sq Reveals Potential Mechanism of RUNx3 Reshaping TME in NSCLC

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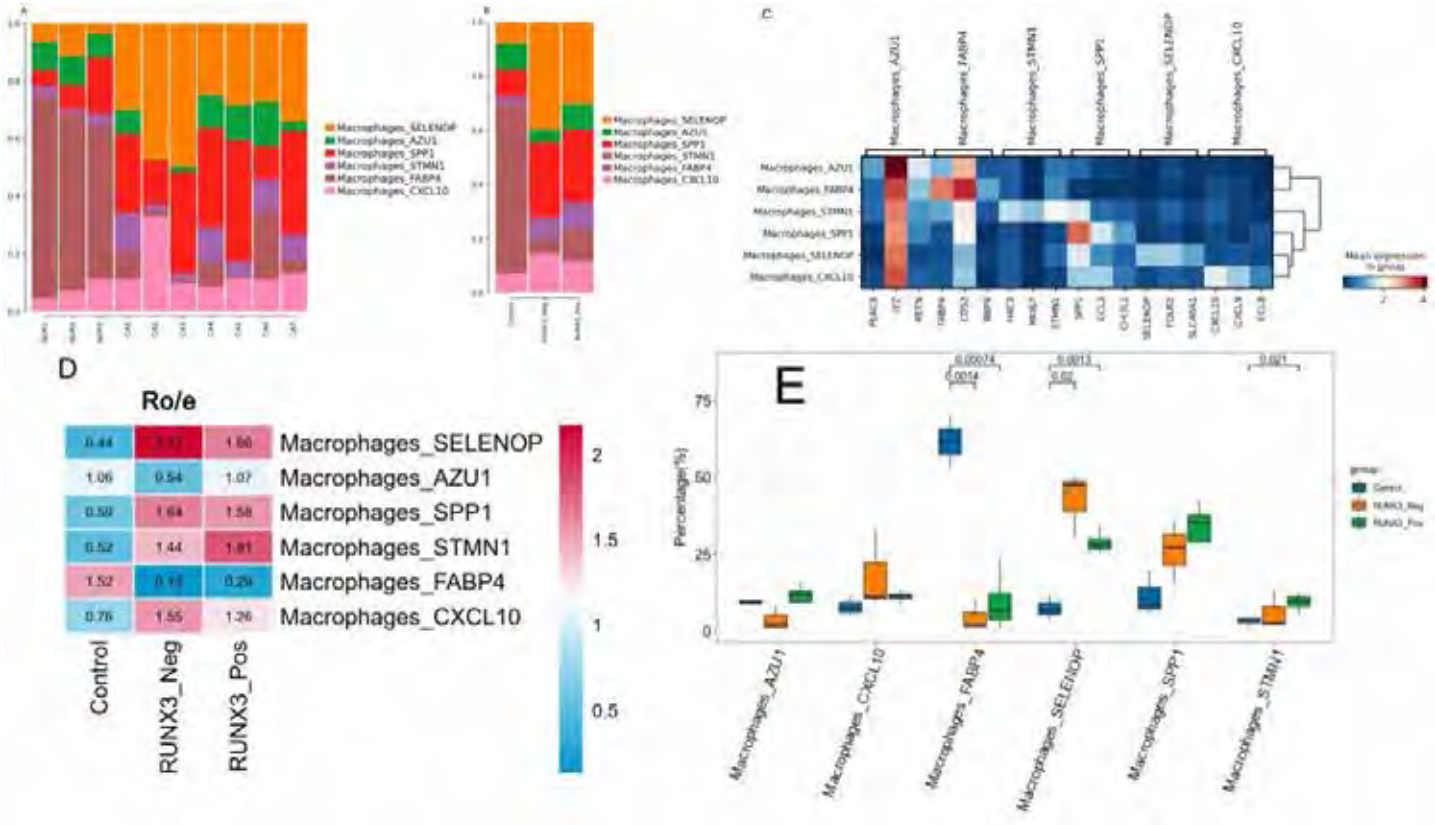
Introduction: RUNX3 plays an important role as a tumor suppressor gene (TSG) in NSCLC, but its specific biological mechanism is not yet clear. The aim of this study is to reveal the changes in tumor microenvironment (TME) in NSCLC with different RUNX3 expression status using single-cell RNA sequencing.

Methods: 7 NSCLC patients with detailed pathological data were included in this study, among which 3 patients provided samples of paracancerous tissue as well as cancerous tissue. After obtaining the sequencing results, the "Seurat" package was used to screen for differentially expressed gene profiles, annotate the cell cluster based on marker genes, and analyze the differences in cell proportions under different RUNX3 expression status. The ratio of observed over expected cell numbers (Ro/e) was used to explore the enrichment tendency of different cell types in three pathological types.

Results: According to immunohistochemical staining of RUNX3, 3 patients were divided into RUNX3 negative group (RUNX3_Neg) and the other 4 RUNX3 positive group (RUNX3_Pos). Based on marker genes, all cells were classified into 13 types. The results of Ro/e showed that the only cell type enriched in RUNX3_Pos cancer tissue was fibroblasts, while the cell types that enriched in RUNX3_Neg cancer tissue were club cells, ciliated cells, fibroblasts, plasma cells, B cells, neutrophils, mast cells and pDCs. From the perspective of immune cells, RUNX3_Neg tissues are more likely to accumulate plasma cells, B cells, mast cells and plasmacytoid dendritic cells compared to RUNX3_Pos tissues. Results of Ro/e demonstrated that RUNX3_Neg cancer tissues are more prone to macrophage depletion, while RUNX3_Pos tissues are more prone to macrophage enrichment.

Conclusions: Via single-cell sequencing technology our findings revealed that the expression status of RUNX3 is highly correlated with TME of NSCLC, and mononuclear phagocytes (MPs) may be an important target cell population for RUNX3 to alter TME, and altering the enrichment status of MPs may be a promising cancer treatment strategy. This study provides valuable insights into the anti-cancer mechanism of RUNX3.



Keywords: single-cell RNA sequencing, RUNX3, tumor-associated macrophage

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.39 Fulzerasib, a KRAS-G12C Inhibitor, Has Synergistic Antitumor Effect With Omeprazole Pretreatment in KRAS G12C NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) harboring the KRAS G12C mutation poses a major challenge for effective and durable treatment. Fulzerasib (GFH925, IBI351), an irreversible KRAS G12C inhibitor, has demonstrated superior efficacy compared to sotorasib and adagrasib, achieving an objective response rate of 49.1% and a median progression-free survival of 9.7 months. Omeprazole, a proton pump inhibitor, has been shown to enhance cytoplasmic retention of cytotoxic drugs and sensitize cancer cells to chemotherapy and some target therapy, such as tepotinib. The current study aims to explore the antitumor effect and underlying mechanisms of fulzerasib in combination with omeprazole pretreatment in KRAS G12C-mutated NSCLC cell lines.

Methods: Three KRAS G12C-mutated NSCLC cell lines (H358, H23 and H2030) were selected to represent fulzerasib-sensitive, mildly resistant and resistant phenotypes, respectively. Cells were treated with varying doses of omeprazole pretreatment (administered 24 hours before fulzerasib) and subsequently treated with fulzerasib. Cell viability was assessed using MTT assays, and synergy was evaluated using Loewe, Bliss, HSA and ZIP models. Western blotting was performed to analyze the expressions of proteins and the regulations of pathways, including KRAS pathway, the MRAS-PP1c-SHOC2 complex, Met pathway, Wnt pathway, and markers like SLUG, HES1, and pEphA2.

Results: Synergistic effects of Fulzerasib and omeprazole pretreatment were observed across all models and cell lines. Combination treatment significantly reduced MRAS expression in the MRAS-PP1c-SHOC2 ternary complex. In cancer-related pathways, pMet and pAKT expression were markedly decreased, while MAPK pathway components (pRaf and pERK1/2) showed no significant changes. Wnt pathway analysis revealed decreased β-catenin expression without notable changes in pLRP6. SLUG, HES1 and pEphA2 expression were also significantly reduced.

Conclusions: This study highlights that fulzerasib exhibits synergistic antitumor effects with omeprazole pretreatment, potentially through the suppression of multiple cancer-related proteins and pathways. Future studies will explore additional mechanisms, including autophagy and ferroptosis, to further elucidate the therapeutic potential of this combination.

Keywords: KRASG12C, Fulzerasib, Omeprazole

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.40 Multiomics Assessment of Lung Adenocarcinoma Subtypes Defined Through Tumor Purity-Adjusted DNA Methylation

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Introduction: Molecular subtypes of lung adenocarcinoma (LUAD), the most common histological subtype of lung cancer, have been proposed based on one or two-dimensional studies and different defining characteristics have been proposed for each of them. LUAD molecular subtypes have been shown to have prognostic value but have not yet been implemented as part of clinical routine. Epigenetic modifications in cancer cells are independent of sequence variants, directly linked to gene and genome regulation, and provide important information to guide subclassification efforts. However, DNA methylation data obtained from tumor samples are influenced by their tumor composition and analyses are often performed without regard for where in the genome such modifications occur.

Methods: We adjusted DNA methylation data from 95 primary LUAD samples from a Swedish cohort to better reflect values from tumor cells alone according to sample purity and subdivided the data according to genomic locations relative to gene coordinates. These data were used to classify samples into four clusters that were then contrasted based on clinicopathological, epigenomic, genomic, transcriptomic, proteomic, and metabolomic data. Findings were validated in two larger independent cohorts containing 418 and 322 samples each. Lastly, 62 LUAD cell lines were classified into the methylation clusters to verify which characteristics were intrinsic to tumor cells.

Results: Of the four methylation clusters, two (M1 and M4) were associated with previously proposed mRNA/protein subtypes showing similar characteristics to what has been published, such as higher percentages of persons without smoking history in M1, the cluster with the best prognosis. The remaining two clusters, however, were a combination of other proposed subtypes. Despite showing similar mRNA/protein subtype compositions, clusters M2 and M3 differed from each other through e.g., higher expression of a napsin A/surfactant metabolism expression metagene in M3, a marker of the LUAD histology. Genes included in this metagene showed lower DNA methylation in M3 compared to M2 despite an aggregate promoter hypermethylation phenotype seen in the former cluster. M2-like and M3-like cell lines recapitulated the metagene expression patterns seen in M2 and in M3 clusters from the three cohorts analyzed. Finally, patients with M3 tumors seemed to have poorer overall prognosis.

Conclusions: Focusing on tumor cell epigenomics, we were able to identify important characteristics of the different LUAD methylation clusters. Dissecting this disease based on combined biological information from multiomics data results in a deeper understanding of the heterogeneity in this complex disease and can hopefully lead to future treatments guided by molecular subtypes.

Keywords: epigenetics, subclassification, primary lung adenocarcinoma

P2.02.41 Feasibility of Flow Super RCA for KRAS Mutation Detection in Liquid Biopsies of Advanced Lung Adenocarcinoma: Pilot Study

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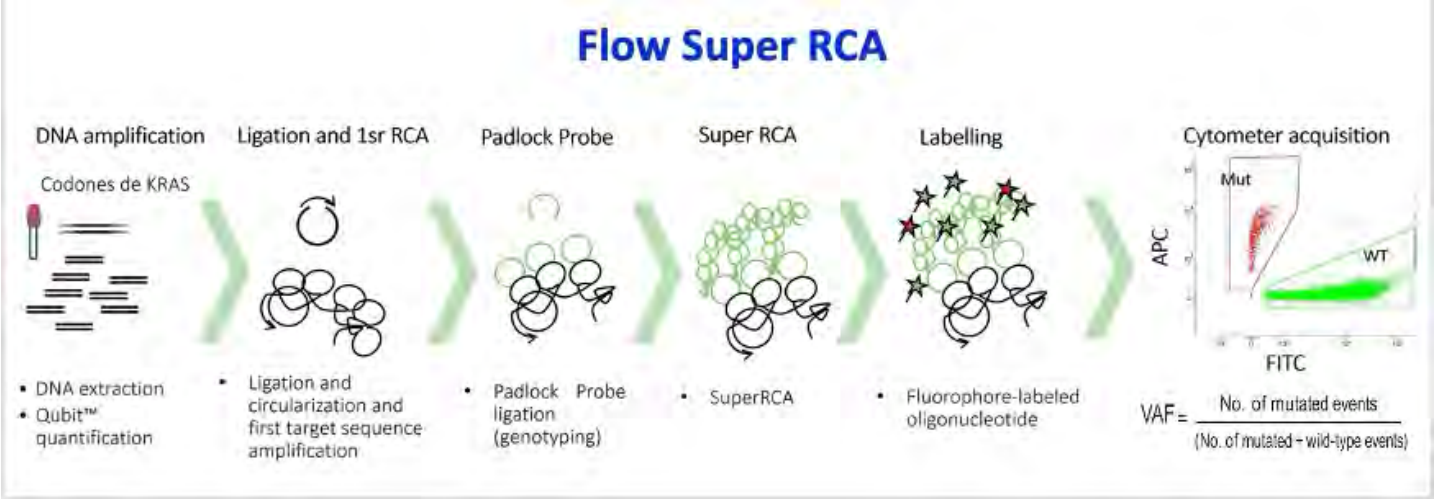
Introduction: KRAS mutations are the most frequent oncogenic alterations in non-small cell lung cancer (NSCLC), particularly in adenocarcinoma. In recent years, considerable research efforts have focused on developing specific KRAS inhibitors. Agents targeting the G12C variant —such as sotorasib and adagrasib— have already been approved, and pan-KRAS inhibitors are currently under investigation. As treatment strategies increasingly rely on molecular profiling, liquid biopsy has emerged as a promising non-invasive tool for real-time mutation detection. In this context, we evaluated the feasibility of a novel rolling circle amplification-based technique (Flow SuperRCA) to detect KRAS mutations in plasma samples and compared its results with conventional tissue biopsy.

Methods: Ten patients with advanced lung adenocarcinoma were included. KRAS mutations (codons G12C, G12D, G12V, and Q61H) were previously analyzed in tumor tissue using conventional molecular methods. Plasma samples were tested using Flow-SuperRCA, which involves target-specific padlock probe ligation, signal amplification, and flow cytometric detection. Cell-free DNA (cfDNA) concentration was quantified, and concordance between tissue and plasma results was assessed.

Results: KRAS mutations were identified in primary tumor tissue in 5 of 10 patients (3 G12C, 1 G12D, 1 G12V). Flow-SuperRCA detected mutations in 3 of these 5 patients (60% concordance), successfully identifying two G12C and one G12D mutation. The G12V and Q61H mutations present in tissue were not detected in blood; both cases had the lowest cfDNA concentrations (0.71 and 2.22 ng/µL, respectively) and a limited number of evaluable variant allele events. Interestingly, Flow SuperRCA detected a third G12C mutation and one Q61H mutation in patients without corresponding tissue alterations. Given that liquid biopsies were performed 4 to 6 weeks after tissue sampling, these findings may reflect temporal tumor evolution or spatial heterogeneity within the (primary vs metastatic) tumor landscape. In total, KRAS mutations were identified in plasma in 5 out of 10 patients.

Conclusions: Flow Super RCA is a promising minimally invasive technique for detecting KRAS mutations in advanced lung adenocarcinoma. The method showed partial concordance with tissue testing and the capacity to reveal additional mutations that may emerge over time or arise in distinct tumor subclones and/or at distinct tumor sites. These preliminary findings support further exploration of this technique in larger prospective cohorts.



Keywords: Liquid biopsy, KRAS mutations, Non-small cell lung cancer

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.42 Effect of MTHFR Gene Mutation on the Efficacy of Tyrosine Kinase Inhibitor Treatment in Lung Cancer Patients

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Introduction: Worldwide, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related deaths. A groundbreaking development in the treatment of lung cancer was achieved with the discovery of mutations that activate the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC). These mutations include a missense mutation in exon 21 and a short frame deletion in exon 19. EGFR-targeted tyrosine kinase inhibitors (TKI) have shown to be more effective than cytotoxic treatment in enhancing tumor response and improving progression-free survival outcomes in NSCLC patients with EGFR mutations. However, targeted therapy eventually leads to drug resistance in patients with EGFR gene mutation, and the underlying molecular mechanism of TKI resistance remains unclear. The MTHFR gene plays an important role in many biological processes. It encodes an enzymatic protein that catalyzes the irreversible reaction of 5-10-methyltetrahydrofolate to 5-methyltetrahydrofolate. This reaction is essential for the conversion of homocysteine to methionine by methionine synthase, where 5-methyltetrahydrofolate is used.

Methods: The Affiliated Hospital of Guangdong Medical University conducted a genetic analysis of 64 patients using next-generation sequencing (NGS) to determine their gene mutation status. In addition, the study also assessed the MTHFR mutation and the baseline characteristics of patients, along with the treatment outcomes such as overall survival (OS) and progression-free survival (PFS).

Results: The study involved 64 patients with advanced non-small cell lung cancer, out of which 30 (46.9%) had EGFR 19 mutations, and 34 (53.1%) had EGFR 19 mutations. The frequency of MTHFR gene mutation in these patients was found to be 31.3% (20/64). The study also revealed that patients with MTHFR gene mutation had a significantly increased median progression-free survival (PFS) of 28.50 months as compared to those without the mutation (11.30 months). However, there was no significant difference in the median overall survival (OS) between the two groups (31.50 months vs. 42.50 months). Furthermore, in NSCLC patients receiving EGFR-TKIs treatment, the study observed significant differences in PFS and MTHFR mutations (p= 0.023).

Conclusions: In NSCLC patients with MTHFR mutation, the benefits of EGFR-TKIs treatment are more significant. MTHFR gene is a predictor for first-line treatment of advanced NSCLC with EGFR-TKIs.

Keywords: MTHFR, tyrosine kinase inhibitors, mutation

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.43 Multi-Omic Approach Elucidates the Underlying Mechanism of HA-Coated Neohesperidin Nanoparticles Against Lung Cancer

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Introduction: Lung cancer (LC) is the leading cause of cancer-related deaths, with an average five-year survival rate of just 13%. Although many synthetic treatments are available, their effectiveness is often compromised by significant resistance issues, making them unsuitable. This therapeutic limitation is largely due to a lack of understanding of the metabolic and mechanistic processes involved in LC. To address this, it is crucial to identify potential molecular metabolites in pre-malignant LC. Therefore, we propose the use of natural products, which may help to mitigate toxicity and resistance-related limitations. In this context, neohesperidin (NHP), a flavonoid, has demonstrated strong anticancer potential. However, its limited bioavailability reduces its therapeutic efficacy. Thus, an NHP polymeric nanoparticle was formulated, and its therapeutic efficacy and underlying mechanisms were evaluated. Additionally, we employed proteomic and metabolomic approaches to investigate the biochemical and molecular differences between malignant LC tissue and normal lung samples in mice.

Methods: Here, we develop the hyalauronic acid (HA) coated PLGA nanoparticle of NHP and comprehensively evaluated its protective effects through histopathological examination of LC mice induced by urethane (1g/kg). Further, proteomics and metabolomics profiling was performed through LC-Orbitrap MS to offer a systematic view of the dynamic alterations in proteins and global endogenous metabolites, together with their disrupted pathways, acquired by applying log≥2 fold change and statistical significance of fold change ($p<0.005$). Later, western blotting was performed to confirm the expression of specific proteins and validate the pathway.

Results: The results demonstrated HA coated NHP nanoparticles could synergistically exert significant preventive effects against LC by notably ameliorating lung histopathological damage in LC mice. Further, approximately 364 differently expressed proteins (DEPs) and 25 differently expressed metabolites (DEMs) were identified, showing significant variation when compared to normal, diseased, and formulation-treated lung tumor tissue. Pathway enrichment analysis of DEMs revealed perturbations in the apoptotic pathway, with the involvement of lipid and amino acid biosynthesis pathways, which are primarily responsible for the therapeutic action of the formulation. Moreover, the expression of proteins involved in the apoptosis pathway (COX6A1, Bcl213, P11103) was confirmed by western blotting.

Conclusions: This research offers valuable insights into therapeutic strategies involving HA-coated NHP nanoparticles and enhances our understanding of antitumor mechanisms, which could be beneficial for future investigations in the clinical treatment of LC. We offer a comprehensive multi-omics foundation for assessing, managing, and detecting health risks associated with lung cancer.

Keywords: Lung Cancer, Neohesperidin, Multi-omics

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.44 Research on the Mechanism of Gut Microbiota Promoting NSCLC Distant Metastasis Through Its Metabolite Testosterone

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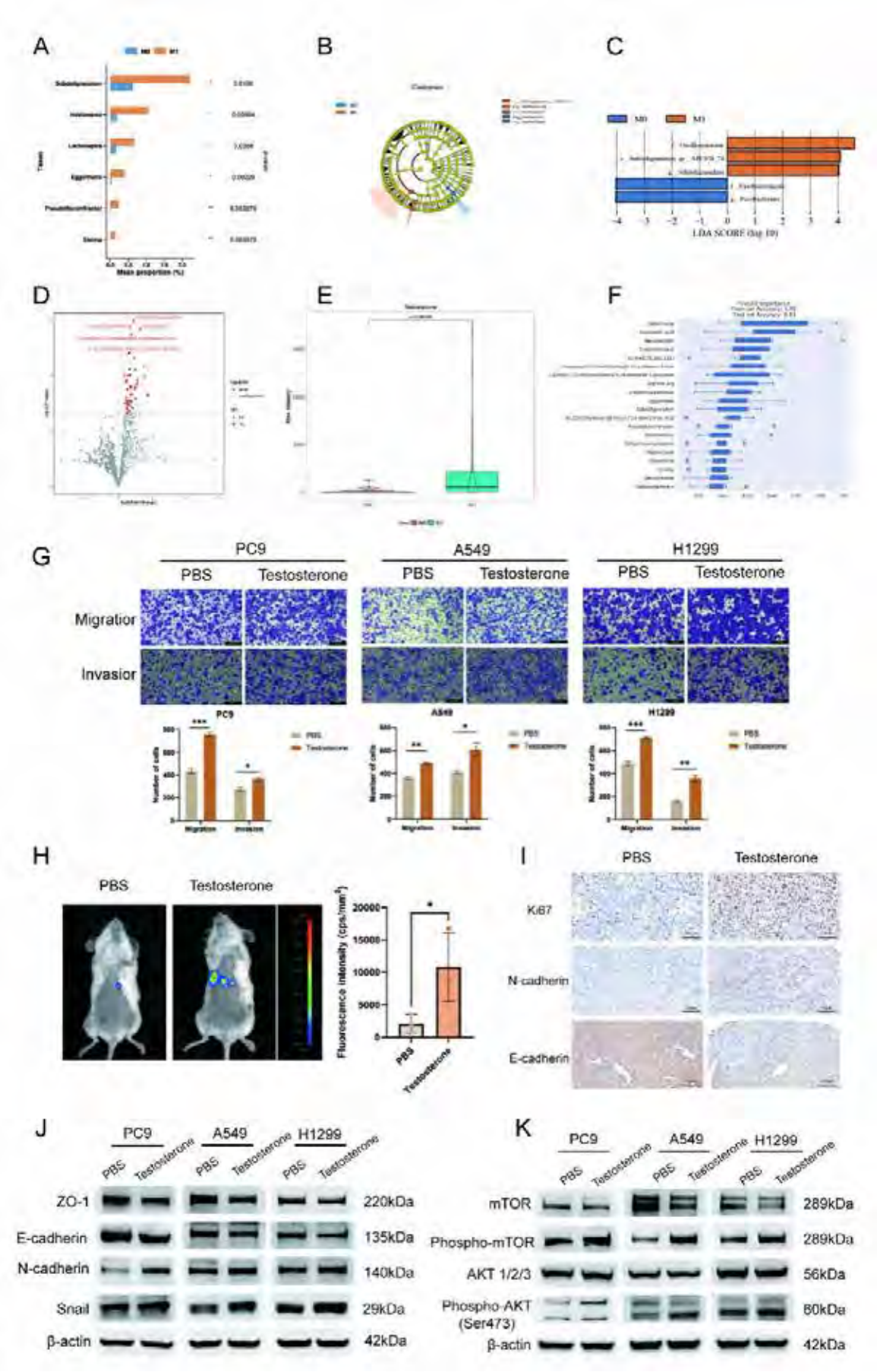
Introduction: Lung cancer ranks among the malignant tumors with the highest morbidity and mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 80-85% of all cases. Over half of NSCLC patients present with metastasis at the time of initial diagnosis, resulting in extremely poor survival rates. Growing evidence suggests that the gut microbiota and its metabolites play crucial roles in tumor initiation, progression, and treatment. However, the underlying mechanisms by which the gut microbiota and its metabolites regulate NSCLC metastasis remain unclear.

Methods: By collecting baseline fecal samples from NSCLC patients prior to treatment for metagenomic and non-targeted metabolomic analysis, multi-omics integrated analysis was performed to identify testosterone as the key metabolite promoting NSCLC metastasis. Wound healing and transwell assays were conducted to verify the effects on migration and invasion of testosterone in NSCLC cell lines. Mendelian randomization demonstrated that testosterone promoted AKT phosphorylation at the genetic level, which was further validated by Western Blot analysis. Tumor metastasis was investigated in a mouse model to reveal whether testosterone could promote NSCLC metastasis in vivo.

Results: Compared to patients with non-metastatic NSCLC, those with distant metastasis exhibited significant gut microbiota dysbiosis and distinct metabolic characteristics. The correlation analysis revealed that Fusobacteria was negatively associated with NSCLC metastasis, suggesting a potential protective role. The metabolite testosterone and its related pathways might play key roles in NSCLC metastasis. Testosterone significantly enhanced the migration and invasion abilities of PC9, A549, and H1299 cells. Testosterone accelerated epithelial-mesenchymal transition (EMT) progression through activation of AKT/mTOR pathway phosphorylation. Additionally, intraperitoneal injection of testosterone promoted malignant progression of NSCLC in mice.

Conclusions: The gut microbiota metabolite testosterone may promote NSCLC metastasis by inducing EMT through activation of AKT/mTOR pathway phosphorylation. This study may provide clinical targets and evidence for the prediction and interventional treatment of NSCLC metastasis.



Keywords: Gut microbiota, Testosterone, NSCLC Metastasis

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.45 Modulated Electro-Hyperthermia Enhances Tumor Cell Susceptibility to Gamma Delta T Cell-Mediated Cytotoxicity and Tumor Infiltration

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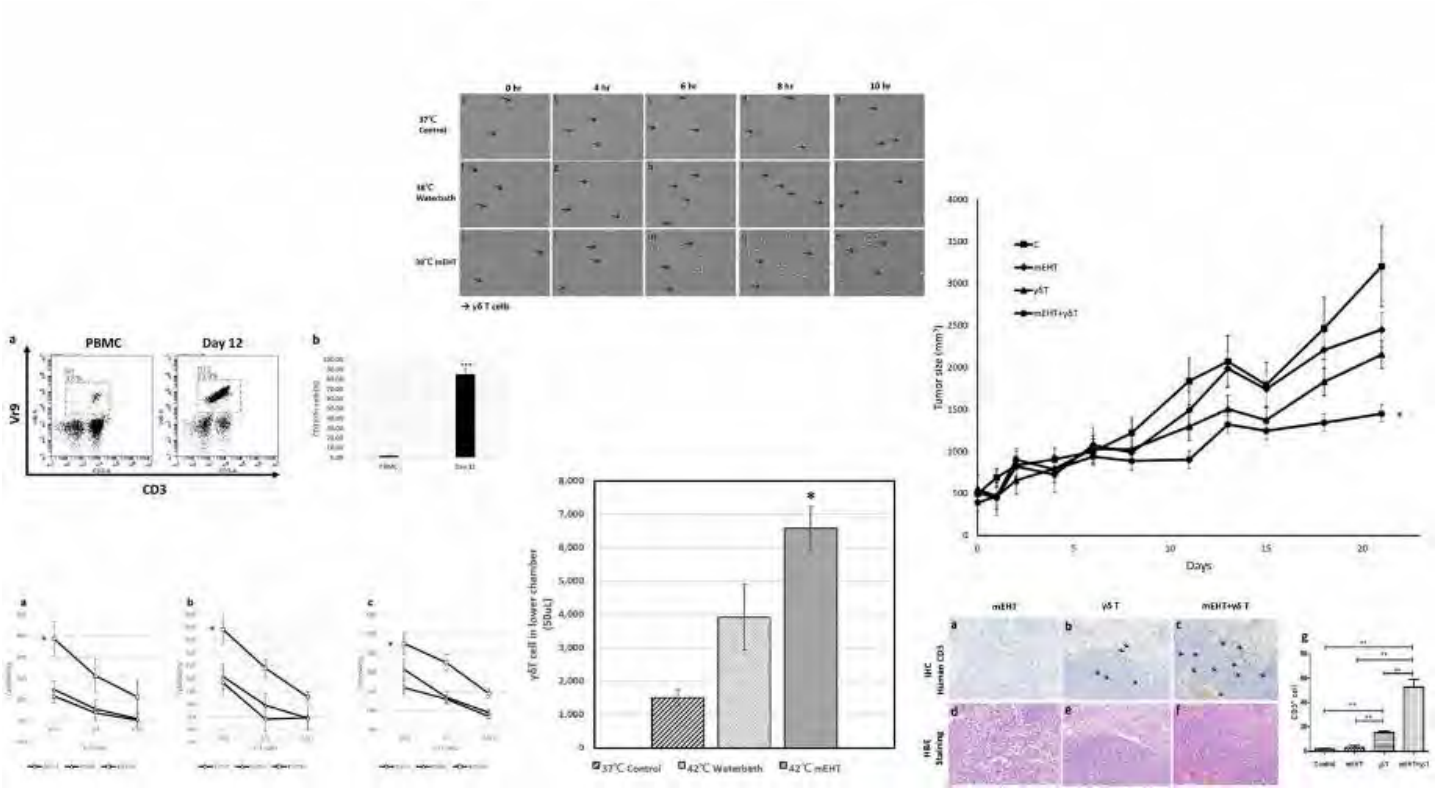
Introduction: Numerous studies reported gamma delta T cell (γδ T cell) therapy as a promising immunotherapy for treating tumors, but little research explored the potentials of γδ T cell in combination with other treatments. Modulate electro-hyperthermia (mEHT) is a significant technological development in hyperthermia, autofocusing electromagnetic power on the cell membrane to create massive apoptosis. However, the synergetic effects of mEHT and γδ T cells for treating tumors remain unclear.

Methods: Therefore, in this study, we hypothesized that mEHT could enhance the therapeutic effects of γδ T cells against tumors. By recruiting γδ T cells to tumor cells, mEHT-treated tumors were more sensitive to these cells and thus increased the cytotoxic functions. The γδ T cells were isolated and co-cultured with mEHT-treated tumors.

Results: The cytotoxic rates were significantly increased compared with control and a conventional heating device. In tumor-bearing NOD/SCID mice, the tumors remained stable until the end of the experiment with intravenous injections of γδ T cells and mEHT treatment. Furthermore, the increased γδ T cell infiltrations within the tumor microenvironment were found in these mice compared with monotherapy.

Conclusions: These results suggested that γδ T cells could mediate a potent anti-tumor effect when combined with mEHT, providing insight for future clinical development of combinational immunotherapy as a novel anti-tumor strategy.



Keywords: gamma delta T cell-mediated cytotoxicity, Modulated electro-hyperthermia, tumor cell

P2.02.46 V-Atpase Inhibitors Enhance the Effect of Tepotinib (c-Met Inhibitor) or RMC-6236 (Pan-Ras(ON) Inhibitor) in KRAS-Mutant NSCLC

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Introduction: KRAS G12C inhibitors (sotorasib or adagrasib) in monotherapy have short-lived response in metastatic KRAS G12C NSCLC patients. Resistance to KRAS G12C inhibitors appear due to the presence of coexisting KRAS mutations, activation mutations of other RAS isoforms, and amplifications or activation mutations upstream or downstream of RTK pathways. We previously reported that targeting c-Met (tepotinib), upstream growth factor signal transducer of KRAS, decreased cell viability in a broad panel of KRAS G12C and non-G12C NSCLC cell lines. The proliferation inhibition was increased when tepotinib was combined with omeprazole, known to act as a V-ATPase proton pump inhibitor. The aims were to first assess the half maximal inhibitory concentration (IC50) of tepotinib versus RMC-6236 in KRAS G12C and non-G12C-mutant NSCLC cell lines. Secondly, the potential synergism of omeprazole + tepotinib versus omeprazole + RMC-6236. Finally, by western blot analysis, to see the behaviour of MRAS and YAP1 among other proteins as biomarkers of adaptive resistance.

Methods: In vitro studies were conducted in NSCLC cell lines, including NCI-H358, a generated H358 line resistant to sotorasib (H358R), NCI-A549, and NCI-H23. Cell lines were treated with tepotinib (c-Met inhibitor) or RMC-6236 (pan-RAS(ON) inhibitor) alone and in combination with omeprazole pre-treatment. Cell viability assays were performed by MTT, and synergism/antagonism analysis was carried out using Combenefit and Sinergy finder + computational programs. Western blot analysis was performed to characterize total and phosphorylated proteins.

Results: RMC-6236 showed a stronger inhibitory effect in H358 than in H358R and H23 cell lines. Omeprazole increased the cell growth inhibition effect of RMC-6236 and showed synergism in all cell lines. RMC-6236 and omeprazole pre-treatment decreased activation of several tyrosine kinase receptors: MET, EGFR, and LRP6, as well as downstream proteins such as AKT, ERK1/2, and YAP1. RMC-6236 treatment alone enhanced the expression of MRAS and translocated β-catenin to the nucleus, however, when omeprazole pre-treatment was added, the upregulation of MRAS and β-catenin disappeared. Of interest is the fact that tepotinib + omeprazole pre-treatment decreased the expression of MRAS, the cancer stem cell marker (Hes1), ERK1/2, AKT, STAT3, and YAP1, as well as EGFR, EphA2, and LRP6.

Conclusions: Early evidence of data points out that omeprazole increases the anticancer effect of either tepotinib or RMC-6236 in KRAS G12C-mutant and non-G12C-mutant NSCLC cell lines. Western blot analysis shows several hints that the combination of omeprazole pretreatment + tepotinib or omeprazole + RMC-6236 both combinations can avoid upregulation of MRAS and YAP1 and several receptor tyrosine kinases. To further discern is the leverage of tepotinib in front of RMC-6236.

Keywords: V-ATPase inhibitors, c-MET inhibitor, KRAS-mutant NSCLC

P2.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.02.47 Hypoxia-Driven SERBP1-SLC25A5-ND6 Axis Regulates Mitochondrial Metabolic Reprogramming to Promote Metastasis in Non-Small Cell Lung Cancer

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Introduction: Metastasis of non-small cell lung cancer (NSCLC) is the core reason for the low survival rate of patients, with metabolic reprogramming serving as a critical adaptive mechanism for tumor survival. SERPINE1 mRNA binding protein 1 (SERBP1), as an RNA-binding protein, is abnormally expressed in a variety of cancers, but its role in NSCLC metastasis has not been clearly defined. By integrating various omics data, this study revealed for the first time the specific mechanism of NSCLC metastasis driven by SERBP1 translocation to mitochondria (mtSERBP1) by binding mitochondrial transporter SLC25A5 under hypoxia conditions, and targeted regulation of mitochondrial metabolism of mt-ND6 mRNA. The clinical translational value of SERBP1 as a potential biomarker was evaluated, and the functional application of SERBP1 as a potential therapeutic target in cancer research was expanded.

Methods: The First Affiliated Hospital of Soochow University collected cancer tissue and matched para-cancer tissue from NSCLC patients to detect SERBP1 expression. The regulatory effect of SERBP1 on NSCLC metastasis was investigated by mouse tail vein lung metastasis model, transwell and wound healing experiments. The OCR and ECAR values of NSCLC cells were measured by Agilent Seahorse XFe24 analyzer. Mitochondrial protein was isolated and the expression of SERBP1 in mitochondria was detected under hypoxia condition. The effect of SERBP1 expression on mitochondrial morphological changes was detected by immunofluorescence and transmission electron microscopy. The mechanism of SERBP1 entering mitochondria was investigated by RIP-seq and Co-IP techniques.

Results: Analysis of 126 clinical cohort studies combined with public databases showed that SERBP1 was highly expressed in cancer tissues and significantly negatively correlated with TNM stage, metastasis, and survival prognosis. Functional phenotype experiments demonstrated that SERBP1 overexpression enhances the migration and invasion ability of NSCLC cells. In the lung metastasis model of nude mice, the number of metastatic nodules increased in SERBP1 high expression group. Mechanistcally,based on high-throughput omics analysis, overexpression of SERBP1 inhibited oxidative phosphorylation and promoted glycolysis. Co-IP experiment confirmed that hypoxia triggers SERBP1 translocation to mitochondria via interaction with the transporter SLC25A5. RIP-seq confirmed that mtSERBP1 targeted regulation of mt-ND6 mRNA, impairing electron transport chain complex I activity and shifting energy production to aerobic glycolysis.

Conclusions: In this study, a complete research system of RNA-binding protein-mitochondrial metabolic axis was established. By focusing on the molecular mechanism that SERBP1 drives NSCLC metastasis by regulating mitochondrial metabolic reprogramming under hypoxic conditions. Under hypoxia conditions, SERBP1 binds to mitochondrial transporter SLC25A5 and transits to mitochondria (mtSERBP1), which degrades the expression of mitochondrial coding gene mt-ND6, destroys the function of electron transport chain complex I, inhibits oxidative phosphorylation, promotes the occurrence of aerobic glycolysis, and accelerates the malignant metastasis of NSCLC.

Keywords: SERBP1, Non-small cell lung cancer, Metabolic reprogramming

P2.05 PULMONOLOGY AND STAGING,
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.01 The Role of Robotic-Assisted Bronchoscopy and Endobronchial Ultrasound in Diagnosing and Staging Pulmonary Carcinoid

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Introduction: Pulmonary carcinoids account for less than 2% of all lung cancers and can present as endobronchial or as parenchymal nodules. The diagnostic yield of robotic-assisted bronchoscopy (RAB) and the accuracy of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) for lymph node staging in pulmonary carcinoids have not been systematically evaluated.

Methods: In this IRB-approved retrospective study (IRB24-2156), we reviewed consecutive patients who underwent RAB evaluation at the University of Chicago for pulmonary nodules and were subsequently diagnosed with pulmonary carcinoids. Records reviewed included demographics, clinical characteristics, nodule imaging features, bronchoscopic techniques, lymph node stations sampled, surgical intervention, and final pathological staging.

Results: Twenty-three patients were diagnosed with pulmonary carcinoids from 2020 until 2024. Most patients were female and white, with a median age of 68 years (Table 1). The mean nodule size was 17.46 mm, predominantly located in the inner or middle third of the lung. Only 6 patients underwent Ga-68 Dotatate scans, all post-bronchoscopic diagnosis. RAB successfully reached the nodules in 100% of cases. A definitive diagnosis was achieved in 21 of 23 patients (91%) (Table 2). Atypical carcinoid diagnosis was made in 3 patients, while a diagnosis of typical carcinoid was made in 20 patients. The tumor was accurately staged by EBUS-TBNA in 17/23 (87%) of cases. Of the three patients with EBUS-TBNA and surgical staging discrepancies, two had non-diagnostic RAB (EBUS-TBNA staging was not performed), and one had intraoperative pleural involvement but not nodal metastasis. Nodal metastases were diagnosed in 4 patients. Bronchoscopic procedures were well tolerated with one case of pneumothorax.

Conclusions: RAB offers a high diagnostic yield for pulmonary carcinoids and EBUS-TBNA, when performed, provides reliable intrathoracic lymph node staging. These findings support the use of RAB and EBUS-TBNA as safe and effective tools for the diagnosis and staging of pulmonary carcinoid tumors.

Table 1: Patient and Nodule characteristics

Patient Characteristics	All patients (N = 23)
Median age at diagnosis (y)	68
Sex	
Female, n (%)	17 (74)
Male, n (%)	6 (26)
Race	
White, n (%)	13 (57)
Black, n (%)	9 (39)
Unknown, n (%)	1 (4)
Ethnicity	
Not Hispanic, n (%)	22 (96)
Unknown, n (%)	1 (4)
Mean body mass index (kg/m^2)	31.60
History of smoking	
Former, n (%)	11 (48)
Current, n (%)	2 (9)
Never, n (%)	10 (43)
Radiographic Characteristics	
Mean nodule size (mm)	17.46
Location of nodule	
Inner third, n (%)	8 (35)
Middle third, n (%)	13 (56)
Outer third, n (%)	2 (9)
Mean distance from the pleura (mm)	35.91
Bronchus sign	
Yes, n (%)	22 (96)
No, n (%)	1 (4)

Table 2: Diagnostic Outcomes

Outcomes	All patients (N = 23) n (%)
RAB Diagnosis	
Yes	21 (91)
No	2 (9)
Complications from RAB	
Pneumothorax	1 (4)
Major bleeding	0
Staging changed after surgery	
Yes	3 (13)
No	20 (87)

Keywords: Carcinoid, EBUS, navigational bronchoscopy

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.02 Evolution and Survival Impact of Endobronchial Ultrasound (EBUS) Adequacy in Two Population-Based Lung Cancer Cohorts

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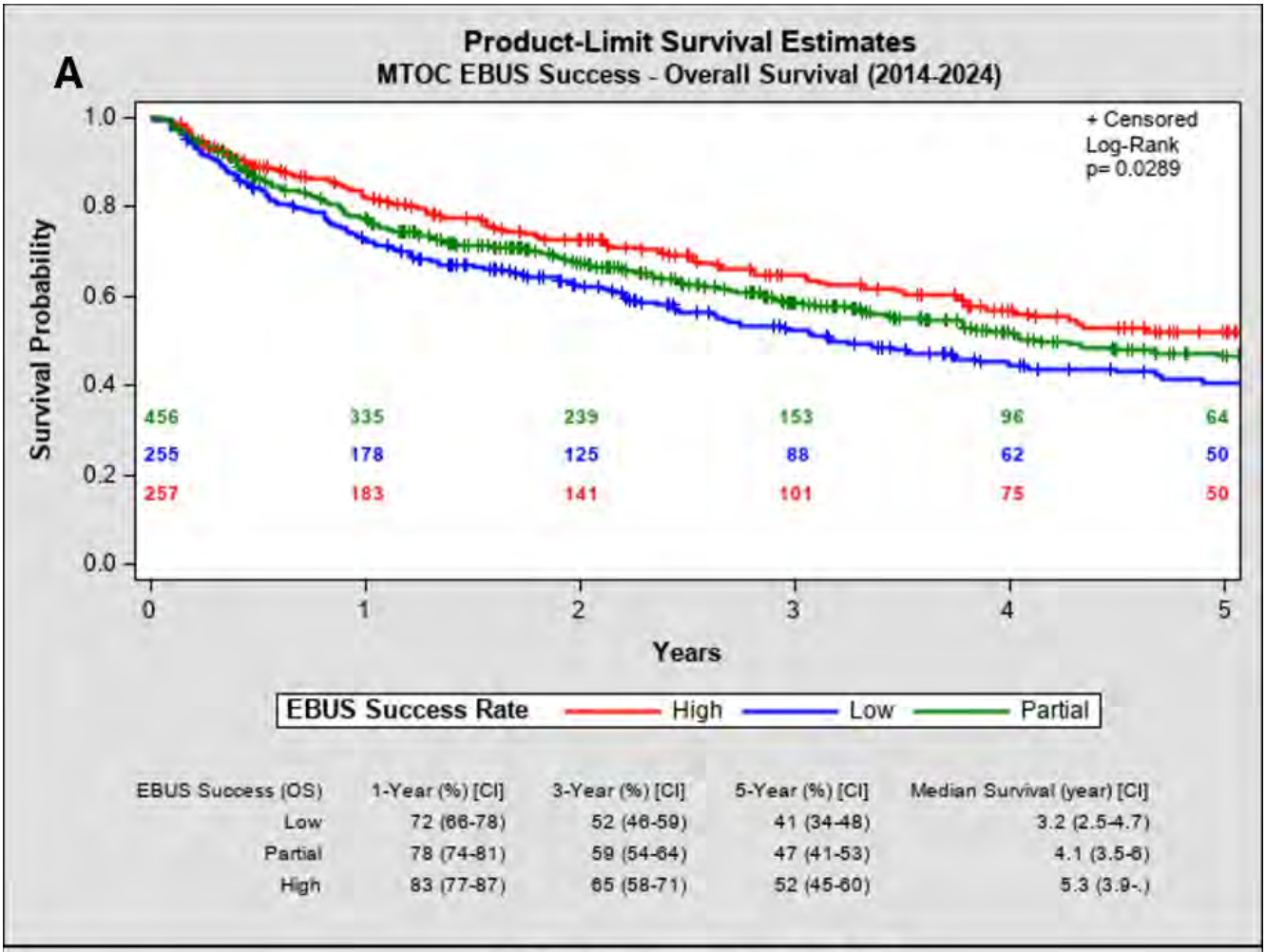
Introduction: EBUS is the standard for mediastinal staging in NSCLC, but variability in nodal sampling adequacy may impact staging accuracy, treatment decisions, and survival.

Methods: We analyzed the pattern of use of EBUS in a Multidisciplinary Thoracic Oncology Program cohort from 2014-2024. EBUS adequacy was categorized as low-adequacy (sampling of 0 or 1 station), partial-adequacy (sampling of 2 or 3 stations), and high-adequacy (examination of all four stations: 4R, 4L, 7, and 10/11). Although other stations (e.g., 2R/L, 12/13) are important, we focused on examination of these hilar/mediastinal stations as a minimum quality standard. We analyzed temporal trends using the Cochran-Armitage test, survival with Kaplan-Meier plots, log-rank tests, and proportional hazards models. Adjusted hazard ratios (aHR) controlled for age, sex, race, insurance, smoking, PET/CT imaging, and clinical stage, with low-adequacy as the reference. Nodal upstaging was calculated by comparing pre-EBUS clinical staging with post-EBUS staging based on nodal sampling results.

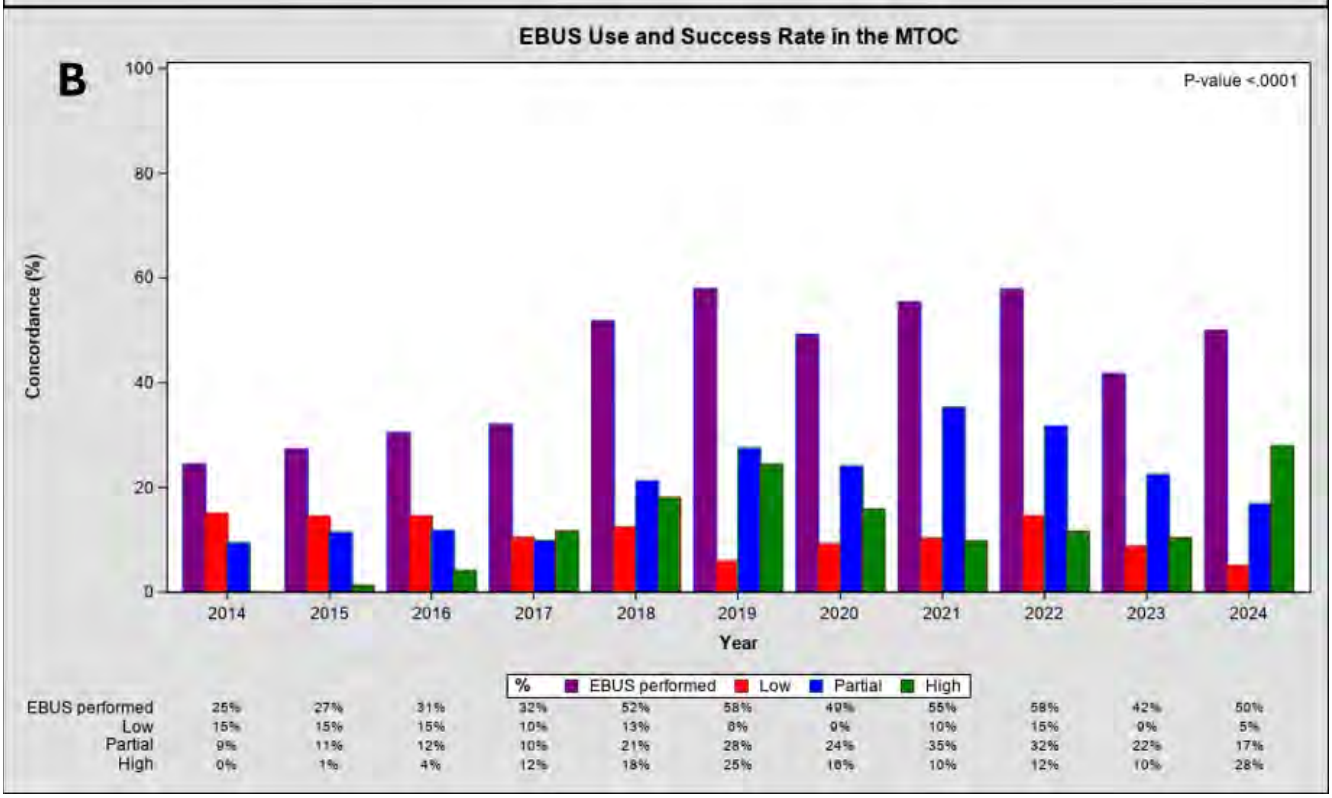
Results: Of 971 patients, 26% had EBUS with low-adequacy, 47% had partial-adequacy, and 27% had high-adequacy. Median age was 67 vs 67 vs 70 (p=0.002); commercial insurance use increased across groups, respectively (35% vs. 44% vs. 49%, p=0.0144). EBUS adequacy significantly improved over time (P<0.0001 Figure 1b). Nodal upstaging was lower within low-adequacy group (2%) compared to partial and high-adequacy groups (8% vs 4%; p=0.0024). EBUS adequacy was associated with improved OS (partial: aHR=0.77, p=0.034; high: aHR=0.75, p=0.022). Stage-stratified analysis showed significant survival benefits for stage III (aHR=0.58, p=0.0329) and intermediate benefits in stage IV (partial: aHR=0.60, p=0.0153; high: aHR=0.58, p=0.0508).

Conclusions: EBUS adequacy significantly improved over time, reflecting advancements in procedural training and feedback. High adequacy was associated with improved OS in stage III-IV disease.

Variable	MTOC (N=971)		
EBUS Adequacy	**Low (26%)**	**Partial (47%)**	**High (27%)**
Age, Median (Q1, Q3)	67 (60, 73)	67 (61, 75)	70 (64, 76)
Nodal Upstaging	5 (2%)	35 (8%)	10 (4%)
Insurance			
Medicare	94 (37%)	150 (33%)	85 (33%)
Medicaid	56 (22%)	73 (16%)	36 (14%)
Commercial	90 (35%)	199 (44%)	127 (49%)
Self-Insured/None	16 (6%)	35 (8%)	10 (4%)
Stations Sampled			
4L	29 (11%)	190 (42%)	258 (100%)
4R	45 (18%)	328 (72%)	258 (100%)
7	96 (38%)	400 (88%)	258 (100%)
10L	-	-	-
10R	36 (14%)	165 (36%)	99 (38%)
11L	-	-	-
11R	39 (15%)	246 (54%)	213 (83%)
Adjusted Hazard Ratio, (95% CI, p-value)			
Overall Survival (OS)	Ref	**0.77 (0.62–0.96, p=0.0217)**	**0.75 (0.58–0.98, p=0.0336)**
Clinical Stage I	Ref	0.70 (0.41–1.19, p=0.1899)	1.25 (0.75–2.08, p=0.4002)
Clinical Stage II	Ref	**2.85 (1.18–6.88, p=0.0203)**	1.55 (0.61–3.95, p=0.3576)
Clinical Stage III	Ref	0.75 (0.52–1.08, p=0.1247)	**0.58 (0.36–0.96, p=0.0329)**
Clinical Stage IV	Ref	**0.60 (0.40–0.91, p=0.0153)**	0.58 (0.34–1.00, p=0.0508)



EBUS Success (OS)	1-Year (%) [CI]	3-Year (%) [CI]	5-Year (%) [CI]	Median Survival (year) [CI]
Low	72 (66-78)	52 (46-59)	41 (34-48)	3.2 (2.5-4.7)
Partial	78 (74-81)	59 (54-64)	47 (41-53)	4.1 (3.5-6)
High	83 (77-87)	65 (58-71)	52 (45-60)	5.3 (3.9-.)



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
EBUS performed	25%	27%	31%	32%	52%	58%	49%	55%	58%	42%	50%
Low	15%	15%	15%	10%	13%	6%	9%	10%	15%	9%	5%
Partial	9%	11%	12%	10%	21%	28%	24%	35%	32%	22%	17%
High	0%	1%	4%	12%	18%	25%	16%	10%	12%	10%	28%

Keywords: Endobronchial Ultrasound (EBUS), NSCLC Staging, Nodal Sampling Adequacy

P2.05.03 Minimizing Atelectasis in ENB: A Propensity-Matched Study of Laryngeal Mask Ventilation Strategy

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Introduction: Atelectasis during electromagnetic navigation bronchoscopy (ENB) can compromise diagnostic accuracy and hamper lesion localization. While endotracheal intubation (ETI) is the traditional airway management approach during ENB, its limitations in ventilation optimization, especially with large-diameter bronchoscopes, have prompted exploration of alternatives. This study aimed to evaluate the feasibility and effectiveness of a laryngeal mask airway-assisted ventilation strategy for atelectasis prevention (LMA-VSAA) during ENB.

Methods: We conducted a single-center, propensity score-matched cohort study comparing LMA-VSAA with conventional ETI in patients undergoing ENB for peripheral pulmonary lesions. Propensity matching was performed based on age, sex, lesion location, and FEV1%. The LMA-VSAA group received optimized ventilation including lung recruitment maneuvers, 6-8 cmH_2O PEEP, and FiO_2 titrated to 40%. The primary outcomes were the degree of atelectasis (measured by CBCT lung volume change) and nodule displacement distance (3D distance between planned and actual lesion position). Secondary outcomes included ENB operation time and complication rates.

Results: Eighty patients were included (40 in each group). Baseline characteristics were well balanced. The LMA-VSAA group showed significantly lower atelectasis compared to the ETI group (8.2 ± 3.4% vs. 28.3 ± 7.6%, P < 0.001). Nodule displacement distances were also significantly smaller in the LMA-VSAA group for both upper (3.2 ± 1.8 mm vs. 11.2 ± 3.4 mm, P < 0.001) and lower lobe lesions (7.4 ± 2.3 mm vs. 24.1 ± 5.2 mm, P < 0.001). ENB procedure times were comparable (25.4 ± 6.8 vs. 27.1 ± 7.5 minutes, P = 0.40). No hypoxemia or serious complications occurred in either group.

Conclusions: The LMA-VSAA strategy significantly reduced intraoperative atelectasis and improved lesion localization accuracy during ENB compared to conventional ETI. These findings demonstrate that LMA-VSAA is a feasible and effective alternative for airway and ventilation management in ENB, with potential to enhance diagnostic yield and patient outcomes. Further randomized trials are warranted to validate these results and explore broader applicability in interventional pulmonology.

Subgroup analysis of primary outcomes stratified by lesion location.

Outcome		LMA-VSAA Group (n=40)	Control Group (n=40)	P
Degree of atelectasis, %	Overall	8.2 ± 3.4	28.3 ± 7.6	<0.001
	Upper lobe lesions	5.6 ± 2.3	19.8 ± 5.4	<0.001
	Lower lobe lesions	11.3 ± 4.1	38.2 ± 9.3	<0.001
Nodule displacement, mm	Upper lobe lesions	5.2 ± 1.8	11.2 ± 3.4	<0.001
	Lower lobe lesions	6.4 ± 2.3	24.1 ± 5.2	<0.001

LMA-VSAA, laryngeal mask airway-assisted ventilation strategy for atelectasis prevention.

Keywords: Electromagnetic Navigation Bronchoscopy, Atelectasis Prevention, Laryngeal Mask Airway

P2.05.04 Electromagnetic Navigation-Guided 3D Conformal Microwave Ablation for High-Risk Peripheral Pulmonary Nodules

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Introduction: Clinically, high-risk peripheral pulmonary nodules (PPNs) identified through imaging follow-up often necessitate surgical resection for pathological diagnosis and therapeutic intervention. However, 5%-10% newly diagnosed patients are not candidates for surgery owing to cardiopulmonary insufficiency or other comorbidities. Traditional alternative therapies exhibit notable limitations in terms of efficacy and safety, underscoring the urgent need for a novel approach. This study aimed to assess the clinical feasibility and safety of electromagnetic navigation-guided three-dimensional conformal microwave ablation (ENB-DCMA) in patients with high-risk PPNs.

Methods: This retrospective study was conducted on consecutive patients who underwent ENB-DCMA of high-risk PPNs between March 2021 and August 2023. Inclusion criteria encompassed medically inoperable patients or those refusing surgery, with PPNs highly suspicious for malignancy. Primary endpoints include local control rate(LCR) and safety.

Results: Sixty-two high-risk PPNs(mean long-axis diameter of 12.26 ± 6.18 mm) in 50 patients were treated with 65 sessions of ablation. All nodules achieved planned ablation zones. No procedure-related mortality occurred. Postoperative complications included pneumothorax 12% (6/50; only 2 cases requiring drainage), post-procedural fever 2%(1/50) and self-limited hemorrhage 4%(2/50). The mean length of hospital stay after surgery was 2.91±1.31 days. Local disease progression occurred in 11 cases during the follow-up. The 1-year local control rate (LCR) was 82.3% (51/62). Median progression-free survival (PFS) was not reached,and the mean PFS for primary NSCLC and metastatic lesions was 40.7 months (95% CI 39.44 to 42.01) and 15.9 months (95% CI 10.58 to 21.31) respectively with a significant difference.(log-rank P<0.001).

Conclusions: ENB-DCMA represented a paradigm-shifting, safe, and effective minimally invasive alternative for the management of high-risk PPNs in medically inoperable patients. This transbronchial approach integrated navigational accuracy with precise 3D thermal field control and may redefine minimally invasive ablation paradigms potentially. Further prospective multicenter trials are needed to confirm its broader clinical applicability and long-term outcomes.

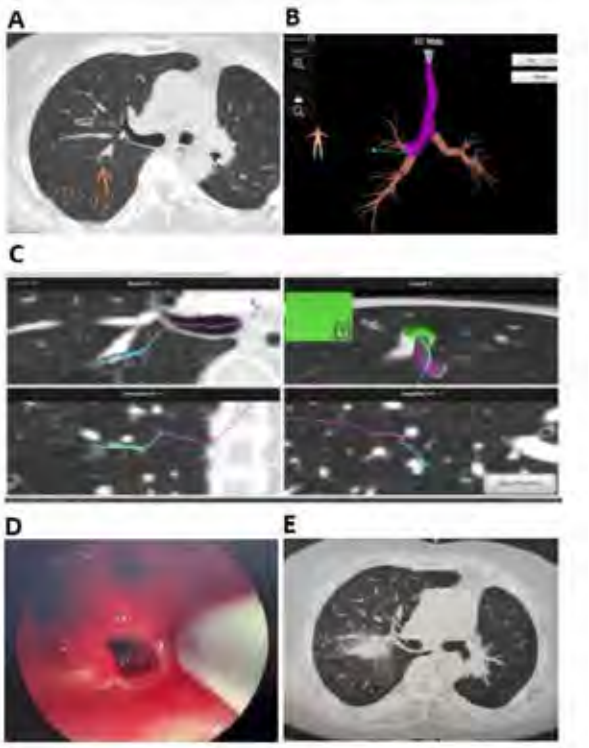

Figure 1: ENB-DCMA procedure: chest computed tomography before microwave ablation (A); planning of targeting nodule (B); real-time electromagnetic navigation screen of the sensor probe aimed at nodule (C); BTPNA was utilized (D); 48h after the microwave ablation (E). *ENB-DCMA*, Electromagnetic navigation-guided three-dimensional conformal microwave ablation; *BTPNA*, Bronchoscopic Trans-Parenchymal Nodule Access

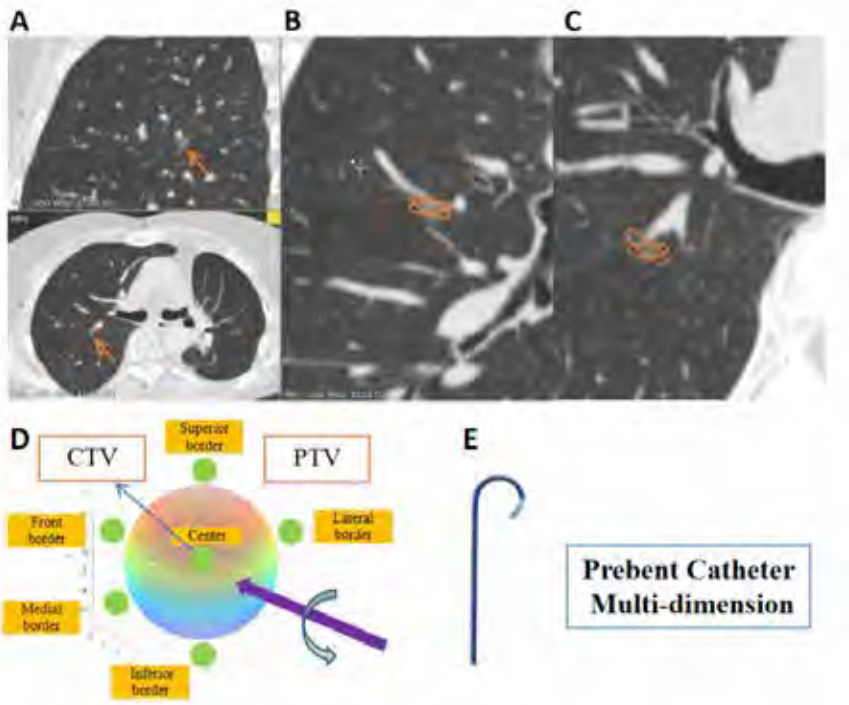

Figure 2: ENB-DCMA concrete operations: chest computed tomography before microwave ablation (A)(B); the nodule was adjacent to vascular structure, a prebent catheter was used for the procedure. the distal end of the catheter could be adjusted by turning the knob until it was parallel to the vascular structure(C); The 3D calibration method was used to ensure the catheter reached the center, superior,inferior,front,medial and lateral margin of the target lesion, thus pathological sampling and sufficient ablation range were confirmed(D); Multi-dimension operation with prebent catheter(E).

Keywords: Electromagnetic navigation bronchoscopy, three-dimensional conformal microwave ablation, High-risk pulmonary nodules

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.05 Prediction of Distant Metastasis Using CT/PET-Based Radiomics in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Introduction: Non-small cell lung cancer (NSCLC) is associated with high rates of distant metastasis (DM), which significantly impacts patients' outcomes. The use of CT/PET-based radiomics has emerged as a promising tool to predict DM, potentially offering more accurate predictions compared to traditional clinical models. We aim to evaluate and compare the predictive performance of radiomics and clinical models in predicting DM in NSCLC patients.

Methods: We conducted a systematic review and meta-analysis following the PRISMA guidelines through PubMed and Scopus databases for studies on radiomics in NSCLC. The protocol was registered on PROSPERO (CRD42025628953). Observational studies and randomized clinical trials on NSCLC patients who underwent CT/PET-based radiomics with distant organ metastasis were included. Non-English articles, reviews, case reports, and animal studies were excluded. Primary outcome included accuracy of CT/PET-based radiomics in predicting DM in NSCLC. Pooled analysis was performed using the inverse variance weighting meta-analysis of single means on evaluation metrics including the area under curve (AUC), and the concordance index (C-index). Secondary outcomes included the comparison of radiomics vs. clinical models in DM prediction.

Results: Seventeen studies, including 1,550 NSCLC patients, were analyzed. Among them, 559 patients had distant metastasis. The mean age was 69.6 ± 7.7 years, and 733 were males. Stage I, II, and III diseases were reported in 450, 316, and 291 patients, respectively. Six studies assessed DM prediction using the C-index, and 11 used the AUC. For radiomics models evaluated with the AUC, low heterogeneity was observed (I^2 = 42%, p = 0.07), with a pooled AUC of 0.73 (95% CI: 0.70-0.77) using a fixed-effect model. Radiomics models evaluated with the C-index showed no heterogeneity (I^2 = 0%, p = 0.83), with a pooled C-index of 0.65 (95% CI: 0.61-0.70). Clinical models assessed using the AUC displayed high heterogeneity (I^2 = 90%, p < 0.01), with a pooled AUC of 0.70 (95% CI: 0.61-0.79) using a random-effect model. In contrast, clinical models evaluated with the C-index showed no heterogeneity (I^2 = 0%, p = 0.61), with a pooled C-index of 0.60 (95% CI: 0.55-0.65).

Conclusions: Our results indicate that radiomics models outperformed clinical models in predicting DM in NSCLC patients, as evidenced by higher pooled AUC and C-index values. Radiomics models also exhibited low heterogeneity across studies, suggesting consistent and reproducible performance. In comparison, clinical models showed greater variability and slightly lower predictive accuracy. These findings suggest that radiomics has the potential to serve as a reliable tool for DM prediction in NSCLC, offering more consistent performance than clinical models.

Keywords: Distant Metastasis Prediction, Radiomics, Predictive Modeling

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.06 Mature Results of a High-Precision Clinical Protocol for Staging Non-Small Cell Lung Cancer (NSCLC) of the Left Lung

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Introduction: Video-assisted mediastinoscopic lymphadenectomy (VAMLA) allows a bilateral mediastinal ymphadenectomy from the superior paratracheal to the hilar nodes. Extended cervical mediastinoscopy (ECM) allows to explore the subaortic and the para-aortic nodal stations. In 2010, VAMLA was included in our staging protocol, based on European Society of Thoracic Surgeons (ESTS) guidelines, for patients with normal mediastinum. We aimed to assess: 1) the accuracy of VAMLA+ECM; 2) the rate of unsuspected (u) N2 in a cohort of patients with left-side NSCLC and normal mediastinum by integrated positron emission tomography (PET) - computed tomography (CT).

Methods: Prospective observational single-center study of 229 consecutive VAMLAs and ECM for staging left clinical (c) N0-1 NSCLC from 2010 to 2023. Systematic nodal dissection (SND) performed during lung resection was considered the reference standard test to validate negative VAMLAs and negative ECM. Those patients with negative VAMLA but without lung resection were excluded (n=29). uN2-3 rates were analyzed in the global series and in the subgroups of tumors according to their clinical nodal and tumor categories by PET-CT. Pathologic findings were reviewed, and staging values, calculated using the standard formulas (including 95% confidence interval [CI]).

Results: 200 patients (152 men; median age 60, range 45-86) underwent VAMLA + ECM. A mean of 4,2 nodal stations and a mean of 16.7 lymph nodes (range 6-39) were sampled. Staging values of the whole protocol (VAMLA + ECM) were: sensitivity, 0.89 (95% CI, 0.74-0.95); negative predictive value, 0.97.6 (95% CI, 0.94-0.99); and diagnostic accuracy, 0.98 (95% CI, 0.98-1). The uN2-3 rate for the whole series was 18%. The uN2-3 rates according to presurgical cT and cN categories by PET-CT were: 6.1% (4/65) in cT1N0; 10.1% (6/59) in cT2N0; 10% (2/20) in cT3N0; 40% (4/10) in cT4N0; 45.6% (21/46) in cN1. Complications related to VAMLA occurred in 9/200 (4.5%) patients, being temporary left recurrent laryngeal nerve palsy the commonest, 3/9 (33%).

Conclusions: This clinical protocol for staging NSCLC of the left lung and normal mediastinum by PET-CT demonstrated a high rate of unsuspected N2-3 disease (specially in cN1 and cT4N0) and a high accuracy. With these results, and especially for the mentioned subgroups, it seems recommendable to increase the precision of invasive staging methods (ideally with a bilateral transcervical lymphadenectomy) to identify the best candidates for neoadjuvant treatments.

Keywords: VAMLA, ECM, Left-sided NSCLC

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.07 The Effect of Adrenal Gland Metastasis on the Course of Lung Cancer

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Introduction: Approximately half of lung cancer patients already have metastases at diagnosis. The adrenal gland is one of the most common metastatic sites for lung cancer. The aim of this study was to investigate the frequency, characteristics and impact on survival of adrenal metastases in patients with lung cancer.

Methods: A total of 1,253 patients with lung cancer were examined between January 1, 2011 and December 31, 2015. All radiologic examinations (chest CT including upper abdomen, PET-CT, dynamic adrenal CT) of all patients from diagnosis to death were retrospectively reviewed. Adrenal lesions were divided into the groups < 1 cm and ≥ 1 cm at diagnosis. Adrenal lesions were classified as benign or malignant based on the compatibility of clinical and radiologic data. However, adrenal lesions in patients with less than one year of follow-up due to death were assessed as indeterminate lesions. The relationship between adrenal metastases and clinical and survival data was analyzed.

Results: The mean age of the patients ± SD was 63.05 ± 9.54 (33 - 90) years, and 89.2% were male. Of the patients with an adrenal lesion of less than 1 cm, 0.7% (7/971) had adrenal metastases at diagnosis and 6% (59/971) during follow-up. Of the patients with an adrenal lesion of 1 cm or more, 54.6% (154/282) had an adrenal metastasis at diagnosis and 45.4% (128/282) had a benign adrenal lesion. The survival time was 12.0 ± 12.5 (11.0 - 13.0) months in patients without metastases at diagnosis, 10.0 ± 3.1 (4.0 - 16.0) months in patients with metastases only in the adrenal gland and 7.0 ± 0.6 (5.9 - 8.1) months in patients with metastases in the adrenal gland and other organs. The survival of patients without metastases was similar to the survival of patients who only had metastases in the adrenal gland (p=0.119). However, the survival of both patients without metastases and patients who only had metastases in the adrenal gland was longer than that of patients who had metastases in other organs in addition to the adrenal gland (p<0.001 and p=0.002 respectively). On multivariate analysis, the determinants of adrenal metastases at diagnosis were nodular structure of the adrenal lesion (OR; 95%CI: 4.97; 2.10-11.87), SUVmax value ≥ 2.5 (5.57; 3.25-9.53), brain (OR: 3.24; 1.17-8.18), bone (3.87; 1.59-9.43) and pleural metastases (2.55; 1.02-6.38). The variables that predicted malignant or benign adrenal lesions were adrenal lesion size (2.98; 1.33-6.67) and SUVmax (8.25; 5.00-13.61).

Conclusions: Although adrenal metastases are common in lung cancer patients, clinical outcomes are better than for metastases in other organs. Curative treatment approaches can have a positive impact on the survival of patients with adrenal metastases.

Keywords: Lung cancer, Adrenal gland metastases, Survival

P2.05.08 Discordance Between Clinical and Pathological Invasive Size in Early Stage Non-Small Cell Lung Cancer

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Introduction: The radiological solid size of part-solid nodules (PSN) is often used to estimate the invasive portion of tumors in non-small cell lung cancer (NSCLC). Consequently, the clinical T stage is defined based on the solid size of PSNs. However, discrepancies between clinical and pathological T staging have been observed. This study aims to analyze the discordance between clinical and pathological staging in NSCLC.

Methods: We retrospectively analyzed early-stage clinical adenocarcinoma lung cancer patients who underwent curative surgery between January 2018 and December 2020. Patients with visceral pleural invasion were excluded. Concordance was defined as matching clinical T stage (based on PSN size) and pathological T stage, while discordance was defined as a mismatch between the two. Among the discordant group, we further classified patients into up-staged and down-staged T status groups. All staging was reviewed according to the ninth edition of the AJCC TNM staging system.

Results: A total of 1,141 patients were included, with 444 (38.9%) in the concordance group and 697 (61.1%) in the discordance group. Among the discordant group, 155 (13.6%) had up-staged T status, and 542 (47.5%) had down-staged T status. Discordance with upstaging was predominantly observed in patients with clinical T1a status. Notably, only pure ground-glass nodules (GGNs) exhibited upstaging discordance. The radiological mean total tumor size in the up-staged group was the largest across all groups, although the solid component size was the smallest (1.9 ± 0.8 cm vs. 1.0 ± 0.9 cm, p < 0.001). The invasive portion's pathological size in the up-staged group was also the largest (1.6 ± 0.9 cm vs. 0.7 ± 0.5 cm and 1.8 ± 0.9 cm, p < 0.001). The acinar type of adenocarcinoma was most frequent in both the concordance and up-staged groups, while the lepidic type was predominant in the down-staged group. Lymphatic invasion was observed in both the concordance and up-staged groups, but none were found in the down-staged group (5.2% vs. 25.8%, p < 0.001). Although the recurrence rate was higher in the up-staged group, no significant difference was found between the concordance and discordance groups (p = 0.004).

Conclusions: Discordance between clinical and pathological staging was particularly notable in pure GGN nodules. For lung nodules close to 2 cm in size, the pathological invasive portion may exceed the radiological solid size, emphasizing the importance of considering both clinical and pathological assessments in staging early-stage NSCLC.

Table. Baseline characteristics

N=1141	Concordance (N=444)	Discordance (N=697)		P value
		Down staging (N=155)	Up staging (N=542)	
Age	63.1 ± 10.0	61.0 ± 9.7	63.7 ± 9.9	0.012
Gender				0.764
Male	183 (41.2%)	59 (38.1%)	223 (41.1%)	
Female	261 (58.8%)	96 (61.9%)	319 (58.9%)	
Clinical T stage				<0.001
T1is	0	0	116 (21.4%)	
T1mi	31 (7.0%)	0	87 (16.1%)	
T1a	85 (19.1%)	35 (22.6%)	140 (25.8%)	
T1b	219 (49.3%)	83 (53.5%)	124 (22.9%)	
T1c	68 (15.3%)	29 (18.7%)	70 (12.9%)	
T2a	41 (9.2%)	8 (5.2%)	5 (0.9%)	
Radiologic size (cm)				
Total	1.8 ± 0.8	1.6 ± 0.8	1.9 ± 0.8	<0.001
Solid	1.6 ± 0.8	1.6 ± 0.7	1.0 ± 0.9	<0.001
Nodule type				<0.001
PSN	136 (30.6%)	15 (9.7%)	275 (50.7%)	
Solid	308 (69.4%)	140 (90.3%)	151 (27.9%)	
pGGN	0	0	116 (21.4%)	
Pathologic T stage				<0.001
T1mi	31 (7.0%)	65 (41.9%)	22 (4.1%)	
T1a	85 (19.1%)	63 (40.6%)	61 (11.3%)	
T1b	219 (49.3%)	23 (14.8%)	190 (35.1%)	
T1c	68 (15.3%)	4 (2.6%)	82 (15.1%)	
T2a	41 (9.2%)	0	171 (31.5%)	
T2b	0	0	14 (2.6%)	
T3	0	0	2 (0.4%)	
Pathologic size (cm)				
Total size	1.8 ± 0.8	1.4 ± 0.7	2.1 ± 0.9	<0.001
Invasive portion	1.6 ± 0.9	0.7 ± 0.5	1.8 ± 0.9	<0.001
Histology				<0.001
AIS	5 (1.1%)	2 (1.3%)	3 (0.6%)	
MIA	26 (5.9%)	51 (32.9%)	17 (3.1%)	
Lepidic	56 (12.6%)	46 (29.7%)	67 (12.4%)	
Acinar	210 (47.3%)	34 (21.9%)	299 (55.2%)	
Papillary	109 (24.5%)	19 (12.3%)	124 (22.9%)	
Micropapillary	8 (1.8%)	0	3 (0.6%)	
Solid	30 (6.8%)	3 (1.9%)	29 (5.4%)	
Lymphatic invasion	23 (5.2%)	0	140 (25.8%)	<0.001

Keywords: NSCLC, Pathological staging, Invasive size

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.09 Proposed Modification of Clinical T Categorization for Early-Stage Lung Adenocarcinoma:A Data-Driven Multicenter Quantitative Analysis

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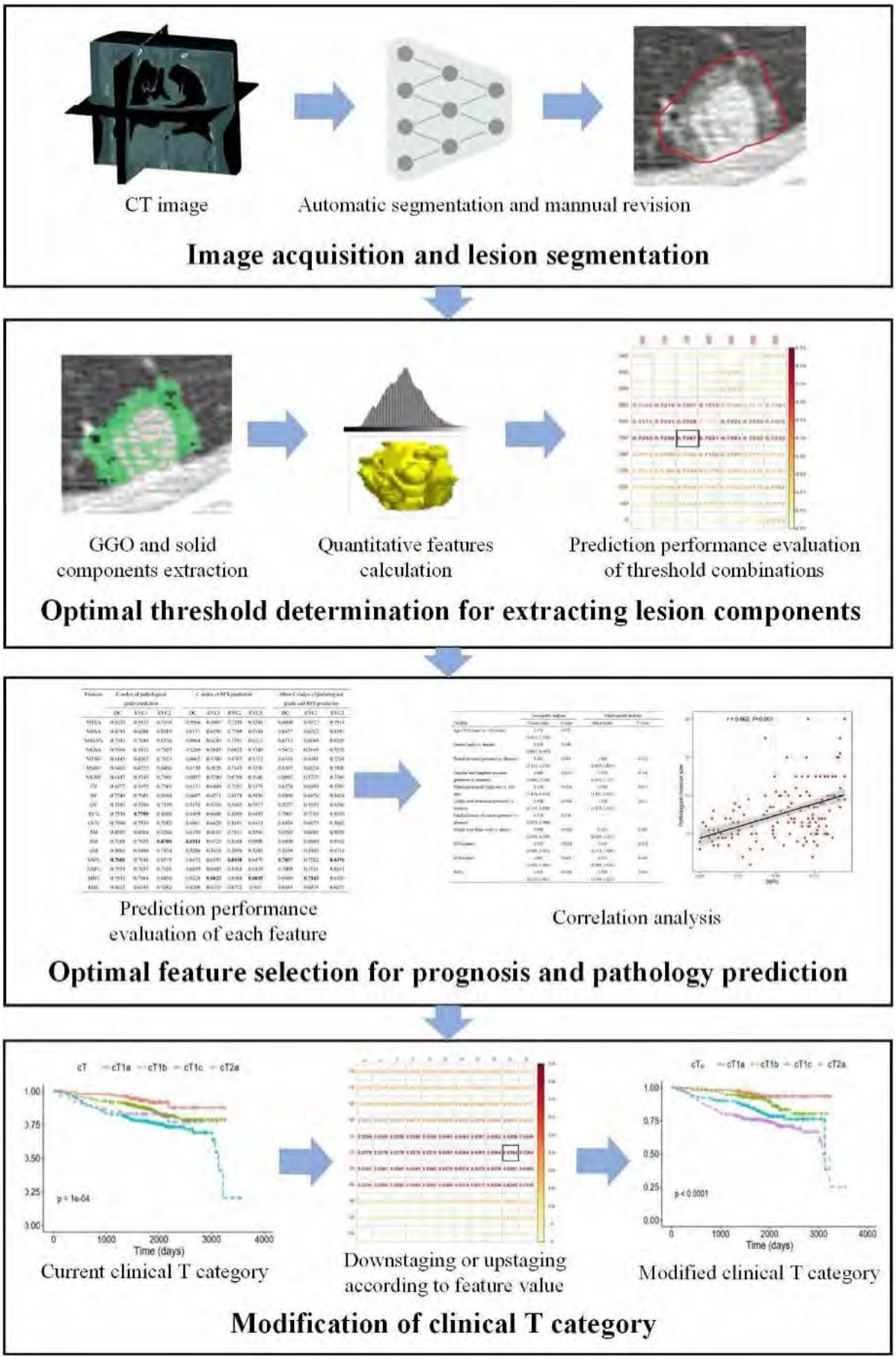
Introduction: The postoperative survival rate for patients with clinical stage I non-small cell lung cancer (NSCLC) remains unsatisfactory even after complete tumor resection. The current clinical T categorization (cT8) may not be optimized for guiding treatment decisions as it does not take into account the ground-glass opacity (GGO) component. This study aim to improve cT8 by considering GGO component that could further optimize the current treatment protocols of early-stage lung adenocarcinoma (LUAD).

Methods: A total of 1289 patients diagnosed with stage I LUAD were included from three hospitals between 2014 and 2017. The study comprised a discovery cohort (DC: n=830) from center I and three external validation cohorts (EVC1: n=186; EVC2: n=176; EVC3: n=97) from centers II, III, and TCIA, respectively. The optimal thresholds for defining GGO and solid components in CT images were determined by a quantitative CT feature predicting both pathological grade and recurrence-free survival (RFS) using a data-driven quantitative analysis method. A modified clinical T category (cTm) was then derived by adjusting the cT8 of patients based on the feature value. The performances of the cTm in predicting pathological grade and RFS were assessed using the concordance index (C-index).

Results: The optimal attenuation thresholds for identifying GGO and solid components on CT were determined to be -650 HU and -250 HU, respectively. The percentage of solid-mass to total-mass (SM%) was the best predictor of both pathological grade and RFS (C-index=0.704). The cTm was derived by downstaging the patients with SM%<45% and upstaging those with SM%>75%, resulting in significantly enhanced C-indexes compared to cT8 in all external validation cohorts: EVC1 (pathological grade: 0.722 vs. 0.686, p<0.001; RFS: 0.654 vs. 0.629, p<0.001), EVC2 (pathological grade: 0.774 vs. 0.720, p<0.001; RFS: 0.831 vs. 0.724, p<0.001), and EVC3 (RFS: 0.613 vs. 0.539, p<0.001).

Conclusions: The proposed cTm has the potential to more precisely tailor surgical interventions and treatment protocols for early-stage LUAD, thus enhancing the prospects for favorable clinical outcomes.



Keywords: lung adenocarcinoma, clinical T category modification, quantitative analysis

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.10 Prognostic Factors in IIB-IIIB Patients With Nodal Involvement Underwent Surgery for NSCLC

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Introduction: The 9thTNM proposal introduced the N2a(single N2 station) and N2b(multiple N2 stations)category as descriptors in stages with nodal involvement and revised the stage groups with new combination of T and N characteristics. However, prognostic factors among these stages are not been investigated yet. Aim of this study is to evaluate different prognostic factors among the new proposed stages.

Methods: Data of patients underwent anatomical surgical resection and lymphadenectomy from 8 centres from 1/1/202015 to31/12/2023 were collected and retrospectively analysed. Only patients with hilar or mediastinal nodal involvement without neo-adjuvant therapy were included. Pathological reports were adapted to the 9thTNM proposal generating the following staging groups: IIB(pT2N1,T1N2a), IIIA(T1N2b,T2-3N2a,T3N1,T4N1), IIIB(T2-3N2b,T4N2a,T4N2b).Pathological factors were correlated to overall survival(OS) and Disease free survival(DFS) using Kaplan-Meier curves.The log-rank test and Cox-regression analysis was used to assess differences between subgroups. The analysis was conducted on the entire population and among the different stages.

Results: The final analysis was conducted on 318 patients. Pathological Stage resulted IIb in108(34.0%),IIIa in168(52.8%) and IIIb in42(13.2%) cases. During follow-up, 132(42.5%) patients experienced a recurrence and 76(20.8%) died. Adenocarcinoma resulted the most frequent histology, resulting in the 67.9% of cases. Pathological T-stage resulted 1 in 137(43.0%),2 in 103(32.4%), 3 in 48(15.1%) and 4 in 30(9,4%) cases, respectively, while pN1 resulted in 138(43.4%) and pN2 in 180(56.6%) patients. Radical mediastinal dissection was performed in 223(70.1%) of cases and Spread through air spaces(STAS) resulted in 64(20.1%) of cases.In the entire cohort, infiltration presence(p=0.008),pN2 (p<0.001),p-stage(p<0.001), total metastatic nodes(p=0.021) and adjuvant therapy resulted significant negative prognostic factors for DFS, while pT(p<0.001), infiltration(p=0.025), vascular invasion (p=0.007), lymphatic invasion (p=0.010),pStage(p=0.002),N2 metastases(p=0.022),total number of metastatic nodes(p=0.044) and adenocarcinoma subtype(p=0.021) significantly correlate with worse OS.Considering the different stages(table),advanced pT stage resulted a significant negative prognostic factor for OS in IIB stages. In stage IIIA, STAS(p=0.022),N2 resected station<3(p=0.041) and N2 metastatic nodes(p=0.046) resulted negative prognostic factors for DFS and lymphatic invasion for OS(p=0.029). In stage IIIB, high grade adenocarcinoma resulted negative prognostic factor for DFS, while pneumonectomy(p=0.019),squamous cell carcinoma (p<0.001),advanced pT(p=0.016), pN2b(p=0.017) and concomitant pN1 involvement(p=0.002) resulted negative prognostic factors for OS.

Conclusions: Our study showed different prognostic factors among the new stages proposed in the new TNM staging system. In this way, it would be possible to stratify the prognosis and plan ad hoc therapies and follow-up schedules tailored on tumor characteristics

	STAGE IIB		STAGE IIIA		STAGE IIIB	
VARIABLE	**DFS p-value**	**OS p-value**	**DFS p-value**	**OS p-value**	**DFS p-value**	**OS p-value**
SURGERY Lobectomy vs pneumonectomy	0.748	0.324	0.106	0.406	0.772	**0.019**
HISTOLOGY Adenocarcinoma Squamous cell carcinoma other	0.872	0.745	0.614	0.586	0.260	**<0.001**
ADENOCARCINOMA HISTOLOGY low vs high grade	0.871	0.366	0.487	0.563	**0.043**	0.882
pT	0.133	**0.045**	0.893	0.084	0.299	**0.016**
INFILTRATION NO vs YES	0.096	0.444	0.799	0.273	0.382	0.153
PLEURAL INFILTRATION NO vs yes	0.570	0.854	0.951	0.279	0.723	0.491
VASCULAR INVASION NO vs YES	0.201	0.707	0.902	0.282	0.871	0.104
LYMPHATIC INVASION NO vs YES	0.237	0.822	0.799	**0.029**	0.855	0.089
STAS NO vs YES	0.627	0.060	**0.022**	0.317	0.931	0.495
PATHOLOGICAL N 1 vs 2	0.210	0.837	0.071	0.501	-	-
PN2 SUBGROUP N2A VS N2B	-	-	0.159	0.755	0.560	**0.017**
LYMPHADENECTOMY Sampling vs radical	0.793	0.317	0.609	0.174	0.748	0.687
N1 RESECTED NODES <3 VS ≥3	0.337	0.901	0.065	0.727	0.535	0.349
N1 METASTASES YES vs NO	0.305	0.589	0.096	0.751	0.051	**0.002**
N2 RESECTED STATIONS <3 VS ≥3	0.864	0.322	**0.041**	0.158	0.481	0.361
N2 RESECTED NODES <6 VS ≥6	0.930	0.293	0.231	0.455	0.308	0.940
N2 METASTASES YES VS NO	0.601	0.911	**0.046**	0.707	-	-
N2 SKIP METASTASES YES VS NO	-	-	0.117	0.216	0.587	0.109
TOTAL RESECTED NODES <10 VS ≥10	0.553	0.502	0.229	0.926	0.538	0.576
TOTAL METASTASTIC NODES <3 VS ≥3	0.469	0.788	0.667	0.300	0.810	0.797
ADJUVANT YES VS NO	**0.029**	0.655	0.160	0.256	0.083	0.238

Keywords: NSCLC, staging, prognosis

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.11 Prognostic Impact of Organ-Specific Metastasis in Non-Small Cell Lung Cancer

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Introduction: Prognostic stratification is essential in non-small-cell lung cancer (NSCLC) to guide treatment decisions. While the TNM staging system has evolved to refine the M category based on metastatic burden, it does not account for differences in prognosis based on the specific organ affected. This study evaluates whether incorporating organ-specific metastasis improves prognostic discrimination in stage IV NSCLC.

Methods: We conducted a retrospective cohort study using data from the Korean Central Cancer Registry (2014-2018). Patients with stage IV NSCLC were classified according to the 9th edition TNM classification: M1b (single-organ, single metastasis), M1c1 (multiple metastases within a single organ), and M1c2 (multiple organ metastases). Survival outcomes were compared across groups using Kaplan-Meier analysis and Cox proportional hazards modeling.

Results: Among 3,165 patients, 56.5% had single-organ metastases, while 43.5% had multiple organ metastases. Median overall survival (OS) was longest in M1b (8.0 months), followed by M1c1 (6.0 months), and shortest in M1c2 (5.9 months) ($p < 0.001$). However, survival varied by metastatic organ. Liver, adrenal, and uncommon-site metastases were associated with significantly worse OS, even among M1b patients. Some M1b and M1c1 patients with high-risk organ metastases had worse survival than M1c2 patients, challenging the TNM-defined prognostic hierarchy.

Conclusions: The current TNM M category does not fully capture the prognostic impact of metastatic organ involvement. Incorporating organ-specific metastases into staging and prognostic models could refine risk stratification and improve personalized treatment approaches for stage IV NSCLC.

Keywords: Non-small cell lung cancer, Metastasis, Prognosis

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.12 Lymph Node Pathologic Grading Strategy: Under the Backdrop of the IASLC Grading System for Invasive Lung Adenocarcinoma

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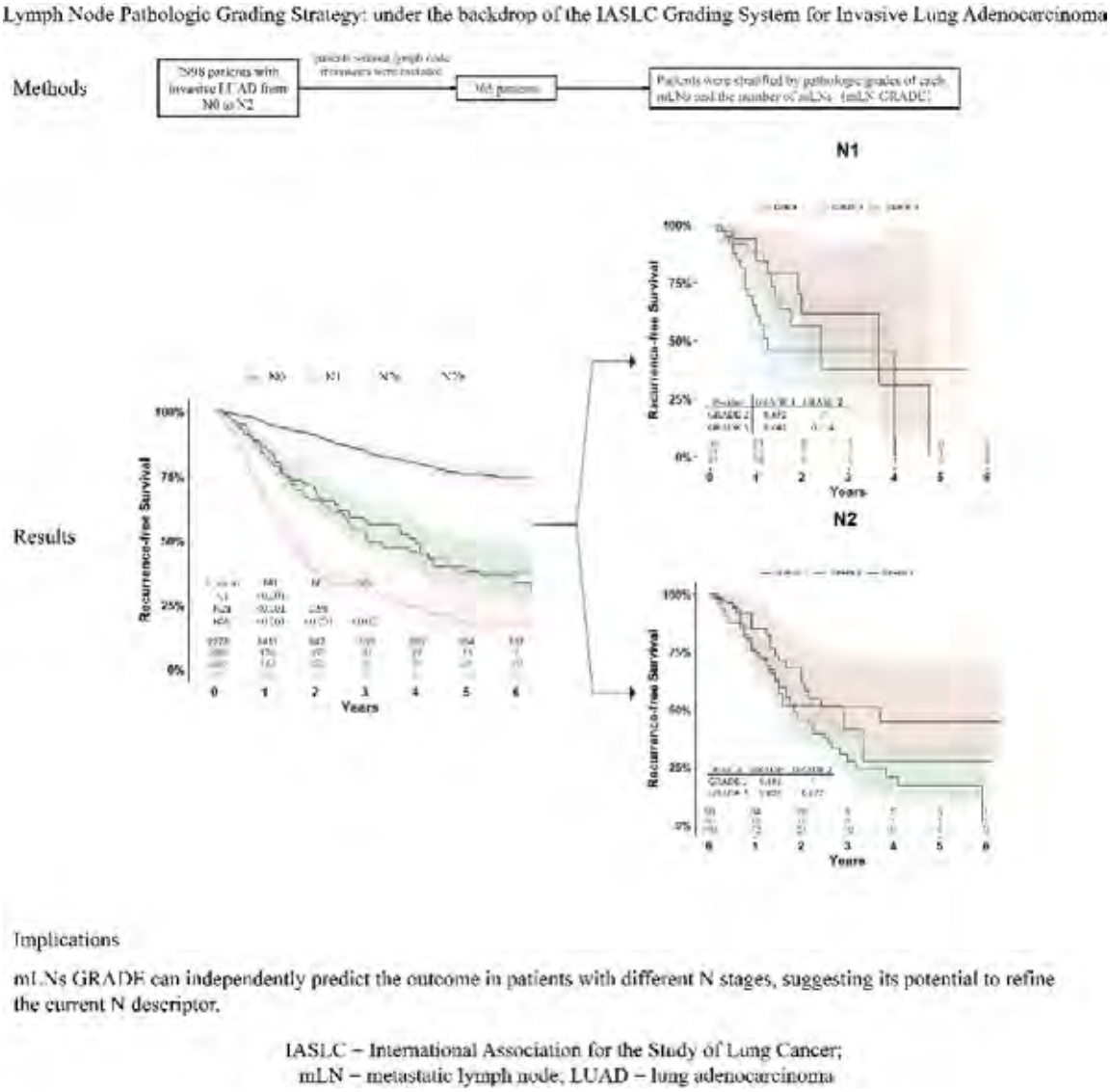
Introduction: We aimed to probe into the pathologic grading system in metastatic lymph nodes (mLNs) based on the IASLC grading system for supplementing the accuracy of N staging in patients with lung adenocarcinoma (LUAD).

Methods: From 2011 to 2021, a large cohort of 2998 patients with invasive LUAD were analyzed and classified according to their N stages. Patients were further stratified according to different pathologic grades for each mLN as well as the quantity of mLNs, which we named GRADEs. And we performed survival analysis to reveal the association between GRADEs and long-term outcomes.

Results: The prognostic differences between N categories were highly significant in terms of recurrence-free survival (RFS). High mLNs GRADE was robustly correlated with higher pathologic grade ($p < 0.001$) in primary tumors, higher p-TNM stage ($p < 0.001$), and worse RFS in patients with different N stages. High mLNs GRADE was linked to higher EGFR mutation ($p = 0.021$) in N1 patients, but not in N2 patients. Multivariate analysis revealed the independent prognostic significance of high mLNs GRADE, correlating with adverse outcomes in both N1 and N2 patients.

Conclusions: High mLNs GRADE is significantly associated with worse outcomes in patients with different N stages. mLNs GRADE may help supplement the current N descriptor.



Keywords: Lung adenocarcinoma, Lymph node, Grading system

P2.05.13 M1a With Pleural or Pericardial Effusion Have Worse Survival Than Those With Pleural or Contralateral Lung Metastasis When Receiving EGFR-TKIs

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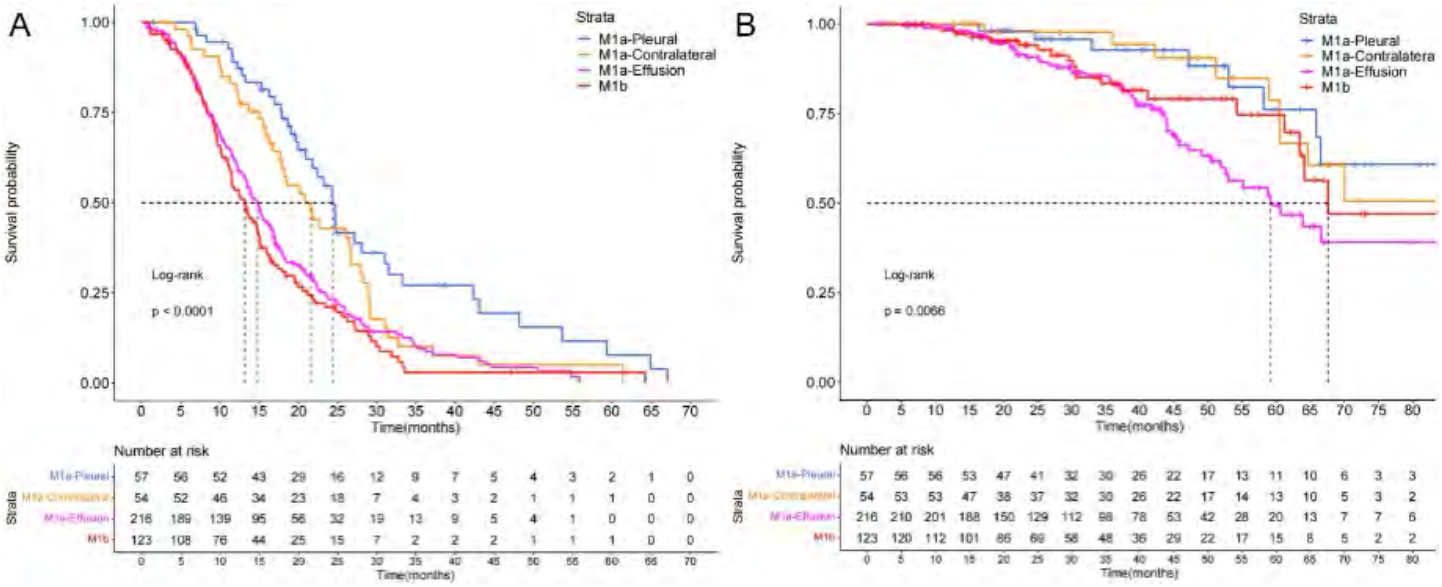
Introduction: The M1a descriptors for non-small cell lung cancer (NSCLC) remain unchanged since 7th TNM staging classification. However, the data from the International Association for the Study of Lung Cancer (IASLC) Staging Project was limited in sample size and uniformity of treatment modalities and lines of treatment. The objective of this study was to evaluate the clinical outcome of NSCLC patients undergoing epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in first-line setting with IVA staging across the different M1a descriptors and M1b descriptors, according to the 9th edition TNM staging manual.

Methods: An electronic medical record search was performed at Shanghai Pulmonary Hospital between Jan 2021 and Dec 2023. NSCLC Patients with IVA staging receiving first-line EGFR-TKIs were analyzed within this retrospective study. The Kaplan-Meier methods were used to evaluate the effect of the different M1a descriptors and M1b descriptors on progression-free survival (PFS) and overall survival (OS).

Results: In total, 450 NSCLC patients with EGFR mutations were evaluated. patients were classified into four groups, including tumors presenting with: 1) pleural or pericardial nodules without effusion ("M1a-Pleural", N=57), 2) contralateral pulmonary nodules with/without pleural or pericardial nodules ("M1a-Contralateral", N=54), 3) pleural or pericardial effusion with/without other M1a descriptors ("M1a-Effusion", N=216), 4) single metastatic lesion in one organ ("M1b", N=123). 274 patients (60.8%) were female and 74 (16.4%) were current or former smokers, with a median age 61 years (range, 19 - 88). Kaplan-Meier survival analyses showed that inferior PFS and OS was observed in patients with M1a-Effusion compared with those with M1a-Pleural (P < 0.001 and P = 0.009, respectively) or M1a-Contralateral (P = 0.016 and P = 0.014, respectively), while sharing a similar prognosis with patients with M1b disease (P = 0.230 and P = 0.130, respectively). Besides, patients with M1a-Pleural had better PFS than those with M1a-Contralateral (P = 0.046), though not significant statistically in OS (P = 0.830).

Conclusions: EGFR-mutated NSCLC patients with pleural, pericardial effusion had similar PFS and OS with M1b disease when treated with EGFR-TKIs, while worse than those with pleural, pericardial or contralateral pulmonary nodules without effusions. These findings may be taken into consideration for the next edition NSCLC staging guidelines.



Keywords: NSCLC, TNM staging system, stage IVA

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.14 Clinical Versus Pathological T Staging in Lung Adenocarcinoma: Discrepancies and Prognostic Implications

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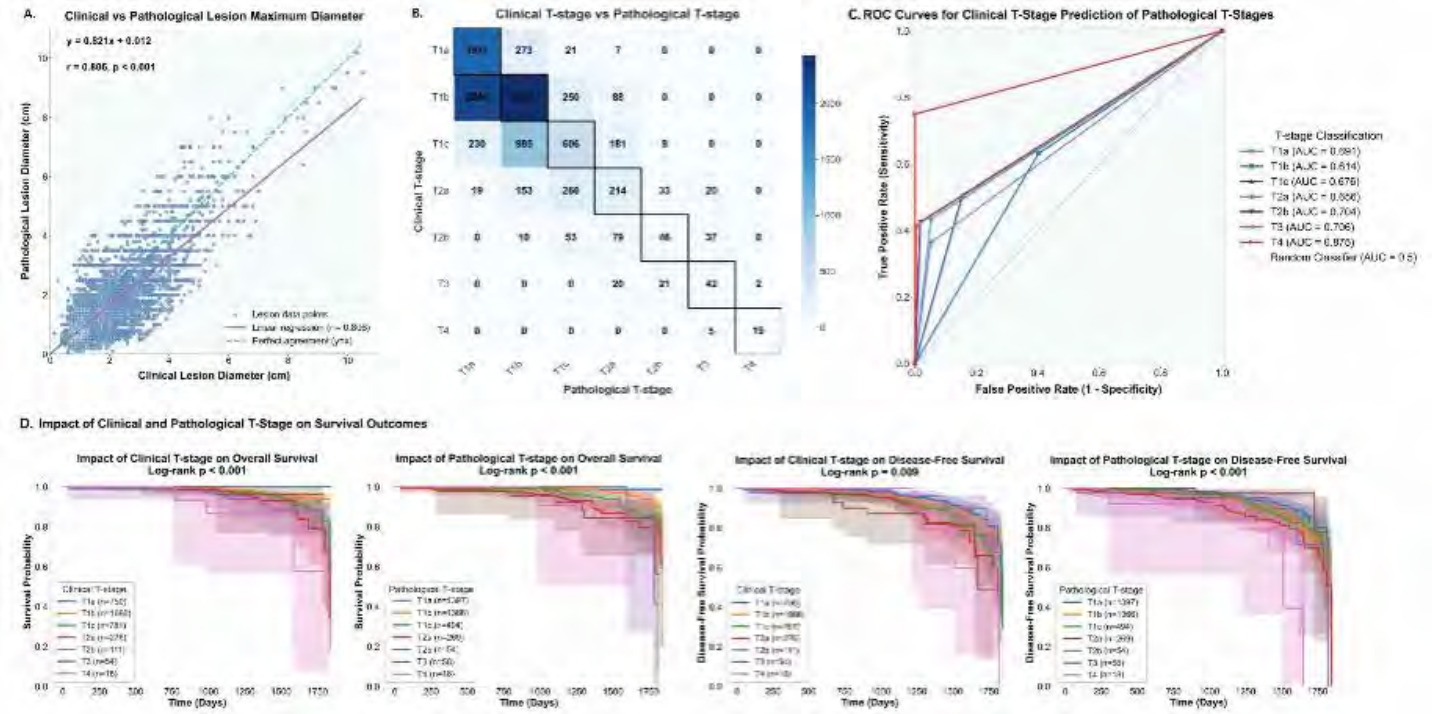
Introduction: Accurate T staging plays a critical role in the management of lung adenocarcinoma, guiding surgical decisions and adjuvant therapy. While pathological T staging is regarded as the gold standard due to its basis in direct tissue examination, clinical T staging based on CT imaging is the primary reference in preoperative settings. However, discrepancies between clinical and pathological assessments are frequently observed and may lead to inappropriate treatment strategies. Despite previous investigations, large-scale studies systematically evaluating these discrepancies and their prognostic implications remain limited.

Methods: This retrospective study included 10,274 patients with resected invasive lung adenocarcinoma from a single tertiary center between 2015 and 2024. Preoperative CT reports and postoperative pathology records were reviewed to obtain tumor size and T stage data. Clinical and pathological measurements were compared to assess agreement in tumor diameter and T classification. A subset of 3,656 patients with available follow-up data was included for survival analysis. The predictive performance of clinical and pathological staging in relation to overall survival (OS) and disease-free survival (DFS) was assessed using Kaplan-Meier curves, log-rank tests, and concordance indices.

Results: Clinical tumor measurements derived from CT were generally larger than those obtained from pathology (mean: 1.80 cm vs. 1.49 cm). Although the two were strongly correlated ($r = 0.806$, $p < 0.001$), the regression line deviated from the identity line, indicating a systematic overestimation by CT. Accordingly, clinical T staging showed a general trend toward overclassification, with only moderate agreement compared to pathological staging ($\kappa = 0.30$). ROC analysis evaluating the ability of clinical T stage to predict pathological T stage revealed a bimodal pattern of performance: predictive accuracy was relatively higher in advanced tumors (T2b-T4), lowest in intermediate stages (T1b-T2a), and modest in early-stage tumors (T1a). Survival analysis further evaluated their prognostic utility, showing that clinical T staging provided slightly better risk stratification in early-stage disease, whereas pathological T staging demonstrated modestly greater prognostic separation in advanced-stage tumors.

Conclusions: Discrepancies between clinical and pathological T staging reflect both biological factors, such as lung tissue shrinkage and tumor heterogeneity, and technical differences in imaging and pathological processing. Although these inconsistencies exist, each staging method offers complementary strengths at different disease stages. Recognizing their respective advantages may improve the accuracy of preoperative assessment and enable more individualized, biology-informed treatment strategies for patients with lung adenocarcinoma.



Keywords: lung adenocarcinoma, clinical T staging, pathological T staging

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.15 Management-Oriented Classification of Lung Neuroendocrine Tumors Based on a French Surgical Cohort of 1,915 Patients From the EPITHOR Database

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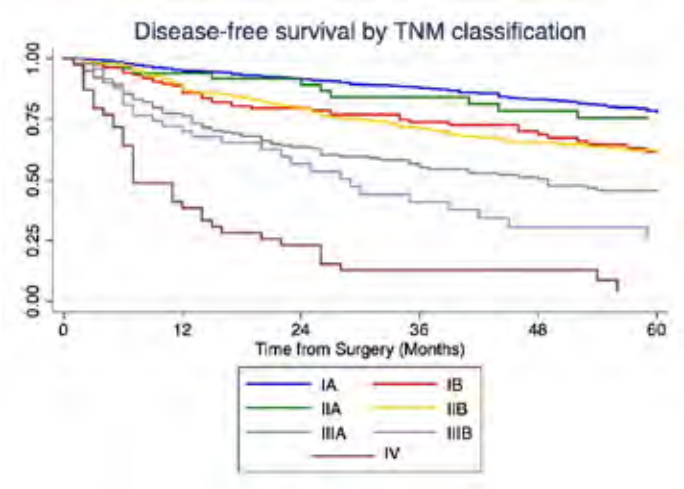
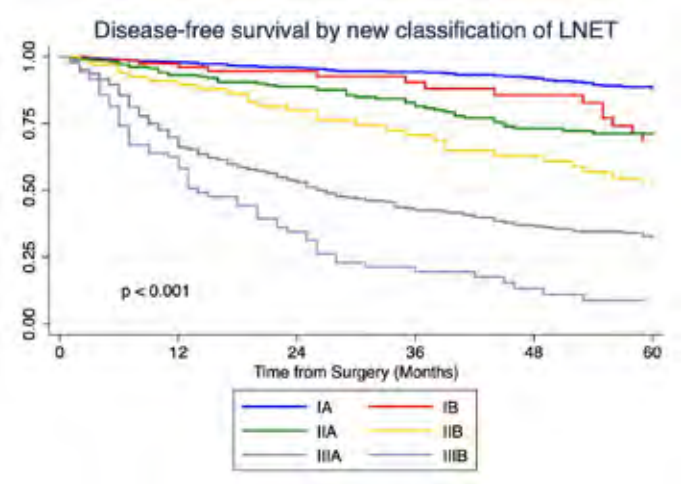
Introduction: Lung neuroendocrine tumors (LNET) are rare malignancies with heterogeneous management, as current strategies are not guided by the TNM classification used for other lung cancers. This study aimed to develop a histopronostic classification capable of predicting survival and recurrence in patients with LNET.

Methods: We conducted a retrospective multicenter study using data from the French national thoracic surgery registry, EPITHOR. The study included French patients who underwent anatomic lung resection or bronchial sleeve resection for LNET (typical carcinoid, atypical carcinoid, and large-cell neuroendocrine carcinoma, excluding small-cell lung carcinoma [SCLC]) between 2008 and 2019. Patients without available pathology reports were excluded. Uni- and multivariable analyses were performed to identify factors predictive of disease-free survival, followed by a recursive partitioning analysis to develop our classification system.

Results: A total of 1,915 patients were analyzed, with extended follow-up and recurrence-free survival data available for 1,406 patients.Our study confirmed that the TNM classification is inadequate for predicting survival in LNET, as some earlier-stage tumors exhibited poorer outcomes than those classified at higher stages.



We established our new classification, based on histological type, tumor size, lymph node involvement, and the proliferation marker Ki-67. The proposed classification is as follows: Stage IA: Typical carcinoid with Ki-67 ≤ 5% Stage IB: Typical carcinoid with Ki-67 > 5% Stage IIA: Atypical carcinoid with tumor size < 4 cm Stage IIB: Atypical carcinoid with tumor size ≥ 4 cm Stage IIIA: Large-cell neuroendocrine carcinoma without mediastinal lymph node involvement (N0 or N1)Stage IIIB: Large-cell neuroendocrine carcinoma with mediastinal lymph node involvement (N2). This classification demonstrated strong discriminatory power for both overall survival and recurrence-free survival(p<0.001).



Conclusions: Our classification system effectively predicts survival and recurrence in patients undergoing surgery for non-SCLC LNET. We propose its implementation in clinical practice to guide surveillance strategies and optimize patient management.

Keywords: neuroendocrine, staging, classification

P2.05 PULMONOLOGY AND STAGING
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.05.16 Comparative Discriminative Performance of Number-Based and 9th Edition N Classifications in NSCLC: Exploring Statistically Valid Cut-offs

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Introduction: The 9th edition of the TNM classification for non-small cell lung cancer (NSCLC) revised the N stage and demonstrated improved prognostic stratification. Interest in number-based N classifications (nN, based on the count of positive lymph nodes) has persisted; however, prior proposals often lacked statistically grounded thresholds. This study aimed to define such thresholds and compare the discriminative ability of the nN classification with that of the 9th edition N stage.

Methods: We retrospectively analyzed NSCLC patients (TanyN0-2bM0) who underwent pulmonary resection between 2005 and 2022. A validation cohort (35%) was randomly selected with stratification by the 9th N stage, and the remaining 65% comprised the training cohort. In the training cohort, all integer threshold combinations were tested to define four nN classes. Combinations showing significant overall survival differences in pairwise log-rank tests were further evaluated using multivariable Cox proportional hazards (PH) models. Final thresholds were selected based on the lowest Akaike Information Criterion (AIC). The nN classification was compared with the 9th N stage using AIC, concordance index (C-index), and integrated discrimination improvement (IDI) in both cohorts.

Results: The training and validation cohorts included 4,802 and 2,586 patients, respectively. Optimal thresholds for the nN classification were 1 and 4, classified four classes: class 0 (0 positive nodes), class 1 (1), class 2 (2-4), and class 3 (≥5). Cox PH models confirmed significant survival differences across all adjacent classes, except class 1 vs. 2 in the validation cohort (p = 0.054).Compared with the 9th N stage, the nN classification showed comparable discrimination. In the training cohort, nN had a slightly lower AIC (17,703.27 vs. 17,726.96) and a higher C-index (0.7569 vs. 0.7539). In the validation cohort, AIC values were nearly identical (nN: 8,843.61; 9th N: 8,843.71), and the C-index was slightly higher for the 9th N stage (0.7368 vs. 0.7345). The IDI values, using the 9th N stage as reference, were 0.00243 at 36 months and -0.00294 at 60 months, indicating minimal overall difference.

Conclusions: The nN classification provided appropriate discriminatory performance and, in some metrics, outperformed the 9th N stage. However, differences were modest, supporting the continued validity of the 9th N stage. Future TNM revisions may benefit from incorporating number-based approaches, particularly in evaluating single-node metastasis.

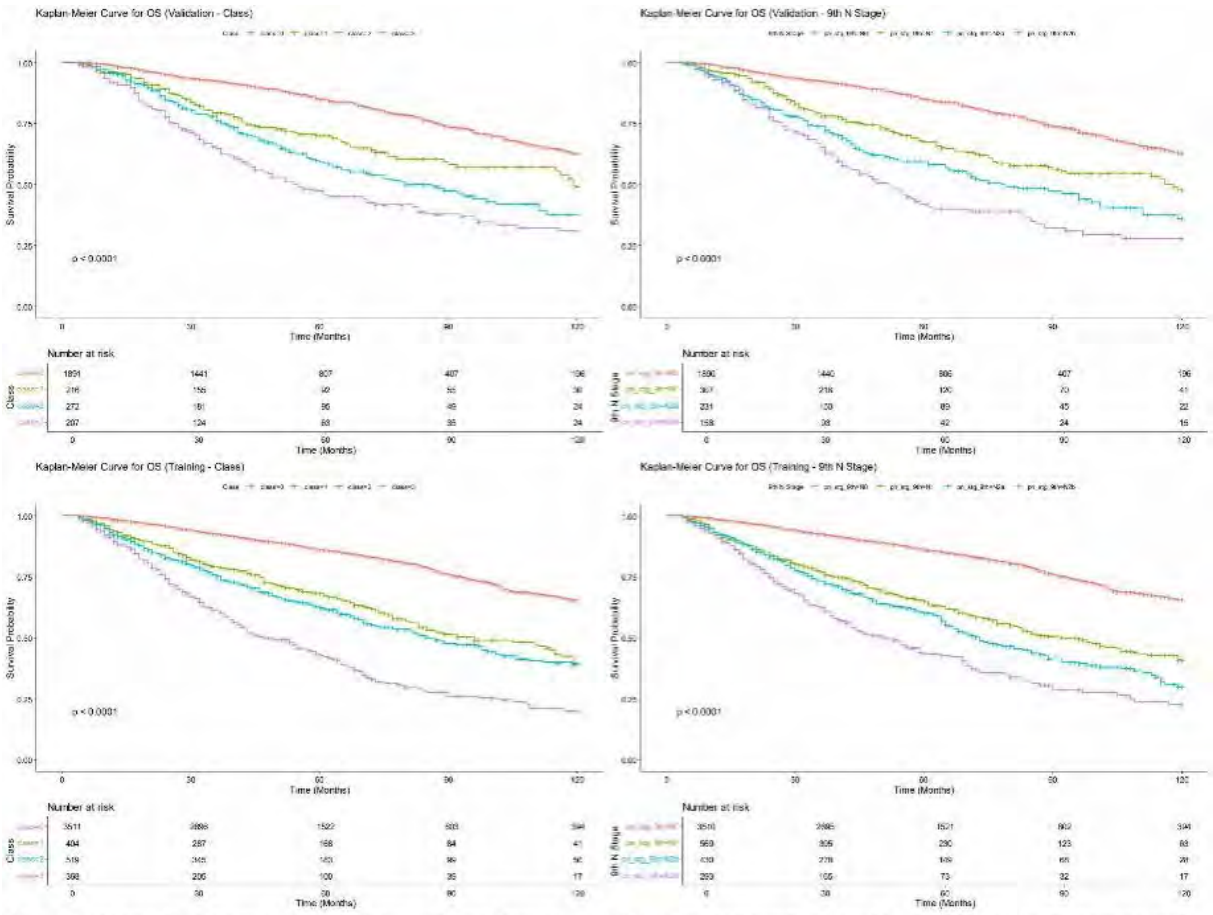

Figure 1. Kaplan–Meier curves for overall survival according to the 9th N stage and number-based N classification in the training and validation sets.

Keywords: Lung cancer, 9th TNM staging system, Number based node evaluation

P2.05.17 European Single-Center Validation of the 9Th TNM Staging System in Over 3,300 Surgically Treated NSCLC Patients

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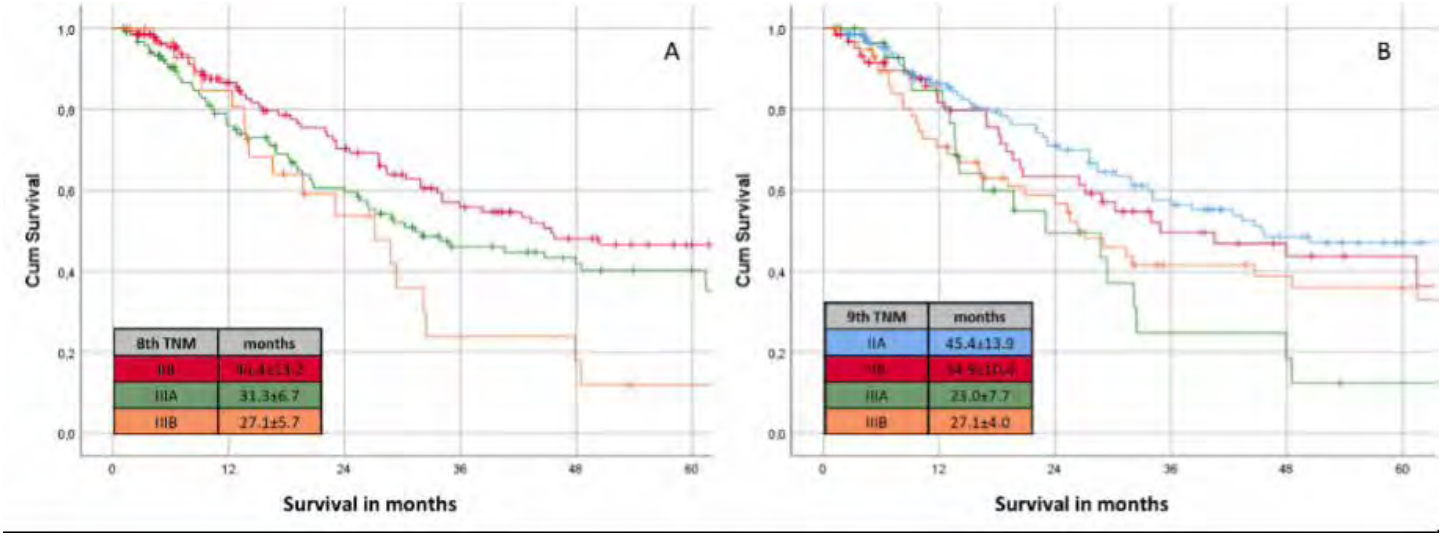
Introduction: IASLC recently introduced the 9th TNM-staging system for NSCLC. This study externally validates the new edition and compares its discrimination power with the previous 8th edition on a large European single-center database.

Methods: A retrospective analysis was conducted on stage I-IIIB patients who underwent anatomical resection and systematic lymph node dissection for NSCLC between 2010 and 2022 at a large European center certified for lung cancer treatment. All patients were treated over time according to applicable guidelines. Overall survival analysis by TNM stages was compared using the Kaplan-Meier method. Akaike Information Criterion (AIC), R2-measure and Concordance index (C-index) were used to compare the predictive ability between the 8th and 9th edition of the TNM-staging system.

Results: A total of 3,313 patients were included in this study. The patients' mean age at time of surgery was 65.6±9.7 years. 61.4% were male patients. The stage of 91.4% of patients (IA: n=1,282; IB: n=513; IIA: n=170; IIB: n=539; IIIA: n=447; IIIB: n=76) remained unchanged according to both TNM-staging systems. Due to the newly introduced changes to the N descriptor, 225 patients (6.8%) were down-staged according to the new TNM-staging system (IIB/IIA: n=134; IIIA/IIB: n=60; IIIB/IIIA: n=31). However, 61 patients (1.8 %) required up-staging from stage IIIA to IIIB. Both TNM-staging systems exhibit comparable predictive power and accuracy for the overall survival of NSCLC patients [8th versus 9th edition AIC: 21,733 vs. 21,146; R2: 0.362 vs. 0.417; C-index (p-value): 0.625 (0.002) vs. 0.627 (0.002)]. This finding remains valid even when analyzing only patients who were either down- or up-staged. In these cases, no significant long-term survival differences were observed.

Conclusions: This study externally validates the 9th TNM-staging system on a large European single-center database. The newly introduced changes to the N-descriptor do not appear to have any significant influence on its prognostic accuracy.



The figure shows the Kaplan-Meier curves of NSCLC patients who were either down- or up-staged according to the 8th edition (A) and 9th edition (B) of the TNM-staging system.

Keywords: TNM 9th. Edition, Staging, Validation

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.01 Prognostic Value of a Combined Model Using CT and PET/CT Parameters for Predicting STAS in Stage I Lung Adenocarcinoma

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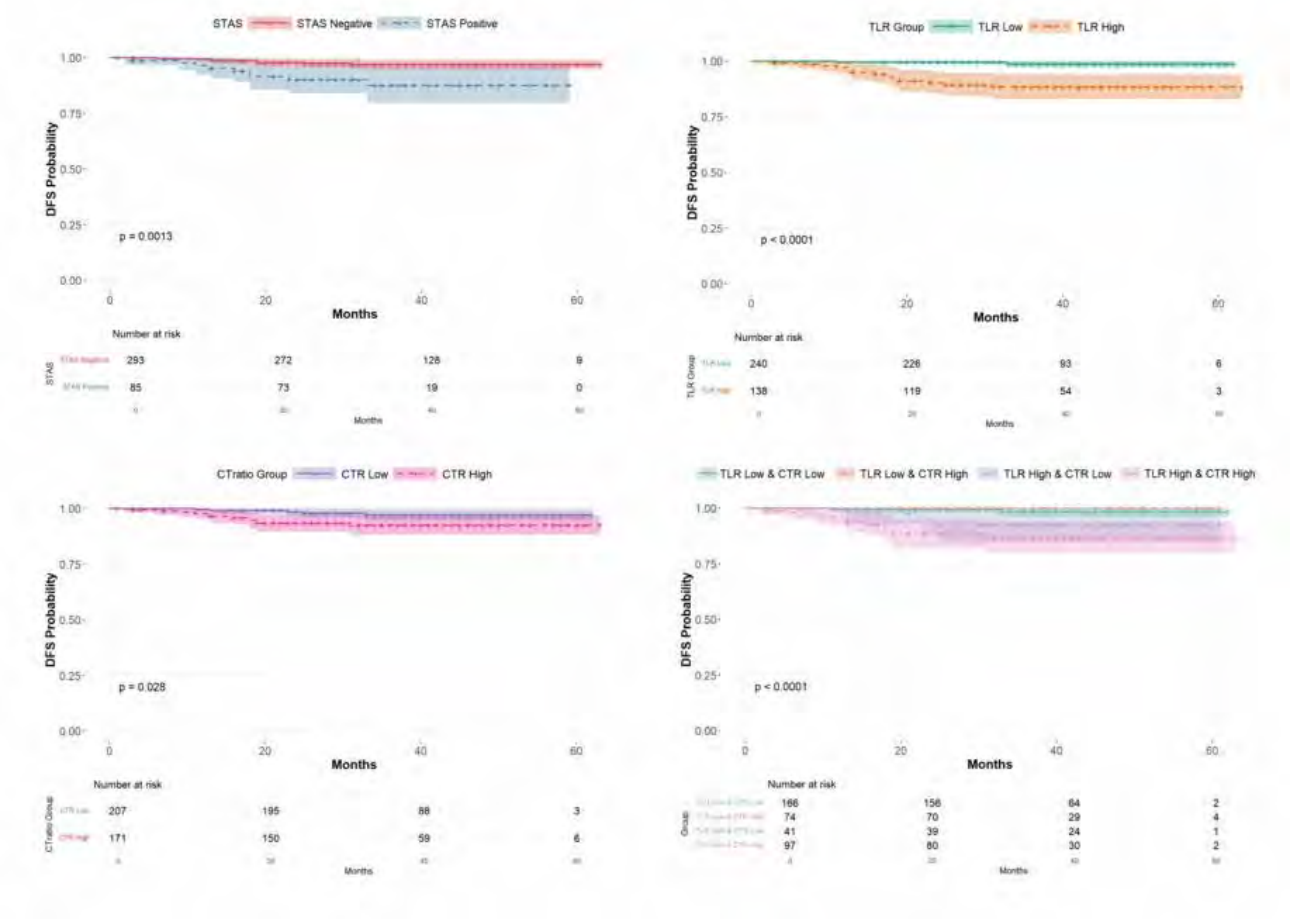
Introduction: This study aimed to develop an imaging-based tumor spread through airspaces (STAS) prediction model using CT and PET/CT and assess its prognostic utility in stage I lung adenocarcinoma.

Methods: 453 patients with pathological stage I lung adenocarcinoma who underwent curative pulmonary resection were retrospectively analyzed. The predictive performance of consolidation-to-tumor ratio (CTR) on chest CT and tumor-to-liver ratio (TLR) on PET/CT for STAS was assessed using receiver operating characteristic (ROC) curve analysis. Kaplan-Meier survival analysis and Cox proportional hazards models were used to evaluate the prognostic significance of STAS, individual imaging parameters, and the proposed combined imaging-based risk model. Associations between the imaging-based risk stratification and established pathological prognostic factors, such as histological grade and lymphovascular invasion (LVI), were also investigated.

Results: STAS was identified in 92 (20.3%) patients and was significantly associated with higher pathological tumor stage ($p < 0.001$), aggressive histologic features, including Grade 3 tumors ($p < 0.001$), and higher rates of LVI ($p < 0.001$). Both CTR (AUC 0.745, cutoff 0.841, sensitivity 77.2%, specificity 68.1%) and TLR (AUC 0.641, cutoff 1.057, sensitivity 67.1%, specificity 72.4%) demonstrated significant predictive ability for STAS. Patients were categorized into four groups based on CTR and TLR cutoffs: G1 (TLR low & CTR low), G2 (TLR low & CTR high), G3 (TLR high & CTR low), and G4 (TLR high & CTR high). Kaplan-Meier analysis revealed that DFS significantly differed among these groups ($p < 0.001$), with no survival difference between G1 and G2 ($p = 0.359$). In multivariate analysis, both the TLR high & CTR low group (HR 8.036, $p = 0.030$) and the TLR high & CTR high group (HR 9.814, $p = 0.006$) remained independent predictors of poor DFS. Additionally, higher imaging-based risk groups correlated with increased Grade 3 tumors ($p < 0.001$) and LVI positivity ($p < 0.001$).

Conclusions: STAS prediction using preoperative CT and PET/CT can provide clinically relevant prognostic insights. The proposed imaging-based risk stratification model, integrating CTR and TLR, effectively identified patients at high risk of recurrence. This model may facilitate individualized treatment strategies, including consideration for more aggressive therapy in high-risk patients.

Figure 1. Prognostic impact of STAS and imaging based risk stratification on disease free survival instage I lung adenocarcinoma



Keywords: STAS, PET-CT, adenocarcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.02 Invading Through External Elastic Lamina Is Predictive of Poorer Outcomes in Pulmonary Non-Mucinous Invasive Adenocarcinoma

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Introduction: Visceral pleural invasion (VPI) of lung cancer is defined as involvement by tumor cells into the elastic laminae of visceral pleura. In both AJCC staging system and CAP cancer protocol, VPI is classified as below: PL-0 for tumors that do not invade the elastic lamina; PL-1 for tumors that invade the elastic lamina but not up to the pleural surface; PL-2 for tumors that invade up to the pleural surface without involvement of adjacent anatomic structures; and PL-3 for tumors that invade the parietal pleura; staging of tumors smaller than 3 cm in size will be upgraded from T1 to T2 if VPI (PL-1 or PL-2) is present. Currently, it is recommended that tumor cell penetration through the thickest and outmost (external/outer) elastic lamina, rather than the internal/inner elastic lamina, serves as the criterion for diagnosing VPI. Nevertheless, there is scarce evidence supporting this recommendation. This study aims to explore the clinical significance of lung cancer invading through internal versus external elastic lamina of visceral pleura with real world experiences.

Methods: We retrospectively reviewed clinicopathological characteristics of 1,217 patients with surgically resected non-mucinous invasive adenocarcinoma at Taipei Veterans General Hospital, Taiwan, between 2011 and 2016. With the scheme of two-layered elastic laminae, VPI was categorized into PL-n (no pleural invasion; tumor involvement beneath internal elastic lamina), PL-i (tumor invading into or beyond internal elastic lamina and beneath external elastic lamina), PL-e (tumor invading into or beyond external elastic lamina but not reaching parietal pleura), and PL-p (tumor invading through elastic laminae and reaching parietal pleura). We analyzed the relationship between categories of VPI and prognosis, along with other pertinent clinical and histopathological parameters.

Results: The 5-year overall survival rates were 89.7% for patients with PL-n, 89.5% for PL-i, 71.3% for PL-e, and 53.3% for PL-p, while 5-year recurrence-free survival rates were 88.1%, 85.8%, 55.8%, and 48.6%, respectively. PL-e showed significant differences in univariate analyses in overall survival analysis whereas in disease-free survival analysis, PL-e showed significant differences in both univariate and multivariate analyses.

Conclusions: Tumor cells invading into or beyond external elastic lamina (PL-e) was a significant prognostic factor for recurrence and associated with worse overall survival for pulmonary non-mucinous invasive adenocarcinoma, compared to tumor cells invading beneath external elastic lamina (PL-i). This study provides evidence supporting the use of external elastic lamina penetration as the landmark to classify pleural invasion in current clinical practice.

Keywords: Lung adenocarcinoma, Visceral pleural invasion, Elastic lamina

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.03 Diagnostic Performance of Frozen Section in Determining Histological Patterns and Spread Through Air Spaces in Lung Adenocarcinoma

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[1]Shanghai Pulmonary Hospital, Shanghai/CN ,[2]The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang/CN ,[3]Anhui Provincial Chest Hospital, Hefei, Anhui/CN ,[4]Shandong Public Health Clinical Center, Jinan, Shandong/CN

Introduction: Precise frozen pathology reports are vital to guide surgical decision-making on sublobar resection and lymphadenectomy selection. We aim to evaluate the accuracy of intraoperative frozen section (FS) in determining the histological patterns and spread through air spaces (STAS) among patients with lung adenocarcinoma.

Methods: In this post-hoc analysis of a randomized, phase 3 trial (STAR 001), patients with invasive peripheral lung adenocarcinoma ≤ 2 cm were randomly assigned to undergo segmentectomy or lobectomy following intraoperative confirmation of micropapillary (MP) and/or solid (S) patterns ≤ 5% by FS. Patients who were excluded due to invasive adenocarcinoma with MP and/or S pattern ≥ 5% by FS diagnosis were also included for post-hoc analysis. The primary outcome was the concordance between FS and final pathology (FP) diagnoses. Fleiss' kappa coefficients were employed to evaluate the inter-observer agreement among three pathologists for pathological diagnosis on FS.

Results: The post-hoc analysis evaluated a consecutive cohort of 900 invasive non-mucinous lung adenocarcinomas. The study population consisted of 645 eligible cases enrolled in STAR001 trial and 255 cases excluded based on MP and/or S patterns exceeding 5% by FS. All subjects were prospectively collected across 13 medical centers in China from August 2019 to December 2023. The best sensitivity for diagnosing the predominant pattern and presence of pattern was 89.6%, and 96.2% in acinar pattern, respectively. While highest specificity for identifying the presence of certain subtype was 93.8% in the evaluation of papillary pattern. The presence of complex glands pattern diagnosed by FS was an independent factor for the discrepancy between FS and FP. Remarkable consistency was demonstrated among the three pathologists in determining the predominant histological pattern on FS, with a kappa value of 0.846. Furthermore, substantial agreement among three pathologists for diagnosing the presence of each certain histological pattern on FS was revealed with all corresponding pattern-specific kappa value exceeding 0.7. The overall accuracy, sensitivity, and specificity of STAS diagnosis on FS were 89.6%, 70.4%, and 95.6%, respectively, with substantial inter-observer agreement (Fleiss' κ=0.707) among three pathologists. (Table 1)

Conclusions: FS demonstrated a favorable concordance in diagnostic accuracy and satisfactory interobserver agreement for intraoperative diagnosis of histological subtypes and STAS. FS may provide surgeons with valuable insights for optimal surgical decision-making.

Table 1. Diagnostic performance of frozen sections on presence of certain histologic pattern, predominant histologic pattern and spread through air spaces in comparison to final pathology.

Patterns	Accuracy	Sensitivity	Specificity	PPV	NPV	Kappa value between FS and FP[1]	Inter-observer Fliess Kappa value[2]
Presence of certain histologic pattern							
Lepidic	85.2%	84.7%	86.3%	93.4%	71.3%	0.671	0.898
Acinar	95.2%	96.2%	66.7%	98.8%	37.8%	0.489	0.864
Papillary	79.4%	44.8%	93.8%	75.2%	80.3%	0.438	0.818
Complex glands	83.8%	69.7%	89.3%	71.8%	88.3%	0.595	0.732
Micropapillary	84.1%	69.7%	91.0%	78.7%	86.3%	0.625	0.701
Solid	90.2%	75.0%	91.1%	34.2%	98.3%	0.426	0.712
Predominant histologic pattern							
Lepidic	90.2%	58.1%	94.5%	58.9%	94.4%		
Acinar	80.6%	89.6%	60.2%	83.5%	71.9%		
Papillary	95.7%	32.4%	99.3%	73.3%	96.2%		Fliess κ for predominant pattern = 0.791
Complex glands	93.2%	55.4%	97.0%	64.6%	95.6%		
Micropapillary	97.3%	26.3%	99.5%	62.5%	97.7%		
Solid	97.6%	75.0%	97.9%	31.6%	99.7%		
STAS							
Presence	89.6%	70.4%	95.6%	83.7%	91.1%	0.690	0.707

PPV, positive predictive value; NPV, negative predictive value; FS, frozen sections; FP, final pathology; STAS, spread through air spaces.
Kappa value[1] was used for assessing diagnostic concordance of frozen section compared to final pathology.
Fliess Kappa value[2] was employed to assess the inter-observer agreement on frozen section slides.

Keywords: Frozen section, Histological patterns, Spread through air spaces

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.04 Artificial Intelligence-Led Characterisation of Lethal Morphologies in Lung Adenocarcinoma

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Introduction: Histopathological grade is the cornerstone of pathological prognostication in lung adenocarcinoma (LUAD). Grade is a quantitative assessment of architectural patterns, but neglects a wealth of information encoded in the tissue such as the tumour microenvironment. Identifying novel morphological markers of risk is time-consuming, given the need for explicit definition of features of interest a priori and substantial manual effort required for the human observer to encode them. Self-supervised artificial intelligence, as applied to histopathological whole slide images (WSIs), has the potential to democratise histopathology and gives us the ability to identify recurrent morphological patterns in WSIs without an up-front hypothesis or human annotation.

Methods: We apply a self-supervised learning pipeline, histomorphological phenotype learning, to a highly characterised set of 4427 WSIs from 1007 patients with surgically resected primary LUAD. This gives us a library of morphological clusters spanning the morphological variance in the dataset. We encode the frequency of each cluster at the patient level and statistically link these to outcome and clinicopathological variables. Each cluster can be interpreted by a pathologist, and given a qualitative description.

Furthermore, we align these clusters to WSIs of tissue microarrays, allowing us to interrogate the local biology underpinning them. This allows us to add a volume of regional molecular signatures to our cluster library.

Results: We discovered 71 clusters which not only independently recapitulate known architectural patterns used in grading but also spotlight variant epithelial and stromal patterns. We group clusters into superclusters, defined by their lymphocyte density and tendency for epithelial discohesion.

In a univariate five-fold cross-validated Cox regression model using supercluster frequency, this achieves an internal test c-index of 0.6-0.65 and 0.61-0.62 in an external cohort (The Cancer Genome Atlas LUAD), exceeding the prognostic power of grade.

Immune-cold discohesive patterns are linked to adverse prognosis in a five-fold cross-validated multivariate Cox regression model (hazard ratio 1.17, 95% CI 1.06-1.28 $p < 0.001$) after adjusting for age, sex, grade and stage. These regions are high in extracellular matrix proteins such as collagen-1A. Immune-hot discohesive patterns are enriched in patients with PD-L1-positive tumours ($p < 0.01$). Additionally, we link the frequency of specific clusters to sex and driver mutations.

Conclusions: We present an unsupervised analysis of tumour morphology in LUAD, identifying under-recognised histopathological features strongly related to outcome. Many of these lethal appearances are of predominantly acinar architecture, highlighting an opportunity to refine the current clinical gold standard.

Keywords: artificial intelligence, lung adenocarcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.05 Diagnosis of the Novel IASLC Grading System Using Intraoperative Frozen Section: A Prospective Multi-Center Trial

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Introduction: The International Association for the Study of Lung Cancer (IASLC) recently proposed a novel grading system for invasive non-mucinous lung adenocarcinoma. This study aimed to assess the accuracy of intraoperative frozen section (FS) in diagnosing IASLC grades in early-stage lung adenocarcinoma and to identify factors associated with misdiagnosis.

Methods: This prospective, multi-center clinical trial (ECTOP-1014) was conducted from July 2022 to August 2023. The diagnoses of new grades were based on the newest grading system released by IASLC. FS diagnoses were compared with final pathology (FP) to evaluate diagnostic concordance. Logistic regression analysis was performed to identify predictors of FS misdiagnosis.

Results: The overall concordance rate between FS and FP for IASLC grading was 79.9%, with a weighted kappa of 0.627, indicating good agreement. Lepidic and micropapillary predominant patterns were independently associated with misdiagnosis of grades using FS ($P < 0.001$). Interobserver agreement among pathologists was excellent ($\kappa = 0.821$). Incorporating FS into a predictive model for Grade 3 tumors improved the Area Under the Curve to 0.907.

Conclusions: FS provides a reliable intraoperative assessment of IASLC grades and may aid in surgical decision-making. However, specific histological patterns, such as lepidic and micropapillary, are associated with increased misdiagnosis rates. Further studies are needed to validate these findings and assess the impact of FS-guided decisions on patient outcomes (NCT05794698).

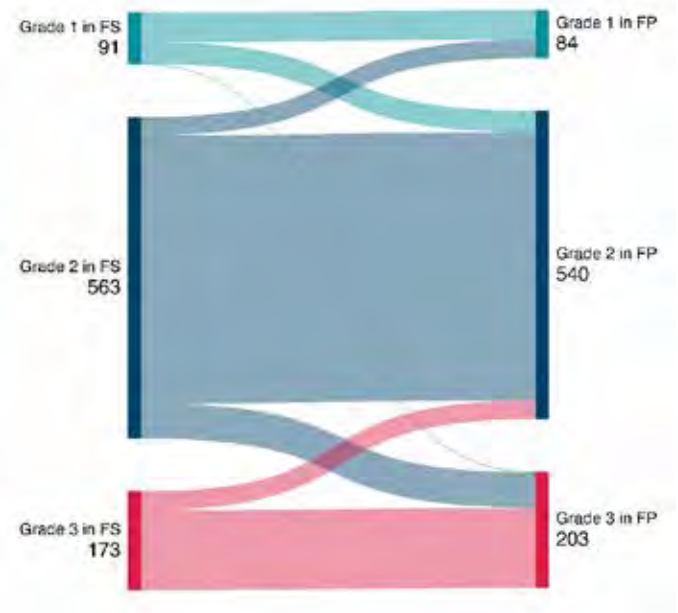

Table 1. The diagnosis of frozen section and final pathology for the IASLC grading system

IASLC grades by FP	IASLC grades by FS, n (%)			Sensitivity	Specificity	Accuracy
	Grade 1	Grade 2	Grade 3			
Grade 1 (N=84)	52 (57.1)	32 (5.7)	0 (0.0)	61.9%	94.8%	91.4%
Grade 2 (N=540)	38 (41.8)	469 (83.3)	33 (19.1)	86.9%	67.2%	80.0%
Grade 3 (N=203)	1 (1.1)	62 (11.0)	140 (80.9)	69.0%	94.7%	88.4%

IASLC: International Association for the Study of Lung Cancer, FS: frozen section, FP: final pathology.

Keywords: Intraoperative frozen section, Grading system, Invasive lung adenocarcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.06 Bronchiolar Adenoma With Malignant Transformation? New Insights Based on Morphologic, Immunophenotypic, and Genomic Analysis of 13 Cases

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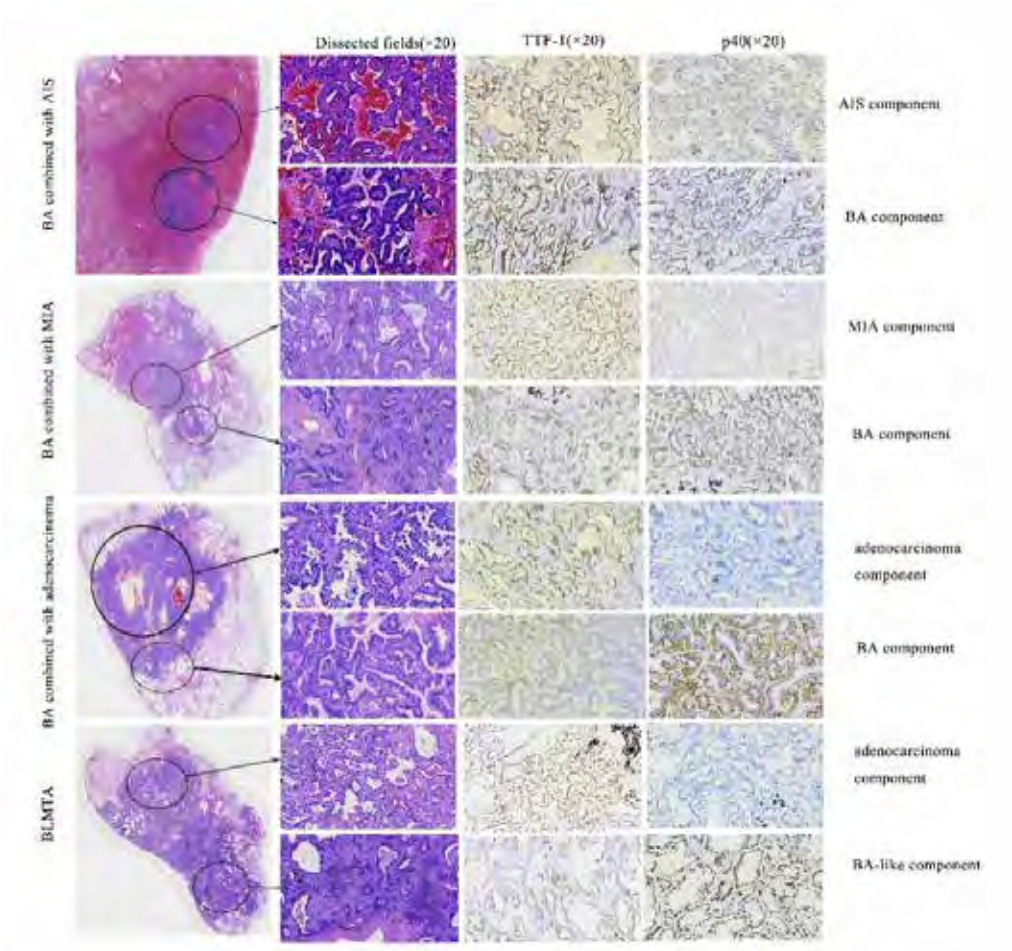
Introduction: In the wide histomorphological spectrum of BAs, it is confusing to pathologists whether there is a close relationship between BAs and lung cancer. Herein, we describe a series of BA with concurrent other lung cancer in the same lesion and to investigate the potential relationship between BA and tumours.

Methods: We described the histomorphological, immunohistochemical and molecular features of 13 cases of bronchiolar adenoma (BA)-like lesions, including four classic BAs, eight mixed type BAs, and one BA-like lesion with malignant transformation to adenocarcinoma (BLMTA). The different components in the mixed type BAs and BLMTA were enriched using the Millisect system. Whole exome sequencing (WES) was performed on the different components.

Results: Of these 13, four were classic distal type BAs with bilayered architecture, eight cases exhibited partial classic bilayered, leaving a monolayer of cuboidal epithelial cells in some areas (mixed type BAs), furthermore, the monolayered areas were diagnosed as AIS (n=4), MIA (n=2), and adenocarcinoma (n=2) base on the histological features. Of note, we also identified one case was composed of homogeneous cuboidal cells with cellular atypia in the BA-like region and cuboidal cells with apocrine secretion in the monolayered adenocarcinoma component (i.e. BLMTA). Immunohistochemical analysis revealed that the TTF1 expression of the luminal cells and basal cells of the bilayered regions of the mixed type BAs and the BLMTA is more heterogeneous than that in monolayered tumour components. Basal cells of BA-like regions expressed p40 continuously. The hotspot map and phylogenetic analysis displayed a distinct difference between the BA and tumour components and there were no branched driver mutations in the two components of the mixed type BAs. However, the two components of the BLMTA shared 459 common gene mutations, including EGFR G719C, TP53, ERBB2, and so on, while the branch driver gene EGFR S768I was only observed in the BA-like component.

Conclusions: Our study demonstrated that BAs and lung adenocarcinoma are entirely distinct entities based on histomorphological, immunohistochemical, and molecular features. BLMTA may represent either a BA-like lesion with malignant transformation potential or a common adenocarcinoma with unique morphological characteristics.



Keywords: bronchiolar adenoma, Millisect, BA-like lesion with malignant transformation to ad

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.08 ERBB2 Mutations in Non-Small Cell Lung Cancer - Findings From a Large UK Cohort

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Introduction: ERBB2 driver mutations are reported in a small fraction of NSCLCs and are amenable to emerging targeted therapies. The rate of ERBB2 mutations has been reported between 1 and 6% in various cohorts. The aim of this project was to determine the frequency of ERBB2 driver mutations in a large retrospective cohort of NSCLCs tested by targeted NGS, predominantly representing samples from the UK's universal 'National Health Service'. There is also limited published data to suggest that certain lung adenocarcinoma morphological patterns of growth may be associated with ERBB2 mutation. Histology was available from a majority of samples and this was reviewed to determine whether particular morphologies were enriched in ERBB2 mutant NSCLC within this cohort.

Methods: The archival database of a molecular diagnostics laboratory, largely serving London and South East England, was interrogated. Samples underwent somatic variant analysis using a custom-built next generation sequencing panel, which included the relevant exons in ERBB2. All samples from patients with a diagnosis of NSCLC which were successfully sequenced were included in the retrospective cohort. All variants classified as being pathogenic from the cohort were exported and full details were extracted for those with ERBB2 mutations.

Results: 4862 NSCLC samples were successfully sequenced over a 5-year period, encompassing 2019-2023 inclusive. 57 ERBB2 mutations were identified within this cohort, representing a mutation rate of 1.2%. 39 Of the 57 ERBB2 driver mutations were insertions, duplications or insertion-deletions in exon 20. Histology was available and lung adenocarcinoma growth pattern assessable in 39 of the 57 samples. The commonest predominant growth pattern in these samples was micropapillary pattern (15/39, 38%) and a further 4 samples had a minor component of micropapillary growth pattern alongside another predominant patter. All 39 cases showed non-mucinous morphology.

Conclusions: This represents the first large cohort of UK NSCLC patients in which ERBB2 mutation rate has been described and, representing a broad cross section of the NSCLC population, is likely to be highly representative. ERBB2 mutation has a similar rate in this cohort to some other less common actionable alterations such as ROS1 fusion, RET fusion and BRAF V600E mutation. There was an enrichment for micropapillary growth pattern in the histology of those harbouring ERBB2 mutation.

Keywords: Molecular pathology, ERBB2, Mutation analysis

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.09 Clinical, Racial, and Genetic Differences in Non-Small Cell Lung Cancer Between Young and Older Patients in the AACR Project Genie Database

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Introduction: The median age for lung cancer diagnosis is 71 years. Approximately 5% of NSCLC cases occur in patients aged 50 years or less. Young patients have distinct clinical characteristics and genetic profiles. This study aims to investigate these differences to improve understanding and inform treatment strategies.

Methods: Data from the AACR, cBioPortal, and Genie databases were retrospectively analyzed. The entire cohort included 1,833 patients with genetic, clinical, and racial data available for analysis. Young patients (< 50 years) were compared with older patients (> 50 years) using Welch's t-test, Mann-Whitney U, chi-square, and Fisher's exact test to identify age-related differences in NSCLC features and their therapeutic implications.

Results: Of the 1,833 patients analyzed, 130 (7.1%) were under 50 years, mostly females 83 (63.8%). The median age was 45.6 years, compared to 67.9 years in older patients. Younger patients had higher proportions of Asians (13.1% vs. 5.9%), Blacks (6.9% vs. 5%), and other racial groups (10.8% vs. 4.5%), while older patients were more likely to be whites (84.6% vs. 69.2%; all p = 0.001). Squamous cell carcinoma is uncommon in young patients compared to older ones (1.5% vs. 11.9%; 2/130 vs. 202/1703; p = 0.005).Younger patients were more likely to present at an advanced stage: stage IV (67.4% vs. 41.2%; p < 0.001), while older patients were more often diagnosed earlier: stage I (28.5% vs. 8.5%), stage II (9.8% vs. 7.0%), and stage III (19.8% vs. 17.1%). Lung (34.5% vs. 22.8%; p = 0.01) and liver (21.8% vs. 13.3%; p = 0.03) were the predominant metastatic sites in younger patients.The prevalence of TP53 mutations was similar between the two groups (overall: 56.76%, older: 54.12%; p = 0.550). Older patients showed a higher prevalence of STK11 mutations (15.47% vs. 6.67%; p = 0.004), KEAP1 mutations (14.28% vs. 4.65%; p = 0.001), and KRAS mutations (31.95% vs. 17.57%; p = 1.96E-04). Among these, the KRAS G12C mutation was significantly more common in older patients (13.49% vs. 3.01%; p = 0.001). In contrast, RB1 mutations were more frequently detected in younger patients (11.11% vs. 6.00%; p = 0.027). Younger patients also exhibited higher rates of ALK rearrangements (20.95% vs. 7.37%; p < 0.001), ERBB2 mutations (11.49% vs. 4.14%; p = 0.0003), and a slightly greater frequency of EGFR mutations overall (27.03% vs. 25.50%; p = 0.696). Among these, the EGFR T790M mutation is notably more common in younger patients (6.77% vs. 2.98%; p = 0.0355)

Conclusions: Lung cancer in young adults has distinctive features, including a predominance of adenocarcinoma, Asian descent, advanced stage at diagnosis, and unique genomic profile. These findings support a tailored approach and comprehensive genetic profiling should be mandatory, as personalized treatment approach with targeted therapy may lead to superior outcomes

Keywords: lung cancer in young, Genie database, racial differences

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.10 Title: Prognostic Impact of TP53 Co-Mutations with EGFR vs KRAS in Advanced Non-Small Cell Lung Cancer: A cBioPortal Analysis

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Introduction: Non-small cell lung cancer (NSCLC) is a genomically diverse cancer, with only a subset of driver mutations with prognostic or predictive significance. Epidermal growth factor receptor (EGFR) and Kisten rat sarcoma viral oncogene (KRAS) are among the most common actionable mutations. While TP53 mutations are generally associated with poor prognosis, their prognostic role in EGFR- and KRAS-mutated NSCLC is still being elucidated. Given distinct biological behaviors and therapeutic approaches for these mutations, we sought to explore the influence of concomitant TP53 mutations on the survival outcomes of patients with EGFR or KRAS mutated NSCLC.

Methods: Information regarding TP53, EGFR and KRAS alterations and patients' survival time in advanced NSCLC was downloaded from the Cancer Genome Atlas Database, an open access database available at http://www.cbioportal.org. We chose MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2023 and MSK, Nat Commun 2023). Patients were stratified into two groups: (1) EGFR-mutated with or without TP53 alterations and (2) KRAS-mutated with or without TP53 alterations. Comprehensive genomic profiling, including next-generation sequencing (NGS) data, was analyzed to correlate mutational profiles with clinical outcomes, particularly overall survival (OS). Kaplan-Meier survival curves and log-rank tests were used to assess differences in survival outcomes between groups.

Results: As expected, overall survival differed by mutational status (log rank p <0.0001) with EGFR mutation positive NSCLC faring better. Among patients with EGFR mutated NSCLC, concomitant TP53 mutation was associated with a worse survival (median OS: 33 months, 95% CI 28-39) compared to those without (median OS: 42 months, 95% CI 33-58; p=0.01). In the KRAS-mutated cohort, median OS was worse in those without TP53 mutation (median OS:15 months, 95% CI:12-22) compared to with TP53 mutation (median OS:24 months, 95% CI:19-35; p=0.049). While TP53 co-mutation was associated with worse outcomes in EGFR-mutant NSCLC, this was not observed in the KRAS group.

Conclusions: Our findings showed mutation-specific prognostic role of TP53 in advanced NSCLC. TP53 mutations were associated with worse overall survival in EGFR-mutated NSCLC. Conversely, in KRAS-mutant NSCLC, TP53 co-mutations conferred a relative survival benefit compared to KRAS mutation alone—suggesting a distinct biological interaction that may influence disease course or therapeutic sensitivity. These results underscore the importance of evaluating TP53 mutational status in the context of the primary oncogenic driver in NSCLC. Specifically, TP53 mutations should be integrated into risk stratification and treatment planning for EGFR-mutated NSCLC, while their role in KRAS-mutant NSCLC suggests a distinct biological interaction warranting further investigation.

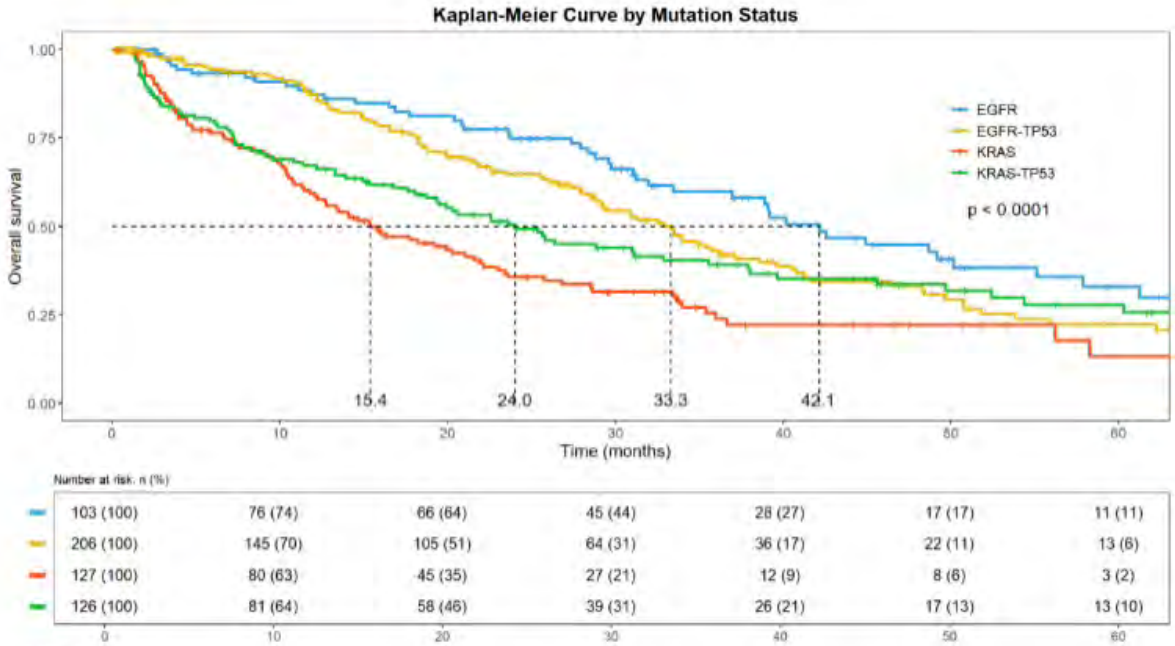

Figure 1:
Kaplan-Meier survival curves for *EGFR*- vs *KRAS*-mutated NSCLC patients with and without concurrent TP53 co-mutations.

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.11 Factors Impacting Receiving EGFR Test Results Before Initial Treatment Among Stage Iv Non-Small Cell Lung Cancer Patients

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Introduction: The study of Compromised Outcomes in Stage IV Non-Small-Cell Lung Cancer (NSCLC) With Actionable Mutations Initially Treated Without Tyrosine Kinase Inhibitors1 demonstrated survival benefit for patients (pts) who initiated targeted therapy for initial treatment compared to those who did not or switched to targeted therapy. We aim to show among stage IV NSCLC pts in the U.S. what factors impact receiving EGFR test results before initial treatment (RBIT).

Methods: Using Integra Connect PrecisionQ's de-identified database, the analysis comprised 1565 pts >=18 years of age who were confirmed via chart abstraction as newly diagnosed with stage IV NSCLC and initiated treatment between 1/1/2022 to 12/31/2024. Pts were assessed based on whether gender, age, race, Eastern Cooperative Oncology Group (ECOG) performance status, histology, stage, site of metastases (mets), testing approach, and test turnaround time (TAT) impacted receiving EGFR RBIT. Descriptive analyses were performed, and chi-squared analysis were used for comparisons.

Results: Among 1565 pts, 1191 (76%) received RBIT, 298 (19%) received results after initial treatment, and 76 (5%) were not tested. The mean age of pts who received RBIT was 70.2 compared to 68.4 for those who did not. Among females, 617/791 (78%) received RBIT compared to 570/769 (74%) for males and 4/5 (80%) for unknown gender pts. Based on race, pts receiving RBIT was 913/1210 (75%) among White pts, 131/172 (76%) among Black/African American pts, 35/39 (90%) among Asian pts, and 112/144 (78%) among other pts. Based on ECOG, pts receiving RBIT was 725/938 (77%) among ECOG 0-1 pts, 205/272 (75%) among ECOG 2+ pts, and 261/355 (74%) among pts with an unknown ECOG. Receiving RBIT by histology was 885/1110 (80%) for adenocarcinoma pts, 211/319 (66%) for squamous cell carcinoma pts, and 95/136 (70%) for pts with other subtypes or unknown histology ($p < 0.01$). Receiving RBIT among stage IVA was 425/577 (74%) compared to stage IVB at 407/512 (79%) ($p < 0.05$). Based on site of mets, receiving RBIT was 479/626 (77%) among pts with bone mets, 325/385 (84%) among pts with brain/central nervous system mets, and 197/250 (79%) among pts with liver mets ($p < 0.01$). Among tested pts, pts receiving RBIT with both solid and liquid testing was 443/509 (87%), those with liquid only testing was 239/285 (84%), those with solid tumor only testing was 325/455 (71%), and those with an unknown modality was 184/240 (77%) ($p < 0.01$). Among tested pts, pts receiving RBIT was 394/454 (87%) for TAT of <7 days, 584/740 (79%) for TAT of 7-to-14 days, and 209/290 (72%) for TAT of >14 days ($p < 0.01$).

Conclusions: The real-world data shows NSCLC stage IV pts who received EGFR RBIT more often had brain/CNS mets, liver mets, stage IVB, adenocarcinoma, both liquid and tissue testing, or results with a shorter TAT compared to those who did not. Factors such as gender, age, race, and ECOG did were not found to be statistically significant in whether patients received EGFR RBIT.

Keywords: EGFR Testing, Stage IV

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.12 TP53/RB1-Mutant Squamous Cell Lung Cancers: Clinicopathologic Features and Outcomes

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Introduction: Loss of TP53 and RB1 disrupts cell cycle regulation, impairs DNA damage repair, and evades apoptosis. Concurrent mutations in the tumor suppressor genes TP53 and RB1 are hallmarks of small cell and neuroendocrine lung carcinomas. Concurrent alterations in TP53 and RB1 also occur in patients with EGFR-mutant lung adenocarcinomas at high risk of histologic transformation to small cell lung cancers. The incidence and significance of TP53/RBI loss in non-small cell lung cancers without actionable oncogenic mutations remain undefined. In this report, we describe the clinicopathologic characteristics and course of patients with TP53/RB1-mutant squamous cell lung cancers with no histologic neuroendocrine features or actionable oncogenic drivers.

Methods: We identified patients at Memorial Sloan Kettering with squamous cell lung cancers with concurrent mutations in TP53and RB1 detected by next-generation sequencing (NGS) using MSK-IMPACT or MSK-ACCESS, performed between January 2014 and 2023. All patients had no actionable driver alterations and no neuroendocrine features noted on pathology reports by histologic examination or immunohistochemistry. Demographic characteristics, clinicopathologic features, treatment histories, survival outcomes, and NGS results were collected.

Results: Among 1011 patients with squamous cell lung cancers with NGS testing by MSK-IMPACT or MSK-ACCESS, we identified 93 patients (9.2%, 95% CI 7.5% to 11.1%) with concurrent TP53 and RB1 mutations with no actionable oncogenic drivers, no neuroendocrine differentiation, and adequate clinical documentation. Their median age at diagnosis was 69 years (range 51 to 91 years), 63% were male, and 97% were current or former cigarette smokers. Seventy-three percent of patients were diagnosed with stages I to IIIB squamous cell lung cancer at diagnosis. The median PDL1 expression was 2% (range 0 to 100%) and 28% had PDL1 values 50% or greater. The median tumor mutational burden (TMB) was 9.8 mutations/megabase (range 3 to 33) and 44% had a TMB score of 10 or greater. Among patients with stages I to IIIB at initial diagnosis, 43% developed progression or recurrence. Among 54 patients with metastatic disease at any time, 15 (28%) had brain metastases. The median overall survival from time of diagnosis of all patients with metastatic disease was 1.3 years, with a median follow up of 9.2 years. Twenty-six patients were treated with immune checkpoint inhibitors (ICI) in any line for metastatic disease. Their median time on treatment with any immunotherapy was 4 months.

Conclusions: We found that patients with TP53/RB1-mutant squamous cell lung cancer without oncogenic drivers, no treatment with target therapies, and no neuroendocrine differentiation by histology, represent a unique group of lung cancers. These individuals had tobacco exposure and a high median TMB. Patients with metastatic disease experienced a short time on ICI with a 15-month median overall survival. We plan to compare patients with squamous cancers with TP53/RB1 loss with matched controls with intact TP53/RB1. We will also analyze tumor tissues from individuals with TP53/RB1-deficient squamous cancers for transcriptional markers (ASCL1, YAP1, POU2F3, NEUROD1) characteristic of small cell lung cancers and markers of neuroendocrine differentiation (chromogranin, synaptophysin, DLL3) to uncover potential therapeutic vulnerabilities.

Keywords: RB1, TP53, Squamous

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.13 Actionable Mutation Profiles and Survival Outcomes in Invasive Mucinous Adenocarcinoma of the Lung

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Introduction: Invasive mucinous adenocarcinoma (IMA) is a rare subtype of lung adenocarcinoma with unique clinicopathologic features and limited therapeutic options. Comprehensive comparisons of genomic profiles and their survival impact between IMA and non-IMA are lacking. This study aimed to evaluate actionable and other clinically significant mutations and their prognostic relevance in IMA versus non-IMA.

Methods: De-identified records of 3,428 patients with primary lung adenocarcinoma and available survival data were retrieved from the Tempus database and stratified by histology into IMA (n=78) and non-IMA (n=3,350) groups. Clinical, biopsy, and molecular characteristics were compared using χ^2 and Fisher's exact tests for categorical variables. Actionable mutations were defined per current NCCN guidelines, including EGFR exon 19, L858R, or G719X mutations, ALK, ROS1, or RET fusions, and ERBB2 alterations. Real-world overall survival (rwOS) was analyzed using Kaplan-Meier curves and Cox proportional hazards models.

Results: IMA showed significantly higher frequencies of KRAS (54% vs. 27%, $p < 0.001$) and ERBB2 mutations (5.1% vs. 1.6%, $p = 0.044$) but a lower frequency of EGFR exon 19 deletions (1.3% vs. 9.6%, $p = 0.013$). Non-IMA patients with actionable mutations had longer median rwOS (35.73 vs. 16.47 months). A similar trend towards improved rwOS was observed for patients with actionable mutations in the IMA cohort (not reached vs. 12.98 months), although the sample size was small (n=14). Additionally, STK11 mutations appeared to be associated with poorer rwOS in non-IMA patients.

Conclusions: IMA exhibits a distinct mutational profile compared with non-IMA, showing differences in both frequency and prognostic impact. While actionable mutations were linked to improved survival in non-IMA, their prognostic value was less evident in IMA. Moreover, STK11 mutations suggested a potentially worse overall survival in non-IMA. Further analyses of clinically significant mutations in a larger IMA cohort will clarify the biological differences underlying these distinct tumor behaviors.

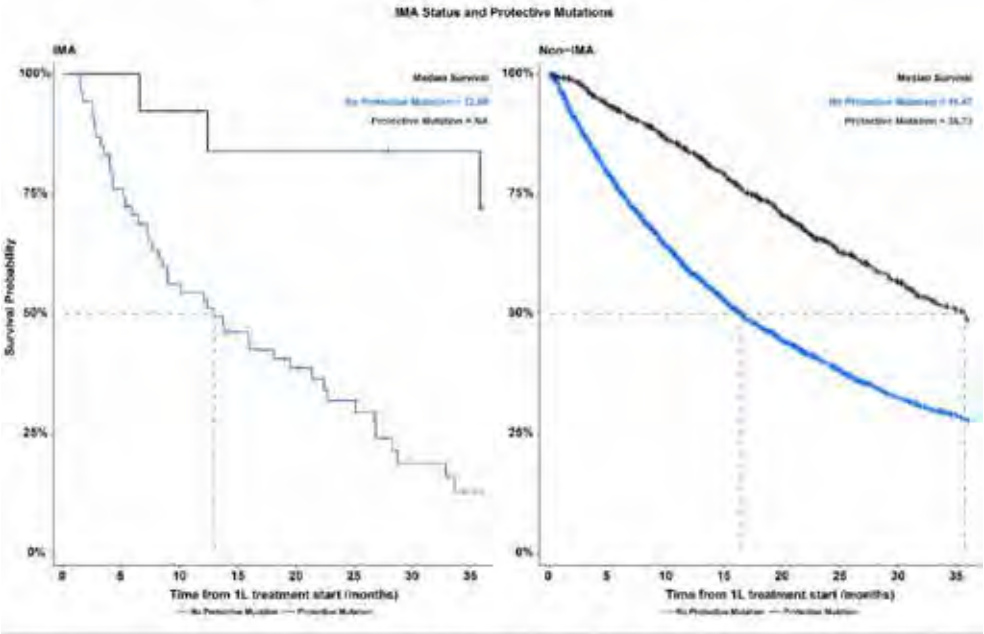
Table 1. Clinical, Demographic, and Molecular Characteristics of IMA vs. non-IMA Patients

Characteristic	Overall N = 3,428[1]	Non-IMA N = 3,350[1]	IMA N = 78[1]	p-value[2]
Age at Diagnosis				0.13
Median (Q1, Q3)	66 (60, 73)	66 (60, 73)	70 (62, 75)	
Mean (SD)	66 (10)	66 (10)	67 (10)	
Min, Max	0, 88	0, 88	41, 84	
Unknown	45	44	1	
Sex				0.021
Female	1,760 (51%)	1,730 (52%)	30 (38%)	
Male	1,668 (49%)	1,620 (48%)	48 (62%)	
Race				0.055
White	2,196 (77%)	2,139 (77%)	57 (88%)	
Black or African American	322 (11%)	320 (12%)	2 (3.1%)	
Other Race	178 (6.3%)	173 (6.2%)	5 (7.7%)	
Asian	151 (5.3%)	150 (5.4%)	1 (1.5%)	
Unknown	581	568	13	
Ethnicity				0.10
Not Hispanic or Latino	2,055 (93%)	2,008 (93%)	47 (87%)	
Hispanic or Latino	156 (7.1%)	149 (6.9%)	7 (13%)	
Unknown	1,217	1,193	24	
Smoking Status				0.2
Ex-smoker	1,827 (56%)	1,780 (56%)	47 (62%)	
Current smoker	740 (23%)	729 (23%)	11 (14%)	
Never smoker	688 (21%)	670 (21%)	18 (24%)	
Unknown	173	171	2	
Stage				0.003
Stage 4	2,922 (88%)	2,869 (88%)	53 (76%)	
Stage 3	316 (9.5%)	302 (9.3%)	14 (20%)	
Stage 1	47 (1.4%)	47 (1.4%)	0 (0%)	
Stage 2	36 (1.1%)	33 (1.0%)	3 (4.3%)	
Unknown	107	99	8	
Metastatic Status at Biopsy				<0.001
Metastatic	2,928 (88%)	2,875 (88%)	53 (73%)	
Pre-metastatic	412 (12%)	392 (12%)	20 (27%)	
Unknown	88	83	5	
Actionable Mutations				
KRAS P/LP	944 (28%)	902 (27%)	42 (54%)	<0.001
EGFR Exon 19 Deletion	322 (9.4%)	321 (9.6%)	1 (1.3%)	0.013
EGFR L858R	233 (6.8%)	231 (6.9%)	2 (2.6%)	0.13
BRAF P/LP	222 (6.5%)	217 (6.5%)	5 (6.4%)	>0.9
ALK Fusion	149 (4.3%)	144 (4.3%)	5 (6.4%)	0.4
MET Exon 14 Skipping	62 (1.8%)	62 (1.9%)	0 (0%)	0.4
ERBB2 P/LP	59 (1.7%)	55 (1.6%)	4 (5.1%)	0.044
EGFR Exon 20 Insertion	48 (1.4%)	48 (1.4%)	0 (0%)	0.6
EGFR G719X	31 (0.9%)	31 (0.9%)	0 (0%)	>0.9
RET Fusion	46 (1.3%)	45 (1.3%)	1 (1.3%)	>0.9
ROS1 Fusion	37 (1.1%)	36 (1.1%)	1 (1.3%)	0.6
EGFR L861Q	24 (0.7%)	24 (0.7%)	0 (0%)	>0.9
EGFR S768I	21 (0.6%)	21 (0.6%)	0 (0%)	>0.9
NTRK3 Fusion	6 (0.2%)	6 (0.2%)	0 (0%)	>0.9
NTRK1 Fusion	3 (<0.1%)	3 (<0.1%)	0 (0%)	>0.9
NTRK2 Fusion	1 (<0.1%)	0 (0%)	1 (1.3%)	0.023
Clinically Relevant Mutations				
STK11	479 (14%)	458 (14%)	21 (27%)	<0.001
KEAP1	293 (8.5%)	284 (8.5%)	9 (12%)	0.3

[1] n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

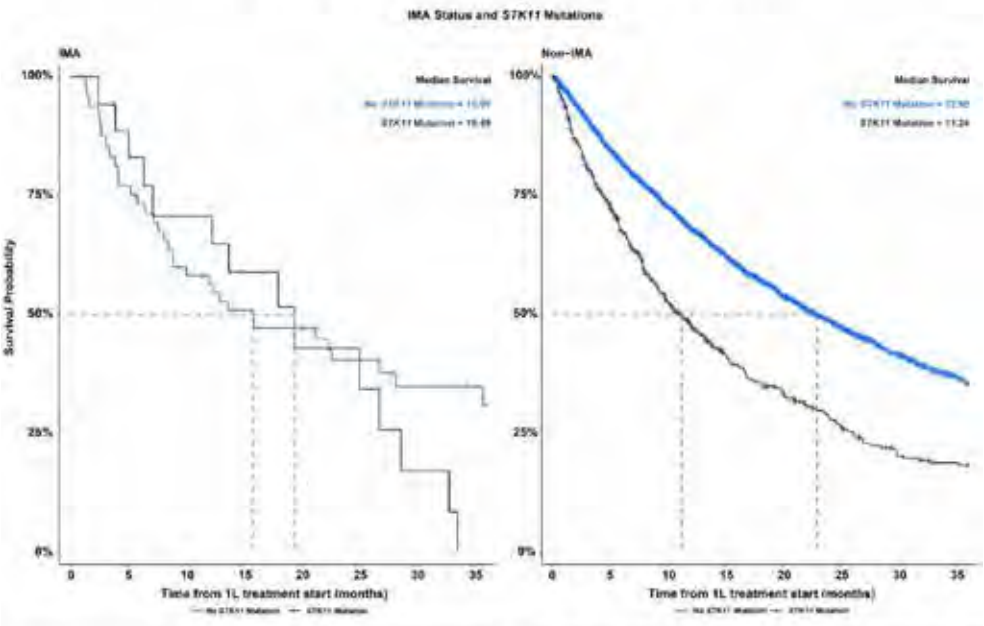
Figure 1. Overall Survival by Mutation Subgroups in IMA and Non-IMA Patients

(a) Overall Survival by Protective Mutation Status in IMA and Non-IMA



Strata	Number of Obs.	Number of Events	Median rwOS	Lower 95% CL	Upper 95% CL
Non-IMA, No Protective Mutation	2490	1334	16.47	15.35	17.85
Non-IMA, Protective Mutation	860	286	35.73	31.49	NA
IMA, No Protective Mutation	64	44	12.98	8.19	22.39
IMA, Protective Mutation	14	3	NA	35.83	NA

(b) Overall Survival by STK11 Mutation Status in IMA and Non-IMA



Strata	Number of Obs.	Number of Events	Median rwOS	Lower 95% CL	Upper 95% CL
Non-IMA, No STK11 Mutation	2892	1336	22.95	21.56	24.75
Non-IMA, STK11 Mutation	458	284	11.24	9.37	13.31
IMA, No STK11 Mutation	57	33	15.88	8.94	35.83
IMA, STK11 Mutation	21	14	19.49	12.36	NA

Keywords: Invasive Mucinous Adenocarcinoma (IMA), Actionable Mutations, Prognostic Biomarkers

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.14 Adoption of a 50-Gene Targeted Next Generation Sequencing Hotspot Panel in Non-Small Cell Lung Cancer in a Tertiary Institution in Singapore

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Introduction: Effective molecular profiling in non-small cell lung cancer (NSCLC) patients is essential to identify actionable genomic alterations (AGAs). Current guidelines recommend the use of next-generation sequencing (NGS) panels. Here we present the clinical outcomes of a newly adopted in-house NGS panel and compared with single gene testing (SGT) for EGFR/ALK/ROS1 alterations.

Methods: Since June 2023, a laboratory developed DNA- and RNA-based 50-gene targeted NGS hotspot panel (APEX Tissue, MiRXES) has been adopted as standard practice for all patients with advanced non-squamous (non-sq) NSCLC. Clinicopathological characteristics and molecular profiling were prospectively collected on all patients with newly diagnosed NSCLC between June 2023 and March 2025 who underwent APEX Tissue testing. The overall response rates (ORR), progression-free survival (PFS) and overall survival (OS) were compared between a subset of patients with advanced non-sq NSCLC with a historic cohort of similar patients who underwent SGT. Descriptive statistics were used to summarise patient demographics and clinical characteristics (SPSS Statistics version 26). Survival outcomes were analysed using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. A p-value of <0.05 was considered statistically significant.

Results: Of the 268 patients who underwent APEX Tissue testing, 227 (84.7%) were successfully sequenced; the remainder had inadequate samples. Of the 227 evaluable patients, the median age was 70 years, majority were males (57.8%), non-smokers (56.8%), Chinese ethnicity (78.0%), adenocarcinoma histology (91.6%) and advanced disease (66.1%) at the time of diagnosis. NGS testing revealed 208/227 (91.6%) patients harboured at least 1 molecular alteration. The commonest alterations were EGFR (44.1%), TP53 (24.7%) KRAS (17.2%), MET (5.3%), ALK (5.3%) and CTNNB1 (5.3%). Some 148 patients (65.2%) had an AGA as defined by NCCN guidelines of which 102/148 (68.9%) patients received molecular targeted therapy during the course of their treatment. A comparison was performed between patients with advanced disease tested with NGS (n=150) and SGT (n=100). Baseline characteristics were well-balanced. The NGS cohort had more AGAs (62.7% vs 23.0%, p<0.01) and received targeted therapy in the 1st line setting (56.7% vs 24.0%, p<0.01). The testing turnaround time was similar (9.01 days vs 7.89 days, p=0.051) between the two groups. In terms of clinical outcomes, patients who underwent NGS testing had a higher ORR (58.9% vs 39.6%, p<0.01). longer PFS (12.4 months vs 5.8 months, HR 0.56, 95% CI 0.40-0.79, p<0.01) and longer OS (21.6 months vs 14.0 months (HR 0.56, 95% CI 0.37-0.85, p<0.01) than patients who underwent SGT.

Conclusions: The integration of a 50-gene targeted NGS hotspot panel was successful in our centre, identifying more AGAs and ultimately improving patient clinical outcomes. To our knowledge, this is also the first study conducted in Asia that has shown improvement in survival of NGS vs SGT in NSCLC. The adoption of broad genomic profiling is essential to optimise therapeutic decision-making.

P2.06.15 Genomic Alterations in Lung Cancers Associated With Fibrosing Interstitial Lung Diseases in a French Multicentric Cohort

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Introduction: Fibrosing interstitial lung diseases (f-ILDs) are rare conditions characterized by chronic inflammation and progressive destruction of the lung parenchyma, leading to end-stage respiratory failure. Epidemiological data indicate that f-ILDs are associated with an increased incidence of lung cancer (LC). However, detailed molecular characteristics of LC associated with f-ILDs (LC/f-ILDs) are lacking. Using Next Generation Sequencing (NGS), we aimed to investigate the genomic alterations of LC/f-ILDs in a large French multicentric cohort, and to compare these genomic alterations with LC from a public database.

Methods: This retrospective study was based on a French multicentric cohort of patients with LC/f-ILD. Histological tumor types were classified according to the 5th edition of WHO classification of thoracic tumours. The pattern of pulmonary fibrosis was based on TDM and/or histopathological criteria according to the ATS/ERS/JRS/ALAT guidelines. DNA and RNA alterations were explored by NGS using using the Oncomine Comprehensive Assay V3 (OCAV3) (Life Technologies, Thermo Fisher Scientific). The genomic alterations of LC/f-ILDS were then compared to the TCGA database of LC. Using Reactome database, we also compared the signalling pathways impacted by the genetic alterations.

Results: A total of 107 samples from 101 patients, representing 102 tumors, were included. Among the 102 LC/f-ILD, 46 (45.1%) were adenocarcinomas (ADC), 43 (42.2%) were squamous cell carcinomas (SCC), 10 (9.8%) were small cell lung cancer (SCLC) and 3 (2.9%) were large cell neuroendocrine carcinoma (LCNEC). DNA NGS was conducted on 95 tumour samples, encompassing 44 ADC, 38 SCC, 10 SCLC, and 3 LCNEC. RNA NGS was conducted on 70 tumor samples. In ADC-SCC/f-ILD, TP53 was the most frequently mutated gene (59.76%), followed by ATM (20.67%), NF1 (17.07%), KRAS (12.20%), and NOTCH1 (10.98%). Mutation of EGFR and KRAS were found in 2 (4,5%) and 9 (20,45%) cases of ADC, respectively. We did not find any fusion transcript of ALK or ROS1 genes. We found a significantly ($p<0,05$) higher frequency of mutations in ADC-SCC/f-ILD compared to TCGA for ATM (20.67% versus 7.17%), NOTCH1 (10.98% versus 5.94%), BRCA1 (13.64% vs 3.16%), PMS2 (6.10% versus 1.33%), TSC2 (6.10% versus 2.77%) and FANCI (6.10% versus 1.43%). Regarding signaling pathways, we found a significantly higher proportion of tumors with molecular alterations in pathways related to DNA repair (especially homolozygous recombination repair, HRR), NOTCH and BRCA pathways in ADC/f-ILD compared to TCGA. In SCCs/f-ILD, we also found a significantly higher proportion of alterations DNA repair pathway compared to TCGA, notably non-homologous end-joining and Homology directed repair pathways.

Conclusions: This study provides significant insights into the genomic alterations of LC/f-ILD. In this large multicentric cohort, we found that ADC/f-ILD seems to harbour specific molecular features, involving NOTCH, HRR and BRCA pathways. These data pave the way for the developpement of new targeted therapies in LC/f-ILD, some of which are currently being investigated in clinical trials.

Keywords: Lung Cancer, Fibrosing interstitial lung disease, Molecular Pathology

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.16 Identification of Molecular Signatures Linked to Early-Stage Lung Adenocarcinoma With STAS Using Spatial Transcriptomics

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Introduction: Spread through air spaces (STAS) is recognized as an invasive histological pattern for tumor invasion in non-small cell lung cancer (NSCLC). It is defined as micropapillary clusters, solid nests, or single cells in the airspaces beyond the edge of the main tumor. STAS has been associated with worse prognosis in patients undergoing surgically resection for NSCLC. However, the molecular basis and potential biomarkers remain unclear. This study utilized spatial transcriptomics to identify the gene expressions patterns specific to STAS, aiming to elucidate its molecular mechanisms and identify candidate biomarkers to support preoperative diagnosis.

Methods: This retrospective, single-center study included 188 patients with pathological stage I lung adenocarcinoma (8th edition TNM classification) who underwent surgical resection at our institution between 2020 and 2021. Overall survival (OS) and recurrence-free survival (RFS) were compared between STAS-positive and STAS-negative patients. A subset of 61 patients (28 STAS-positive, 33 STAS-negative) was selected for spatial transcriptomic profilling using GeoMx Digital Spatial Profiler (DSP). Region of interest (ROIs) were defined in the tumor core, tumor border, tumor microenvironment (TME), and adjacent normal lung tissue. Transcriptomic data were analyzed using R (version 4.4).

Results: Among the 188 patients, 56 (29.8%) were identified as STAS-positive. While OS did not differ significantly between the two groups, RFS was significantly worse in STAS-positive patients ($p < 0.01$). In univariate analysis, both STAS and the papillary histologic subtype were associated with an increased risk of tumor recurrence. In multivariate analysis, only STAS remained as an independent prognostic factor for recurrence ($p = 0.01$). Spatial transcriptomic analysis was conducted on 791 ROIs from STAS-positive and STAS-negative tumors. Differential gene expression analysis revealed that specific pathways and molecular signatures, particularly those associated with tumor proliferation and invasion, were enriched in the STAS-positive tumor and TME ROIs.

Conclusions: STAS is an independent prognostic factor for recurrence in early-stage NSCLC patients following surgical resection. Spatial transcriptomic analysis identified distinct molecular features, including changes in the TME of STAS-positive tumors, that may contribute to recurrence. These findings enhance our understanding of the molecular basis of STAS and may aid in identifying biomarkers to support preoperative diagnosis.

Keywords: Lung adenocarcinoma, STAS, Spatial transcriptomics

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.17 Cellular Heterogeneity and Tertiary Lymphoid Structure Dynamics Predict Overall Survival in Immune Checkpoint Therapy-Treated NSCLC Patients

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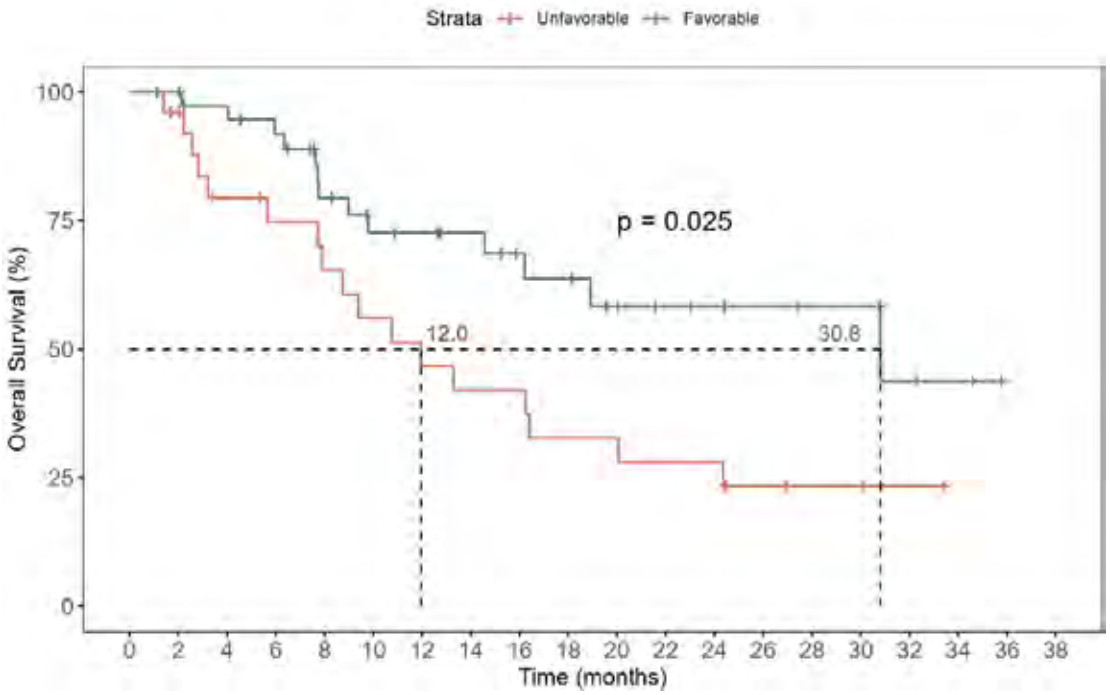
Introduction: Despite the promise of immune checkpoint inhibition (ICI) in non-small cell lung cancer (NSCLC), precise methods for predicting patient response remain limited. An understanding of each patient's tumor microenvironment (TME) is essential for identifying robust biomarkers to improve treatment outcomes. We present a novel framework integrating patient-specific TME composition and Tertiary Lymphoid Structure (TLS) dynamics from bulk RNA-sequencing to predict immunotherapy response.

Methods: Methods: Cellworks previously developed and cross-validated an algorithm for deconvolution of cell proportions and cell-type-specific gene expression from bulk transcriptomic data. This approach was enhanced by incorporating a TLS Score derived from 34 key genes representing various facets of TLS dynamics, including cellular interplay and maturity. A Cox proportional hazards model was trained to predict OS in primarily advanced NSCLC patients treated with ICI (n=63, SU2C-MARK cohort), using TME cell proportions (TCP) and TLS score derived from tumor-derived bulk transcriptomic data. The model was then locked and validated on an independent set of 66 ICI-treated NSCLC patients from the same study.

Results: The integrated TCP and TLS model demonstrated high predictive significance for overall survival (OS) in the training cohort (HR=0.36, C-Index=0.768, p < 0.001) and retained significance in the independent validation cohort (HR=0.66, C-Index=0.628, p < 0.001). When dichotomized, the model demonstrated clinically meaningful separation in the validation cohort (HR=0.45, p=0.025; median OS: 12 vs. 30.8 months, Figure 1). Analysis of TLS components revealed that expression of genes involved in immune cell recruitment (CCL19, CCL21, CXCL13, CXCR3), T-cell infiltration and activation (CD3D, CD3E, ICOS, IL21R), and mature B-cell/dendritic cell presence in germinal centers (CD19, CD79B, CD20, FCER2, CR1/CD35, CD83) was significantly associated with improved survival. Notably, the survival benefit was not limited to fully mature TLS but extended to intermediate-mature TLS, suggesting that organized B-cell follicles, even without fully developed germinal centers, may confer ICI benefit. Among TME cellular components, a high ratio of CXCL9+ M1-like macrophages to SPP1+ M2-like macrophages was positively correlated with OS across both sets. A specific cluster of antigen-experienced CD8 + T-cells (CXCR6+ CXCR3+ KLRK1+) strongly predicted favorable outcomes, while tumor-associated neutrophils predicted poor survival. Both structural (TLS) and cellular (TCP) parameters contributed independently and complementarily to predictive accuracy.

Conclusions: The integration of TLS dynamics with specific immune and stromal cell populations provides collective insight into how structural organization and cellular composition cooperatively determine ICI efficacy. Further validation in larger cohorts is necessary to translate these findings into clinical practice.



Keywords: immunotherapy, tumor microenvironment, tertiary lymphoid structure

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.18 Computational Modeling of Comprehensive Genomic Profiling to Predict Chemotherapy Benefit in Advanced NSCLC

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Introduction: Combination chemo-immunotherapy is a primary treatment option for patients with advanced non-small cell lung cancer (NSCLC). Although PD-L1 is a biomarker for selecting patients for therapy, it is imperfect, and the benefit of adding chemotherapy varies among patients. To address this, Cellworks developed a mechanistic computational biology model that integrates a patient's tumor-specific genomic profile, identified through comprehensive genomic profiling (CGP). This model reveals signaling pathway dysregulation and predicts variable immune checkpoint inhibitor (ICI) and ICI + chemotherapy (ICI+C) responsiveness. The model's output is translated into a quantitative score called the delta Therapy Response Index (ΔTRI), which represents the likelihood of chemotherapy benefit regardless of PD-L1 status.

Methods: The TRI algorithm was developed using two real-world retrospective cohorts (total n=1519) of patients with metastatic NSCLC who underwent CGP using the Foundation One CDx panel1. The TRI, computational model and clinical thresholds were locked and then prospectively tested in an independent set of 222 advanced NSCLC treatment naïve patients receiving either ICI monotherapy (n = 66) or ICI+C combination therapy (n = 156) with complete clinical and genomic information, derived from the nationwide (US-based) de-identified ConcertAI Genomics360 database. All patients in the validation cohort had Foundation One CDx CGP associated with first-line (1L) therapy. Right-censored survival times were generated as the difference between the date of diagnosis and the last date of clinical observation. The ΔTRI clinical threshold was selected to represent 1.5 standard deviations from the estimated standard deviation in ΔTRI observed in the clinical development set.

Results: In the overall, independent validation population, continuous TRI was significantly associated with OS after adjustment for clinical and genomic risk factors in a multivariable model, including across PD-L1 levels (LR p = 0.022). Patients in the ΔTRI High Benefit Group (ΔTRI ≥ 16, n = 86), had an incremental benefit in median OS of ~ 7.63 months with the addition of chemotherapy to ICI (logrank p = 0.002, median OS ICI = 6.84 months vs ICI+C = 14.47 months, Figure 1). In contrast, patients in the ΔTRI No Benefit Group (ΔTRI < 16, n = 136) showed no improvement in OS when receiving ICI+C (logrank p = 0.78, median OS ICI = 11.02 months vs ICI+C = 12.63 months). After adjustment for clinical and genomic risk factors, a likelihood ratio test of interaction between ΔTRI and treatment (ICI versus ICI+C) was significant (LR p = 0.036).

Conclusions: In this study, continuous TRI predicted overall survival (OS) while ΔTRI predicted the incremental benefit of chemotherapy in an independent real-world cohort of patients with NSCLC receiving 1L ICI or ICI+C. These findings support the use of CGP in conjunction with computational modeling to identify patients who may benefit from combination immunotherapy and chemotherapy, as well as those unlikely to respond to ICI alone, regardless of PD-L1 levels. Future studies will aim to prospectively validate the hypothesis that ΔTRI can guide decisions on whether to add chemotherapy. 1Klein, M. et al. MA09.06,2024 Journal of Thoracic Oncology, Volume 19, Issue 10, S89.

Keywords: immunotherapy, chemothrerapy, biosimulation

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.19 A Multi-Source Pathology-Based Model for Gene Mutation and Recurrence Risk Prediction in Lung Cancer

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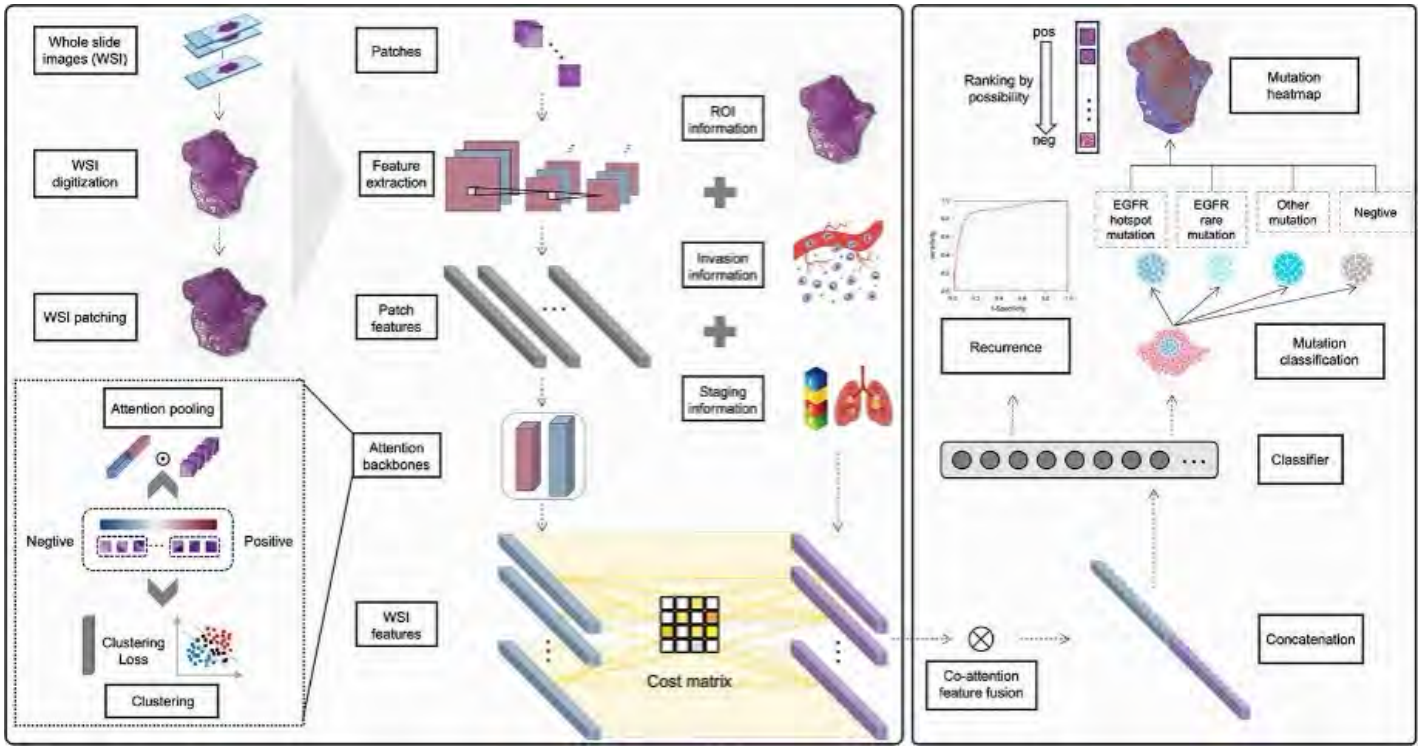
Introduction: Histopathologic analysis remains the cornerstone of lung cancer diagnosis, yet morphological patterns alone cannot reliably predict gene mutations or clinical outcomes. Gene sequencing, while informative, relies on high-quality tissue samples and is further limited by prohibitive costs, prolonged turnaround times, and restricted accessibility, particularly in economically underdeveloped regions. To address these challenges, we propose a deep convolutional neural network (DCNN)-based multi-source pathology model.

Methods: We collected 2,767 hematoxylin and eosin (H&E)-stained whole slide images (WSIs) from surgical resection samples (447 cases) at Fudan University Shanghai Cancer Center with complete genetic mutation profiles. A subset of 1,150 WSIs (336 cases) contained progression free survival (PFS) data. Utilizing a clustering-constrained attention multiple instance learning (CLAM) framework with cross-attention, we fused histopathological features, pathologist-annotated regions of interest (ROIs), tumor invasion patterns, and TNM staging. Histopathological annotations and ROIs identification were performed by two pathologists and reviewed by a senior pathologist. Mutations were classified into four categories based on sequencing results: epidermal growth factor receptor (EGFR) hotspot mutation (EGFR Exon 19), EGFR rare mutation (EGFR non-Exon 19), other mutations (non-EGFR), and negative (no mutation). Model performance was evaluated using confusion matrices, receiver operating characteristic curves, classification maps, and heatmaps.

Results: The prediction model based on DCNN exhibited outstanding performance, achieving an overall accuracy of 0.89 across the four categories of mutation classification within the test dataset. Specifically, the area under the receiver operating characteristic curve (AUC) for predicting EGFR hotspot mutations, EGFR rare mutations, other mutations, and negative samples was 0.80, 0.89, 0.79, and 0.74, respectively. In contrast, the baseline model, which lacked ROIs, cancer cell invasion information, and staging information, only achieved an accuracy of 0.81 and an average AUC of 0.68. Furthermore, our DCNN model demonstrated robustness in WSIs of lung cancers for the prediction of five-year PFS, achieving an overall accuracy of 0.89. The AUC for predicting five-year PFS was 0.89 in the validation set and 0.85 in the test set. In contrast, the baseline model achieved an accuracy of 0.70 and an AUC of 0.65 in the test set.

Conclusions: Our study highlights the potential of a DCNN-based multi-source pathology model for predicting both gene mutation and recurrence risk, providing a cost-effective tool to guide clinical decisions in resource-limited settings.



Keywords: Deep convolutional neural network (DCNN), Gene mutation and recurrence prediction, Lung cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.20 Assessment of Molecular Testing in Stage IV Non-Small Cell Lung Cancer Patients Across American Oncology Network

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Introduction: The NCCN guidelines recommend non-small cell lung cancer (NSCLC) patients (pts) who are stage IV receive comprehensive biomarker testing that includes evaluating for EGFR, ALK, ROS1, RET, MET, NTRK1/2/3, KRAS, ERBB2, and BRAF. The American Oncology Network (AON) has conducted quality initiatives (QI) with Integra Connect PrecisionQ focused on improving testing for stage IV pts. This study aims to show testing practices over the past 4 years in pts with stage IV NSCLC at AON.

Methods: 915 newly diagnosed stage IV pts from AON were randomly selected among 4,841 pts >=18 years of age who started first-line treatment between 1/1/2021 and 12/31/2024. The 915 pts were evaluated through manual chart abstraction to confirm their stage, diagnosis, and molecular testing results. In 2023, Integra Connect worked with AON medical leadership to generate an initial analysis of testing in stage IV and those results were shared with the practice. Testing rates were evaluated in each calendar year and additional analyses were performed to assess testing by histology, smoking status, gender, race, and age. Descriptive analyses were performed to analyze the data.

Results: Among the 915 stage IV NSCLC pts the median age was 70 (IQR 62.5-77), 49.5% were female, 76.2% identified as White, 11.8% identified as Black/African American, and 3.3% identified as Asian. Among the pts, 71% had adenocarcinoma, 21% had squamous cell carcinoma, and the remainder were undefined. In 2021, 84.9% (N = 218) of pts received comprehensive testing, which increased to a high of 93.8% (N = 194) in 2023 and was 89.8% (N = 177) in 2024. Among pts with adenocarcinoma, 91% (N = 652) received comprehensive testing compared to 81% (N = 193) in pts with squamous cell carcinoma. In 2021, 72% (N = 50) of squamous cell carcinoma pts received comprehensive testing which increased to 89% (N = 35) in 2024. No noticeable changes in testing rates over time were found among pts with adenocarcinoma. Comprehensive testing rates by smoking status were as follows: those who never smoked at 88.6% (N = 140), those who were previous smokers at 89.4% (N = 463), and those who identified as active smokers 86.5% (N = 311). Among male pts, 88.5% received comprehensive testing whereas among female pts 87.9% received comprehensive testing. Comprehensive testing rates by race were as follows: 88.2% for White (N = 697), 88% for Black/African American (N = 108), 90% for Asian (N = 30), and 87.5% for Other (N = 80). Comprehensive testing by age was as follows: pts <=50 at 92.7% (N = 41), pts 51-60 at 85% (N = 120), pts 61-70 at 88.3% (N = 300), pts 71-80 at 88.1% (N = 328), and pts >=81 at 89.7% (N = 126).

Conclusions: AON has driven increases in comprehensive testing among stage IV NSCLC pts, notably improving testing rates in pts with squamous cell carcinoma. While pts who were <=50 years of age had the highest rates of testing, no noticeable differences were observed by race, smoking status, or gender.

Keywords: Quality Improvement, Stage IV, Molecular Testing

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.21 Differential Gene Expression and Pathway Analysis of Invasive Mucinous Adenocarcinoma

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Introduction: Invasive mucinous adenocarcinoma (IMA) is a distinct lung adenocarcinoma subtype with unique clinical behavior, including immunotherapy resistance and high metastatic potential. However, the molecular pathways linking these pathological features to clinical outcomes remain unclear. In this study, we conducted a comprehensive gene expression and pathway analysis to investigate whether mucin-related genes are associated with survival outcomes, evaluating their potential roles as prognostic biomarkers and therapeutic targets in IMA.

Methods: De-identified data records from 17,885 patients with lung adenocarcinoma were identified, including 558 with IMA and 17,327 with non-IMA subtypes. Differential gene expression (DGE) was assessed using Wilcoxon rank-sum tests with Benjamini-Hochberg correction ($|\log_2 FC| \geq 1.0$; $q \leq 0.05$ considered significant), excluding genes with low expression (TPM sum ≤ 20). Real-world overall survival (rwOS) was evaluated with Kaplan-Meier curves and Cox proportional hazards models. Gene set enrichment analysis was conducted via the Enrichr-KG platform using GO, KEGG, and Reactome libraries ($q \leq 0.05$ considered significant).

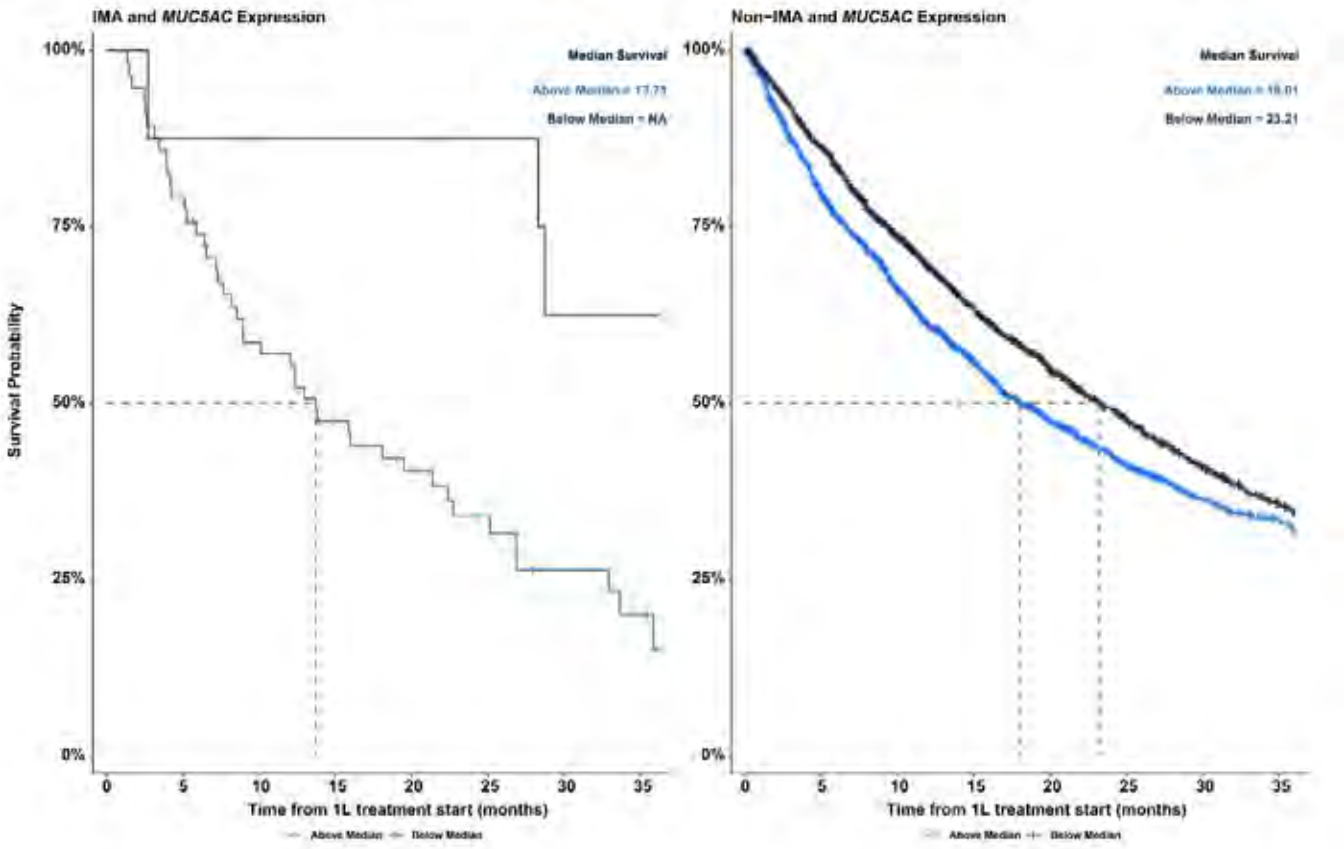
Results: DGE analysis identified 366 genes that were significantly differentially expressed in IMA (342 upregulated, 24 downregulated). Subsequent enrichment analyses identified 96 significantly enriched pathways: 94 linked to upregulated genes and two with downregulated genes. Furthermore, pathway analysis indicated that MUC5AC is closely linked to IL33 and SOX9, while MUC13 shares pathways with CXCL3 and CXCL5, all four of which were significantly upregulated in IMA (Table 1). Among the upregulated genes, elevated MUC5AC expression correlated with poor survival in both IMA and non-IMA cohorts (Figure 1).

Conclusions: These findings suggest that mucin-related genes in IMA modulate immune and metabolic pathways beyond mucin production, as evidenced by their strong network connectivity to regulators such as IL33, SOX9, CXCL3, and CXCL5. Our data highlight that the interconnected pathways among these upregulated genes could underlie the aggressive clinical behavior observed in IMA, warranting further mechanistic and clinical investigation.

Table 1. Selected Differentially Expressed Genes in IMA vs. Non-IMA

Gene	Log_2 Fold Change	*q*-value	Regulation
MUC5AC	4.44358	<0.001	Upregulated
MUC13	3.15044	<0.001	Upregulated
SOX9	1.33527	<0.001	Upregulated
IL33	1.32646	<0.001	Upregulated
CXCL5	1.22091	<0.001	Upregulated
CXCL3	1.00121	<0.001	Upregulated

Figure 1. Kaplan-Meier survival curves for MUC5AC overexpression in IMA and non-IMA patients



Strata	Number of Obs.	Number of Events	Median rwOS	Lower 95% CL	Upper 95% CL
Non-IMA, Above Median	1646	804	18.01	16.57	20.15
Non-IMA, Below Median	1704	816	23.21	21.47	25.28
IMA, Above Median	68	44	13.71	8.94	22.72
IMA, Below Median	10	3	NA	28.73	NA

Keywords: Invasive Mucinous Adenocarcinoma (IMA), Pathway Enrichment Analysis, Mucin-related genes

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.22 Pathological Characterization of Molecularly Screened Diffuse Pleural Mesothelioma

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Introduction: The genetic landscape of pleural mesothelioma (PM) exhibits a significant degree of heterogeneity, with BAP1, NF2, and CDKN2A recognized as the most frequently altered tumor suppressor genes. Histology remains the paramount factor in determining prognosis and guiding treatment selection. However, information about the correlation between pathological and genomic features is lacking.

Methods: Between June 2020 and December 2024, 217 PM cases were prospectively screened for the UNITO-001 study (NCT04940637) using a DNA-based NGS assay. The Oncomine Comprehensive Assay v3, which identifies point mutations, deletions, insertions, and copy number variations in 161 genes, including BAP1, NF2, CDKN2A, and genes associated with homologous recombination repair (HRR), was used. All cases were reviewed for comprehensive morphological analysis of growth variants and grading.

Results: A total of 161 patients were male, and 56 were female. The average age was 71 years. Of the 217 patients, 176 (81%) were classified as epithelioid, 16 (7%) as biphasic, and 8 (4%) as sarcomatoid (the remaining were not available). 108/217 (50%) cases harbored genetic alterations. The most common altered gene was BAP1 (42/108, 39%), followed by NF2 (21/108, 19%) and CDKN2A (12/108, 11%). Other altered genes included TP53 (6/108, 6%), common BRAF, KRAS and STK11 oncogenes (13/108, 12%) and nonconventional genes (ARID1A, ATM, BRCA2, CHEK2, FBXW7, FGFR1, IDH1, MSH6, NF1, PALB2, PIK3CA, POLE, RAD51, SLX4 and SMAD4) in 23/108 (21%) cases. Co-mutations occurred in 14/108 cases (13%), primarily involving BAP1 (11/14 cases, 78%). Additionally, 2/108 were germline mutations in the MSH6 and BAP1 genes, and 26/108 (24%) were somatic mutations in HRR genes. Overall, 86/176 (49%) epithelioid, 11/16 (69%) biphasic, and 2/8 (25%) sarcomatoid cases harbored mutations. Histological slides from 176 surgical pleural biopsies were available for revision. Among the epithelioid tumors, the main architectural variants were solid (73/156, 47%), tubule-papillary (68/156, 44%), and trabecular (18/156, 11%). The solid pattern characterized the majority of mutated cases (42/73, 58%), while the tubule-papillary growth pattern was found in 29/68 (42%) mutated cases, and the trabecular pattern in 9/18 (50%) mutated cases (Fisher test p=not significant). No significant correlation between mutated genes and growth patterns was found. Regarding grading, 56/156 (36%) cases were high, and 100/156 (64%) were low-grade cases. The high-grade cases exhibited the highest mutation rate (31/56, 55%), while among the low-grade cases, 49/100 (49%) were mutated cases (Fisher test p= not significant). No significant correlation between mutated genes and grade was found.

Conclusions: Although a significant correlation between growth patterns, grading, and molecular profiles was not established, the high heterogeneity of PM highlights the need for further studies to explore alternative genetic pathways, identify surrogate biomarkers, and evaluate the potential for novel personalized therapies.

Keywords: mesothelioma, genetic landscape, histology

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.23 CDKN2A Deletion Is an Independent Predictive Biomarker for Immunotherapy Response in Patients With Advanced NSCLC

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Introduction: While immune checkpoint inhibitors (ICIs) have transformed the treatment landscape of non-small cell lung cancer (NSCLC), identifying reliable predictive biomarkers remains a critical challenge. Currently used markers such as PD-L1 expression and tumor mutational burden (TMB) offer limited predictive value when applied in isolation. Genomic alterations that influence the tumor immune microenvironment may provide additional insights into immune resistance. In this study, we focused on CDKN2A deletion as a candidate biomarker and evaluated its clinical impact using real-world data.

Methods: We retrospectively reviewed clinical and genomic data from 321 NSCLC patients treated with ICIs at Severance Hospital between July 2019 and February 2023. All patients underwent targeted next-generation sequencing using the TSO500 panel. Associations between genomic alterations and progression-free survival (PFS) were assessed using univariate, subgroup, and multivariate analyses. In addition, H&E-stained tissue sections were reviewed to assess immune cell infiltration in relation to CDKN2A status.

Results: CDKN2A alterations were identified in 14% of patients, with deletions accounting for 6.5%. CDKN2A deletions were significantly associated with shorter progression-free survival (PFS) compared to cases without deletion (p = 0.002). The adverse prognostic effect of CDKN2A deletion was comparable to that of other poor-risk features, including nonsquamous histology (p = 0.001), low PD-L1 expression (≤50%, p = 0.001), low tumor mutational burden (<20/Mb, p = 0.001), and receipt of chemoimmunotherapy versus immunotherapy alone (p = 0.007). Notably, despite these associations Multivariate Cox regression analysis confirmed CDKN2A deletion as an independent poor prognostic factor (HR 2.24, 95% CI 1.38-3.65, p = 0.001) showing a greater adverse effect than even low PD-L1 expression (HR 1.42, 95% CI 1.08-1.89, p = 0.014), one of the most established poor-risk biomarkers. Moreover, histopathological review revealed reduced immune infiltration in tumors harboring CDKN2A deletion, consistent with an immune-cold tumor microenvironment. Although the TSO500 panel does not include the MTAP gene, its close genomic proximity to CDKN2A on 9p21.3—coupled with prior reports of frequent co-deletion—suggests a broader immunogenomic mechanism. Importantly, we also observed concurrent deletion of CDKN2B in 6.2% of patients, further supporting the hypothesis that large-scale chromosomal loss in the 9p21.3 locus contributes to immune evasion.

Conclusions: Our findings suggest that CDKN2A deletion is a clinically meaningful and potentially predictive biomarker for resistance to immune checkpoint therapy in NSCLC. The concurrent loss of neighboring genes such as MTAP and CDKN2B reinforces the role of the 9p21.3 chromosomal region in modulating the tumor immune landscape. As next-generation sequencing becomes increasingly integrated into clinical care, incorporating 9p21.3 status may enhance patient stratification and guide the development of rational combination strategies, including agents targeting epigenetic or innate immune pathways.

Keywords: Predictive biomarker, Immunotherapy, CDKN2A

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.24 Primary Pulmonary Neuroendocrine Immunophenotype Carcinoma Harboring Driver Gene Mutation/Fusions: Neuroendocrine Neoplasm?

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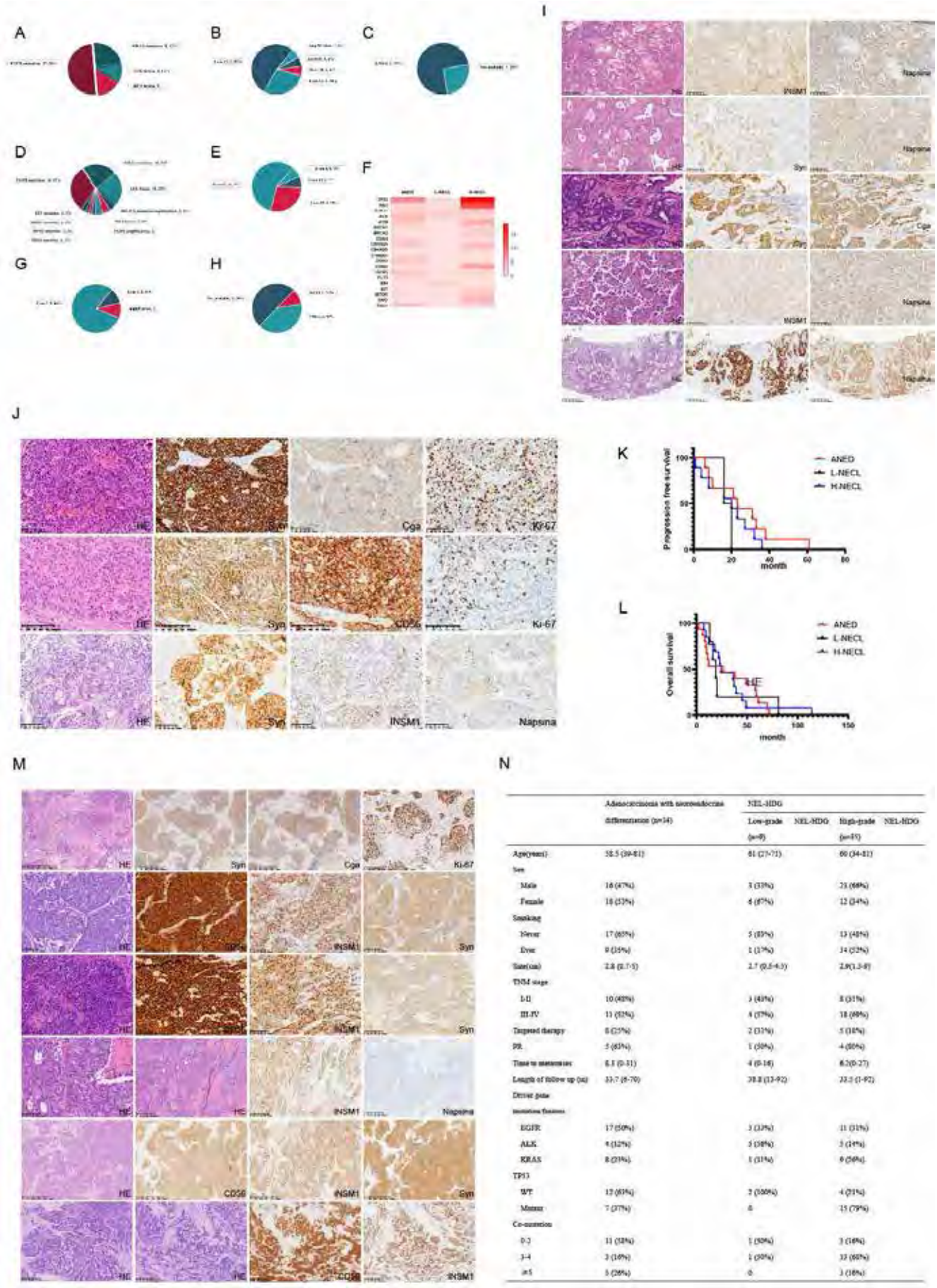
Introduction: Driver mutations in tyrosine kinase receptors are key genomic alterations in a subset of lung adenocarcinomas. However, these mutations are extremely rare in primary pulmonary neuroendocrine carcinomas (NECs), with only a few cases reported. We identified multiple cases of primary pulmonary neuroendocrine immunophenotype carcinoma harboring driver gene mutations or fusions, which could be classified into adenocarcinoma with neuroendocrine differentiation (ANED) and neuroendocrine-like carcinoma (NELC). Notably, NELC exhibited morphologic characteristics that do not align with the current classification system. To clarify its classification, we conducted a comprehensive clinicopathologic and molecular analysis of all identified cases at our institution.

Methods: A retrospective review was conducted using the electronic pathology database of a tertiary hospital between January 2018 and June 2024 identify cases of primary pulmonary neuroendocrine immunophenotype carcinoma harboring driver gene mutations or fusions. Diagnoses were confirmed by a pathologist, and specimens were analyzed for EGFR mutations, ALK translocations, and KRAS/RET expression. Clinical data were also collected and analyzed.

Results: Seventy-eight cases of pulmonary neuroendocrine immunophenotype carcinoma with EGFR, ALK, and other receptor tyrosine kinase mutations or fusions were identified. Among them, 34 were classified as ANED, with EGFR mutations detected in 50% of cases and additional occurrences of KRAS, RET, and ALK alterations. The remaining cases were high-grade NELC (HNELC), where TP53 mutations were present in 79% of advanced cases (A-H). Histological findings revealed that ANED exhibited typical adenocarcinoma patterns, including lepidic, acinar, papillary, micropapillary, and solid growth (I). In contrast, low-grade NELC (LNELC) displayed atypical morphologic features, such as irregular trabecular and nest-like growth with a fibrotic rather than sinus-rich interstitium (J). HNELC differed from conventional neuroendocrine neoplasms and exhibited a higher nuclear-to-cytoplasmic ratio than large cell neuroendocrine carcinoma but lower than small cell lung carcinoma, with spindle-shaped and polygonal cells and irregular nest-like structures (M). Clinically, most cases of HNELC were diagnosed at Stage III-IV, while ANED and LNELC cases were more evenly distributed across disease stages (N). Compared with ANED, HNELC showed significantly worse progression-free and overall survival (K-L). The majority of patients who received targeted therapy exhibited partial responses, reinforcing the need for routine driver gene testing in neuroendocrine-like tumor.

Conclusions: Lung NELC with driver gene mutations or fusions differs clinically and molecularly from traditional lung neuroendocrine neoplasms. However, it remains appropriate to classify these tumors within the neuroendocrine category. The findings emphasize the necessity of routine molecular testing in tumors with neuroendocrine features and atypical morphology.



	Adenocarcinoma with neuroendocrine differentiation (n=14)	NEL-HDG			
		Low-grade (n=8)	NEL-HDG	High-grade (n=33)	NEL-HDG
Age(years)	52.5 (39-81)	61 (27-71)		60 (34-81)	
Sex					
Male	16 (47%)	3 (33%)		23 (69%)	
Female	18 (53%)	6 (67%)		12 (34%)	
Smoking					
Never	17 (65%)	5 (83%)		13 (48%)	
Ever	9 (35%)	1 (17%)		14 (52%)	
Size(cm)	2.8 (2.7-5)	2.7 (0.5-4.3)		2.9(1.3-8)	
TNM stage					
I-II	10 (48%)	3 (43%)		8 (31%)	
III-IV	11 (52%)	4 (57%)		18 (69%)	
Targeted therapy	8 (27%)	2 (33%)		5 (16%)	
PR	5 (63%)	1 (50%)		4 (66%)	
Time to metastasis	8.3 (0-31)	4 (0-16)		8.2(0-27)	
Length of follow up (m)	33.7 (8-70)	39.8 (13-92)		33.3 (1-92)	
Driver gene mutation features					
EGFR	17 (50%)	3 (33%)		11 (31%)	
ALK	4 (12%)	3 (38%)		3 (14%)	
KRAS	8 (23%)	1 (13%)		9 (56%)	
TP53					
WT	12 (63%)	3 (100%)		4 (21%)	
Mutant	7 (37%)	0		15 (79%)	
Co-mutation					
0-2	11 (32%)	1 (50%)		3 (16%)	
3-4	3 (16%)	1 (50%)		33 (60%)	
≥5	3 (26%)	0		3 (16%)	

Keywords: lung neuroendocrine-like carcinoma, driver gene mutation, ALK rearrangement

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.25 Clinical Implications of TROP2 Expression in Lung Adenocarcinomas

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Introduction: Trophoblast cell surface antigen 2 (TROP2) is a cell surface glycoprotein expressed in various types of cancers, and its overexpression is associated with a negative prognosis. Antibody-drug conjugates targeting TROP2 show potential of treating TROP2-expressing cancers. Recently, TROP2 overexpression has been linked to poorer progression-free and overall survival (OS) after PD-L1 blockade therapy in patients with non-small cell lung cancer. In addition, TROP2 overexpression has been reported to correlate with gefitinib resistance in EGFR-mutated lung cancers. However, the clinical implications of TROP2 expression in lung adenocarcinoma (LUAD) remain unclear.

Methods: Immunohistochemical staining with an anti-TROP2 antibody (SP295) was performed on 1067 surgically resected LUAD tissue microarrays. The intensity of TROP2 expression was scored as 0 (absent), 1 (weak-to-moderate), or 2 (strong). The H-score was calculated as the product of the intensity and proportion of positive tumor cells. TROP2 expression positivity was evaluated based on the intensity (0 vs. 1/2), proportion of positive tumor cells (<25% vs. ≥25%), and H-score (<50 vs. ≥50). Statistical analysis was performed to examine the association of TROP2 overexpression with clinicopathological and molecular characteristics and prognosis. Subset analyses of the role of TROP2 expression were performed in PD-L1 positive LUADs and EGFR mutated LUADs.

Results: TROP2 overexpression was observed in 823 patients (77%) showing intensity 1/2, 373 (35%) with ≥25% positive tumor cells, and 273 (22%) with H-score ≥50. TROP2 overexpression was significantly associated in males, individuals partaking in smoking, elevated serum CEA level, advanced pathological stage, larger tumor size, histologically high-grade tumors, lymphatic permeation, pleural invasion, EGFR wild-type, and PD-L1 positive expression. The OS and relapse-free survival (RFS) of patients with TROP2 positive LUADs were worse than those with TROP2 negative LUADs. No differences were found in clinicopathological and molecular characteristics, OS, and RFS between TROP2 positive and negative cases of PD-L1 positive LUADs and EGFR-mutated LUADs.

Conclusions: TROP2 overexpressed LUADs are biologically aggressive tumors and good candidates for TROP2-targeting therapy. There were no biological differences between TROP2 positive and negative cases of PD-L1 positive LUADs and EGFR mutated LUADs.

Keywords: TROP2, lung adenocarcinoma, ADC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.26 The Clinicopathological Characteristics and Prognostic Analysis of SMARCA4-Deficient Non-Small Cell Lung Cancer

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Introduction: To investigate the clinicopathological features of SMARCA4 deficient non-small cell lung cancer (NSCLC), and to evaluate the value of SMARCA4 gene mutation and its protein expression loss in clinical prognosis.

Methods: Advanced NSCLC patients diagnosed from January 2022 to January 2024 were selected, including 32 cases with BRG1 deficient and 64 cases with BRG1 intact expression. TCGA and MSKCC databases contained SMARCA4 gene mutation profile, mRNA expression level and the clinical prognostic information were downloaded.

Results: The main mutation types of SMARCA4 gene included missense mutation (52%), nonsense mutation (23%), frameshift deletion (12%), frameshift insertion (3%), and splice site mutation (10%). BRG1-deficient NSCLC is predominantly male (68.8%) with a history of tobacco exposure (65.6%) and a poor prognosis (Median OS of 12.0 months). The histopathological types were diverse, with poorly differentiated adenocarcinomas, The tumor stroma exhibits significant inflammatory cell infiltration and necrosis, with easily observable mitotic figures in tumor cells. Additionally, TTF-1 is negatively expressed in 76.1% of cases. The median level of proliferation index Ki-67 was 70%, and the positive rate of PD-L1 expression accounted for 68.7% (53.1% of which had an expression range of 1-49%, and 25% showed high expression). The co-deficient rate of BRG1 and BRM was 6.2%, and no co-deficient of BRG1 and ARID1A/ARID1B were found. In 954 NSCLC patients, there was no significant difference in overall survival between the SMARCA4 mutant group and the non-mutant group ($p>0.05$), while low expression of SMARCA4 mRNA ($p<0.05$) , especially BRG1 protein deficient ($p<0.0001$) predicted a worse clinical prognosis.

Conclusions: SMARCA4/BRG1-deficient NSCLC exhibits a highly aggressive clinicopathological phenotype. The loss of BRG1 protein serves as a more robust prognostic stratification factor compared to SMARCA4 gene mutations, warranting in-depth basic research and clinical trials to identify precise and effective therapeutic strategies.

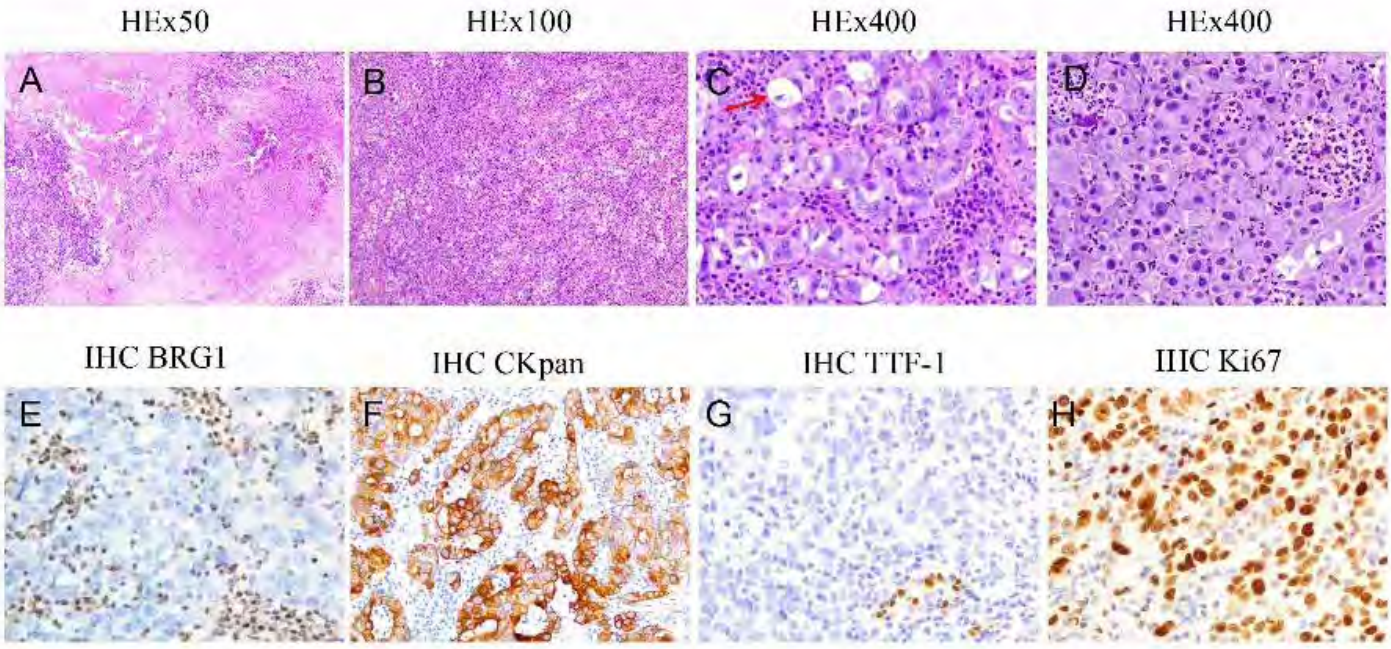

Figure 1. Pathological characteristics of BRG1-deficient adenocarcinoma. (A) HE staining shows poorly differentiated morphology with solid sheet-like arrangement and extensive necrosis (50× magnification). (B) HE staining shows some tumor cells with clear cytoplasm and an inflammation-rich background (100× magnification). (C) HE staining shows significant cellular atypia, prominent nucleoli, frequent mitotic figures, and poorly formed glandular structures (red arrow) (400× magnification). (D) Rhabdoid tumor cells with distinct eosinophilic nucleoli and a high mitotic rate (400× magnification). (E) Immunohistochemical staining shows loss of BRG1 expression in tumor cells with positive expression in background inflammatory cells (400× magnification). (F) Immunohistochemical staining shows CKpan is positive in tumor cells (400× magnification). (G) Immunohistochemical staining TTF-1 is negative in tumor cells (400× magnification). (H) immunohistochemical staining shows approximately 80% Ki67 positivity in tumor cells (400× magnification).

Table 1. Clinicopathological features of 32 cases of BRG1-deficient non-small cell lung cancer

Characteristic	Percentage(%)	Characteristic	Percentage(%)
Age		**histological type**	
Median age	63	ADC	26(81.3)
Range	37-83	SCC	3(9.4)
Gender		ASC	1(3.1)
Male	22(68.8)	PC	1(3.1)
Female	10(31.2)	LCC	1(3.1)
Smoking history		**TTF-1 expression(N=26)**	
Current or ever	21(65.6)	Positive	6(23.1)
Never	11(34.4)	Negative	20(76.9)
Clinical stage		**NapsinA expression(N=26)**	
IIIB-IIIC	5(15.6)	Positive	6(23.1)
IV	27(84.4)	Negative	20(76.9)
Distant metastasis		**Ki-67 expression**	
Yes	25(78.1)	Median	60%
No	7(11.9)	Range	30-95%
Systemic therapy		**Differentiation**	
Chemotherapy	11(34.4)	Poorly	27(84.4)
Chemo-immunotherapy	20(62.5)	Moderately	5(15.6)
Target therapy	1(3.1)	Highly	0(0)
Follow-up time. months		**BRM expression**	
Median time	12.0	Yes	30(93.8)
Range	6.0-26.0	No	2(6.2)
Prognosis		**ARID1A expression**	
Survival with tumor	7(11.9)	Yes	32(100)
Dead	25(78.1)	No	0(0)
Overall survival. months		**ARID1B expression**	
Median	12.0	Yes	32(100)
95%CI	9.5-14.5	No	0(0)
Driver gene		**PD-L1 expression**	
EGFR L858R (+)	1(3.1)	<1%	7(21.9)
KRAS exon2/3 (+)	4(12.5)	1-49%	17(53.1)
ALK/ROS-1 (+)	0	≥50%	8(25.0)

Abbreviations: ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; PC, pleomorphic carcinoma; LCC, large cell carcinoma.

Keywords: SMARCA4-deficient NSCLC, clinicopathological features, prognostic analysis

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.27 Unlocking the Genetic Link: Exploring Germline EGFR T790M Mutations in NSCLC and Implications for Targeted Treatment and Familial Screening

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Introduction: The EGFR T790M mutation in non-small cell lung cancer (NSCLC) is most commonly acquired and associated with resistance to first-and second-generation EGFR tyrosine kinase inhibitors (TKIs). However in less than 1% of NSCLC cases, this mutation occurs as a germline alteration, significantly increasing the risk of developing lung cancer, particularly in non-smokers. Third-generation EGFR TKIs like osimertinib are effective for acquired T790M mutations, but their role in germline mutations is underexplored. The INHERIT trial showed that germline EGFR mutations can lead to an earlier age of diagnosis and may impact clinical outcomes. This study presents four rare cases of NSCLC patients with germline EGFR T790M mutations, providing insights into treatment responses, familial screening, and potential for region-specific genetic counseling and early detection.

Methods: This retrospective study analyzes four female patients who do not smoke diagnosed with NSCLC between 2017 and 2022, all with germline EGFR T790M mutations identified through tissue and plasma circulating tumor DNA biopsies. First-line therapy with osimertinib was initiated for all patients, and genetic screening was offered to first-degree relatives to assess familial risk. CT scans were recommended for relatives with positive test results. Clinical data were collected to evaluate disease progression, response to therapy, and the impact of genetic findings on clinical practice. Descriptive statistics were used to analyze treatment responses, survival outcomes and the correlation between variant allele frequencies (VAF), and treatment efficacy.

Results: All four patients demonstrated the germline EGFR T790M mutation. Patient A, diagnosed in 2022, initially responded well to osimertinib but developed pneumonitis, leading to treatment cessation. After disease progression, reduced-dose osimertinib was reintroduced, leading to disease stabilization. Patient B, diagnosed in 2020, achieved stable disease on osimertinib combined with stereotactic radiosurgery for brain metastasis. Patient C, diagnosed in 2021, showed progression despite osimertinib monotherapy, but responded favorably to osimertinib and amivantamab. Patient D, diagnosed in 2017, remained stable on osimertinib after radiation therapy. Genetic testing of family members revealed several first-degree relatives who tested positive for the T790M mutation and were enrolled in CT screenings for early detection. Although genetically unrelated, these patients were suspected to have inherited the mutation based on high VAFs observed in molecular testing of their tumors.

Conclusions: Germline EGFR T790M mutations, though rare, significantly impact NSCLC management. Osimertinib was effective for these patients, with most achieving disease stability, though the responses were not always sustained. This study emphasizes the importance of genetic testing for patients with suspected germline mutations and their first-degree relatives. Given the increased 50-60% risk of lung cancer in these individuals, as reported in the literature, we recommend family members undergo lung cancer screening to facilitate early detection. The findings suggest the need for region-specific genetic counseling and targeted screening programs for high-risk families. Further research into osimertinib's efficacy in germline EGFR T790M mutations is essential. Larger cohort studies and clinical trials are needed to establish standardized protocols for familial screening and treatment strategies. Enhanced understanding of germline EGFR T790M mutations will improve both treatment outcomes and early detection in at-risk families.

Keywords: Germline EGFR T790M, Non-Small Cell Lung Cancer, Osimertinib

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.28 GPC3 Upregulation After Neoadjuvant Chemoimmunotherapy Associates With Adverse Outcomes and Tumor Heterogeneity in Squamous NSCLC

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Introduction: Lung squamous cell carcinoma (LUSC) accounts for approximately 20%-30% of non-small cell lung cancer (NSCLC). With breakthroughs from studies such as KEYNOTE-671, neoadjuvant immunochemotherapy has become the standard treatment for resectable LUSC. However, current efficacy evaluation systems (e.g., major pathological response, MPR) exhibit significant individual variability in predicting long-term outcomes. Glypican-3 (GPC3), a member of the heparan sulfate proteoglycan family, has been confirmed as a prognostic biomarker in hepatocellular carcinoma, yet its role in the tumor microenvironment (TME) remodeling of LUSC and therapy-induced expression dynamics remain unclear.

Methods: This study enrolled 24 LUSC patients who underwent direct surgical resection (without neoadjuvant therapy) and 44 patients who received neoadjuvant immunochemotherapy followed by surgery at Guangdong Provincial People's Hospital between 2021 and 2024. Additionally, 15 patients with histopathologically confirmed LUSC bone metastases were included. GPC3 expression was independently assessed by two blinded pathologists (positivity defined as H-score ≥10). Statistical analyses included Fisher's exact test (categorical variables) and Mann-Whitney U test (continuous variables). Survival analysis was performed using Cox proportional hazards models adjusted for clinical staging factors.

Results: In the direct surgery group (n=24), 13 (54%) were GPC3-positive, whereas in the neoadjuvant immunochemotherapy group (n=44), 32 (73%) were GPC3-positive. In contrast, only 2 (13%) of the bone metastasis cases (n=15) exhibited GPC3 positivity. Statistical analysis revealed that GPC3 positivity increased post-neoadjuvant therapy, though not significantly (p=0.18, 95% CI [0.14, 1.43]). Notably, GPC3 expression was significantly lower in bone metastases compared to primary lung lesions (p=0.017, 95% CI [1.23, 80.32]). Using the Mann-Whitney U test, we compared GPC3+ cell proportions between the direct surgery and neoadjuvant groups. The neoadjuvant group exhibited significantly higher values (W=702, p=0.013). Descriptive statistics showed that the median GPC3+ cell proportion in the neoadjuvant group was 50 (IQR: 5-70), significantly higher than that in the direct surgery group (median=15, IQR: 0-40), suggesting that neoadjuvant immunochemotherapy induces GPC3 upregulation. To assess prognostic differences, patients were stratified by GPC3 IHC results. Among 24 GPC3-positive patients, 18 (75.0%) experienced recurrence, whereas only 1 of 11 (9.1%) GPC3-negative patients relapsed (p=0.00056, 95% CI=[2.84, 1358.96]). Postoperative adjuvant therapy did not influence recurrence risk (overall p=1.0; within the GPC3-positive subgroup, p=0.649). Kaplan-Meier analysis (median follow-up: 20.1 months) showed that the GPC3-positive group had a median event-free survival (EFS) of 17.7 months (95% CI: 14.6-not reached), whereas the negative group did not reach median EFS. The log-rank test confirmed significant survival curve divergence (p=0.0117).

Conclusions: This study is the first to demonstrate that neoadjuvant immunochemotherapy induces GPC3 upregulation in the LUSC TME, with GPC3+ phenotype strongly associated with early postoperative recurrence. The heterogeneity in GPC3 expression between primary and metastatic lesions suggests potential epigenetic reprogramming during metastatic progression. However, due to the limited sample size (n=83) and lack of multi-omics validation, future studies integrating single-cell RNA sequencing and spatial transcriptomics are warranted to elucidate the functional role of GPC3.

Keywords: LUSC, Neoadjust Therapy, GPC3

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.29 Bridging Histopathology and Molecular Profiling: AI-Powered Virtual Multiplex Immunofluorescence Staining for LUAD Prognosis

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Introduction: Multiplex immunofluorescence (mIF) is widely used in tumor research to simultaneously visualize multiple biomarkers, providing detailed insights into the tumor immune microenvironment. However, mIF is costly and time-consuming, with limited histopathological context. Consequently, hematoxylin and eosin (H&E)-staining remains the primary method for cancer diagnosis. Here, we introduce HEMIFuse, a generative artificial intelligence-based platform that rapidly synthesizes virtual mIF images solely from routine H&E images.

Methods: The HEMIFuse platform was developed using the pix2pixHD generative adversarial network model. A total of 133 patients with stage I-III lung adenocarcinoma (LUAD) who underwent surgery were retrospectively enrolled and randomly divided into the training (n=100) and validation set (n=33). Formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections were initially subjected to mIF staining, followed by high-resolution whole-slide imaging. The same sections were then restained with H&E and scanned. This procedure yielded spatially aligned, cell-level paired H&E and mIF images from identical histological regions (Fig. 1a), providing a high-quality dataset for applying AI to integrate histopathology with multiplex molecular information.

Results: Comprehensive image evaluation demonstrated that virtual mIF images generated by the HEMIFuse platform were of high quality and showed strong concordance with ground-truth images (Fig. 1c and d). Specifically, the highest SSIM and corresponding PSNR values on the validation set for the four LUAD-related biomarkers—CD3 (0.91 ± 0.05, 32.86 ± 4.13), CD20 (0.88 ± 0.08, 35.21 ± 3.05), CD68 (0.90 ± 0.05, 33.61 ± 3.55), and PD-L1 (0.85 ± 0.06, 31.26 ± 5.78). Additionally, the biomarker expression levels derived from virtual mIF images enabled prognostic stratification in LUAD patients ($p < 0.05$), achieving performance comparable to chemically stained mIF images. (Fig. 2).

Conclusions: The HEMIFuse platform enables rapid and accurate conversion of routine H&E images into virtual mIF images, significantly reducing cost of mIF staining and streamlining histopathology workflows.

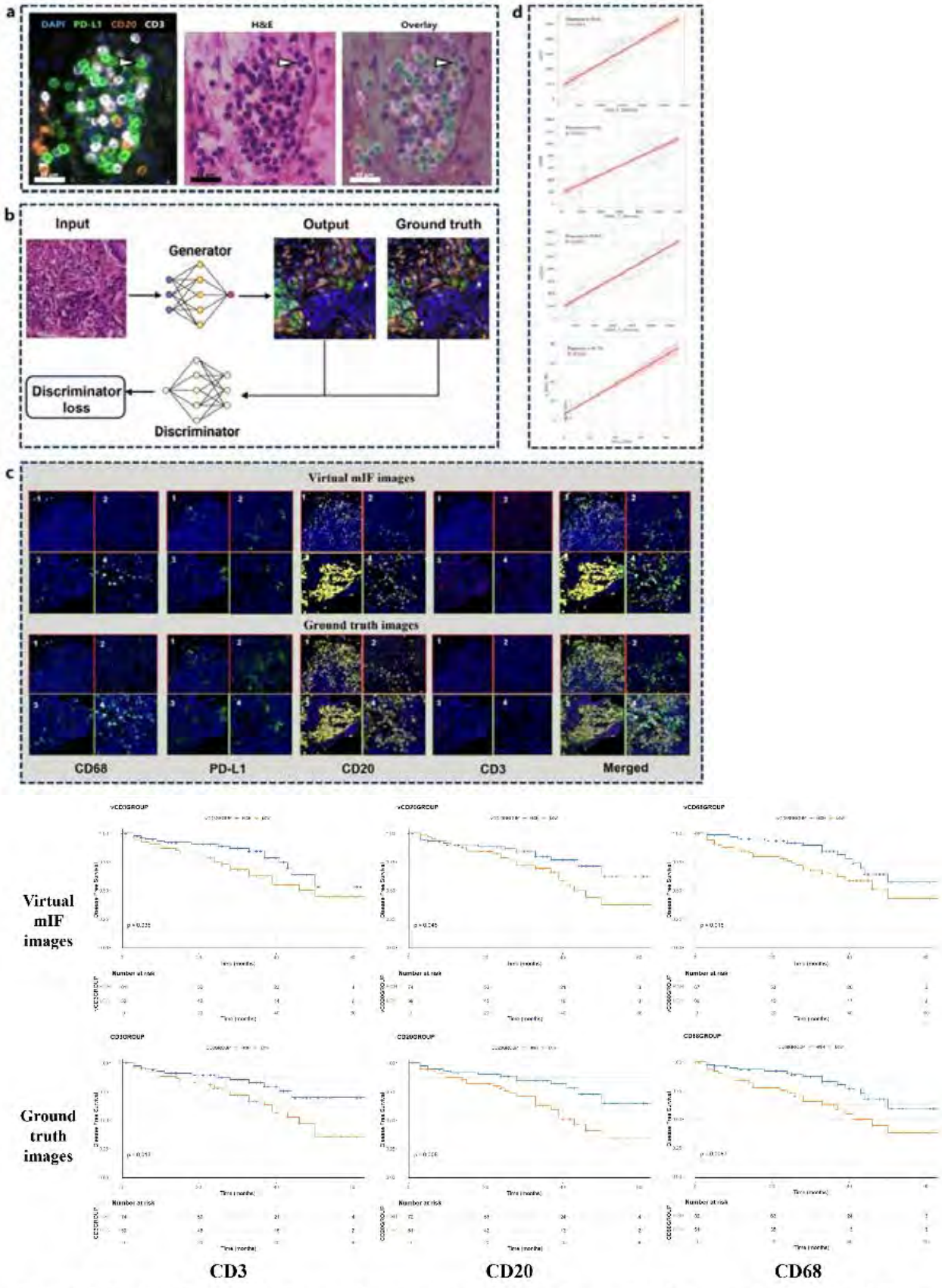

Figure 2: Kaplan–Meier survival curves based on virtual mIF and ground truth images, labeled with different biomarkers, for patients with LUAD.

Keywords: Virtual staining, Multiplex immunofluorescence, Lung adenocarcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.30 ITGBL1: A Predictive Biomarker for IPF-LUSC Comorbidity Risk in Lung Transplant Candidates

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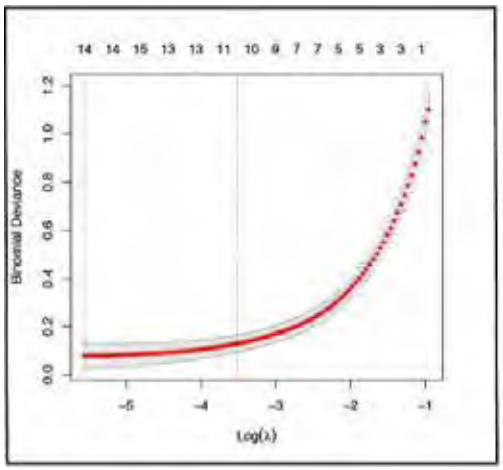
Introduction: Lung transplantation has become a primary treatment for end-stage lung diseases, including idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). IPF patients face a significantly elevated risk of developing lung squamous cell carcinoma (LUSC), though the underlying mechanisms remain unclear. Since lung cancer is an absolute contraindication for transplantation, there is an urgent need for biomarkers to assess malignant transformation risk in IPF patients pre-transplant. This study aims to identify predictive biomarkers for lung cancer risk in transplant candidates.

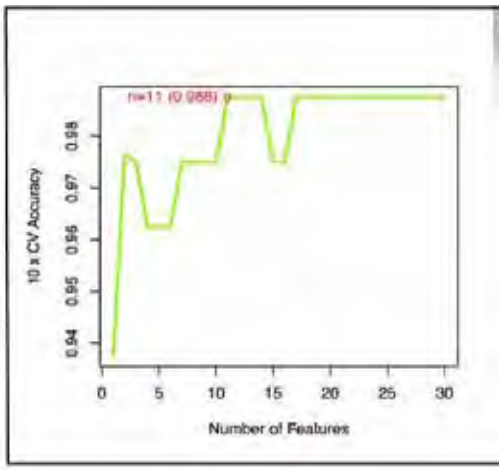
Methods: Using single-cell RNA sequencing data from IPF-LUSC lung samples, IPF datasets from GEO, and LUSC data from TCGA, we identified common differentially expressed genes (DEGs) between two diseases. LASSO regression and SVM-RFE algorithms were applied to screen core candidate genes. SHapley Additive exPlanations (SHAP) interpretability analysis evaluated gene importance and model contribution. Kaplan-Meier survival analysis assessed prognostic impacts. PPI networks, GSEA functional enrichment, and immune cell infiltration analyses were performed for core genes. Single-cell RNA data further validated gene specificity in IPF-LUSC tumor tissues. All analyses used R language (v4.4.1).

Results: Cross-analysis revealed 409 shared DEGs. LASSO and SVM-RFE identified five core genes: BCHE, C1orf210, ITGBL1, PLLP, and SCG5. The XGBoost model (AUC-ROC=0.982) highlighted ITGBL1 as a key gene via SHAP analysis. Survival analysis showed high ITGBL1 expression correlated with reduced overall survival in LUSC patients (p=0.0014) but not in IPF cases. GSEA linked high ITGBL1 to cell cycle and proliferation pathways. Immune infiltration analysis revealed positive associations between ITGBL1 and naïve B cells/M1 macrophages in IPF (p<0.05). Single-cell data confirmed ITGBL1 overexpression in smooth muscle cells of IPF-LUSC tumor samples.

Conclusions: High ITGBL1 expression in IPF-LUSC patients may serve as a critical risk factor for malignancy. This finding could refine lung transplant recipient selection and enable perioperative interventions to improve long-term outcomes.



A



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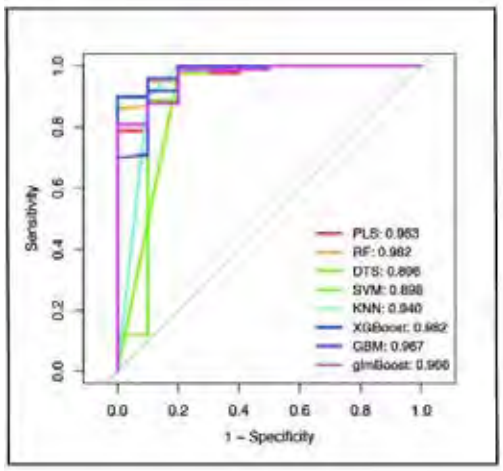

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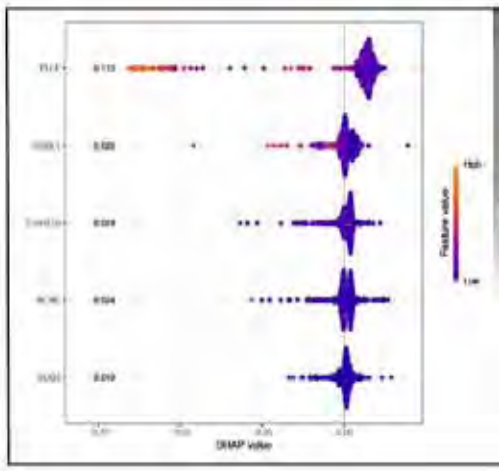

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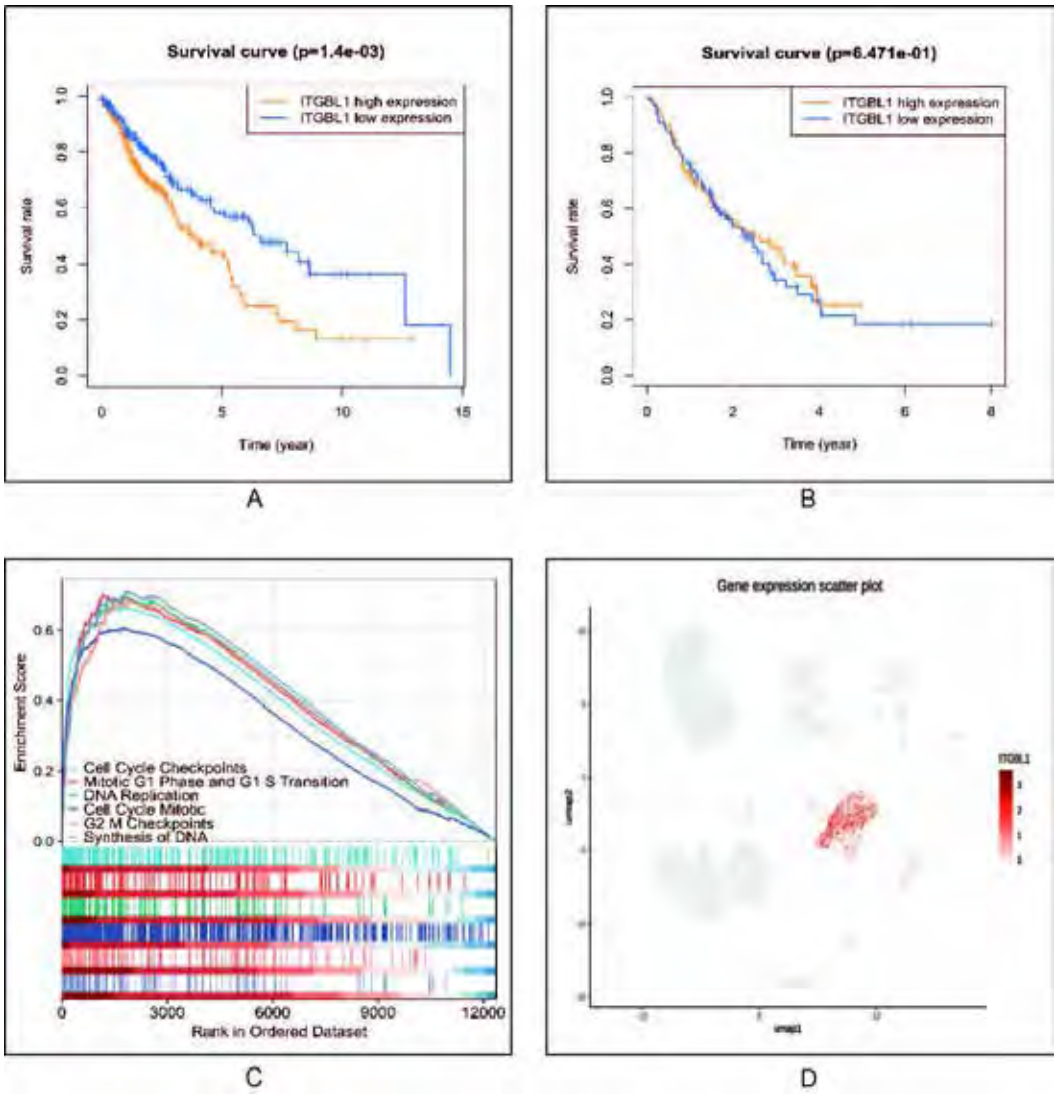

Keywords: ITGBL1, Idiopathic pulmonary fibrosis, Lung squamous cell carcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.31 Translational Analysis of NSD3 Gene Amplification in Lung Squamous Cell Carcinoma: Clinical Impact and Prognostic Insights From Histopathology

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Introduction: Nuclear receptor-binding SET domain 3 (NSD3), a histone H3 lysine 36 methyltransferase, has been implicated as a driver of lung squamous cell carcinoma (LUSC) in preclinical studies. However, the clinicopathological characteristics and prognostic significance of NSD3 amplification in LUSC remain unclear. To address this, we performed histopathological analysis of patient tissue samples.

Methods: The NSD3 gene copy number was evaluated using fluorescence in situ hybridization in 268 surgically resected LUSC cases, categorized into the amplification (Amp) and diploidy (Diploidy) groups. Clinicopathological characteristics were compared, and artificial intelligence-based image analysis was used to investigate the correlation between NSD3 amplification and protein expression, cancer cell proliferation, and tumor-infiltrating lymphocytes through immunohistochemistry.

Results: NSD3 amplification was detected in 106 (39.6%) patients. NSD3 protein expression was positively correlated with the NSD3 gene copy number ($R = 0.528$, $P < 0.001$). The Amp group exhibited higher mitotic counts ($P = 0.004$) and MIB-1 labeling index ($P = 0.009$) than the Diploidy group. No significant differences in the numbers of CD8-, Forkhead box P3-, or CD20-positive tumor-infiltrating lymphocytes were observed between the two groups. The Amp group had shorter overall survival than the Diploidy group ($P = 0.030$), and multivariable analysis revealed that NSD3 amplification is an independent poor prognostic factor ($P = 0.049$).

Conclusions: Our study highlights the clinical relevance of NSD3 amplification in LUSC using patient tissue analyses. These findings emphasize the potential of NSD3 as a prognostic biomarker and therapeutic target, bridging the gap between preclinical research and clinical application.

Keywords: Nuclear receptor-binding SET domain 3 (NSD3), Lung squamous cell carcinoma, Potential therapeutic target

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.32 Impact of piR_004530 Reactivation in Lung Cancer: Implications for Recurrence and Survival of Lung Squamous Cell Carcinoma Patients

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Introduction: PIWI-interacting RNAs (piRNAs) are germline-characteristic small non-coding RNAs whose reactivation has been recently observed during carcinogenesis as a consequence of the germline reactivation program, which can be considered a hallmark of cancer. We have evaluated the prognostic impact of piR_004530 reactivation in non-small cell lung cancer (NSCLC) patients and studied its functional role in cell lines and organoid models.

Methods: A total of 243 NSCLC resected patients were analyzed. PiR_004530 expression was quantified in tumor (n=243) and normal tissue (n=31) using qRT-PCR. Tumor recurrence after surgery, disease-free survival (DFS), and overall survival (OS) were used as clinical endpoints in survival analysis. Cox regression models were generated and decision curve analysis for assessment of clinical benefit on disease prognosis was used. The effect of piR_004530 overexpression was assessed in squamous cell carcinoma (SCC) cell lines by cell migration, invasion, proliferation, apoptosis, and colony formation analysis. Patient-derived organoids from SCC patients were generated and cell viability was evaluated after piRNA overexpression.

Results: PiR_004530 became reactivated on the tumor compared to normal tissue and was overexpressed in SCC patients. The prognosis analysis in the whole cohort showed that patients with high levels of piR_004530 had shorter DFS and OS. However, the subanalysis by histology revealed that the true prognostic impact of piR_004530 was specifically on SCC patients. SCC patients with high piR_004530 had a higher relapse rate and shorter DFS and OS. piR_004530 emerged as an independent prognostic factor in the multivariate analysis. Since the SCC patients that received adjuvant treatment had the best post-surgical prognosis, we focused on the role of piR_004530 on non-treated patients, which allowed us to identify a high-risk group where the piRNA ameliorated patient's risk stratification, highlighting superior clinical benefit in postsurgical relapse prediction. piR_004530 overexpression was associated with increased migration, invasion, and proliferation, while apoptosis was inhibited in SCC cell lines. Moreover, the overexpression induced stem cell gene activation. In patient-derived organoids, the overexpression boosted organoid cell viability.

Conclusions: PiR_004530 became reactivated in NSCLC where it played a role as an oncogene and its higher levels correlated with disease recurrence and shorter survival in SCC patients.

Keywords: Lung Squamous Cell Carcinoma, PIWI-interacting RNAs, Recurrence

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.33 Prognostic Significance and Therapeutic Potential of LILRB4 in Mdsc-Mediated Immunosuppression in NSCLC

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Introduction: Recently, a pro-tumor role of immunosuppressive MDSCs (myeloid-derived suppressor cells) is, at least partly, attributed to the presence of leukocyte Immunoglobulin-like receptor B4 (LILRB4/ILT3 in humans and its murine ortholog, gp49B) which are expressed on MDSCs, and some recent pieces of literature report that B4 is associated with cancer progression and prognosis. Previously, we investigated the mechanism by which B4 expressed on MDSCs promotes cancer progression in a mouse model and reported that inhibition of the B4 immune checkpoint suppresses metastasis (Su MT, Kumata S, et al. Oncoimmunology. 2022;11:2060907). However, no studies were examined the significance of the B4 immune checkpoint in non-small cell lung cancer (NSCLC) patients.

Methods: A retrospective study was conducted on 239 patients who underwent curative lung resection for NSCLC between 2011 and 2017. B4 expression levels in tumor-infiltrating stromal cells were assessed by immunohistochemistry and scored. The relationship between B4 expression and clinicopathological factors, as well as prognosis, was analyzed retrospectively. Whether the blocking of B4 on human PBMC-derived CD33+ MDSCs inhibited the migration ability of lung cancer cells was also examined using transwell migration assay.

Results: The median age of the patients was 70 years (range: 41-86 years), and 85 (35.6%) were female. The predominant histological type was adenocarcinoma (142 cases, 59.4%). High: B4 expression was observed in 75 patients (31.4%), including 26 (34.7%) with adenocarcinoma. The median follow-up period was 69.5 months (range: 1.7-119.6 months). Patients with high B4 expression had significantly shorter overall survival (OS) and recurrence-free survival (RFS) ($p = 0.013$ and $p < 0.005$, respectively). Multivariate analysis identified high B4 expression as an independent prognostic factor for poor OS and RFS ($p = 0.04$ and $p < 0.005$, respectively). Even in the cohort background aligned by propensity score matching, OS ($p = 0.023$) and RFS ($p = 0.0046$) in the B4 high group were shorter than in the B4 low group. Some of the B4 positive cells were positive for MDSC markers, CD33 and CD14. Transwell migration assay demonstrated that blocking B4 significantly inhibited the migration of human lung cancer cells cocultured with CD33+ MDSCs.

Conclusions: The results suggested that B4/gp49B participates in MDSC-mediated immunosuppression in the tumor microenvironment and that the targeting of B4 could be a novel strategy to improve immune checkpoint therapy.

Keywords: LILRB4, Immune Checkpoint Inhibitor, NSCLC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.34 Tumor Heterogeneity Based Prognostic Score: What the Specimen Tells Us in the Intelligent Era?

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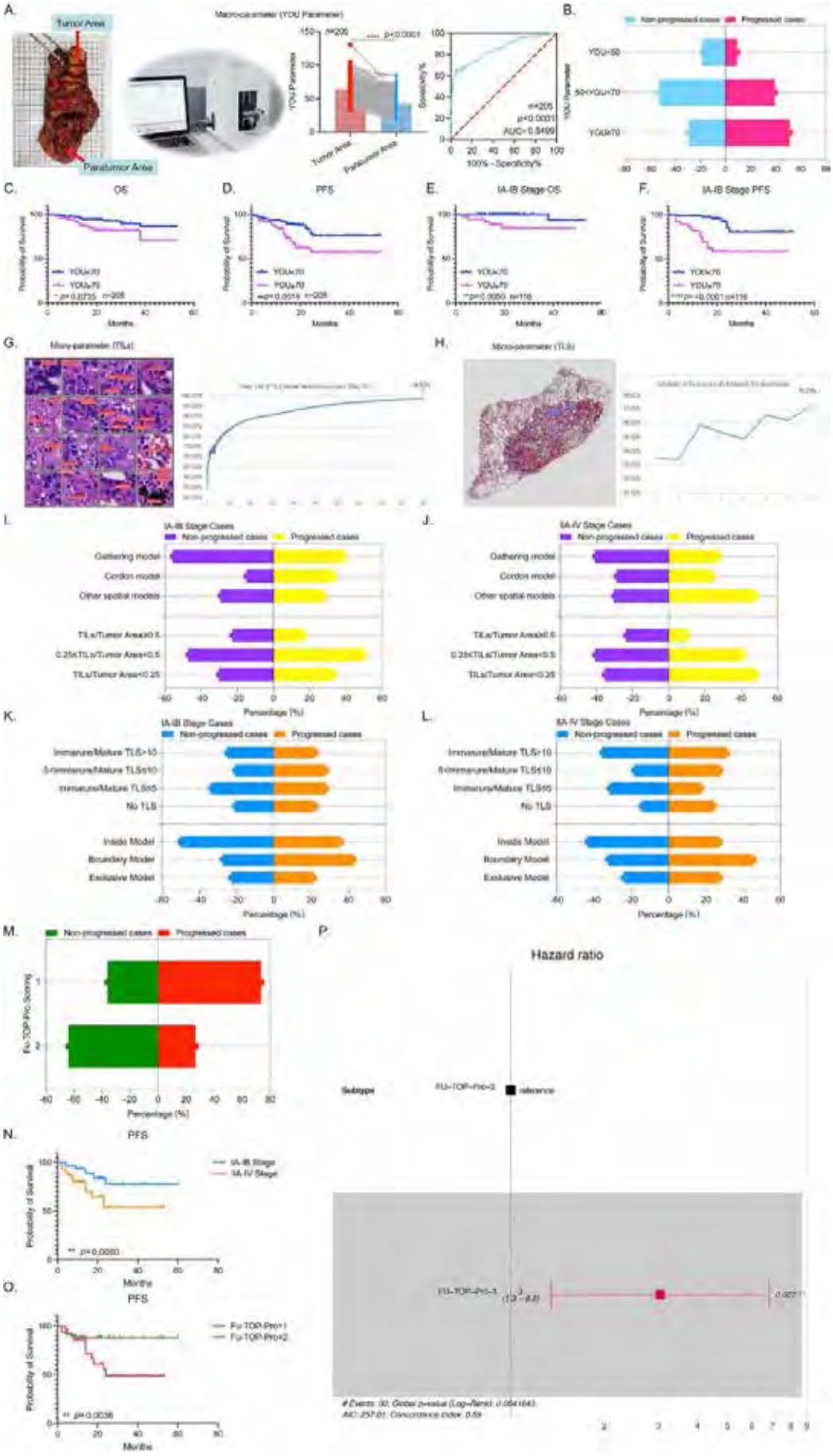
Introduction: Tumor heterogeneity plays key role in regulating tumor recurrence and therapy resistance. Especially microenvironmental heterogeneity is clearly suggestive of recurrence and death risk. Further studies are needed to determine whether tumor heterogeneity-based score can predict prognosis and guide future treatment strategies.

Methods: To investigate the relationship between prognostic outcome and tumor heterogeneity-based score, a total of 205 non-small cell lung cancers (NSCLCs) are collected. First, the specimen is measured and recorded as a novel macro-parameter (YOU parameter, optimal from Young modulus). Then we build an optimized AI model for micro-parameters detection, including tumor-infiltrating lymphocytes (TILs) and tertiary lymphoid structure (TLS). The percentage of TILs/tumor area is scored as 1 point (<0.25), 2 points (≥0.25 and <0.5) and 3 points (≥0.5). Cordon model between TILs and tumor is marked as 1 point. Intra-tumor gathering model is marked as 2 points. Other spatial models are marked as 0. Besides, no TLS, immature TLS and mature TLS are marked as 0, 1, 2 separately. The TLS number/10HPF is identified as 0 (1-5), 1 point (6-10) and 2 points (>10). The spatial construction model is defined as the inside model (inside tumor area=2), boundary model (0.785mm2 area centered on the tumor border =1), and exclusive model (outside tumor area=0). Finally, the multi-dimensionality Fu-TOP-Pro scoring is built to predicate recurrence risk post-operation. This Fu-TOP-Pro scoring consists of the macro-parameter (YOU parameter) and micro-parameters (TILs+TLS).

Results: Differences in tumor composition result in different macro-parameter (YOU parameter) values. Obviously, YOU parameter performs well in distinguishing tumor and non-neoplastic adjacent tissues. It shows a dramatically high level in tumor (A). Progressed cases tend to have higher YOU parameter, especially in early stage cases (B-F). Besides, for micro-parameters, AI-based reorganization accuracy of TILs and TLS reach 98.53% and 97.23% respectively (G and H). Both gathering model and cordon model of TILs, and inside model of TLS are positively related to good prognosis (I-L). Finally, the Fu-TOP-Pro scoring model performs better in PFS prediction compared to TNM stage (M-O). Fu-TOP-Pro score is an independent prognostic factor (P, Fu-TOP-Pro=1, HR=3, p=0.007).

Conclusions: To sum up, the findings of both macro- and micro-parameters are of great significance to identify the post-operation recurrence risk. It provides new ideas and AI views for prognosis prediction, indicating the potential of broad application prospects.



Keywords: NSCLC pathohistological heterogeneity, prognostic score (Fu-TOP-Pro scoring), YOU parameter and AI

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.35 Extracellular Vesicle RNA Diversity in Lung Adenocarcinoma: Driving Immunosuppression and Metastasis

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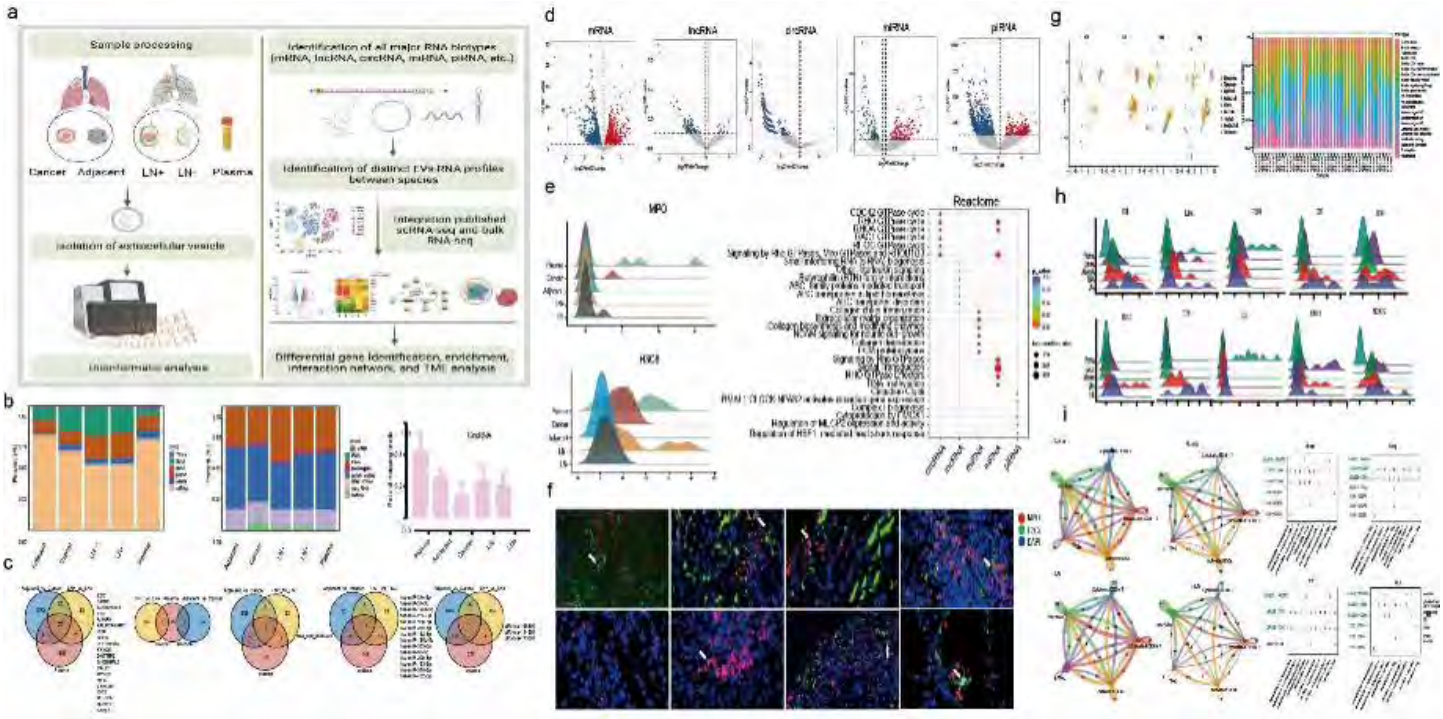
[1]The Affiliated Qingyuan Hospital of Guangzhou Medical University, Qingyuan/CN ,[2]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN

Introduction: Lung adenocarcinoma (LUAD), the predominant subtype of non-small cell lung cancer (NSCLC), utilizes lymph node involvement as a key prognostic determinant. Although tumor-draining lymph nodes (TDLNs) coordinate antitumor immunity, the spatial heterogeneity of extracellular vesicle (EV) RNA profiles across primary tumors, TDLNs, and systemic circulation remains undefined. This study investigates EV RNA dynamics to elucidate their roles in establishing immunosuppressive niches.

Methods: We conducted multi-tissue EV RNA profiling of primary tumors, TDLNs (node-positive: TDLN+), and plasma from LUAD patients. Integrated bioinformatics analyses characterized RNA diversity, functional pathways, and immune-stromal crosstalk.

Results: Primary tumor-derived EVs (Ti-EVs) preferentially retained long non-coding RNAs (lncRNAs) and transfer RNAs (tRNAs) within the tumor microenvironment (TME), whereas plasma EVs displayed distinct mRNA and miRNA profiles. Functionally, primary Ti-EVs promoted neutrophil extracellular trap (NET) formation and systemic dissemination, while TDLN+ Ti-EVs activated insulin-like growth factor (IGF) signaling. Both primary and metastatic niches exhibited stromal-epithelial-myeloid enrichment but lacked immune infiltration. Strikingly, EV-mediated LGALS9-HAVCR2 signaling in TDLN+ engaged activated dendritic cells (aDCs), monocyte-derived macrophages (mo-Macs), and exhausted CD8+ T cells, establishing a potent immunosuppressive axis.

Conclusions: Our study uncovers EV RNA heterogeneity as a driver of multidimensional immunosuppressive TME in LUAD. Conserved lncRNA/tRNA signatures in Ti-EVs and plasma EVs highlight their potential as liquid biopsy biomarkers. Therapeutic targeting of the LGALS9-HAVCR2 axis may disrupt immunosuppressive signaling in nodal metastases, offering clinical translation opportunities. These findings illuminate EV-mediated intercompartmental crosstalk in cancer progression.



Keywords: tumor tissue-derived extracellular vesicles, tumor-draining lymph nodes, lung adenocarcinoma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.36 Proteomic Atlas Reveals Organ-Specific Metabolic and Functional Shifts in Preclinical Icb-Related Pneumonitis and Colitis

Z-X. Rong, Z-N. Wu, X-T. Cai, K-M. Zhuang, Z-P. Xu, H-T. Qu, Y-P. Zhang, Z-Y. Dong
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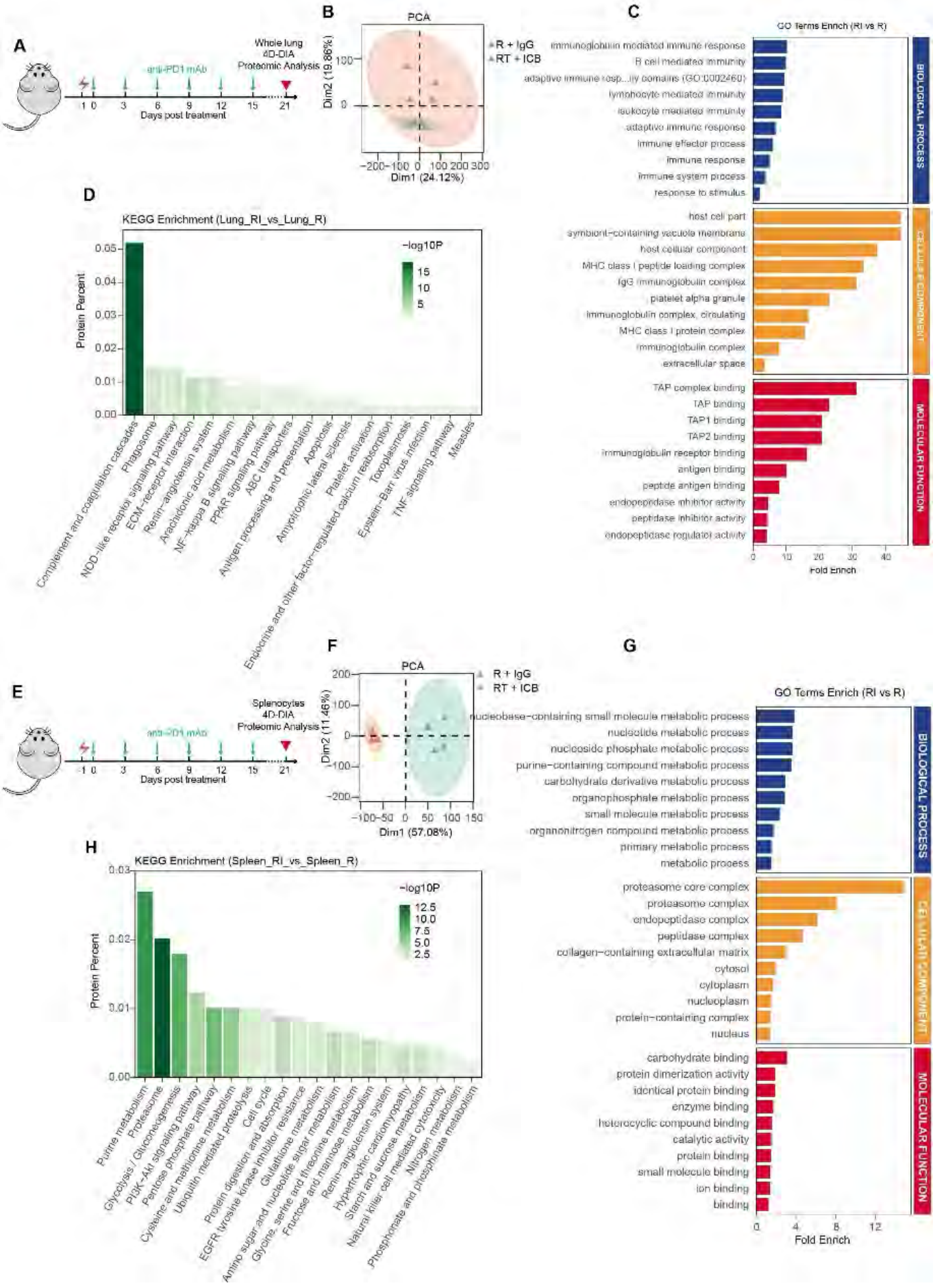
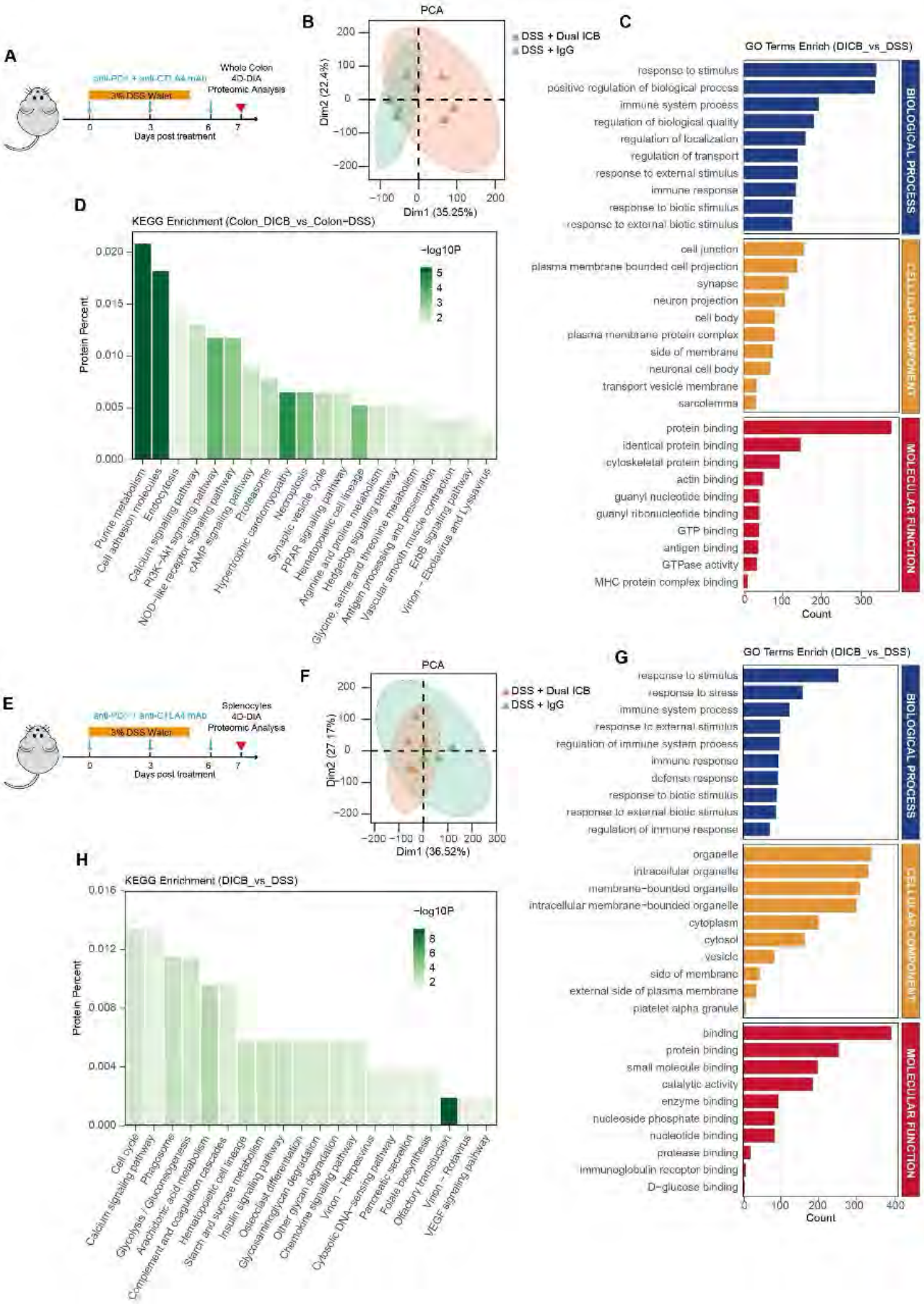
Introduction: Immune checkpoint blockade (ICB)-associated colitis and pneumonitis are clinically significant immune-related adverse events (irAEs), yet insights in their systemic and tissue-specific proteomic alterations remain unclear.

Methods: We performed label-free 4D-DIA proteomic analysis on colon, lung, and splenocytes from murine models of radiation-induced pneumonitis (radiation ± ICB) and DSS-induced colitis (DSS ± ICB). Gene Ontology (GO) and KEGG enrichment analyses were used to identify altered pathways.

Results: In pneumonitis, lung tissues exhibited adaptive immune activation, dysregulated complement/coagulation cascades, and enhanced intracellular pathogen processing (symbiont-containing vacuole membrane and TAP binding). Spleens showed systemic metabolic reprogramming with upregulated nucleoside, carbohydrate, and cysteine/methionine metabolism. In colitis, inflamed colons displayed neuron-epithelial alterations (synapse, neuron-projection, and cell adhesion) concurrent with immune activation, while spleens exhibited enriched carbohydrate and arachidonic acid metabolism.

Conclusions: This study maps organ-specific proteomic landscapes of irAEs, highlighting systemic metabolic rewiring and functional alterations of local proteins. These findings underscore the tissue-specific nature of irAE pathogenesis and potential therapeutic targets.


A
anti-PD1 mAb
Whole lung
4D-DIA
Proteomic Analysis
1 0 3 6 9 12 15 21
Days post treatment
B
PCA
R + IgG
RT + ICB
Dim2 (19.86%)
Dim1 (24.12%)
C
GO Terms Enrich (RI vs R)
immunoglobulin mediated immune response
B cell mediated immunity
adaptive immune resp...ity comains (GO:0002460)
lymphocyte mediated immunity
leukocyte mediated immunity
adaptive immune response
immune effector process
immune response
immune system process
response to stimulus
BIOLOGICAL PROCESS
host cell part
symbiont-containing vacuole membrane
host cellular component
MHC class I peptide loading complex
IgG immunoglobulin complex
platelet alpha granule
immunoglobulin complex, circulating
MHC class I protein complex
immunoglobulin complex
extracellular space
CELLULAR COMPONENT
TAP complex binding
TAP binding
TAP1 binding
TAP2 binding
immunoglobulin receptor binding
antigen binding
peptide antigen binding
endopeptidase inhibitor activity
peptidase inhibitor activity
endopeptidase regulator activity
MOLECULAR FUNCTION
Fold Enrich
D
KEGG Enrichment (Lung_RI_vs_Lung_R)
Protein Percent
-log10P
Complement and coagulation cascades
Phagosome
NOD-like receptor signaling pathway
ECM-receptor interaction
Renin-angiotensin system
Arachidonic acid metabolism
NF-kappa B signaling pathway
PPAR signaling pathway
ABC transporters
Antigen processing and presentation
Apoptosis
Amyotrophic lateral sclerosis
Platelet activation
Endocrine and other factor-regulated calcium reabsorption
Toxoplasmosis
Epstein-Barr virus infection
TNF signaling pathway
Measles
E
anti-PD1 mAb
Splenocytes
4D-DIA
Proteomic Analysis
1 0 3 6 9 12 15 21
Days post treatment
F
PCA
R + IgG
RT + ICB
Dim2 (11.46%)
Dim1 (57.08%)
G
GO Terms Enrich (RI vs R)
nucleobase-containing small molecule metabolic process
nucleotide metabolic process
nucleoside phosphate metabolic process
purine-containing compound metabolic process
carbohydrate derivative metabolic process
organophosphate metabolic process
small molecule metabolic process
organonitrogen compound metabolic process
primary metabolic process
metabolic process
BIOLOGICAL PROCESS
proteasome core complex
proteasome complex
endopeptidase complex
peptidase complex
collagen-containing extracellular matrix
cytosol
cytoplasm
nucleoplasm
protein-containing complex
nucleus
CELLULAR COMPONENT
carbohydrate binding
protein dimerization activity
identical protein binding
enzyme binding
heterocyclic compound binding
catalytic activity
protein binding
small molecule binding
ion binding
binding
MOLECULAR FUNCTION
Fold Enrich
H
KEGG Enrichment (Spleen_RI_vs_Spleen_R)
Protein Percent
-log10P
Purine metabolism
Proteasome
Glycolysis / Gluconeogenesis
PI3K-Akt signaling pathway
Pentose phosphate pathway
Cysteine and methionine metabolism
Ubiquitin mediated proteolysis
Cell cycle
Protein digestion and absorption
Glutathione metabolism
EGFR tyrosine kinase inhibitor resistance
Amino sugar and nucleotide sugar metabolism
Glycine, serine and threonine metabolism
Fructose and mannose metabolism
Renin-angiotensin system
Hypertrophic cardiomyopathy
Starch and sucrose metabolism
Natural killer cell mediated cytotoxicity
Nitrogen metabolism
Phosphonate and phosphinate metabolism



Keywords: irAE, Proteomic Atlas, Metabolism

P2.06.37 NGS Testing in Lung Cancer Within the Catalan Precision Oncology Program: The ICO-HUB Comprehensive Cancer Center Experience

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Introduction: NGS testing is essential for the clinical management of patients with NSCLC, and equitable access to molecular diagnosis, especially NGS, should be ensured. In Catalonia, the public payer (CatSalut) launched the Precision Oncology Program (POP) to cover NGS testing costs for adult patients diagnosed with stage IB-IV non-squamous NSCLC or squamous NSCLC if younger than 50y or those with low tobacco exposure.

Methods: This observational study aimed to capture the clinicopathological and molecular characteristics of patients with NSCLC who participated in the POP within our campus. Molecular testing was conducted at the Molecular Core of the Bellvitge Universitary Hospital (HUB) and the Catalan Institute of Oncology (ICO), covering a large population area and collaborating with eight affiliated regional hospitals. Patients were eligible if they underwent a single NGS test to identify actionable genomic alterations. All cases were discussed in a multidisciplinary tumor board.

Results: 1653 patients were registered who participated in the POP from February 2020 to March 2025. Two sequencing platforms were used: Trusight Oncology 500 (TSO500) in 299 patients (18.1%) and Oncomine Precision Assay (OPA) in 1354 patients (81.9%). Median age was 67 years and most patients were males (66.1%), ECOG PS 0-1 (66.5%) and had stage IV disease (61%). Most patients were current or former smokers (84.1%). The most frequent histology was lung adenocarcinoma (74.5%), followed by squamous (7.2%). The median tumor cell infiltration was 40% (range, 5-100%) and NGS was not informative only in 37 cases (2.2%). The following drivers were detected in the whole cohort: KRAS mutations 526 (31.8%), being G12C 217 (13.1%); EGFR mutations 192 (11.6%), including exon 19 deletions in 97 (5.9%), L858R in 57 (3.4%) and other mutations 38 (2.3%); BRAF mutations 77 (4.7%), being V600E 24 (1.5%); ALK fusions 33 (2.0%); ERBB2 mutations 33 (1.9%); MET exon 14 skipping mutations 28 (1.7%); ROS1 fusions 14 (0.8%), RET fusions 8 (0.5%), NTRK fusions (0.06%). Actionable drivers were detected in 550 patients (33.3%) and were more frequently observed in patients with non-squamous histology (35.1%) compared with those with squamous cell carcinoma (9.3%). More information on clinical outcomes will be presented at the conference.

Conclusions: NGS testing is feasible in a public health system to enable equitable access to treatment. The frequency of actionable driver alterations is consistent with the known prevalence in Europe. The POP of Catalonia allowed the identification of patients to receive targeted therapy within the ICO-HUB network.

Table 1. Frequency of actionable driver alterations according to histology

Actionable genomic alterations	Non squamous NSCLC (n=1534)	Squamous NSCLC (n=119)
KRAS G12C	213 (13.9%)	4 (3.4%)
EGFR	187 (12.2%)	5 (4.2%)
ALK fusions	33 (2.2%)	0 (0.0%)
ERBB2 mutations	32 (2.1%)	1 (0.8%)
MET ex14 mutations	27 (1.8%)	1 (0.8%)
BRAF V600E	24 (1.6%)	0 (0.0%)
ROS1 fusions	14 (0.9%)	0 (0.0%)
RET fusions	8 (0.5%)	0 (0.0%)
NTRK fusion	1 (0.06%)	0 (0.0%)

Keywords: NGS, NSCLC, targeted therapy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.38 BTN1A1 and Nuclear YAP1 Co-Expression as Predictive Biomarkers for Nelmastobart Efficacy in Lung Cancer: Findings From a Phase 1 Trial

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Introduction: Butyrophilin 1A1 (BTN1A1) is a novel immune checkpoint protein expressed in various human tumors and immune cells. It has been shown to be co-expressed with Yes-associated protein 1 (YAP1), a central effector of the Hippo signaling pathway that translocates to the nucleus under stress conditions. The co-expression of BTN1A1 and nuclear YAP1 is thought to promote tumor growth, immune evasion, and chemoresistance. High levels of BTN1A1 and nuclear YAP1 expression have been observed in lung cancer, highlighting their potential as therapeutic targets. Recently, a first-in-human Phase 1 clinical trial of Nelmastobart, a BTN1A1-targeting antibody, was completed. This study compared immunohistochemical profiles and tumor microenvironment characteristics between responders and non-responders to Nelmastobart in a cohort of patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The goal was to inform the design of future clinical trials based on BTN1A1 and YAP1 expression and CD8+ T cell infiltration.

Methods: Tissue samples from four lung cancer patients (three SCLC and one NSCLC) were analyzed to evaluate BTN1A1 expression and tumor microenvironment features. A non-small cell lung cancer tissue microarray (TMA) was included for broader comparative analysis. Multiplex immunofluorescence staining was performed using the Akoya OPAL 6-color system, with a panel including BTN1A1, PD-L1, CD8, Ki-67, PanCK, and YAP1. Slides were scanned using the Akoya PhenoImager HT 2.0, and image analysis was conducted using QuPath and R.

Results: Analysis of the NSCLC TMA revealed BTN1A1 expression in approximately 60% of cases. Co-expression analyses showed that tissues with strong BTN1A1 expression had a higher proportion of cells co-expressing nuclear YAP1 (8-12%), while co-expression with PD-L1 was rarely observed. Treatment with Nelmastobart was well-tolerated, with the most common adverse events being low-grade fatigue and infusion-related reactions. Among enrolled SCLC and NSCLC patients, those with high nuclear YAP1 expression and BTN1A1 positivity in baseline tissue achieved stable disease (SD). Notably, patients with high nuclear YAP1 expression demonstrated improved progression-free survival compared to those with low YAP1 expression.

Conclusions: Preliminary results from the TMA analysis and Phase 1 trial suggest that targeting BTN1A1 with Nelmastobart is safe and shows early signs of clinical activity in lung cancer, particularly among patients with high nuclear YAP1 expression. These findings support further investigation in larger, biomarker-enriched clinical trials to validate BTN1A1 and YAP1 as predictive biomarkers and confirm the therapeutic efficacy of Nelmastobart in lung cancer.

Keywords: BTN1A1, YAP1, Nelmastobart

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.39 Predicting Relapse and TKI Response Using DNA and RNA EGFR VAF in EGFR-Mutant Lung Adenocarcinoma

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Introduction: Driver mutations in the epidermal growth factor receptor (EGFR) gene are highly prevalent in non-smoking lung adenocarcinoma (LUAD) patients, particularly in Asian populations; however, their impact on relapse-free survival (RFS) remains controversial. While some studies associate EGFR mutations with a better prognosis, others report no significant difference or even worse outcomes, suggesting that a binary classification of EGFR genotype may be insufficient for patient stratification. Emerging evidence highlights the role of EGFR variant allele fraction (VAF) in predicting tyrosine kinase inhibitor (TKI) efficacy in advanced LUAD, yet its relevance for prognosis or TKI response in early-stage disease remains unexplored. Moreover, previous studies have exclusively relied on DNA VAF, overlooking potential insights from RNA VAF, which may reflect allele-specific expression or other transcriptional influences. In this study, we aim to analyze both DNA and RNA VAF in resected LUAD patients to evaluate their prognostic value for relapse risk and TKI response. This study marks the first investigation of RNA VAF as a clinical biomarker in this context.

Methods: We analyzed 133 untreated stage I-III EGFR-mutant LUAD patients for relapse-free survival (RFS). Additionally, we evaluated progression-free survival (PFS) under TKI treatment in a subset of 48 patients. Whole-exome sequencing data from tumor and adjacent normal tissue (NAT) were used for somatic variant calling, and these data were integrated with tumor RNA sequencing to estimate mutant and wild-type gene expression using a newly developed bioinformatic pipeline. Cox proportional hazards models were applied to calculate hazard ratios (HR) adjusted for clinical variables (sex, age, smoking status, and pathological stage) and molecular profiles (EGFR mutation types, and TP53 genotype).

Results: Both DNA and RNA EGFR VAFs significantly stratified patients' RFS (log-rank tests, $p < 0.0001$), but they identified distinct high- and low-risk subsets. Integrating both models resulted in a three-tier risk group classification with significant adjusted hazard ratios (adj. HR [95% CI]: mid-risk, 3.03 [1.15-7.99]; high-risk, 4.42 [1.56-12.54], compared to low-risk). EGFR-wildtype patients exhibited an intermediate risk (2.03 [0.6-6.89]), underscoring the heterogeneity of EGFR-mutant LUAD. Our model also identified high-risk stage I patients who may require more urgent intervention ($p = 0.0021$). In TKI-treated patients, those who relapsed prior to therapy exhibited the same PFS trend as observed in RFS ($p = 0.047$), whereas non-relapsed patients showed an inverse trend.

Conclusions: These findings highlight the clinical relevance of VAFs beyond EGFR genotype alone and emphasize the importance of evaluating both DNA and RNA VAFs to enable more precise and informed TKI treatment decisions.

Keywords: epidermal growth factor receptor (EGFR), variant allele fraction (VAF), tyrosine kinase inhibitor (TKI)

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.40 Integrated Molecular Analysis of Advanced NSCLC Depicts Molecular Signatures Associated With Tyrosine Kinase Inhibitors Efficacy

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Introduction: Tyrosine kinase inhibitors (TKI) are the mainstay of treatment for advanced oncogene addicted non-small cell lung cancer (NSCLC). However, resistance to TKI invariably occurs during treatment course but data on drug resistance-related mechanisms are largely missing. Therefore, we designed a retrospective study to deeply characterize the genomic and epigenetic signatures associated with TKI response in epidermal growth factor receptor mutation positive (EGFR+) and anaplastic lymphoma kinase rearranged (ALK+) advanced NSCLC patients.

Methods: Samples from patients with advanced NSCLC treated with first-line next-generation TKIs (osimertinib or alectinib) were analyzed for genomic profiling using the Oncomine Comprehensive Assay Plus (ThermoFisher Scientific) panel. Cases were also analyzed using a PCR-based global miRNome assay (miRCURY LNA miRNA PCR kit, Quiagen). Potential targets of significantly deregulated microRNA and their biological functions were predicted by STRING and MirDIP softwares. Clinical characteristics including best response to treatment and progression-free survival (PFS) to 1st line TKI were collected. An exploratory analysis of subgroups of short-term responders (STR) and long-term responders (LTR) was also performed.

Results: Genomic profile was performed in 60 samples (44 EGFR+, 16 ALK+), while miRNome analysis in 52 cases (46 in overlap with NGS testing, 36 EGFR+ and 16 ALK+) (table 1). After a median follow-up for PFS of 14 months (range 4-52), univariate analysis of EGFR+ cases showed significantly shorter PFS in those harboring TP53 co-mutations (HR 3.63, 95% CI 1.55-8.49, p=0.0029) and gain in Chr7p (no gain vs gain: HR 0.36, 95% CI 0.15-0.86, p=0.029). In ALK+ cases a significantly shorter PFS was observed in cases with HLA A gene loss (HR 45.26, 95% CI 3.44-545.2, p=0.004) and those without RMS gains (HR 6.97, 95% 1.27-38.11, p=0.025). MicroRNA profiling clustered both EGFR+ and ALK+ cases into 3 main clusters without significant association with treatment responses. However, LTR and STR showed significant deregulation of a set of microRNA. In EGFR+, the most differentially regulated miRNAs were miR-423-3p, miR-744-5p and miR-455-3p, with a main predicted interference of the transforming growth factor-β pathway, whereas in ALK+ cases immune-related chemokine pathway was deregulated through the modulation of miR-135a-5p, miR-331-3p and miR-196a-5p.

Conclusions: The present data suggest the potential role of extended molecular testing to predict benefit of first-line next-generation TKIs in EGFR+ and ALK+ advanced NSCLC. Data from larger populations are warranted to confirm these preliminary findings.

Table 1 Clinical characteristics of patients

	EGFR+ (n: 44)	ALK+ (n:16)
Median age at diagnosis (range)	72 (35-91)	57(43-83)
Sex (male vs female)	15(34.1%) vs 29(65.9%)	9(56.2%) vs 7(43.8%)
Smoking habits (never vs former vs current)	28(63.6%) vs 11(25%) vs 5(11.4%)	7(43.8%) vs 7(43.8%) vs 2(12.4%)
EGFR mutation subtype (ex19 del vs ex21 L858R vs others) / ALK rearrangement partner (EML4 vs others)	22(50%) vs 21(47.7%) vs 1 (2.3%)	14(87.6%) vs 2(12.4%)
TP53 co-mutation (yes vs no)	26(59.1%) vs 18(40.9%)	13(81.2%%) vs 3(18.8%)
Best response to treatment (CR vs PR vs SD vs PD vs NE)	1(2.3%) vs 30(68.1%) vs 11(25%) vs 1(2.3%) vs 1 (2.3%)	0(0%) vs 13(81.2%) vs 2(12.5%) vs 0(0%) vs 1(6.3%)

EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ex19 del: exon 19 deletion; ex21 L858R: exon 21 L858R point mutation; EML4: EMAP Like 4; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE; not evaluable.

Keywords: Resistance mechanisms, miRNA, Oncogene addicted NSCLC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.41 Real-World Data and Utility of Newly Proposed Grading System From IASLC for Invasive Lung Adenocarcinoma in Japan

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Introduction: The IASLC has proposed a new pathological grading system for lung adenocarcinoma. In this classification, tumors primarily showing lepidic growth with less than 20% high-grade components are grade 1; tumors predominantly acinar or papillary with less than 20% high-grade components are grade 2; and tumors with ≥20% high-grade components are grade 3. However, limited data are available on its clinical utility.

Methods: To evaluate the utility of the new IASLC grading system in surgically treated lung adenocarcinoma cases in Japan. We retrospectively reviewed 2,266 lung adenocarcinoma cases, surgically resected with complete (R0) resection and EGFR testing from January 2015 to December 2018 across 21 institutions. Tumors were graded into grades 1-3 using both the previous predominant pattern grading system (old classification) and the new IASLC grading system (new classification), and clinicopathological features were compared.

Results: Using the old classification, 686 cases were grade 1, 1,259 grade 2, and 321 grade 3. The new classification identified 678 grade 1, 1,028 grade 2, and 560 grade 3 cases, showing a decreased proportion of grade 2 and increased proportion of grade 3. Survival analysis revealed clear stratification between grade 2 and grade 3 cases, particularly in stage I disease ($p<0.001$). The proportion of EGFR mutations in the new classification decreased with increasing grade, 55.5%/49.3%/27.7% for grade1/2/3, respectively.Among pN0M0 cases, grade 3 tumors classified as pT1mi-1b had survival outcomes comparable to pT1c, while grade 3 tumors classified as pT2 showed survival similar to pT3 tumors.

Conclusions: The new IASLC grading system effectively stratifies tumors previously classified as grade 2 into distinct prognostic groups. Grade 3 tumors identified in early-stage lung adenocarcinoma under the new system may warrant an upgrade in T classification.

Keywords: IASLC Grading System, Adenocarcinoma, Real-World Data

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.42 NSD3 Overexpression Predicts Prognosis and Immune Cell Infiltration Patterns in Lung Squamous Cell Carcinoma: A Bioinformatics Analysis

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Introduction: Nuclear receptor-binding SET domain protein 3 (NSD3) is a histone methyltransferase involved in chromatin remodeling and gene transcription regulation, with dysregulated expression reported in various malignancies. This study aimed to investigate the expression of NSD3 in lung squamous cell carcinoma (LUSC) using bioinformatics approaches and to explore its association with clinicopathological features, immune cell infiltration, and patient survival outcomes.

Methods: Expression levels of NSD3 in LUSC and adjacent normal tissues were analyzed using TCGA and GTEx data via the GEPIA2 platform. Kaplan-Meier survival analysis was performed to evaluate the prognostic significance of NSD3 expression. The UALCAN platform was used to assess correlations between NSD3 expression and clinicopathological parameters, including patient age, tumor stage, histological subtype, and TP53 mutation status. Associations between NSD3 expression and chemokines, chemokine receptors, immune subtypes, and molecular subtypes were evaluated using TISIDB. The relationship between NSD3 expression and immune cell infiltration, as well as its prognostic implications, was further explored using TIMER2.0.

Results: NSD3 expression was significantly upregulated in LUSC tumor tissues compared to adjacent normal tissues. High NSD3 expression was associated with favorable survival outcomes, including overall survival (HR = 0.6699, p = 0.007), disease-specific survival (HR = 0.648, p = 0.045), progression-free survival (HR = 0.678, p = 0.004), and progression-free interval (HR = 0.680, p = 0.028). NSD3 expression positively correlated with $CD4^+$ T cell infiltration ($\rho = 0.153$, $p < 0.001$), and negatively with $CD8^+$ T cells ($\rho = -0.108$, $p < 0.05$) and myeloid dendritic cells ($\rho = -0.12$, $p < 0.01$). Notably, NSD3 expression exhibited negative correlations with several chemokines and chemokine receptors, including CCL3, CCL4, CXCL16, CCR1, CCR5, and CCR6 (all $p < 0.001$). Significant variation in NSD3 expression was observed across immune and molecular subtypes ($p < 0.001$).

Conclusions: NSD3 is significantly overexpressed in LUSC and is associated with a favorable prognosis and distinct patterns of immune cell infiltration. These findings suggest that NSD3 may serve as a promising prognostic biomarker, potential therapeutic target, and predictive indicator of treatment response in LUSC.

Keywords: Lung Squamous Cell Carcinoma (LUSC), Prognostic Biomarker, Nuclear receptor-binding SET domain protein 3 (NSD

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.43 Estimating Tumour Microenvironment Cellular States From Bulk RNAseq Produces Biomarkers of Clinical Outcome Across Stages

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Introduction: Lung cancer is a complex and heterogeneous disease for which better predictive biomarkers of response are still lacking to guide personalized therapies. A better understanding of the tumor microenvironment (TME) is needed to improve patient outcomes. Here, we propose a novel computational approach that leverages bulk RNA-seq to infer clinically relevant patient-specific cell groups and states, which are normally detectable only with more costly and complex single-cell assays.

Methods: We developed an integrated computational approach based on cell type deconvolution and transcription factor activity estimation combined with an advanced machine learning framework to extract clinically relevant features from bulk RNAseq data. We analyzed a cohort of 62 primary lung adenocarcinoma (LUAD) samples from IUCT patients across disease stages (Hurtado et al. 2024). As validation, we use an independent RNA-seq cohort of early-stage LUAD with 77 RNAseq and 15 scRNA-seq samples collected at Vanderbilt University (Senosain et al. 2023). To assess the potential for this approach in late stage samples, we applied it to a multicenter French cohort with 130 advanced NSCLC patients treated with immunotherapy (IT) (N=90) or chemotherapy (N=40) in first-line setting (E. Gobbini, GFPC and UNICANCER).

Results: Our results identified cell populations associated with immune response and evasion (Hurtado et al. 2024). In early-stage samples, we observed a dual role of natural killer cells, suggesting their involvement in both immune activation and suppression. This dual behavior was linked to patient survival, highlighting natural killer cells as important players (Figure 1AB). In the late stage cohort we identified cell type groups significantly associated with immunotherapy response (p-value = 0.025, F-statistic = 5.188, effect size = 0.051) which predicted response with better performance than several existing approaches (Figure 1C).

Conclusions: Our approach characterizes RNA-seq based TME profiles through immune cell states and interactions, which enhances patient stratification. It identifies immune cell phenotype and interaction biomarkers linked to survival and progression that are validated across independent

cohorts.

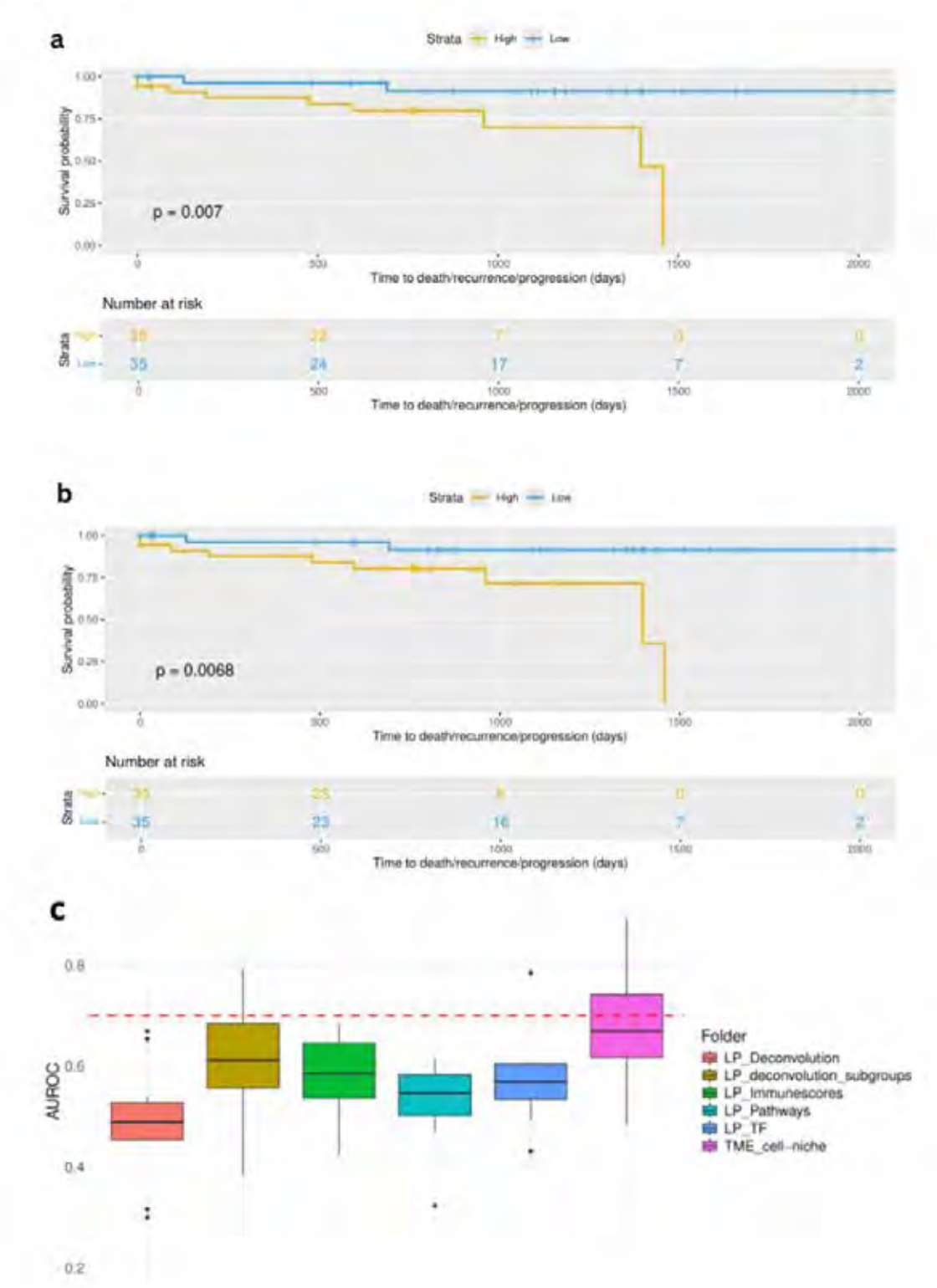

Figure 1. AB. Multivariate cox proportional hazards models across selected TME patient profiles in the early-stage Vanderbilt cohort to evaluate recurrence-free-survival. Survival curves based on high and low risk groups using linear predictors after fitting Cox PH model using cell type groups as covariates (p-value = 0.007, p-value = 0.0068). C. Machine learning models performance (AUC-ROC) to predict immunotherapy response in the late-stage cohort using different approaches to estimate TME features (our approach is named TME_cell-niche, line red = AUC = 0.7).

Keywords: immunotherapy, tumor-microenvironment, cell-type deconvolution

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.44 More Than a Mutation: Prevalence of HER2 Overexpression, Amplification, and Mutations by Histology in NSCLC

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Introduction: HER2-directed therapies have gained tumor-agnostic approval and have demonstrated clinical activity in HER2-mutated lung adenocarcinoma with limited data in benefit for HER-2 overexpressing tumors. The prevalence of this therapeutic target in non-small cell lung cancer (NSCLC) remains poorly characterized with evolving and complicated testing guidelines. Here we evaluate the prevalence of HER2 genomic alterations and HER2 overexpression in adenocarcinoma and squamous cell carcinoma (SCC) of the lung.

Methods: We retrospectively analyzed a database of 9,395 NSCLC samples tested at NeoGenomics Laboratories. HER2 protein expression by immunohistochemistry (IHC) was performed using ASCO/CAP breast cancer scoring guidelines (0/1+/ 2+/ 3+). HER2 amplification (amp) was defined by fluorescence in situ hybridization (FISH; HER2/CEP17 ≥ 2.2). Next-generation sequencing (NGS) was used to identify HER2 mutations. Identified genetic variants were annotated according to the American College of Medical Genetics and Genomics standards. Fisher's exact test compared HER2 overexpression, amplification, and mutation rates by histology.

Results: Among 4,875 tissue samples, 3,761 were adenocarcinoma and 941 were SCC. In adenocarcinoma, IHC 2+ was detected in 32.5% (n=1,222) and IHC 3+ in 2.7% (n=100) of cases; whereas in SCC, 15.4% were IHC 2+ (n=145) and 1.3% (n=12) were IHC 3+, confirming the higher prevalence in adenocarcinoma histology (p<0.00001). HER2 amp by FISH occurred in 8.5% of adenocarcinoma (318/3,761) and 3.9% of SCC (37/941) and was more common in adenocarcinoma compared to SCC (p=0.003). Among amplified adenocarcinoma, 41.2% were IHC 2+ (n=131) and 1.9% were IHC 3+ (n=6); in amplified SCC, 43.2% were IHC 2+ (n=16) and none were IHC 3+.

In 7,576 cases assessed by NGS, HER2 mutations were detected in 3.4% of adenocarcinomas (261/7,576) and 3.0% of SCC (55/1,819). Pathogenic HER2 mutations were more common in adenocarcinoma (1.4%, 107/7,576) than SCC (0.3%, 6/1,819; p<0.00001). In adenocarcinoma, 63.6% of pathogenic mutations (68/107) were HER2 exon 20 insertions and 36.4% were other HER2 domain variants (39/107). No exon 20 insertions were identified in SCC. Of cases with HER2 pathogenic mutations in adenocarcinoma (n=107), 1.9% also had IHC 3+ (n=2) and 15.9% had IHC 2+ (n=17), respectively, whereas for SCC, only 1 of 6 had IHC 2+.

Conclusions: HER2 overexpression, amplification, and activating mutations were more prevalent in adenocarcinoma compared to SCC, however within adenocarcinoma, we observed diverse representations of each HER-2 subcategory. These findings emphasize the importance of systematic HER2 testing in NSCLC to identify patients who may benefit from HER2-targeted therapies.

Keywords: Non-small Cell Lung Cancer, HER2, Histology

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.45 A Novel Predictive Gene Signature for Liver Metastasis (LM) in NSCLC Using a Comprehensive Linked Clinical-Molecular Database

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Introduction: Among patients with non-small cell lung cancer (NSCLC), LM is associated with poor prognosis. However, it remains difficult to predict LM and questions remain around the biology underlying LM. We leveraged a real-world (RW) clinical-molecular database to identify a gene expression signature predictive of LM among patients with advanced NSCLC and adenocarcinoma histology (advNSCLC-AC) to inform patient care.

Methods: This study used the US-based deidentified Flatiron Health (FH)-Caris Life Sciences (Caris) NSCLC Clinical-Molecular Database (CMDB), with clinical data from the FH Research Database linked to whole exome sequencing, whole transcriptome sequencing (WTS), and immunohistochemistry data derived from Caris tumor profiling tests (data cutoff, September 30, 2024). Patient characteristics were summarized using descriptive statistics. Among patients with advNSCLC-AC who received first-line (1L) chemoimmunotherapy, a univariate competing-risk Fine-and-Gray model assessed the association between gene expression in lung biopsies collected at advanced diagnosis and time to LM, with death as a competing event. LM-associated genes were selected through cross-validation and aggregated into a composite risk score using single-sample Gene Set Enrichment Analysis. Gene ontology enrichment analysis was conducted to identify biological processes associated with the predictive signature. RW overall survival (rwOS) was estimated using the Kaplan-Meier method.

Results: Among 8697 patients with NSCLC, 1121 met study criteria. Patients had a median age of 67 years at 1L start, 56% were White, 52% were male and the majority had stage IV disease (84%) and a history of smoking (91%). rwOS analysis confirmed that LM at 1L initiation was associated with poorer prognosis (P<.001) (Figure 1A). Leveraging WTS data from 407 patients with no LM at biopsy, we identified genes significantly associated with LM risk (FDR < 0.05). A composite risk score stratified patients into high- and low-risk groups, showing significant separation in cumulative incidence of LM (Gray's P<.01) (Figure 1B). Analysis demonstrated specificity to LM, with no significant association with brain metastases observed (Figure 1C). The signature included 259 genes, enriched for genes involved in organelle fission, cellular division, meiosis, and homologous recombination (Figure 1D).

Conclusions: Analyses of comprehensive and longitudinal multimodal RW data from the CMDB replicated the known association of LM with poor prognosis and identified a composite biomarker for LM risk stratification in the advNSCLC-AC setting. This novel gene signature may inform surveillance and treatment strategies to optimize patient outcomes and elucidate biological mechanisms underlying the development of LM. Further validation in independent cohorts is needed.

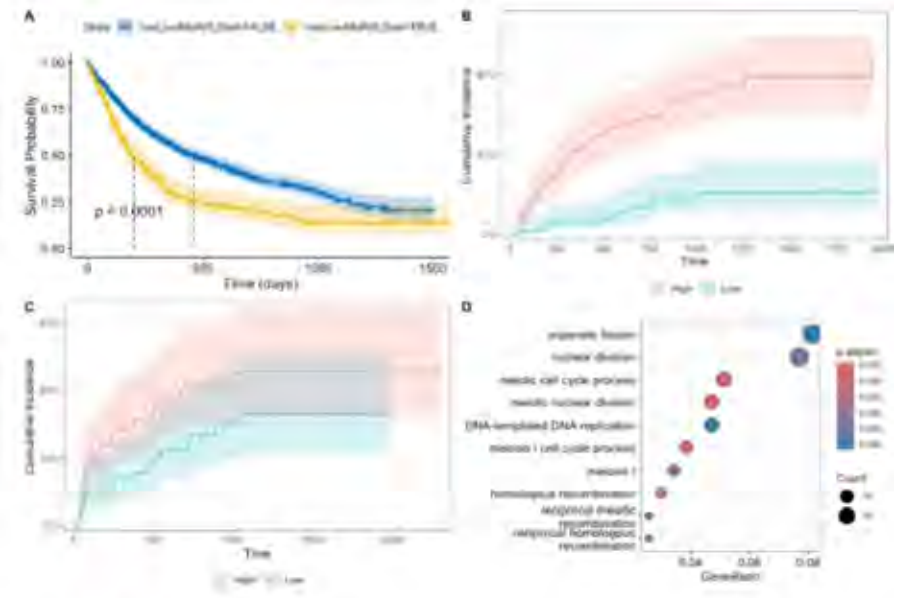

Figure 1. Prognostic value of liver metastasis and characterization of a novel LM predictive signature in NSCLC-AC
A) Kaplan-Meier curve of rwOS on total cohort (N = 1121) stratified by presence of LM at 1L start (true= LM reported at 1L start, false= LM not reported at 1L start)
B) Cumulative incidence function (CIF) of time to first liver metastasis accounting for death as a competing risk stratified by LM composite risk score (high vs. low score)
C) CIF of time to first brain metastasis accounting for death as a competing risk stratified by LM composite risk score (high vs. low score)
D) Gene ontology enrichment analysis of genes included in the LM predictive signature

Keywords: multiomics, real-world data, liver metastasis

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.46 Multi-Omics Analysis Reveals Genomic Features Associated With Combination Immunotherapy Benefit in Advanced NSCLC

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Introduction: Combination immunotherapy has become the standard first-line treatment for patients with untreated advanced non-small cell lung cancer (NSCLC). However, reliable biomarkers predictive of combination immunotherapy outcome remain unclear.

Methods: In this prospective study, we enrolled a total of 54 patients with advanced NSCLC receiving PD-1/PD-L1 blockade plus chemotherapy as first-line treatment. Pretreatment tumor biopsy samples were collected from 45 patients. Blood samples were collected before 1st (C1D1; n=51), 2nd (C2D1; n=45), 3rd (C3D1; n=36), 4th (C4D1; n=29) cycles of combination immunotherapy, as well as at disease progression (n=7). Comprehensive genomic profiling of tissue and circulating tumor DNA (ctDNA) was performed using a 437-gene panel. Transcriptomic profiling on tissue (n=14) was conducted via RNA-seq.

Results: At baseline, patients with STK11 mutations exhibited a trend towards lower PR rate compared to those without (0.0% vs. 60.0%; P=0.085). LRP1B mutations were associated with longer progression-free survival (PFS) (HR=0.35, P = 0.034). In contrast, patients with FBXW7 mutations had shorter PFS than those with wild-type FBXW7 (HR=5.39, P=0.001). Gene set enrichment analysis of the TCGA-NSCLC dataset revealed that FBXW7-mutated NSCLC exhibited upregulation of cell cycle pathway genes, including MYC and E2F, thereby promoting tumor proliferation. In addition, immune pathways related to IFN-α and IFN-γ responses were downregulated, leading to impaired immunity. Analysis of the tumor immune microenvironment indicated that FBXW7 mutations were associated with reduced infiltration of CD4+ memory T cells (p=0.017) and NK cells (p=0.040). Transcriptomic analysis showed that patients with low SPP1 expression, involved in the suppression of CD8+ T cells and tumor evasion of the immune response, has markedly longer PFS (P=0.008). Our longitudinal analysis revealed that at the C2D1, C3D1 and C4D1 time points, patients with detectable ctDNA (ctDNA+) exhibited worse PFS (HR=5.18, P=0.004; HR=17.81, P<0.001; HR=3.91, P=0.018). Patients with early ctDNA clearance, testing negative across C2D1, C3D1 and C4D1, had better PFS compared to those without ctDNA clearance at C4D1 time points (NR vs. 5.6 months, P<0.001).

Conclusions: The multi-omics analysis illuminates the genomic and transcriptomic features of tissue and peripheral blood associated with combination immunotherapy outcomes in patients with advanced NSCLC, highlighting potential predictive biomarkers.

Keywords: non-small cell lung cancer, combination immunotherapy, biomarker

P2.06.47 Axl Receptor Shedding and EMT in Lung Adenocarcinoma: Prognostic Implications Based on STAS

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Introduction: Axl receptor tyrosine kinase promotes epithelial-mesenchymal transition (EMT), facilitating tumor invasion and metastasis. Proteolytic shedding of Axl's extracellular domain (ECD) is not fully understood, especially its role in lung cancer progression. Given the potential relationship between spread through air spaces (STAS) and EMT, we aimed to investigate the prognostic significance of Axl shedding and its association with EMT in lung adenocarcinoma, stratified by STAS status.

Methods: We conduct a retrospective study of 202 patients with surgically resected lung adenocarcinoma. Dual-domain immunohistochemistry (IHC) was utilized to evaluate both ECD and phosphorylated intracellular domain (pICD) of Axl using tissue microarrays. Patients were categorized into shedding and non-shedding groups based on staining intensity (Figure 1). Recurrence-free probability (RFP) was assessed by Kaplan-Meier analysis, stratified by STAS status. A cancer proteogenomic database (LinkedOmicsKB) was used to assess correlations between Axl RNA expression and EMT signatures.

Results: The Shedding pAxl group exhibited significantly worse prognosis than the non-shedding group (5-year RFP: 54% vs. 79%, p<0.001). Notably, when stratified by STAS status, the negative prognostic impact of Axl shedding was significant only in STAS-positive patients (5-year RFP: 38% vs. 73%, p<0.001), but not in STAS-negative patients (Figure 2). Multivariable analysis confirmed shedding Axl (HR=2.28, p=0.008) and pathological stages II/III (HR=2.39, p=0.013) as independent predictors of recurrence. Additionally, significant positive correlation between Axl expression and EMT signature was observed at the RNA level (ρ=0.50, p<0.001).

Conclusions: Our findings demonstrate a significant association between Axl receptor shedding, EMT, and STAS in lung adenocarcinoma, highlighting the prognostic importance of Axl shedding, particularly in STAS-positive tumors. These insights may offer potential pathways for personalized treatment and targeted therapeutic strategies.

Figure 1. Schema of Axl shedding

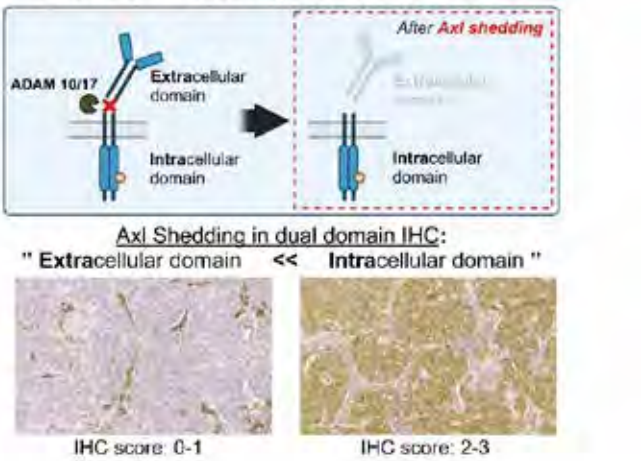
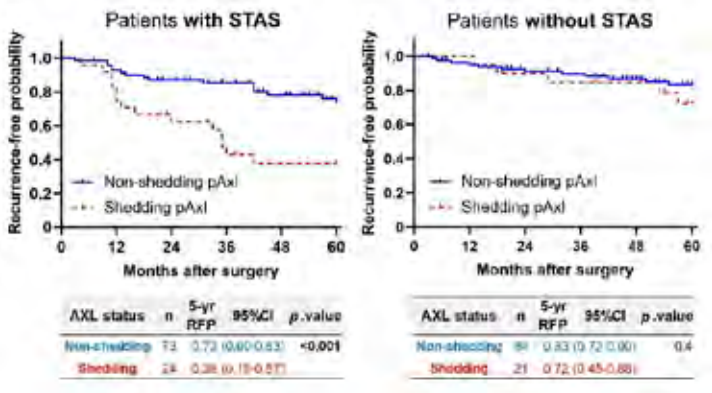


Figure 2. Prognostic impact of Axl Shedding by STAS status



Keywords: Lung adenocarcinoma, Axl, Spread Through Air Space

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.48 Histology-Specific Genomic and Immune Predictors of Resistance to Neoadjuvant Chemoimmunotherapy in Early-Stage Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant chemoimmunotherapy (nCIT) improves outcomes in early-stage NSCLC, yet biomarkers for guiding patient selection prior to treatment remain insufficiently defined. Given the distinct biology of adenocarcinoma (LUAD) and squamous carcinoma (LUSC), we investigated how genomic and immune predictors influence treatment response, with an emphasis on histology-specific resistance mechanisms.

Methods: In this prospective cohort study (NCT06907160), 72 patients with stage IB-III EGFR/ALK wild-type NSCLC (37 LUSC, 34 LUAD, 1 sarcomatoid) received neoadjuvant platinum-doublet chemotherapy plus PD-(L)1 blockade, planned for curative resection. Pre-treatment tumors underwent next-generation sequencing and AI-based tumor-infiltrating lymphocyte (TIL) analysis (Lunit-SCOPE IO) to assess somatic mutations, copy-number variations (CNVs), and the immune microenvironment. Primary endpoints were major pathologic response (MPR), pathologic complete response (pCR), and treatment resistance, defined as (1) no radiologic tumor shrinkage per RECIST 1.1, including progression precluding surgery, or (2) ≥60% residual viable tumor post-surgery.

Results: Twenty-six patients (36%) met resistance criteria—7 due to radiologic progression and 19 due to poor pathologic response. Genome-wide screening identified recurrent copy loss in cytobands 9p24.1 (including CD274) and 19p13.3 (including STK11) associated with treatment response (Fig. 1A-B). Loss of 9p24.1 (23%) correlated with non-inflamed immunophenotype (Fig. 1C), significantly lower MPR/pCR rates ($p<0.001$), and a higher resistance rate across both histologies (Fig. 1D). In LUAD, 16% had 19p13.3 loss and/or STK11 mutations, linked to reduced MPR/pCR rates and increased resistance rate (Fig. 1E); these associations were absent in squamous histology. Integrating genomic features into clinical-immunophenotype variables significantly improved MPR prediction (AUC: 0.87 vs. 0.67, $p=0.007$), with a greater gain observed in adenocarcinoma. (Fig. 2A-C).

Conclusions: This study highlights histology-specific associations between pre-treatment genomic alterations, immune contexture, and pathologic response. CNVs—particularly 9p24.1 and 19p13.3—contributed to resistance in a histology-dependent manner. These findings support pre-treatment molecular stratification to optimize patient selection and identify individuals less likely to benefit from nCIT.

Figure 1

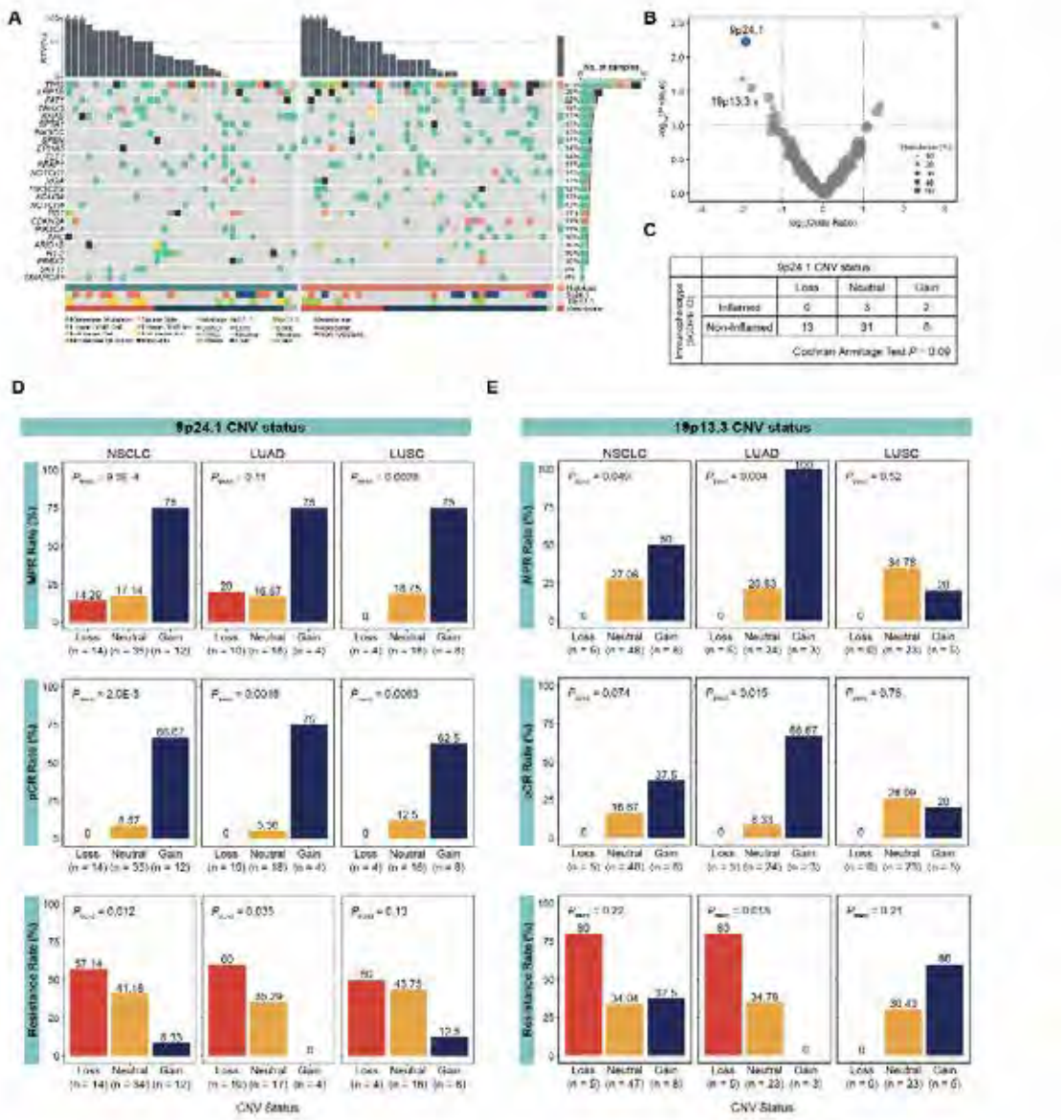
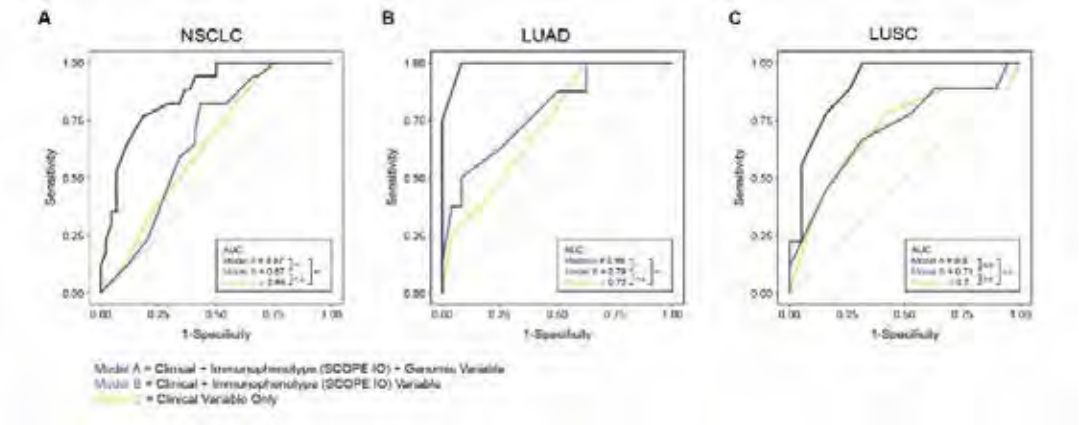


Figure 2



Keywords: Neoadjuvant immunotherapy, Biomarker, Copy number variations

P2.06.49 Spatial Metabolomic Profiling Reveals Dynamic Metabolic Reprogramming During Lung Squamous Cell Carcinoma Evolution

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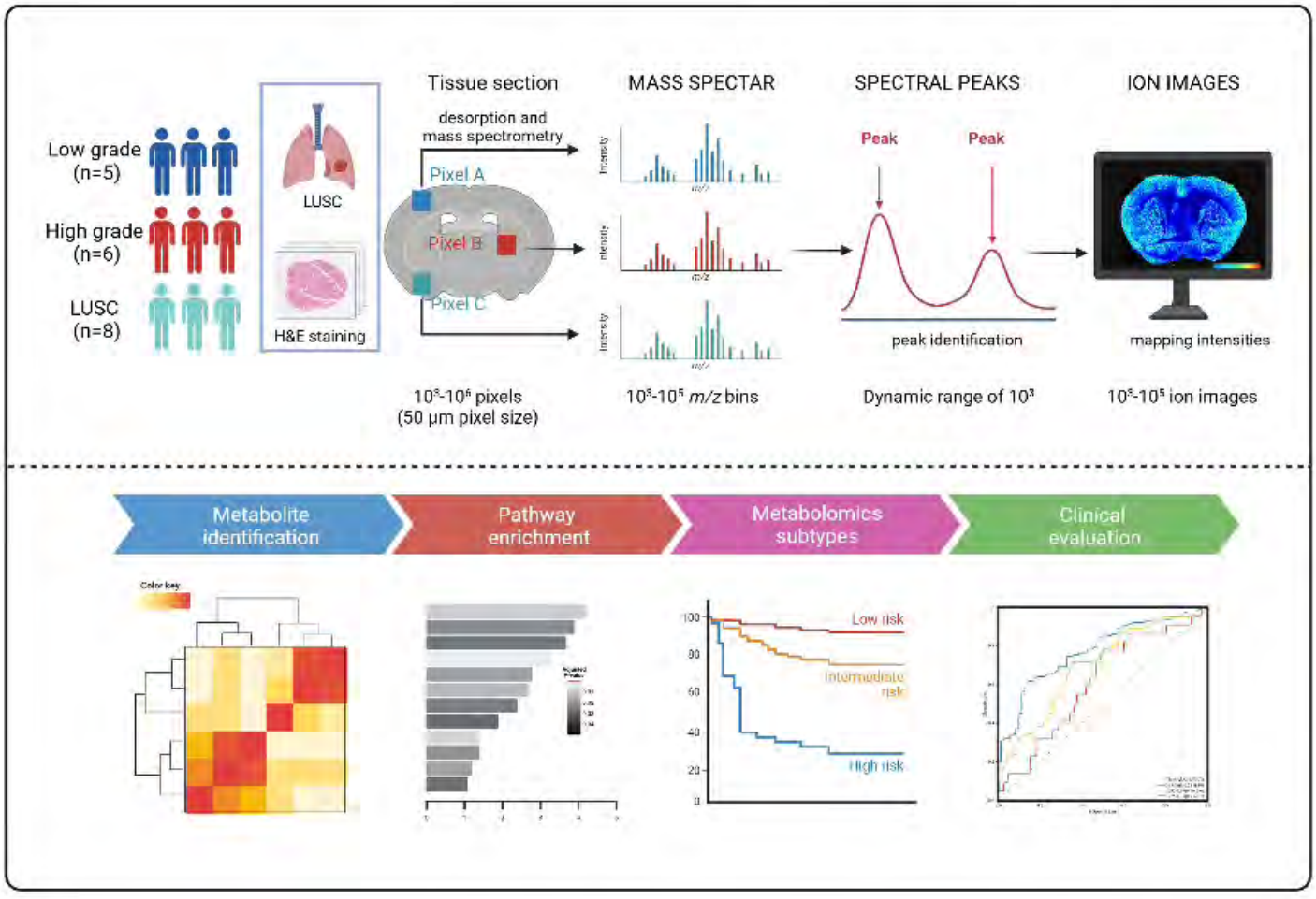
Introduction: Metabolic reprogramming undergoes dynamic evolution throughout cancer initiation and progression. However, the metabolic landscape underlying the transition from precancerous lesions to invasive lung squamous cell carcinoma (LUSC) remains poorly characterized. To elucidate the spatial distribution and temporal evolution of metabolic alterations during pulmonary carcinogenesis, we performed large-scale spatial metabolomic profiling on surgically resected specimens.

Methods: We conducted large-scale spatial metabolomic profiling of surgically resected specimens spanning precancerous lesions (atypical hyperplasia and carcinoma in situ) to invasive LUSC. This approach enabled the systematic mapping of metabolic pathway dysregulation across distinct stages of pulmonary carcinogenesis.

Results: Our findings reveal that dysregulated metabolic pathways emerge as early as the precancerous stage, with distinct metabolic trajectories observed from atypical hyperplasia through carcinoma in situ to invasive LUSC. Spatial metabolomics demonstrated remarkable metabolic similarity between atypical hyperplasia and carcinoma in situ, which significantly diverged from the metabolic profile of invasive carcinoma. This divergence highlights extensive reprogramming during LUSC invasion. Additionally, retinol metabolic dysregulation correlated with adverse pathological features. Functional validation confirmed that disrupted retinoic acid metabolism promotes cancer cell migration.

Conclusions: The comprehensive characterization of metabolic evolution during LUSC progression uncovers critical insights into early detection and precision therapy. The identification of retinol metabolism as a driver of invasion suggests its dual potential as a therapeutic target and prognostic biomarker. These findings lay a foundation for improving early detection strategies and developing tailored interventions for LUSC patients.



Keywords: Lung Squamous Cell Carcinoma, Spatial Metabolomic, Cancer Evolution

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.50 Transcriptomic Profiling Identifies a Prognostic and Predictive Immune Signature in Patients (Pts) With Lung Squamous Cell Carcinoma (LUSC)

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Introduction: Intra-tumoral immune infiltration and inflammation have been strongly proposed as promising prognostic and predictive biomarkers in non-small cell lung cancer (NSCLC). However, a transcriptomic approach is not well validated in this setting. Herein, we developed a transcriptome-based score and validated its prognostic and predictive value in LUSC.

Methods: The transcriptomic counts and clinical data were obtained from The Cancer Genome Atlas Lung Squamous Cell Carcinoma (TCGA-LUSC, n = 487). Immune genes were obtained from the molecular signature database and validated genes from the literature. The pts were clustered based on their expression of immune genes into high vs low immune profiles using unsupervised K-means clustering. The Differentially Expressed Genes (DEGs) between the two groups were identified, and then we intersected the DEGs with the immune genes to obtain the immune DEGs. The immune DEGs were fitted into uni- and multi-variate cox regression models to find the independent predictors of survival. An immune score (IS) was calculated using the expression of these genes multiplied by the cox regression coefficients. Pts were split using the median IS into high- and low-IS groups in all datasets. Log-rank tests and Kaplan Meier analysis were used to correlate the score with Overall Survival (OS) and Progression-Free Survival (PFS). Tumor microenvironment using 'CIBERSORT' algorithm, and the proteomic landscape were also analyzed between the two groups. To further validate our findings, we examined the IS on the following GEO cohorts: GSE157009 with 249 LUSC pts and GSE135222 with 27 NSCLC pts treated with immune checkpoint inhibitors (ICI).

Results: We identified 3,616 DEGs, of which 344 immune DEGs were obtained and fitted into the univariate and multivariate Cox regression models. CCL21, CD48, and IL2RB were identified as independent predictors of survival. The high- and low-IS groups included 378 and 375 pts, respectively. The high IS group demonstrated worse outcomes compared to the low IS group in all datasets. In TCGA-LUSC, pts with high IS had worse OS and PFS (P<0.05). Similar results were seen in the external validation dataset, with high IS group showing worse OS in GSE157009-LUSC (P=0.0082). Moreover, high IS predicted for worse PFS in pts treated with ICI in GSE135222-ICI cohort (P=0.018). Notably, these associations remained significant after adjusting for stage, gender, and age, confirming the IS as an independent predictor of survival in all of the cohorts (HR>2, P<0.001). High IS correlated with higher infiltration of M2 macrophages, activated dendritic and mast cells, while low IS correlated with higher M1 macrophages, resting mast cells, cytotoxic T-cells, and activated NK cells infiltration (P<0.05). Low IS correlated with higher protein expression of BCL2, BCL2L11, MSH2, MSH6, PARP1, and LCK, while high IS correlated with higher expression of AKT pathway and mTOR pathway activation proteins (P<0.05).

Conclusions: We developed a transcriptome-based immune score in LUSC that is prognostic and predictive of responses to ICI. The score was based on 3 immune-related genes. Pts with high immune score had worse outcomes, worse PFS after ICI and higher levels of immune inhibitory cells.

Keywords: Immune biomarkers, immunotherapy, NSCLC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.51 Tumour Tissue Extracellular Vesicle (EV) Biomarkers of Lung Cancer in Patients With or Without Heavy Smoking Histories

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Introduction: Lung cancer in individuals who have never smoked (LCINS) remains an under-recognised and growing phenotype of lung cancer, necessitating the development of innovative early detection methods beyond current screening programs. Extracellular vesicles (EVs) have emerged as leading candidates for early cancer detection for their pro-tumorigenic effects at early disease stages and stability when in circulation, making them prime candidates for liquid biopsy. In order to characterise a tumour EV signature, this study aims to analyse tumour and non-tumour lung tissue-derived EV-RNA from LCINS and lung cancer in individuals who have a heavy smoking history (LCIHS) to: (a) identify tumour EV biomarkers of LCINS and LCIHS, and (b) identify markers expressed in lung tumours irrespective of smoking history.

Methods: Resected tumour and non-tumour specimens of early-stage (I and II) primary adenocarcinoma from LCIHS (n=6) and LCINS (n=3) were analysed. EVs were isolated from tumour and non-tumour lung tissue using a collagenase-dispase digestion buffer and EV samples were purified using differential centrifugation, ultracentrifugation, and size exclusion chromatography. Total EV-RNA was extracted and sequenced (Illumina NovaSeqX) at a target depth of ~40M reads per sample. Gene expression was analysed by tissue type and smoking history, with significance thresholds of an FDR-adjusted p-value<0.01 and a fold change>±10 (HREC/2023/MNHA/89121).

Results: In LCINS, 53 genes were significantly differentially expressed in tumour tissue, compared to non-tumour tissue. The most statistically significant of these was CEACAM5, a protein coding gene which is associated with lung and other cancers. Similarly, in LCIHS, 587 differentially expressed genes were identified in tumour tissue when compared to non-tumour tissue. The most statistically significant of these was XAGE1A, an antigen which has been associated with lung cancer in many studies. Of the genes identified in tumour tissues, 12 were significantly differentially expressed in tumour tissues of both LCINS and LCIHS, when compared to their respective non-tumour tissues (8 upregulated, 4 downregulated). Among these was SPP1, a gene that is well characterised as upregulated in plasma in patients with lung cancer.

Conclusions: Our data indicate the viability of using EVs to detect clinically relevant biomarkers of lung cancer. Differentially expressed genes were identified in tumour-derived EVs in LCINS and LCIHS. Among these genes are known biomarkers of lung and other cancers. Further, our data indicate LCINS tumours are unique to those arising in patients with a heavy smoking history, with the presence of numerous significantly differentially expressed genes between tissues. However, we also observed overlapping differentially expressed genes in tumour tissues. We have identified potential markers unique to LCINS and commonly expressed in tumours from patients with an absent and a heavy smoking history. These findings provide the foundation for the development of a lung cancer biomarker panel, inclusive of people who have never smoked, that can detect early-stage adenocarcinoma. Identifying biomarker candidates in tissue EVs enables translation into blood EVs, potentially offering early cancer detection via blood sampling. These findings are presently being validated in a larger cohort.

P2.06.52 Survival and Mutational Differences of GPER and Estrogen Receptor (ER) in NSCLC

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Introduction: G-protein coupled estrogen receptor 1 (GPER) is a protein involved in the estrogen signaling pathway and a tumor promoter in non-small cell lung cancer (NSCLC). ER positivity is increased in females and epidermal growth factor receptor (EGFR) mutant (-mt) NSCLC. Here, we evaluated differences based on ER-alpha (ESR1), ER-beta (ESR2), and GPER RNA expression with survival in NSCLC.

Methods: NSCLC samples (n = 52,690) were analyzed by NGS (NextSeq or NovaSeq) andRNA (NovaSeq) (Caris Life Sciences, Phoenix, AZ). Spearman's correlation coefficient (r) was used. GPER, ESR1, and ESR2 expression was split into quartiles (top (-H) and bottom (-L)). Real-world mOS was obtained from insurance claims and calculated from collection to last contact. Hazard ratio (HR) was calculated by Cox proportional hazards model, and P values calculated by log-rank test. Multivariate Cox regression analysis was used.

Results: Females comprised a greater percentage of GPER-H (51.1%) versus (vs) GPER-L (47.7%) ($p < 0.05$). GPER-H had decreased mt in STK11 (10.4% vs 18.6%) and KEAP1 (9.76%vs 16.3%) vs GPER-L but higher in EGFR-mt (14.1% vs 8.68%) ($q < 0.05$). No difference in BRAF, KRAS, HRAS or NRAS-mt was seen. GPER was weakly correlated with ESR1($r = 0.384$) and ESR2 ($r = 0.424$). Longer mOS was seen in ESR1-H and ESR2-H, while, GPER-H had shorter mOS overall and in females and males, separately (Table 1). GPER-H had shorter mOS in females that are ESR1-L and ESR1-H tumors, while males only had shorter mOS in ESR1-L but not ESR1-H tumors. In ESR2-L tumors, GPER-H has shorter mOS in both females and males. In ESR2-H tumors, GPER-H had shorter mOS in females and in males buta smaller Δ mOS (Table 1). GPER-H had shorter mOS in ESR1/2-L tumors adjusting for histology, gender, and EGFR, BRAF, KRAS, HRAS, NRAS, STK11, and KEAP1-mt status (ESR1-L: adjusted HR (aHR): 1.21 (1.03-1.43), $p = 0.02$; ESR2-L: aHR: 1.33 (1.14-1.55),$p = 3.84E-04$).

Conclusions: Our results show unique and biologically meaningful correlations of GPER with ESR1 and ESR2 expression. GPER-H had a greater prevalence of EGFR-mt but decreased STK11-mt and KEAP1-mt. GPER-H was associated with worse mOS in ESR1-H tumors in females but not males. Our results suggest that targeting GPER and ER may help survival in female and EGFR-mt NSCLC patients.

Table 1. Survival by GPER/ESR1/ESR2 Status.

Comparison			mOS	HR (95% CI)	P-value
Overall		ESR1-H/-L	22.2 vs 15	0.77 (74-0.8)	<0.0001
		ESR2-H/-L	23.2 vs 14.5	0.75 (0.72-0.78)	<0.0001
		GPER-H/-L	18.4 vs 19.6	1.06 (1.02-1.1)	4E-03
GPER: -H/-L		Female	22.3 vs 23.9	1.07 (1.01-1.13)	3.1E-02
		Male	15 vs 16.3	1.07 (1.02-1.13)	0.01
ESR1-L	GPER-H/-L	Female	13 vs 20.2	1.27 (1.12-1.44)	3E-04
		Male	10.4 vs 15.2	1.27 (1.14-1.42)	<0.0001
ESR1-H		Female	26.3 vs 32.7	1.2 (1.02-1.41)	0.03
		Male	19 vs 17.5	0.96 (0.82-1.13)	0.563

Keywords: estrogen receptor, g-protein coupled estrogen receptor 1, ESR

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.53 TP53 Mutations Drive Therapeutic Resistance in ALK-Rearranged Lung Adenocarcinoma

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Introduction: While TP53 mutations and EML4-ALK variants influence ALK inhibitors efficacy. The impact of concurrent genomic alterations on outcomes remains incompletely characterized.

Methods: This retrospective study utilized next-generation sequencing data(NGS) from ALK-mutant lung cancer patients treated at Guangdong Provincial People's Hospital. Clinical data were combined with somatic mutation profiles to investigate associations between TP53, RB1 mutation status, and other genomic characteristics.

Results: Of 219 patients, 4 (1.8%) receiving adjuvant ALK inhibitors after surgery achieved durable responses without requiring first-line therapy, 2 (0.9%) were lost to follow-up. Among 143 treatment-naïve patients with baseline NGS, TP53 alterations (33%) were the most common event associated with decreased first-line progression-free survival and decreased overall survival, along with KEAP1, BRAF, CDKN2A and TYMS 6BP alterations. In addition to pretreatment TP53 alterations, patients with TP53 alterations detected at any time point had shorter PFS (mPFS:17.067m vs 11.833m, HR=1.457, 95% CI: [1.062,1.999], p=0.019) and reduced OS(mPFS: 72.767m vs 43.800m, HR=1.809,95% CI: [1.197,2.734], p=0.004). In patients with primary progressors, TP53-altered tumors showed reduced radiographic responses (CR/PR rate: 31.91% vs 68.09% in wild-type, Fisher's exact test p<0.000), indicating accelerated acquired resistance. Further investigation of the effect of TP53 alterations revealed an association with worse outcomes even in patients with good initial radiographic response (CR/PR) (PFS:HR=1.955,95% CI: [1.193,3.201], p= 0.007; OS:HR=3.008, 95% CI: [1.366, 6.621], p= 0.004). Our analysis revealed that in ALK-rearranged tumors, co-alterations of TP53 and RB1 were not associated with inferior PFS (HR=1.143, 95%CI: [0.951,1.373], p=0.11) but showed a significant trend toward worse OS (HR=1.267, 95% CI: [1.004,1.598], p=0.042), differentiating with known EGFR/TP53/RB1 co-alteration patterns in the past studies.

Conclusions: TP53 mutations drive therapeutic resistance in ALK-rearranged lung adenocarcinoma, with RB1 co-mutation exhibiting context-dependent effects distinct from EGFR-mutant disease. These findings highlight the need for mechanism-tailored combinatorial strategies.

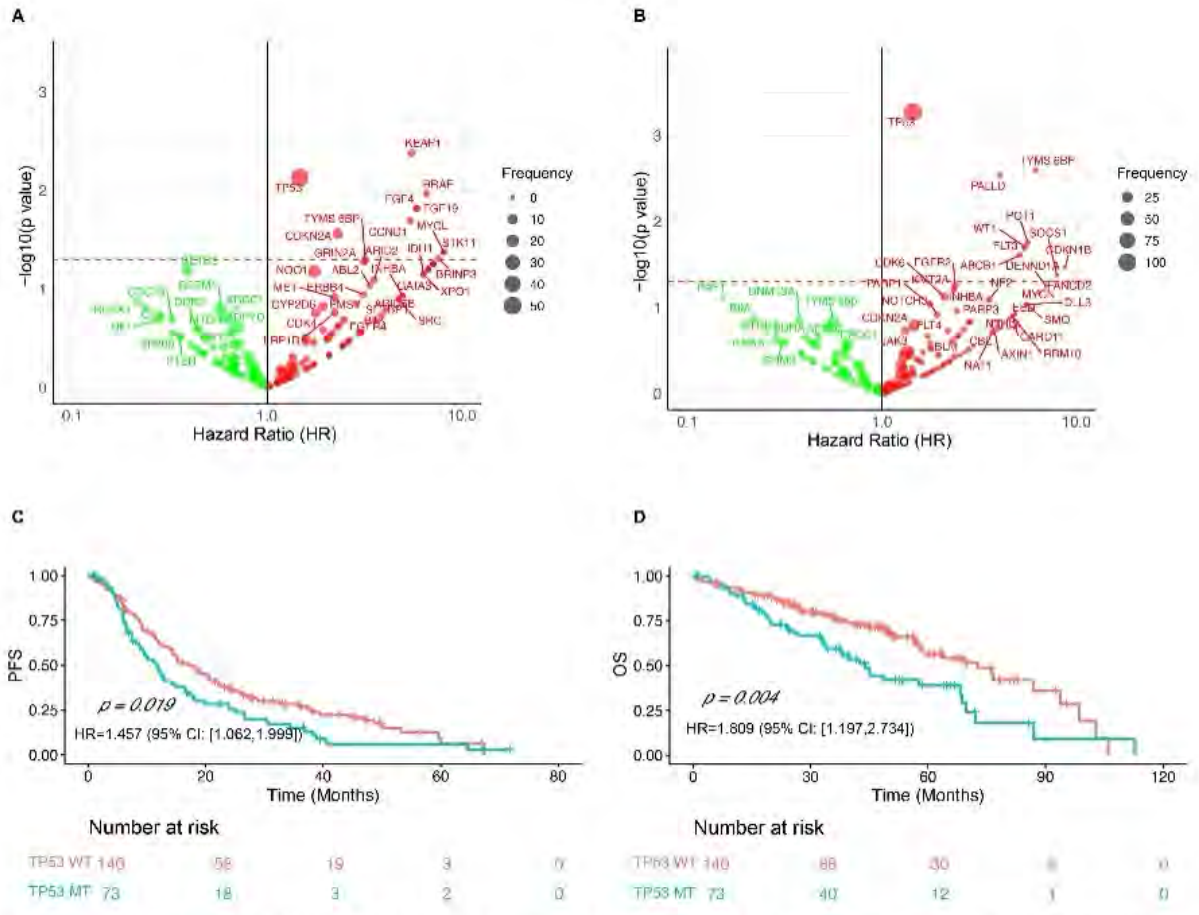

Figure 1. Genomic and clinical correlates of treatment outcomes in ALK-mutant NSCLC. Volcano plots depict associations between co-occurring alterations and (A) PFS (n = 143) or (B) OS (n = 213). Hazard ratios (HRs; x-axis) and −log10-transformed p values (y-axis; univariate Cox model) are shown, with data points color-coded by genetic event. Alterations present in <7 samples were excluded. Association between TP53 alteration detected at any time point and (C) PFS, (D) OS. HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

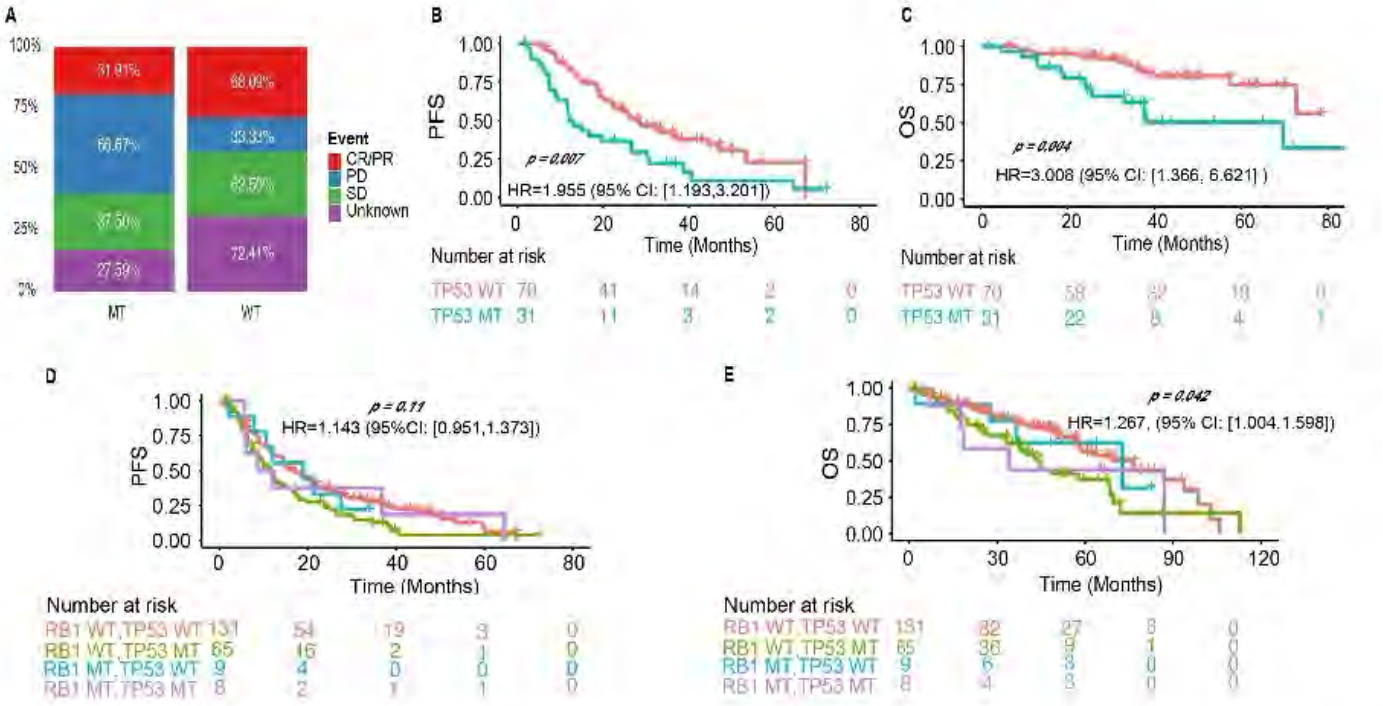

Figure 2. Impact of TP53 alterations on treatment outcomes and resistance mechanisms in ALK-mutant NSCLC. (A) Radiographic response distribution comparing TP53-mutant (MT) versus wild-type (WT) tumors at baseline (Fisher's exact test). (B-C) Kaplan-Meier curves of (B) progression-free survival (PFS) and (C) overall survival (OS) in patients achieving complete/partial response (CR/PR), stratified by TP53 status. (D-E) Survival outcomes in the full cohort (n=213): (D) PFS and (E) OS by combined RB1/TP53 mutation status. WT, wild type; MT, mutant; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; CI, confidence interval; PFS, progression-free

Keywords: ALK rearrangement, TP53 mutation, Therapeutic Resistance

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.54 miR-Roring IFN-Gamma Pathway Activity as a Predictive Tool for Immunotherapy Response in Non-Small Cell Lung Cancer

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Introduction: Non-small-cell lung cancer (NSCLC) is a leading cause of cancer-related deaths, due to late diagnosis and therapy resistance. Immune checkpoint inhibitors (ICIs), either alone or in combinations with chemotherapy (CT), achieve durable responses in approximately 20% of patients with advanced disease, while the remaining majority fail to respond or acquire resistance. Although several biomarkers have been proposed in literature, PD-L1 expression remains the only widely accepted clinical marker for NSCLC. However, its predictive value is limited by technical variability (different anti-PD-L1 antibodies, inconsistent expression thresholds, and intra-/inter-tumor heterogeneity all undermine its reliability). Consequently, the lack of robust biomarkers for identifying responder patients represent a major challenge to optimizing immunotherapy. MicroRNAs have emerged as promising biomarker candidates due to their exceptional stability in harsh conditions. We recently identified a novel miRNA-based signature that accurately predicts response to neoadjuvant CT in NSCLC. Notably, this miRNA signature hallmarks metastases with an active IFN-γ response pathway, which has emerged as a critical factor in shaping immunotherapy response. Based on these findings, we hypothesized that IFN-γ-related miRNAs could be exploited as predictive biomarkers of response to ICIs/ICIs+CT.

Methods: To identify IFN-γ-related miRNAs, commercially available NSCLC cell line were treated with 100ng/ml for 24 hours and subjected to miRNA-sequencing (Qiaseq). Moreover, we leveraged TCGA dataset to analyze miRNA expression in NSCLC tumors stratified in IFN-γ high and IFN-γ low activity, as determined by CytoSig tool. Finally, spatial transcriptomics (Visium,10x) was carried out in treatment naïve NSCLC samples (n=3) to map the spatial correlation between miRNA activity and IFN-γ signaling within tumor cells versus the surrounding microenvironment. To evaluate whether IFN-γ-related miRNAs could predict response to ICI based therapies, a retrospective cohort (n=34) of stage IV NSCLC patients prior treatment with ICIs/ICIs+CT was collected and subjected to miRNAseq (Qiaseq), digital mRNA-seq and DNA-seq (Oncopanel, Vazyme).

Results: In vitro treatment with IFN-γ significantly altered the miRNome of NSCLC cells, with a total of 67 miRNAs that are differentially expressed (FC>|1,2|; p<0,05). Of these, 7 miRNAs showed an altered expression (FC>|1,2|; p<0,05) in patient-derived samples (TCGA-LUAD, n=507; TCGA-LUSC, n=473) with a predicted different IFN-γ activation status. Moreover, spatial transcriptomics analysis of treatment naïve NSCLC (N=3) confirmed the association between the 7-miRNA signature and IFN-γ activity specifically in tumor cells. Strikingly, the 7-miRNA signature demonstrated higher predictive accuracy for ICIs response than PD-L1 in a cohort of stage IV NSCLC patients (n=34) treated with first-line ICIs-based therapy (AUCmiRNA=0.87 vs AUCPD-L1=0.69). Validation in a second independent cohort of ICIs treated NSCLC patients (N=30) is currently ongoing, together with comprehensive genomic profiling and immunophenotypic characterization, to further refine and validate the predictive power of this signature.

Conclusions: IFN-γ-related miRNAs hold the potential to serve as robust predictive biomarkers for immunotherapy response in NSCLC. If validated in larger cohorts, this miRNA signature could improve patient stratification and the development of more effective therapeutic strategies in NSCLC.

Keywords: miRNA, Immune Checkpoint Inhibitors, IFN-gamma

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.55 Association Between Pathologic Necrosis and Postoperative Recurrence in Stage IA Non-Small Cell Lung Cancer

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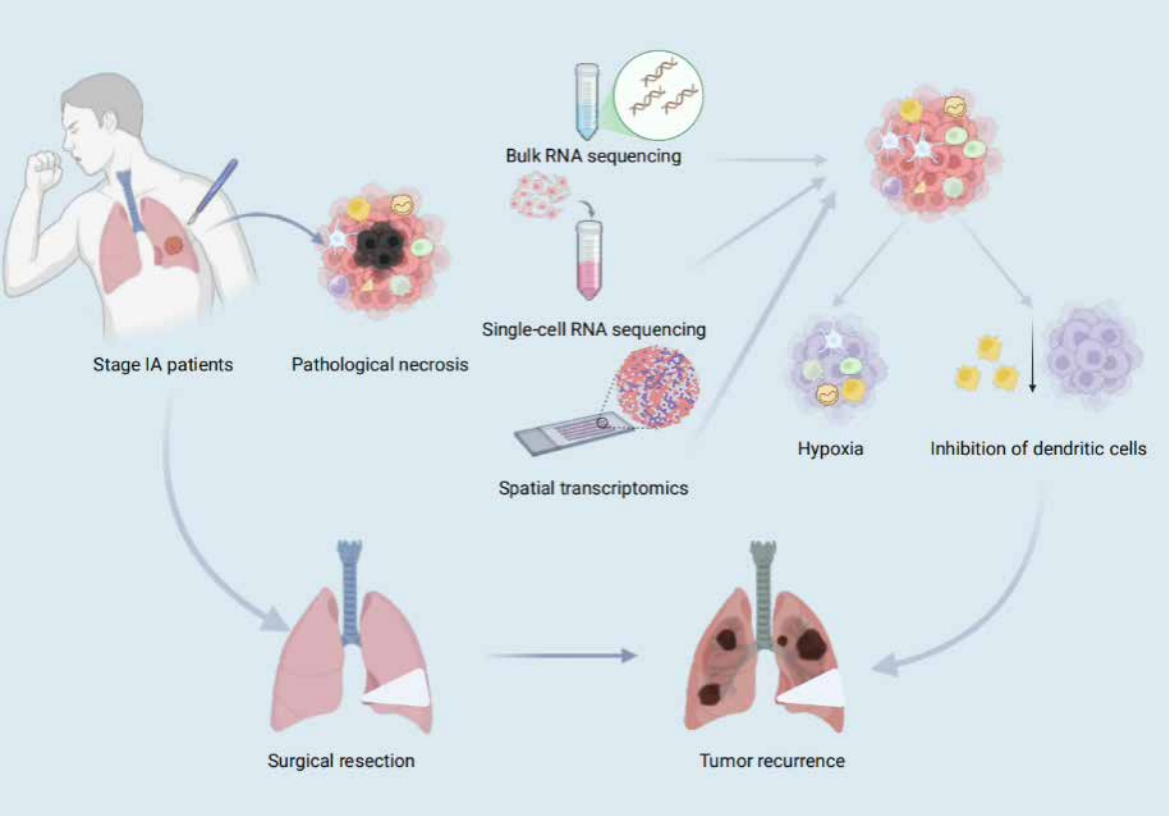
Introduction: Currently, there is insufficient evidence to definitively establish pathological necrosis in stage IA non-small cell lung cancer NSCLC) patients as a high-risk factor for postoperative recurrence.

Methods: In this study, clinicopathological data from stage IA NSCLC patients were retrospectively collected, and the association between histopathological necrosis and both overall survival (OS) and recurrence-free survival (RFS) was evaluated using Kaplan-Meier analysis and univariate and multivariate Cox regression models. The tumor microenvironment (TME) characteristics associated with histopathological necrosis in stage IA NSCLC were investigated using a combination of bulk RNA sequencing (RNA-seq), single-cell RNA sequencing (scRNA-seq), and spatial transcriptomics. Additionally, the intersection of necrosis-related genes (NRGs) and recurrence-associated genes (RAGs) was analyzed to explore the transcriptional relationship between pathological necrosis and postoperative recurrence. Experimental validation of key genes was performed to elucidate their functional roles in NSCLC.

Results: Kaplan-Meier analysis of 1,311 stage IA NSCLC patients demonstrated that OS and RFS were significantly worse in histopathological necrosis than in non-pathological necrosis. Univariate and multivariate Cox regression analyses identified histopathological necrosis as an independent risk factor for postoperative recurrence. TME analysis revealed that upregulated NRGs were associated with tumor cell cycle progression, increased proliferation, and hypoxia, while downregulated NRGs were linked to dendritic cell dysfunction. Nine genes were identified as being associated with both histopathological necrosis and postoperative recurrence. Cox proportional hazards regression analysis revealed ANLN as a key gene. In vitro experiments demonstrated that silencing ANLN expression in NSCLC cells suppressed tumor proliferation, invasion, and migration, while inducing apoptosis. In vivo studies further confirmed that ANLN inhibition significantly reduced tumor size.

Conclusions: Our study reveals the genetic link between pathological necrosis and postoperative recurrence in stage IA NSCLC, establishing its role as an independent high-risk factor. These findings support incorporating necrosis into risk stratification and developing targeted strategies to reduce recurrence.



Keywords: histopathological necrosis, postoperative recurrence, stage IA non-small cell lung cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.56 Enhancing Lung Cancer Diagnosis and Early Recurrence Risk Detection via Bedside Atomic Force Microscopy

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Introduction: Lung cancer remains a leading cause of cancer-related mortality; only 16% of cases are diagnosed at a localized stage. Approximately 75% of patients receive treatment, with advances focusing on personalized approaches through mutations like EGFR for targeted therapies or PD-L1 expression for immunotherapy. Treatment decisions rely on molecular profiling, which often takes over two weeks and is complicated by limited tumor sample availability. Beyond genetic markers, tumor physical properties significantly influence cancer progression. Tumor stiffness and extracellular matrix have been proposed as factors affecting treatment penetration and response. The Atomic Force Microscopy (AFM)-based Automated and Reliable Tissue Diagnostics (ARTIDIS) platform offers a rapid, standardized method to evaluate tumor nanomechanical properties. This study demonstrates the feasibility of measuring these properties and explores how nanomechanical signatures (NS) can enhance diagnosis, predict recurrence risk, and improve treatment response assessment.

Methods: This study involved 70 patients diagnosed with non-small cell lung cancer (NSCLC), all indicated for surgical resection at the Hospital Clinic. We procured 140 fresh tumor samples (involved) and paired uninvolved pulmonary tissue samples, meticulously preserved in formalin for subsequent histopathological and molecular analyses. Utilizing the ARTIDIS platform, we evaluated the NS of the collected tissues, employing blinded measurements to minimize bias. Comprehensive clinical and pathological characteristics, treatment responses, and outcomes were documented, with follow-up data available for up to 36 months.

Results: Of the patients analyzed, four had prior neoadjuvant therapy, while 66 were treatment-naïve. Clinical stage distribution: 45.7% stage IA-B, 28.6% stage IIA-B, 22.9% stage IIIA, and 2.9% stage IIIB. Tissue samples included 52 patients (104 samples) with matched tumor-involved and non-involved lung tissue, 17 patients (34 samples) with non-involved tissue only, and one patient (2 samples) classified as tumor-involved. ARTIDIS NS system effectively distinguished malignant tumors from uninvolved pulmonary tissue, achieving 88% sensitivity, 86% specificity, and 87% accuracy (n=52). It identified histological subtypes (adenocarcinoma vs squamous cell carcinoma) with 100% sensitivity and 83% specificity. NS correlated with molecular alterations, showing a higher Young's modulus in KRAS-mutant tumors. In adenocarcinoma cases, high stiffness, marked by increased collagen deposition (Picrosirius red staining), was associated with low CD8+ cell infiltration, suggesting stiffness-driven immune exclusion. Among the 17 patients with recurrence, 47% (8 patients) received first-line treatment (chemotherapy +/- immunotherapy). Twelve patients died (10 due to cancer progression). Notably, ARTIDIS NS predicted tumor progression within 10 months post-surgery, achieving 100% sensitivity and 93% specificity in identifying at-risk patient, even in non-involved tissue, while preserving tissue integrity for further analysis.

Conclusions: The ARTIDIS platform effectively differentiates malignant from non-malignant tissues by measuring tumor physical properties. This tool accurately predicts early recurrence and disease progression, enabling the identification of high-risk patients, including early physical changes in non-involved tissue associated with high-risk recurrence. Notably, high stiffness correlates with specific mutations and immune exclusion, could guide treatment decisions. To validate this, a 200-patient extension study is underway, focusing on neoadjuvant treatment patients to refine strategies for NSCLC and improve patient outcomes.

Keywords: Nanomechanical signature, Mechanical biomarker, Tumor Aggressiveness

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.57 TIM-1+ B Cells Promote Immune Suppression and Predict Poor Prognosis in Lung Adenocarcinoma

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Introduction: T-cell immunoglobulin and mucin domain-containing protein 1 (TIM-1) has been identified as a promoter of tumor cell viability, migration, and invasion. However, the precise role and distribution characteristics of TIM-1 within the tumor microenvironment (TME) remain critical areas of investigation. This study aimed to explore the distribution characteristics of TIM-1 within TME and the prognostic value of TIM-1 Positive immune cells in patients with lung adenocarcinoma (LUAD).

Methods: In this study, multiplex immunofluorescence (mIF) was performed on tissue slides from 126 patients with LUAD to investigate the distribution patterns of TIM-1 and the prognostic significance of three TIM-1 positive immune cell populations in both the primary tumor and tumor-draining lymph nodes (TDLN). Panel 1 (DAPI, CK, CD4, CD8, CD20, TIM-1) assessed TIM-1 distribution, and Panel 2 (DAPI, CD20, CD21, CD23) evaluated tertiary lymphoid structures (TLS).

Results: Compared to the primary tumor, TIM-1+CD8+T cells and TIM-1+B cells exhibited significantly greater infiltration in the TDLN ($p<0.0001$, $p<0.0001$ respectively). In the primary tumor, lower TIM-1+B cell infiltration was associated with longer overall survival (OS) (mOS, 84 vs. 54 months; $p<0.0001$, HR=2.574, 95% CI 1.356 to 4.889) and DFS (mDFS, 53.0 vs. 23.1 months; $p=0.018$, HR=1.721, 95% CI 1.035 to 2.862). In the TDLN, lower TIM-1+B cell infiltration was also correlated with longer OS (mOS, not reached vs. 64.7 months; $p=0.0019$, HR=2.350, 95% CI 1.323 to 4.172) and DFS (mDFS, 68.5 vs. 28.9 months; $p=0.016$, HR=1.707, 95% CI 1.081 to 2.696). Higher TIM-1+B cell infiltration in the TDLN was associated with a lower proportion of mature TLS ($p=0.0009$, $r=-0.3990$, 95% CI -0.5895 to -0.1666) and increased infiltration of TIM-1+B cells in the tumor was linked to reduced CD8+ T cell infiltration ($p=0.016$, $r=-0.2788$, 95% CI -0.3598 to -0.0233).

Conclusions: Our findings confirm the immunosuppressive role of TIM-1+B cells in LUAD and suggest that TIM-1+B cells exert immune suppression by inhibiting TLS maturation and CD8+ T cell infiltration and predict poor prognosis of LUAD patients. These findings highlight TIM-1+ B cells as a potential therapeutic target.

Keywords: TIM-1+B cell, lung adenocarcinoma, prognosis

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.58 Predictive Value of Tumor Microenvironment Biomarkers in Neoadjuvant Immunotherapy Combined With Chemotherapy for Locally Advanced NSCLC

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Introduction: Neoadjuvant immunochemotherapy represents a pivotal treatment strategy for locally advanced non-small cell lung cancer (LA-NSCLC). Pathological response rate serves as a critical prognostic indicator, with emerging evidence suggesting its intimate correlation with the functional dynamics of immune cells within the tumor microenvironment (TME). Despite growing interest, comprehensive insights into TME biomarkers remain limited. This study aims to elucidate the prognostic significance of TME biomarkers through a multidimensional analytical approach.

Methods: This retrospective cohort study investigated 77 patients with stage IIIA-IIIB NSCLC who underwent surgical resection following neoadjuvant immunochemotherapy (2018-2024). The methodological framework comprised four systematic approaches: (1) Immunohistochemical quantification of TME biomarker expressions in pathological specimens; (2) Comprehensive H-score calculation analyzing correlations with pathological response and prognosis; (3) Development of a predictive model for assessing Major Pathological Response (MPR); and (4) Validation of biomarker-response correlations using single-cell sequencing from the GEO database. Statistical analyses were conducted using SPSS 25.0 and R statistical software.

Results: Pretreatment H-scores revealed significant predictive value for CD8+ T cells (P=0.047) and CD20+ B cells (P=0.041) as independent MPR predictors. Single-cell sequencing validation corroborated the correlation between elevated CD8+ T and CD20+ B cell expressions and enhanced MPR rates. Post-neoadjuvant therapy, we observed notable immunological remodeling: significant increases in activating immune cell populations (CD4+ T cells, CD8+ T cells, CD20+ B cells, CD56+ NK cells, and CD86+ M1 macrophages) and concurrent reductions in immunosuppressive cell populations (FOXP3+ Treg cells and CD163+ M2 macrophages). The predictive model integrating CD8+ T and CD20+ B cell immune scores demonstrated superior prognostic accuracy (AUC: 0.761) compared to individual biomarkers.

Conclusions: Pretreatment CD8+ T and CD20+ B cell TME immune scores predict MPR in LA-NSCLC patients receiving neoadjuvant immunochemotherapy. Single-cell RNA sequencing validates the correlation between elevated immune cell expressions and enhanced MPR rates, highlighting biomarkers' predictive potential. The treatment dynamically modulates immune cell functionality, inducing TME immunological remodeling. Our multivariate model integrating immune signatures demonstrates superior prognostic precision compared to single biomarker approaches.

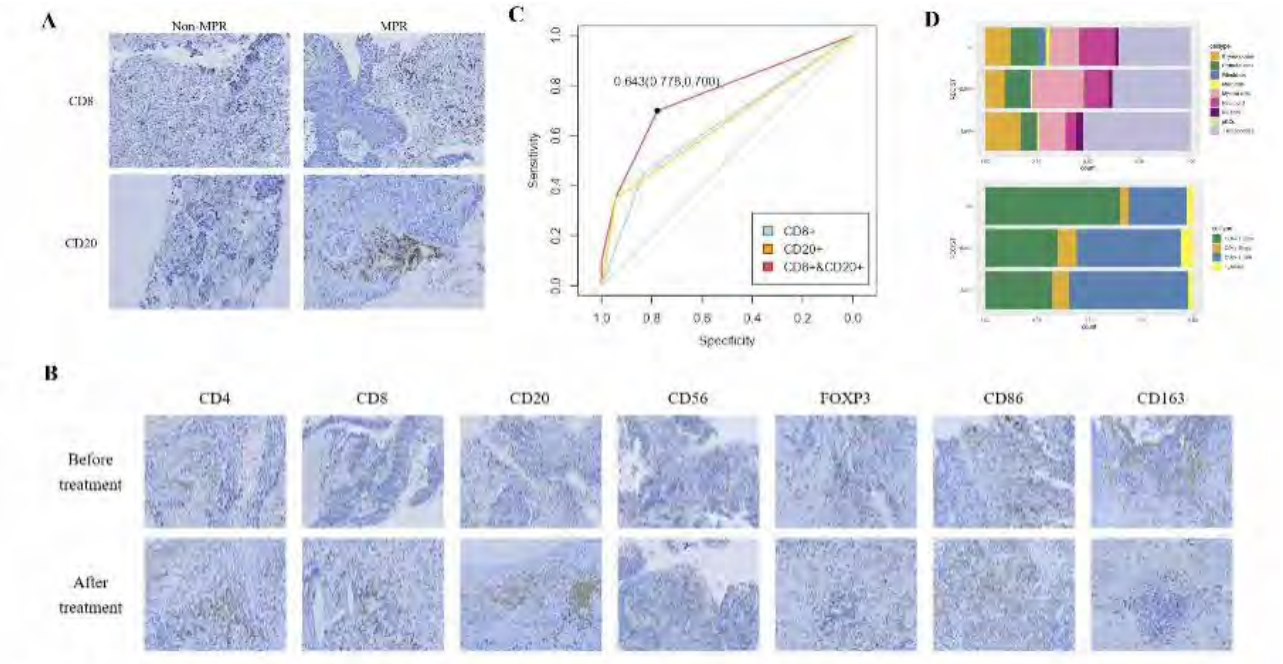

Fig.1 A, Expression of CD8+ T cells and CD20+ B cells in MPR and non-MPR groups before treatment (positive staining manifested as brown granules on cell membrane). **B**, Dynamic H-score changes of immune cells (positive staining of CD4+ T, CD8+ T, CD20+ B, CD56+ NK, CD86+ M1 macrophages, CD163+ M2 macrophages as membrane-distributed brown granules; FOXP3+ Treg positive staining as nuclear brown granules). **C**, ROC curves of CD8+ T cells, CD20+ B cells, and combined prediction model. **D**, Single-cell clustering: Cell type proportions before treatment

Keywords: Neoadjuvant immunotherapy, Tumor microenvironment, Biomarkers

P2.06.59 Multi-Level Screening of MET Aberrations in Treatment-Resistant Non-Small Cell Lung Cancer: A Report From LC-SCRUM-TRY

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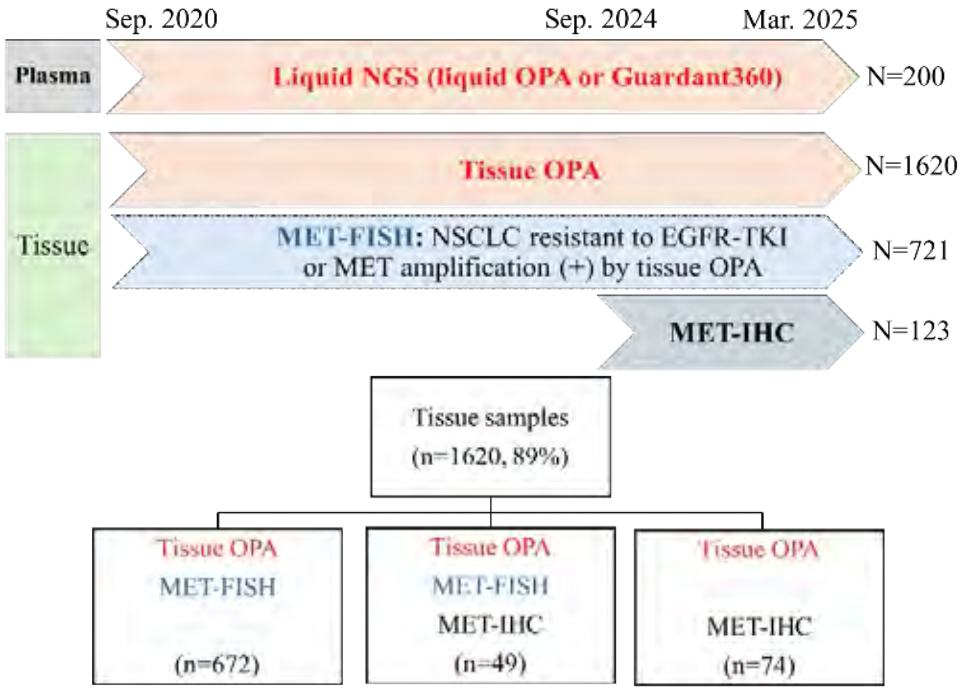
Introduction: MET aberrations are druggable targets in cancer treatment including non-small cell lung cancer (NSCLC) which can occur from both genetic and epigenetic alterations. We have established a nation-wide genomic screening project in treatment-resistant NSCLC (LC-SCRUM-TRY; UMIN000041957) to identify the characteristics of patients with resistant alterations including MET aberrations.

Methods: Tissue/ Plasma samples from patients with NSCLC registered in LC-SCRUM-TRY were analyzed. Tissue samples were subjected to a rapid NGS analysis, Oncomine Precision Assay (tissue OPA). Plasma samples were analyzed by liquid NGS (liquid OPA or Guardant360). MET-FISH was performed for NSCLC resistant to EGFR-TKI or harboring MET amplification by tissue OPA. MET-IHC screening was implemented since Sept. 2024 (Figure 1). MET amplification by NGS was defined as MET copy number ≥4 (tissue OPA), ≥1.2 (liquid OPA), ≥2.12 (Guardant360). MET amplification by FISH was defined as MET/CEP7 ratio ≥2. MET protein staining was graded based on the intensity of the staining in tumor cells (0 to 3+). MET overexpression was defined as ≥25% of tumor cells expressed 3+ staining assessed by two pathologists independently.

Results: As of Mar. 2025, a total of 1868 patients were enrolled, and 1820 treatment-resistant samples were analyzed. Sample type were tissue (89%), and plasma (11%). The median age was 70 (range, 19-90), with 51% male. A total of 1083 (59.5%) were already identified to have oncogenic driver at enrollment, including EGFR mutation (45.0%), and ALK/ ROS1/ RET rearrangement (6.6/1.9/1.5%, respectively). Tissue samples were analyzed by NGS (n= 1620), MET-FISH (n= 721), MET-IHC (n=123), respectively (Figure 1). Any MET aberration was detected in 195/1820 (10.7%). MET amplification was detected in 5.5% by liquid NGS, 5.4% by tissue NGS, and 16.0% by FISH analysis, respectively. MET amplification by tissue NGS was frequently observed in EGFR-mutated NSCLC compared with ALK/ROS1/RET-rearranged and driver-negative NSCLC (7.9% vs 3.8% and 3.4%, p<0.001). MET protein overexpression was detected in 44.7% by IHC. The frequency of MET overexpression was not significantly different between EGFR-mutated, ALK/RET/ROS1-rearranged, and driver-negative NSCLC (47%, 61%, and 38% respectively, p=0.21). Of 195 MET aberration-positive patients, 32 (16.4%) patients were enrolled into clinical trial as 2nd or later line of chemotherapies, including 13 patients into MET-targeted therapies.

Conclusions: MET amplification was predominantly detected in EGFR-mutated NSCLC, while MET protein overexpression was relevantly observed across NSCLC regardless of driver gene status. Multi-level screening of MET aberration in LC-SCRUM-TRY contributed to enrollment into clinical trial of MET-targeted therapies.

Figure 1. Multi-level screening of MET aberration in LC-SCRUM-TRY.



Keywords: MET aberration, amplification, overexpression, non-small cell lung cancer, reistance mechanism

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.60 Multimodal Diagnostic Model for Intraoperative Diagnosis and Surgery Strategy in Stage Ia LUAD (SuRImage V2): A Prospective, Multicentric Study

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Introduction: Intraoperative frozen section analysis is critical for guiding surgical decisions in stage IA lung adenocarcinoma (LUAD), including resection extent and lymph node dissection. However, its reliance on limited, suboptimal samples and time-consuming protocols risks diagnostic inaccuracy. To address these limitations, we propose an artificial intelligence framework leveraging preoperative chest CT and intraoperative resection images to enable rapid, precise diagnosis and risk stratification. This approach aligned with the diagnostic protocol by thoracic surgeons and aims to reduce reliance on traditional frozen section constraints, enhancing surgical decision-making accuracy and efficiency for early-stage LUAD.

Methods: This study prospective enrolled patients with stage IA lung adenocarcinoma underwent complete resection between June 2020 and September 2023 in Guangdong Provincial People's Hospital (GDPH), Affiliated Hospital of Guangdong Medical University (GDMUAH), Meizhou People's Hospital (MZPH).Preoperative CT within 3 months before surgery were collected and registration with each patient. Surgical resection images of the LUAD were taken by smartphones in operating theaters under natural lighting condition in operating theater. Artificialintelligence models (SuRImage v2) based on preoperative CT, intraoperative surgical resection images and clinical characteristics were established for three tasks. Task1 tend to differentiate invasive lung adenocarcinoma (IAC) from non-IAC lesions. Task2 tend to classify pre-invasive lesion (PIL), minimally invasive adenocarcinoma (MIA) and IAC. Task3 tend to more specifically classify IAC grading according to 2021 IASLC Grading system in LUAD. The study was registered in Chinese Clinical Trial Registry (ChiCTR2300075999).

Results: We prospectively collected 2344 surgical resection images of 1638 lung nodules in 1516 patients from GDPH and 1421 non-enhanced chest CT scans. For each task, we developed three models including CT model, SuRImage and SuRImage v2. In task1 the diagnostic performances were 0.79 for CT model, 0.80 for SuRImage and 0.81 for SuRImage v2. In task2 the diagnostic performances were 0.79 for CT model, 0.82 for SuRImage and 0.84 for SuRImage v2. In task3 the diagnostic performances were 0.77 for CT model, 0.80 for SuRImage and 0.82 for SuRImage v2. Incorporating with CT images, SuRImage v2 could reach better diagnostic performance, demonstrating the critical role of multimodal imaging in optimizing intraoperative decision support.

Conclusions: We developed rapid intraoperative diagnostic models based on preoperative CT, intraoperative surgical resection images and clinical information, which comprehensively combined the macroscopic and radiomic features of lung adenocarcinoma. Compared with frozen section diagnosis, this study could avoid the disturbance of sampling and reach a diagnosis rapidly to assist the decision of surgical strategies.

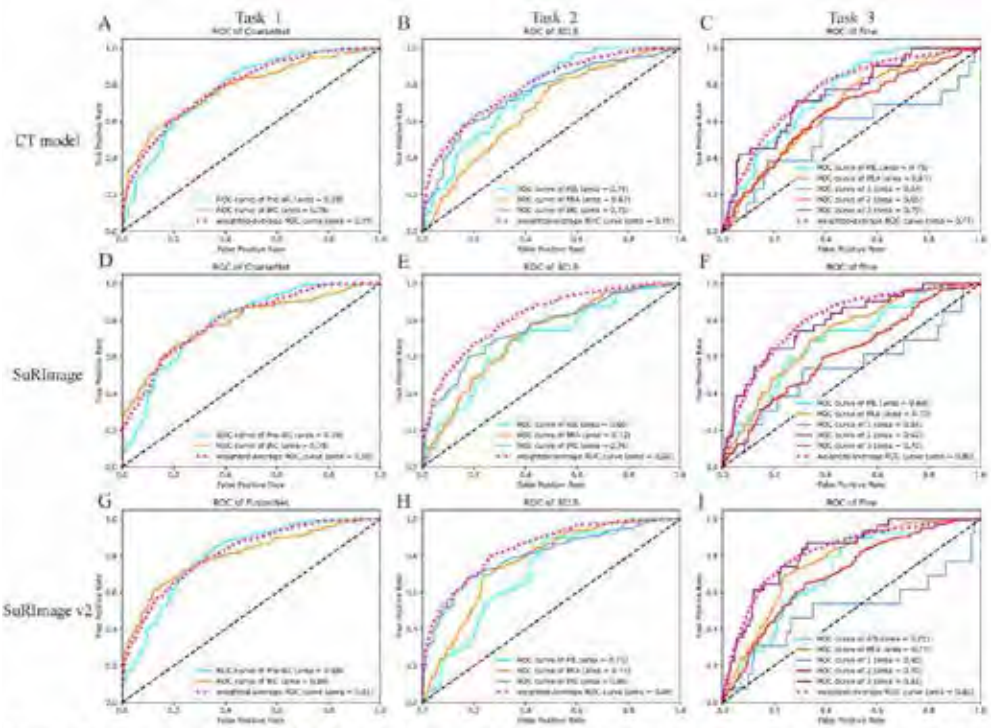

Figure 1. The diagnostic performance of CT model, SuRImage and SuRImage v2. Tasks 1 to 3 refer to different clinical scenarios for IAC identification, diagnosis and grading. CT model (A-C) were established with preoperative chest CT within 3 months, while SuRImage (D-F) were developed with intraoperative surgical resection images. This study enhanced the multimodal intraoperative diagnostic model SuRImage v2 (G-I) by incorporating preoperative CT and intraoperative macroscopic features. Area under the curve (AUC) were calculated for evaluation of model performance.

Keywords: Intraoperative diagnosis, Surgical strategy, Macroscopic feature

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.61 ASPiRATION. Australian Nationwide Cohort Study to Assess Impact of Comprehensive Genomic Profiling in Metastatic Lung Cancer

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Introduction: The importance of comprehensive genomic profiling (CGP) for metastatic non-small cell lung cancer (mNSCLC) is well-established but access to testing is not universal. ASPiRATION, an Australian study, investigated the feasibility and clinical impact of upfront CGP testing nationally, alongside standard of care (SoC) testing (i.e. minimum of EGFR, ALK, ROS1), to inform systemic therapy in community settings including regional, rural and remote (RRR) areas via a remote consent/Telehealth model.

Methods: Patients with newly-diagnosed, pathologically-confirmed, non-squamous mNSCLC with adequate tumour tissue for CGP and SoC testing were recruited. CGP was performed prospectively on archival tissue using FoundationOne® CDx or TruSight Oncology 500 panels. Molecular Tumour Boards (MTB) provided treatment recommendations based on genomic driver alterations in the first-line setting, classified as Tier 1 if they had Level 1 or 2 evidence of actionability according to OncoKB or TOPOGRAPH (Australian-developed database). Turnaround time (TAT) was measured from tissue request to MTB report.

Results: Between December 2020-June 2023, 1000 Australians with advanced NSCLC (median age 66yo; 14% Asian, 26% never-smokers, 49% female, 36% ECOG 0) were recruited from 85 hospitals across all states and territories, 27% from RRR areas, reflective of Australia's population distribution (28% RRR per 2023 census). TAT interquartile range was 22-36 days; 23% required additional biopsies within 90 days before CGP results. Twenty-eight (2.8%) participants were ineligible; 779 (80%) had evaluable results by both SoC and CGP. The most common driver alterations were KRAS (G12C, 13%; non-G12C, 18%), EGFR (17%), ERBB2 (5.5%), MET exon 14 skipping mutations (2.6%) and ALK fusions (4.2%). Tier 1 alterations were detected in 293 (38%) by SoC and 385 (49%) by CGP. Tier 1 alterations detected by CGP but not SoC included KRAS G12C (3.9%), MET mutations/amplifications (2.6%), EGFR (1.9%), ALK fusions (1.0%), all but one RET (1.3%) and all NRG1 fusions (0.8%). In 779 participants, 705 were treated with systemic therapy, but 79% commenced prior to receiving CGP results: 52% on chemo/IO and 27% on targeted agents. 16% enrolled in a clinical trial, 12% with targeted agents. Amongst those with Tier 1 alterations, 65% received targeted therapy, including 18% in RRR areas. Ninety-eight (13%) had actionable alterations by CGP but not SoC, of which 45% received targeted therapy. With 27 months follow-up, median overall survival (OS) for participants who received targeted treatment, non-targeted treatment and best supportive care was 34 months (95% CI, 30 - not reached), 16 months (95% CI, 13-20) and 8.1 months (95% CI, 2.7-13), respectively.

Conclusions: Tissue-based CGP testing detects 13% more actionable alterations than SoC testing, demonstrating the value of upfront comprehensive genomic screening in patients with mNSCLC. Considering CGP TAT, a formal utility analysis comparing universal upfront versus reflex testing would inform implementation to guide precision medicine at national scale.

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The Investigators thank the patients and their families. ASPiRATION was a collaboration between TOGA, the NHMRC Clinical Trials Centre, University of Sydney, and Omico.

Keywords: NSCLC, Comprehensive genomic profiling, tissue

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.62 Integrin-ß6 Modulates the Tumor Microenvironment and Serves as a Prognostic Marker in Lung Squamous Cell Carcinoma

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Introduction: Integrin-β6 (ITGB6) is a member of the integrin family implicated in tumor proliferation and metastasis in non-small cell lung cancer (NSCLC), making it a compelling therapeutic target. Interest in ITGB6 has recently grown with the development of sigvotatug vedotin, an ITGB6-targeted antibody-drug conjugate (ADC) conjugated to monomethyl auristatin E (MMAE), which has shown promising efficacy in heavily pretreated NSCLC. In this analysis, we investigate the prognostic relevance of ITGB6 expression and its impact on the tumor microenvironment (TME) in lung squamous cell carcinoma (LUSC).

Methods: We analyzed bulk RNA sequencing data from the TCGA-LUSC cohort and single-cell RNA-seq data from GSE131907, GSE148071, and GSE162498. ITGB6 RNA and protein expression in tumor vs. normal tissues were evaluated using GEPIA2 and UALCAN, respectively. Differential gene expression between high (top 25%, n =135) and low (bottom 25%, n =135) ITGB6 expressors was performed using DESeq2. Immune cell infiltration was assessed via XCell and EPIC deconvolution algorithms. Gene set enrichment analysis (GSEA) was conducted using Enrichr. Single-cell data were processed in Seurat following standard QC and normalization workflows. Correlation analyses were performed using the CSCORE algorithm. Prognostic value was assessed using a multivariate Cox regression model adjusting for stage, age, and gender.

Results: The TCGA-LUSC cohort included 512 patients with full transcriptomic and survival data. Patients with higher ITGB6 expression, stratified by median expression level, had worse overall survival (OS) compared to those with lower expression (logrank p = 0.0019). Moreover, a multivariate Cox regression for OS confirmed high ITGB6 expression as an independent predictor of poor prognosis (HR = 1.39, P = 0.0201). Bulk RNA and protein analysis revealed no significant difference in ITGB6 expression between tumor and normal samples. However, single-cell analysis demonstrated significantly lower ITGB6 expression in malignant LUSC epithelial cells compared to normal lung epithelium (log2FC = -0.96, P < 0.0001). High ITGB6 expressors showed upregulation of genes involved in epithelial-to-mesenchymal transition (EMT) and cancer-associated fibroblast (CAF) activation, including ANGPTL4, FN1, FAP, VIM, and CAV1. GSEA revealed enrichment in pathways such as EMT, extracellular matrix (ECM) organization, CXCR chemokine receptor binding, and collagen remodeling. Immune deconvolution showed that high ITGB6 expression was associated with increased infiltration of CAFs, dendritic cells, monocytes, M1 and M2 macrophages, T regulatory cells, and higher immune and microenvironment scores. Conversely, infiltration of Th1 and Th2 CD4+ T cells was reduced (all p < 0.01). Single-cell analysis further revealed elevated ITGB6 expression in CAFs from LUSC tumors compared to normal lung fibroblasts (log2FC = 1.97, P < 0.0001).

Conclusions: High ITGB6 expression is an independent poor prognostic marker of OS in LUSC and is associated with an immunosuppressive and fibrotic TME characterized by active CAFs and increased ECM remodeling. These findings suggest that ITGB6 may not only serve as a therapeutic target but also as a biomarker for patient stratification in LUSC, particularly in the context of ADC therapy.

Keywords: Integrin B6, Biomarker, Tumor microenvironment

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.63 The Role of the Lower Airway Microbiome in Predicting Treatment Response to Immunotherapy in Patients With Non-Small Cell Lung Cancer

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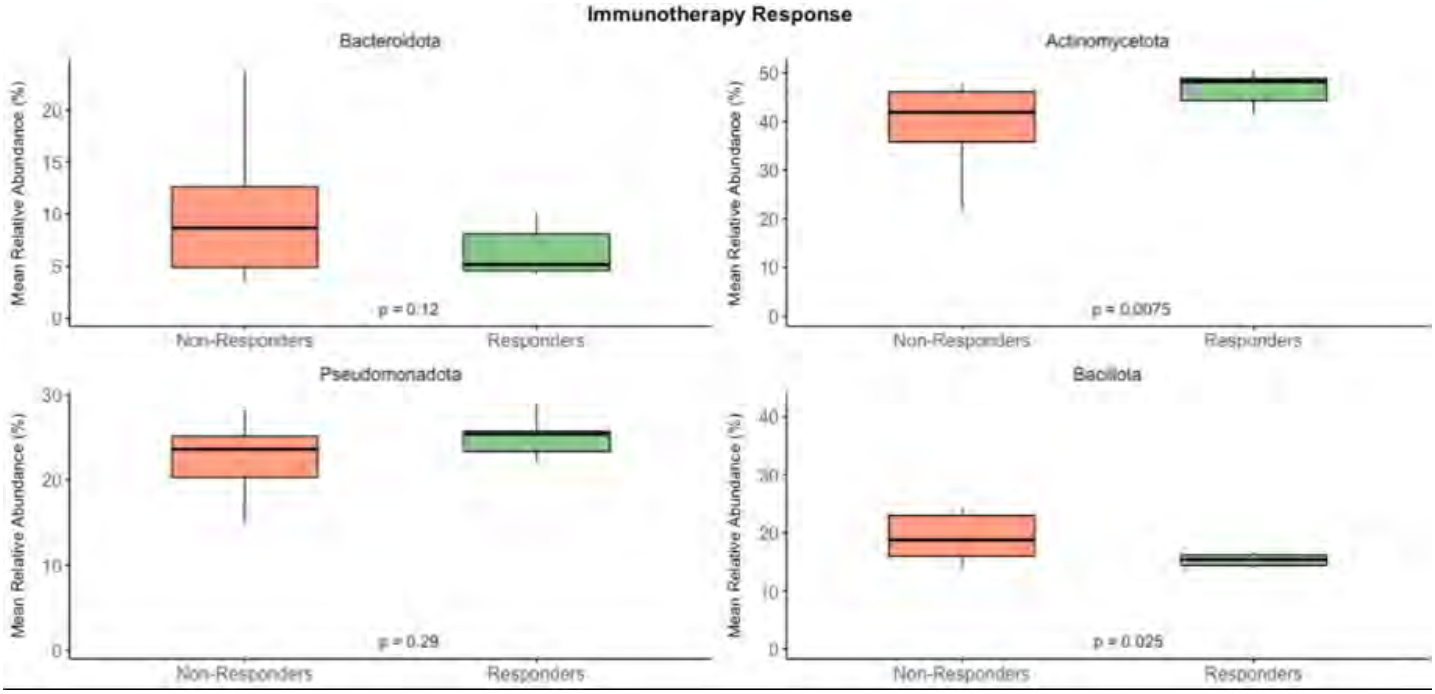
Introduction: Endobronchial ultrasound guided biopsy(EBUS) is standard of care to diagnose and stage patients with suspected lungmalignancy. Current biomarkers availableto predict treatment response to therapy are imperfect. Recently, the gutmicrobiome has been shown to modulate treatment response to immunotherapy innon-small cell lung cancer (NSCLC). However, despite the lower airwaymicrobiome interacting directly with the tumour microenvironment and multiplestudies suggesting a role for the airway microbiome in tumorigenesis, there arefew studies to date investigating the effect of the airway microbiome ontreatment response in NSCLC.

Methods: Patients attending our tertiary referralcentre for EBUS with suspected lung malignancy from June 2021 to December 2023were consecutively recruited to the study. Clinicopathological and demographicdata as well as information on antibiotic and antacid use were collected.Bronchoalveolar fluid was sampled from the site of the suspected tumour in 74participants. 58 participants were diagnosed with NSCLC and of those, 38patients received systemic therapy, with 24 from this group receivingimmunotherapy. We performed whole genome metagenomic sequencing to obtain the lungmicrobiome profiles from these patients.

Results: Patients treated with immunotherapy were stratifiedinto responders (n = 8; 33%) and non-responders (n= 16; 67%)using Durable Clinical Response criteria. The Simpson index, a measure of alphadiversity was reduced in responders, but this did not reach significance (p =0.06). Compositional differences were also noted. Phylum-001 was significantlyincreased in non-responders (p = 0.004) while Phylum-002 was enriched inresponders (p = 0.003). Multivariate analysis at a species level demonstrated asignificant negative effect on immunotherapy response for two microbial species(p = 0.01-0.02) although this did not remain significant on Benjamini Hochbergcorrection for multiple comparisons.

Conclusions: Few studies have investigated the impact ofthe lower airway microbiome on immunotherapy response in NSCLC. Increasedabundance of firmicutes has previously been associated with the development oflung cancer, as have oral colonisers at the genus levels. Our study is thefirst to suggest that differences in thelocal airway microbiome at the species level may also have a role in modifyingimmunotherapy responses. Larger multicentre studies are needed to furtherexplore its potential as a novel biomarker and therapeutic target. .



Keywords: lung microbiome, immunotherapy response, non-small cell lung cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.64 Fusion Transcript Burden Is Associated With Clinical Outcomes in Patients With Resected NSCLC

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Introduction: Disease-free survival (DFS) varies considerably in patients with non-small cell lung cancer (NSCLC) following an anatomic resection, with few validated prognostic biomarkers guiding systemic adjuvant therapy selection. Here, we explore fusion transcript burden (FB), or the total number of unique fusions detected at the RNA level, as a means to prognosticate DFS, based on the premise these events result in increased neoantigen production and heightened immunosurveillance in tumors.

Methods: Paired-end RNAseq was performed by Tempus on 536 FFPE NSCLC tumors, stage IA-IIIB, resected at RUMC between 2010 and 2021, with those receiving neoadjuvant therapy excluded. The overall cohort consisted of patients with resected NSCLC and was 59.1% (317) female and 40.9% (219) male, ranging in age from 41-93 (median 70) yrs. STAR-Fusion was used in parallel to STAR genome alignment, and differential gene expression between groups based on Fusion Burden performed using edgeR with GLM and quasi-likelihood. Kaplan Meier plots were performed using Survival/Survminer. Primary endpoint was DFS, with fusion burden as categorical.

Results: Median follow-up time in the study was 42.4 months. Fusion Burden (FB) followed a right-skewed distribution in the overall cohort, with a range of 5 to 47 (med. value = 14). Wilcoxon rank-sum test showed a difference in FB distribution that was stage-dependent, comparing stage II to III cases ($p = 0.035$), but was independent of histology (Adenocarcinoma vs. Squamous Cell Carcinoma (SCC), $p= 0.25$). However, when a FB threshold of 10 unique transcripts was applied, those with SCC histology had a significant difference ($p=0.037$; $n=100$) in DFS as early as the 2-yr timepoint, versus those with non-squamous histology ($p=0.24$, $n=434$). When we applied this same FB threshold to the full stage II /III sub-cohort, a superior DFS was observed for those with a FB ≥10 at the 1-, 2-, and 5-yr timepoints (all $p \leq 0.05$), relative to those below the threshold. Notably, the prognostic value of FB with respect to benefit from adjuvant therapy was most pronounced for patients with SCC histology, where adjuvant therapy provided a ~20% increase in DFS at the at 5-yr timepoint for those with a FB ≥10 ($p=0.031$, $n = 78$). Finally, when we examined differential gene expression in the full cohort grouped by FB (threshold at 10), there were a total of 2,908 modulated genes with a FDR < 0.05. Among the top 50 results, 22% are implicated in inflammatory/immune response and 20% are implicated in apoptosis.

Conclusions: Our findings support that fusion transcript burden may have value for prognosticating benefit from adjuvant chemotherapy and may hold promise for the improved prognostication of patients with early stage lung cancer and/or guiding selection of immune checkpoint inhibitors as part of their treatment strategy. Efforts are now focused on cohort expansion and contextualizing these findings to the tumor immune microenvironment.

Keywords: Fusion Burden, Clinical Outcome

P2.06.65 An Ensemble Approach to Predict Three-Class PD-L1 Expression From H&E Whole-Slide Images

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Introduction: Hematoxylin and eosin (H&E) digital pathology slides (DPS) hold valuable information for predicting complex medical tasks, as immune checkpoint inhibitor (ICI) response. While PD-L1, assessed via immunohistochemistry, remains the most reliable clinically-approved biomarker, H&E slides offer a cost-effective, widely-available alternative for computational decision support. We incorporate finer classification of PD-L1 status using single-modality data, adressing a critical gap in the field.

Methods: The I3LUNG (NCT05537922) is a global EU project aiming to predict response to ICIs using artificial intelligence (AI), incorporating data from centers in Italy, Germany, Greece, Spain, US, and Israel. The cohort includes individuals in a non-curative setting who have received first-line treatment for advanced or metastatic NSCLC with ICIs, alone or in combination with chemotherapy or other agents. We used H&E DPS, paired with patient's PD-L1 status. DPS were tiled into squares (224x224px) at 10x magnification. From each tile, we extracted embeddings from UNI foundation model (embedding dimension 1x2024) to be fed as input to an attention-based multiple instance learning (ABMIL) algorithm to predict three-class PD-L1 expression status (<1%, 1-49%, ≥50%). ABMIL treats a DPS as a bag of tiles, using attention mechanisms to identify key tiles influencing the slide-level prediction. We compared multiple model variations, including DP1, using a single ABMIL mode and DP5 and DP15 using an ensemble of 5 and 15 ABMIL, respectively, to assess the impact of ensemble size. We also tested DP5L, a variant replacing the attention mechanism with random sampling and averaging over up to 50 tiles, and a baseline dummy model DM predicting the majority class.

Results: We used 419 pts with available DPS and PD-L1 status (144 pts <1%, 140 pts 1-49%, and 135 ≥50%). The models were evaluated using balanced and per-class accuracy (ACC), precision (PRE), recall (REC), and F1-score (F1). The results are presented in Table 1. All the models outperformed the dummy model DM. Comparing DP5 and DP15, a larger ensemble size appears beneficial for PD-L1 expression classification. Both models significantly outperform DP1, further emphasizing the advantage of the ensemble approach. Additionally, DP5L underperforms compared to DP5 and DP15, highlighting the importance of the attention mechanism in the ABMIL method.

Conclusions: To our knowledge, this is the first AI-based study effectively demonstrating three-class PD-L1 expression classification directly from H&E slides. All models significantly outperformed the baseline model. This approach can assist clinical decision-making without requiring PD-L1 immunohistochemistry, particularly if access to PD-L1 testing is limited.

Table 1. Metrics on the 3-class classification of PD-L1 expression

Metric	DP_5	DP_{15}	DP_1	DP_5L	DM
ACC	0.50	0.43	0.33	0.50	0.33
PRE	0.50	0.43	0.33	0.50	0.12
REC	0.50	0.43	0.33	0.52	0.34
F1	0.50	0.43	0.33	0.49	0.18
PD-L1<1% PRE	0.51	0.43	0.34	0.58	0.34
PD-L1<1% REC	0.55	0.45	0.40	0.44	1
PD-L1<1% F1	0.53	0.36	0.36	0.50	0.51
PD-L1 1-49% PRE	0.47	0.38	0.36	0.43	0
PD-L1 1-49% REC	0.63	0.36	0.39	0.69	0
PD-L1 1-49% F1	0.54	0.37	0.32	0.53	0
PD-L1 ≥50% PRE	0.54	0.47	0.33	0.58	0
PD-L1 ≥50% REC	0.30	0.47	0.33	0.36	0
PD-L1 ≥50% F1	0.39	0.44	0.33	0.45	0

Keywords: Digital Pathology, PD-L1 Expression, Immunotherapy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.66 Novel Predictive Spatial Biomarker in NSCLC: Discriminant of Niches Unlocking Treatment Sensitivity (DONUTS)

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Introduction: We previously showed that CD8+FoxP3+ cells predict response to anti-PD-1-based therapy in melanoma. Here, we leveraged large-scale mIF analyses (~35M individually mapped cells; 50,000 high power fields) and novel spatial modelling techniques to characterize these cells and their niche as predictive features of a treatment-responsive tumor microenvironment in NSCLC. We benchmark their performance to PD-L1 IHC and tertiary lymphoid structures (TLS).

Methods: A total of 75 pre-treatment biopsy specimens were obtained from 4 cohorts of patients with NSCLC; Cohort 1 (n=25) from the first neoadjuvant clinical trial of anti-PD-1(NCT02259621); Cohort 2 (n=14) from a landmark trial of advanced NSCLC receiving second-line anti-PD-1(NCT01673867); Cohort 3 (n=20) patients received second-line standard of care anti-PD-1; and Cohort 4 (n=16) from a landmark trial of advanced NSCLC receiving second-line chemotherapy (docetaxel) following progression on first-line platinum doublet chemotherapy(NCT01673867). Slides were stained with a previously-validated 6-marker multiplex immunofluorescence (mIF) panel. The AstroPath platform was used to generate comprehensive cellular maps from whole-slide scans. A probabilistic model was trained on the contact neighbours of ~50,000 CD8+FoxP3+ cells in NSCLC resections, and the niche surrounding these cells was defined using CD8, CD163, FoxP3, and cytokeratin. Receiver-operating characteristic curves were used to test the association of patient outcomes with (1) the densities of CD8+FoxP3+ cells and (2) the CD8+FoxP3+ cell niche (i.e. the surrounding ring of cells or "DONUTS").

Results: CD8+FoxP3+ cell densities showed strong predictive value for patient outcomes in all four cohorts. DONUTS defined by using only 4 mIF lineage markers were ~150-fold more abundant than CD8+FoxP3+ cells themselves and met or outperformed the actual cells (Figure 1, AUCs of 0.73-0.86 in all cohorts tested). When benchmarked against other biomarkers, both CD8+FoxP3+ cell densities and the DONUTS were additive to PD-L1 IHC results, and served to further stratify patient outcomes. Additionally, resection specimens were used to show that the density of both CD8+FoxP3+ cells and the DONUTS associated with TLS density (p=0.001), the latter of which are rarely captured on pre-treatment specimens.

Conclusions: Our study identifies CD8+FoxP3+ cells and their immunoactive niche as robust predictive biomarkers of treatment outcome across diverse disease stages and treatment types. Importantly, the DONUTS are more prevalent than the CD8+FoxP3+ cells themselves, reducing concern of sampling error. Further, this biomarker only requires four markers, is additive to PD-L1 and is a surrogate for TLS. Taken together, the DONUTS represent a next-generation predictive biomarker poised for clinical implementation.

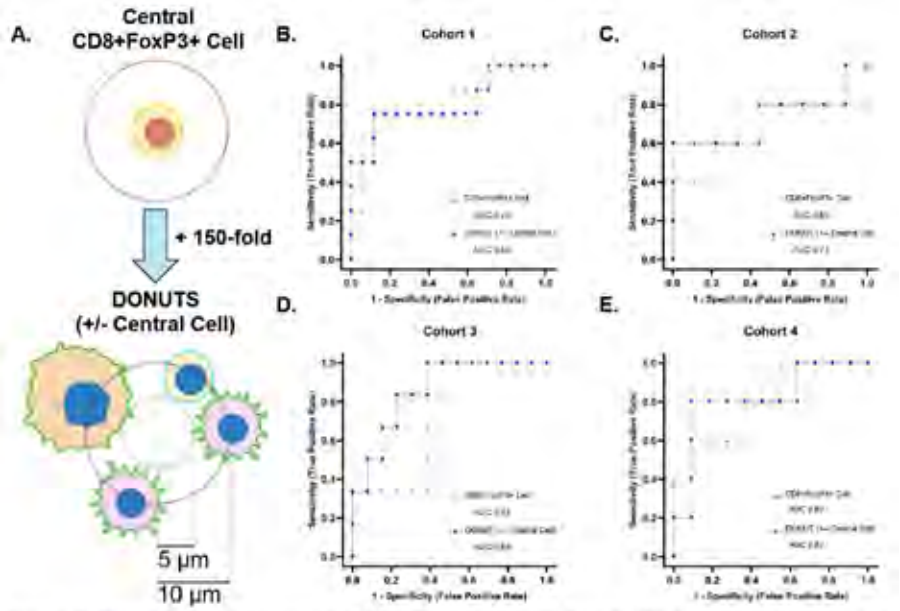

Figure 1. Novel spatial biomarker (DONUTS) validates in four NSCLC cohorts. Densities of CD8+FoxP3+ cells and the CD8+FoxP3+ cellular niches (DONUTS) were used to predict outcome in NSCLC. **A.** The DONUTS (bottom) occur at ~150-fold greater frequency than CD8+FoxP3+ cells themselves (top). **B-E.** Receiver-operator characteristic curves are plotted for four testing cohorts. The DONUTS outperform CD8+FoxP3+ cells in predicting major pathologic response (**B**; AUC=0.80 vs 0.79), overall survival (**C**; AUC=0.73 vs 0.69), radiographic response (**D**; AUC=0.86 vs 0.73), and progression free survival (**E**; AUC=0.82 vs 0.80).

Keywords: Biomarker, Spatial, NSCLC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.67 Retrospective Analysis of 124 LCNEC Tumors With Targeted Expression Profiling of 111 Samples Identifies Candidate Chemo-Sensitivity Biomarker

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Introduction: Pulmonary large cell neuroendocrine carcinomas (LCNECs) are high-grade, poorly differentiated lung neuroendocrine neoplasms. LCNECs are rare, representing ~3% of all lung malignancies, but convey poor prognosis, with only 16.7% 5-year survival. Previous genomics profiling of LCNEC has identified prognostic groups: carcinoid- or non-small cell-like (EGFR, STK11, KEAP1 mutations) with improved survival and small cell-like (RB1, TP53 mutations) with worse survival. Despite heterogeneity and poor survival, LCNEC continues to be staged and managed like non-small cell lung cancer (NSCLC). This study aimed to use a single-institution bio-banked LCNEC registry to evaluate clinical and molecular features associated with survival, metastasis, and response to platinum-based chemotherapy.

Methods: A retrospective cohort of 124 cases of LCNEC prospectively consented for RNA profiling were identified in the Duke Biorepository. Diagnosis was reviewed and confirmed by a thoracic pathologist. Patients were included regardless of pathologic stage. Patient- and tumor-related clinical features associated with overall survival (OS) were examined using multivariable Cox proportional hazards including landmark analyses to adjust for time bias experienced by patients who received adjuvant chemotherapy. To identify associated molecular features, 111 of these 124 cases were profiled with a 1,392 immuno-oncogene panel. Differentially gene expression analysis was performed contrasting short and long survivors (separated by median survival: 5.1 years) who received chemotherapy and contrasting pathologic stage I tumors with eventual metastasis vs no metastasis. Significantly differentially expressed genes were identified using a quasi-likelihood F-Test on the relevant coefficient of a generalized linear model (FDR < 0.10).

Results: In our cohort of 124 LCNEC cases with median follow-up of 17.27 years, the median age at time of surgery was 68 (IQR:58-72) and all pathologic stages were represented (I:57, II:36, III:25, IV:6 patients). The incidence of recurrence or metastasis was 31.6% in patients with pathologic stage I disease. Most patients underwent lobectomy. Thirty-seven patients received adjuvant chemotherapy, primarily with a platinum-backbone. We identified age at surgery (HR:1.03, 95%CI:1.01-1.05), ECOG performance status 1 (HR:1.94, 95%CI:1.15-3.30), receipt of platinum-based chemotherapy (HR:0.52, 95%CI:0.29-0.91) and stage III pathology (HR: 2.61, 95%CI 1.39-4.91) as significantly associated with OS. However, chemotherapy was not significantly associated with overall survival (HR: 0.58, 95%CI 0.32-1.05) in a landmark analysis (landmark time: 3 months). We found two significantly differentially expressed genes associated with long survival, BMP7 (log2FC: -1.36, FDR:0.009). and CGREF1 (log2FC: -0.94, FDR=0.057). Median survival after receipt of chemotherapy was 8.43 and 1.79 years for patients with high (above median) and low (below median) BMP7 expression, respectively. No genes were significantly differentially expressed between stage 1 tumors with or without metastasis after multiple hypothesis correction.

Conclusions: In this clinical and immune-oncologic gene expression study of 124 cases of LCNEC, the receipt of platinum-based adjuvant chemotherapy was not associated with OS with adjusted landmark analysis. However, we identified BMP7 and CGREF1 as candidate biomarkers for sensitivity to platinum-based chemotherapy. If validated, these biomarkers could inform clinical decisions regarding perioperative chemotherapy and surgery. Future work will profile candidate biomarkers in banked tissue with immunohistochemistry and aim to validate these findings in an orthogonal cohort.

Keywords: Large Cell Neuroendocrine Carcinoma, Biomarkers, Chemosensitivity

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.68 Enhancing Precision Medicine in NSCLC - the Importance of Tumor Metabolic Spatial Profiling in Immunotherapy Biomarker Discovery

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Introduction: Immune checkpoint blockade (ICB) therapies provide durable benefits to a subset of patients with non-small cell lung cancer (NSCLC), though the majority do not respond. This study aims to spatially profile the tumor-immune contexture and metabolic activity in ICB-treated patients to gain insights on how spatial organization of cells, activation states and cellular interactions can be utilized predict ICB response and resistance.

Methods: Using a multiplex immunofluorescence (mIF) panel of 44 proteins, encompassing immune and metabolic cell states, we profiled tumor microarrays (TMA) from two large cohorts of NSCLC patients treated with ICB (n=117, 72 with relevant clinical annotations). Employing Nucleai's deep learning (DL)-based analysis pipeline, marker positivity was determined by a DL-classifier for each segmented cell, followed by assignment to 14 cell types by known protein expression profiles. Cell subtypes were established by clustering of positive prediction probabilities of metabolically and immunologically relevant proteins, outputted from the DL-classifier. Spatial features were calculated by integrating cell types, phenotypic states, and spatial context. Welch's T-test identified spatial features linked to clinical outcomes within each metabolic subgroup, distinguishing responders (objective response or prolonged progression-free survival (PFS)) from non-responders. A multivariate model predicting clinical benefit was developed from spatial features within tumor subtypes in a training set (n=53) and validated on an independent test set (n=19).

Results: We identified 5 distinct tumor clusters which differed in their cellular composition, immune and metabolic states, and clinical outcomes following ICB. Key proteins differentiating these clusters included CD44, G6PD, Hexokinase-1, HLA-A, and oxidative phosphorylation (OXPHOS) proteins. All patients in the CD44+ tumor cluster demonstrated clinical benefit, with extended PFS (23.2 months vs. 3.0 and 3.3 months for G6PD+ and HEX1+ clusters, p=0.02) and a trend towards prolonged overall survival (OS). Within the tumor metabolic subtypes, different immune and metabolic states were associated with treatment outcomes - within the G6PD+ and HEX1+ tumor clusters, positivity for OXPHOS proteins was associated with better clinical outcome, while in the HLA+ and OXPHOS- tumor clusters, high expression of immune activation related proteins, such as HLA-A and PD-L1, were more significantly associated with clinical outcome. Thus, the metabolic phenotype of the tumor is critical for accurate ICB response biomarkers identification. A multivariate ICB outcome predictor based on tumor subtypes demonstrated high accuracy (AUC 0.93, p=0.001) in an independent set, with predicted responders showing higher clinical benefit rates (84.6% vs. 16.7%, p=0.01) and prolonged PFS and OS.

Conclusions: In this study we present the analysis results of one of the largest clinically annotated mIF dataset from pre-treatment biopsies of NSCLC patients treated with ICB. Our findings reveal that the clinical relevance of spatial features is intricately linked to the tumor's metabolic phenotype, emphasizing the necessity of integrating metabolic phenotyping into prediction models for improved prediction of ICB outcomes. This research underscores the potential of multiplex imaging and advanced spatial biology tools to significantly advance biomarker discovery and enhance personalized treatment strategies, paving the way for more tailored and effective therapeutic interventions in NSCLC.

Keywords: Immunotherapy, biomarker, spatial

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.69 Metabolite Enrichment Patterns Correlate With Race, Gender and BMI in Lung Cancer Patients

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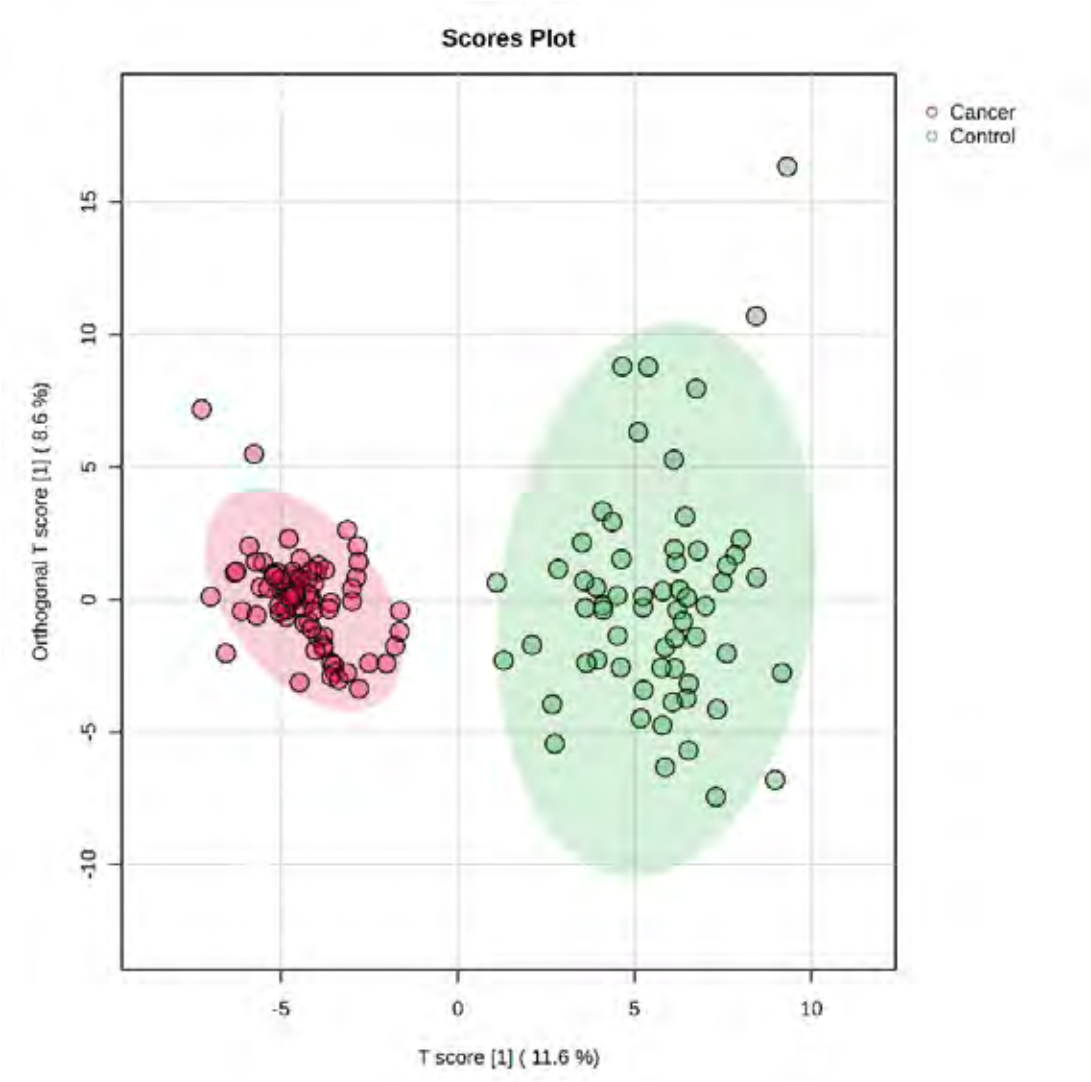
Introduction: Despite the high incidence of lung cancer (LC), the effect of patient demographics on metabolic pathway activity remains poorly understood. Understanding these metabolic differences will provide insight into how patient anthropometric data affects LC development and progression, and could uncover novel therapeutic and preventative strategies, offering the potential for more personalized and effective treatments.

Methods: This retrospective cohort study collected plasma from 62 patients with confirmed LC and 80 control patients without LC. Metabolomic profiling was performed using ultra-high performance liquid chromatography - mass spectrometry (UHPLC-MS). Analysis was conducted using MetaboAnalyst 5.0 to identify distinct metabolite enrichment patterns. Orthogonal partial least squares discriminant analysis (OPLS-DA) was employed to assess significant differences in metabolite levels between LC and control groups. We then determined the most significant metabolite differences, using Variable Importance in Projection (VIP) scores for discrete variables (e.g. race and gender), and a random forest algorithm for continuous variables (e.g. body-mass index (BMI)).

Results:

Figure 1



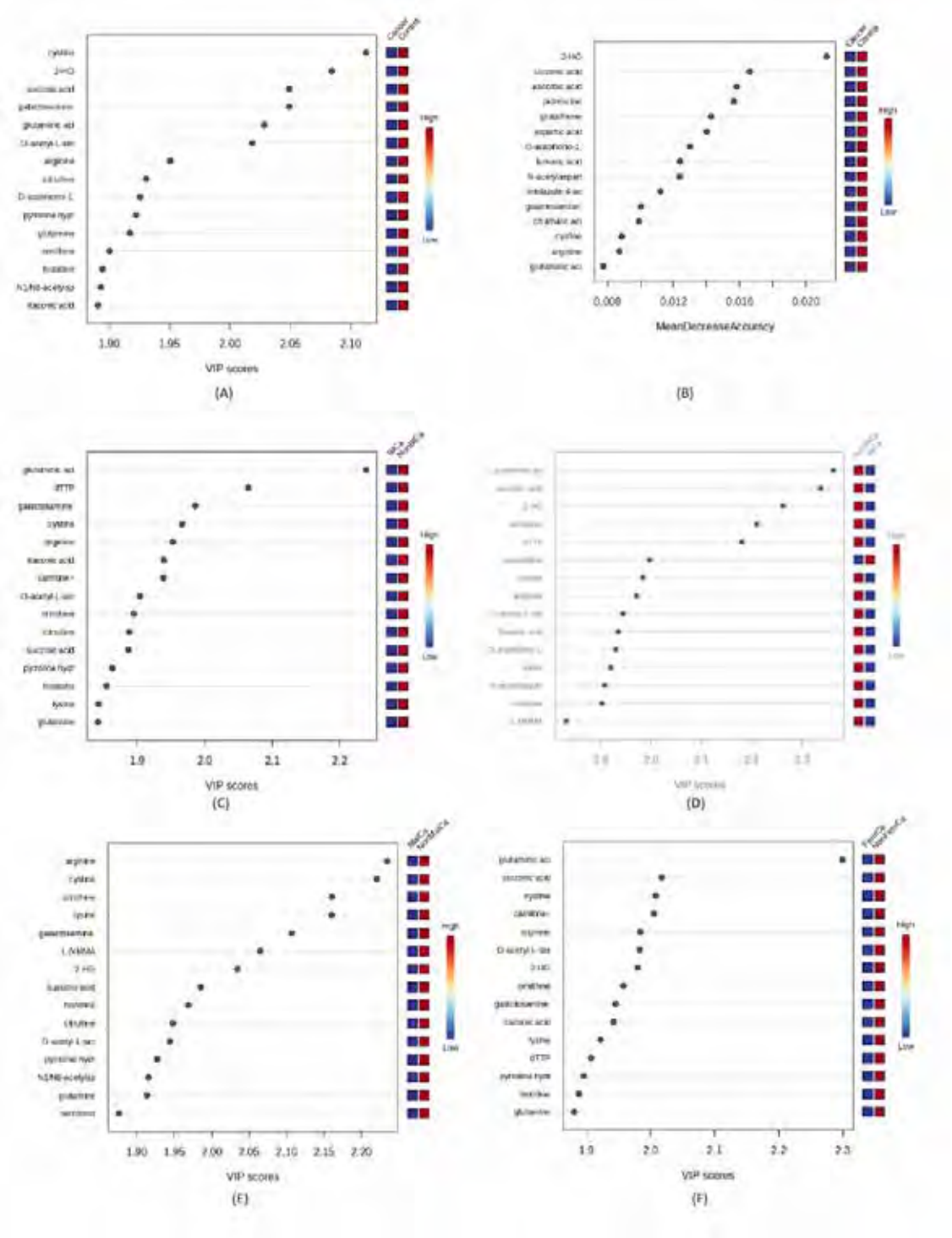


Figure 2

We found significant differences in metabolite expression between cancer and control samples (Figure 1), with decreased metabolite enrichment seen in LC (Figure 2A). We then found the most significant metabolite differences in subgroup analyses for BMI (2B), black race (2C), white race (2D), male gender (2E) and female gender (2F).

Conclusions: Our analysis demonstrates significant differences in metabolite expression between LC and control samples, with most metabolites showing decreased plasma enrichment in LC. This may be attributed to heightened tumor metabolite consumption. Additionally, different patient subsets had different patterns of metabolite enrichment, such as lower plasma levels of 2-hydroxyglutarate in cancer patients with higher BMIs. Future research exploring the relationship between metabolite enrichment and factors such as geospatial location, epigenetic gene expression and social determinants of health will deepen our understanding of how both biological and external factors modulate tumor metabolism.

Keywords: lung cancer, biomarkers, metabolomics

P2.06.70 Concurrent Tissue and ctDNA-Based Genomic Profiling in Advanced Lung Cancer: A Prospective, Single-Institution Study

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Introduction: Liquid biopsy (LB) is a valuable tool for detecting actionable molecular alterations in advanced non-small cell lung cancer (aNSCLC), facilitating genotype-matched therapies. While LB is recommended for cases with inadequate/inaccessible tumor tissue, its routine integration into the diagnostic workflow for all newly diagnosed aNSCLC patients remains limited. This study evaluated whether concurrent plasma circulating tumor DNA (ctDNA) next-generation sequencing (NGS) alongside tissue-based NGS improves the time to molecular results and treatment initiation in newly diagnosed aNSCLC patients.

Methods: This single-center, prospective, quality improvement study included two cohorts of patients. The 'ctDNA cohort' underwent plasma ctDNA NGS in addition to standard tissue-based NGS, and the 'reference cohort' received standard tissue-based NGS alone. Both cohorts underwent tissue biopsy and reflex tissue NGS. ctDNA NGS was done on a 31 gene hotspot panel, DNA only, FindIt by Canexia Health. The primary outcome was time from medical oncology consultation to initiation of first-line systemic therapy.

Results: A total of 215 patients were analyzed, 90 in ctDNA cohort and 125 in control cohort. Patient characteristics are shown in table 1. Compared to the reference cohort, the ctDNA cohort had significantly shorter median time to molecular results (14 vs. 35 days; p=0.01); time to molecular results from first respirology/thoracic surgery consultation (22 vs. 48 days; p=0.01); time to treatment initiation from first medical oncology consultation (12 vs. 22 days; p=0.01). Lack of molecular results at the first medical oncology consultation led to treatment delay in 13% (11/86) of patients in the ctDNA cohort, compared to 23% (28/122) in the reference cohort (p=0.06) (Figure 1).

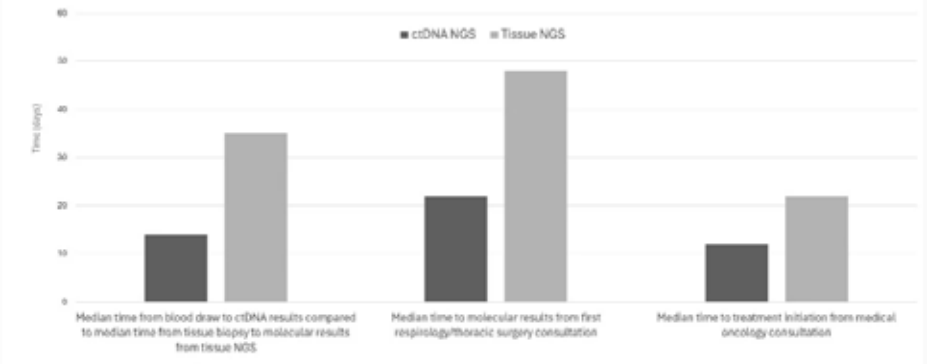
Conclusions: In a publicly funded, single-payer healthcare system, concurrent ctDNA and tissue-based NGS significantly accelerates molecular result acquisition and reduces time to treatment initiation compared to tissue testing alone. These findings support incorporating ctDNA testing early in the diagnostic pathway for aNSCLC.

Table 1: Demographic characteristics of the ctDNA and reference cohorts.

Characteristic	ctDNA cohort (No. (%) of patients, N=90)	Reference cohort (No. (%) of patients, N=125)
Age, years (median)	71	72
Sex		
Male	39 (43)	72 (58)
Female	51 (57)	53 (42)
Histology		
Adenocarcinoma	60 (67)	78 (62)
Squamous cell carcinoma	23 (26)	31 (25)
NSCLC NOS	7 (7)	16 (13)
Clinical stage		
4	65 (72)	125 (100)
3	25 (28)	0 (0)

No., number; NSCLC NOS, non-small cell lung cancer not otherwise specified.

Figure 1. Outcome measures



Keywords: Liquid biopsy, ctDNA, NSCLC

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.71 Clonal Hematopoiesis and Its Association With Lung Cancer Incidence and Immunotherapy Response: A Meta-Analysis

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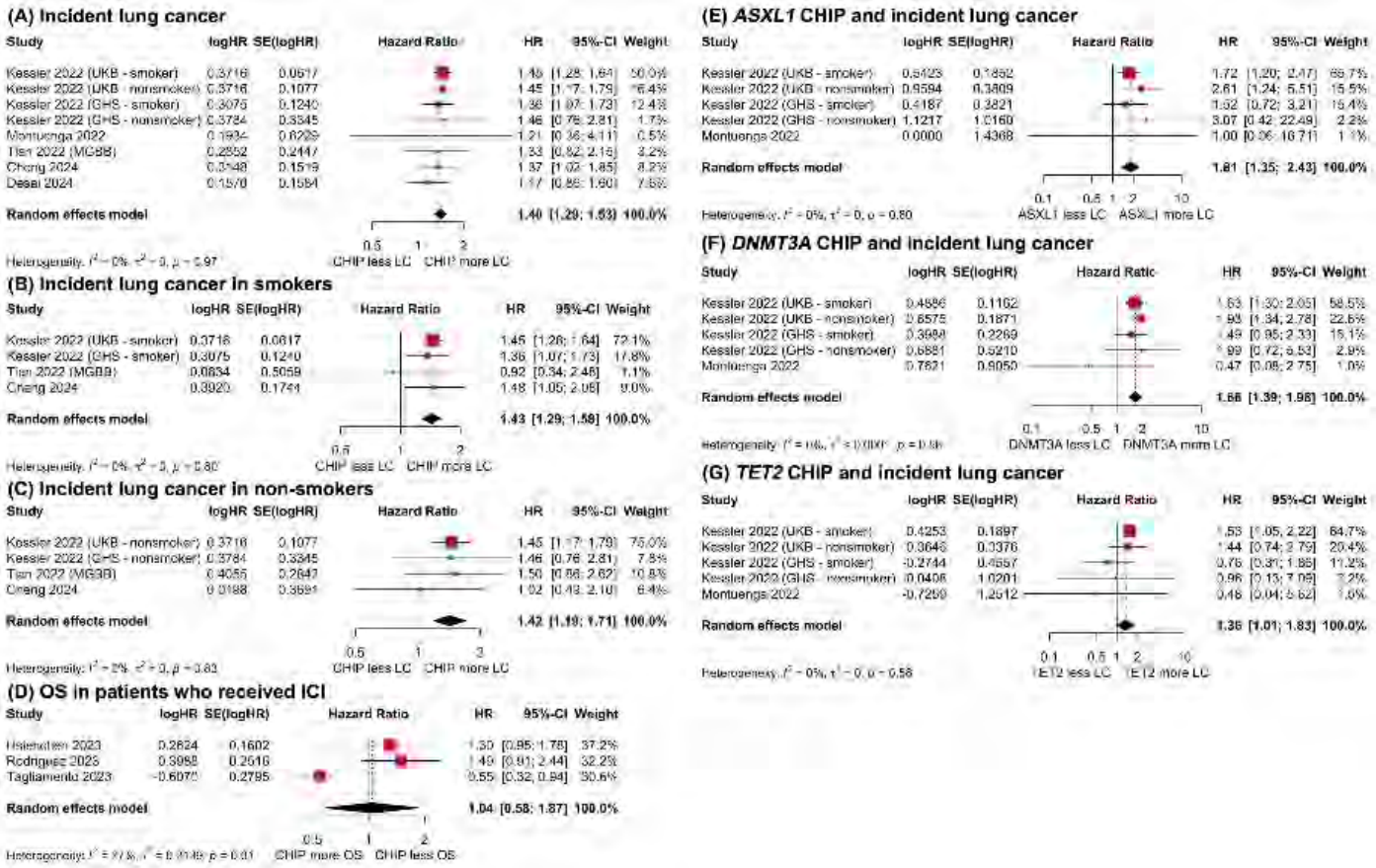
Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is a form of acquired somatic mutation that occurs in the hematopoietic stem cell without detectable hematologic malignancy. It is known to increase the risk of developing solid tumors, including lung cancer, through heightened inflammation and altered antitumor immunity. This may affect the efficacy of immune checkpoint inhibitors (ICI). We performed meta-analyses to evaluate (1) the association between CHIP and the incidence of lung cancer and (2) whether CHIP affects the survival outcome in patients with lung cancer who received ICI.

Methods: Studies indexed in Medline and Embase databases were identified using search terms related to "CHIP" and "lung cancer" from inception to February 2025. We included all observational studies that compared individuals with and without CHIP. For studies evaluating the risk of developing lung cancer, all patients must not have had prior lung cancer diagnoses, then followed for incident lung cancer. For studies evaluating ICI response, all patients with lung cancer must receive ICI, then followed for overall survival (OS). Hazard ratios (HR) or odds ratios (OR), with associated 95% confidence intervals (CI), were pooled using the generic inverse variance method. We conducted subgroup analyses based on smoking status and gene mutations.

Results: In total, eight studies were included in the meta-analysis. The presence of CHIP was associated with an increased incidence of lung cancer (HR 1.40, 95%CI 1.29-1.53; Figure 1A). The elevated risk did not differ between individuals with a history of smoking (HR 1.43, 95%CI 1.29-1.58) and those without (HR 1.42, 95%CI 1.19-1.71) (Figure 1B-C). Among patients with lung cancer who received ICI, CHIP was not associated with an adverse OS (HR 1.04, 95%CI 0.58-1.87; Figure 1D). Based on the involved gene, differential risks were noted, with ASXL1 being associated with the highest risk, followed by DNMT3A and TET2 (HR for ASXL1 1.81, 95%CI 1.35-2.43 vs. HR for DNMT3A 1.66, 95%CI 1.39-1.98 vs. HR for TET2 1.36, 95%CI 1.01-1.83; Figure 1E-G).

Conclusions: CHIP was associated with an elevated risk of incident lung cancer regardless of smoking status. All CHIP genes conferred increased but differential risks, further warranting studies to evaluate risk stratification using CHIP genetic makeup for this at-risk population. Although antecedent CHIP did not worsen overall survival in lung cancer patients treated with ICI, future studies are needed to confirm this finding and identify potential mechanistic vulnerabilities in this patient subgroup, which could potentially guide more individualized screening strategies.



Keywords: clonal hematopoiesis, lung cancer, immunotherapy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.72 Impact of Peripheral Electrolyte on Equilibrium Between Immunotherapy Toxicity and Survival in Advanced NSCLC Treated With PD-L1 Blockade

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Introduction: Peripheral electrolyte homeostasis is emerging as a critical regulator of immune cell function and systemic immunologic balance. Understanding how these ions shape the balance between autoimmune versus antitumor response in the context of immune checkpoint blockade may provide novel insights into predicting and managing immune-related adverse events (irAEs).

Methods: Individual participant data of 1,137 patients with non-small cell lung cancer (NSCLC) from two randomized trials (OAK [n=850] and POPLAR [n=287]) treated with atezolizumab versus docetaxel were analyzed. Logistic regression and Cox proportional hazards models were employed to assess the associations between baseline peripheral electrolyte levels (calcium, chloride, magnesium, sodium, phosphorus, and potassium) and the risk of irAEs and survival outcomes (durable clinical response, progression-free survival, and overall survival); significant ions in univariate analyses were further evaluated in multivariate models. Subgroup analyses examined associations with organ-specific (endocrine, neurological, gastrointestinal, cutaneous) and severe (grade ≥3) irAEs. Additionally, parallel analyses in the chemotherapy arm were conducted to examine whether these associations are immunotherapy-specific.

Results: Elevated serum calcium levels at baseline were associated with significantly higher irAE risk while remaining independent of survival and response to immunotherapy, underscoring its toxicity-specific predictive value. Conversely, higher chloride levels predicted both increased irAE incidence and improved clinical efficacy, indicating a dual modulatory role for autoimmune and antitumor response (Figure 1). Organ-specific analyses linked calcium to endocrine irAEs and chloride to neurological and gastrointestinal irAEs. Patients experiencing severe irAEs exhibited higher calcium and chloride levels compared to those without severe irAEs (Figure 2). In contrast, no significant association was observed between these electrolytes and adverse events in the chemotherapy arm, emphasizing their specificity for immunotherapy-induced toxicity.

Conclusions: Baseline electrolyte ions exerted differential impacts on irAE risk and efficacy outcomes in NSCLC immunotherapy. Notably, calcium specifically associates with irAEs, may offering a potential biomarker to guide toxicity mitigation strategies.

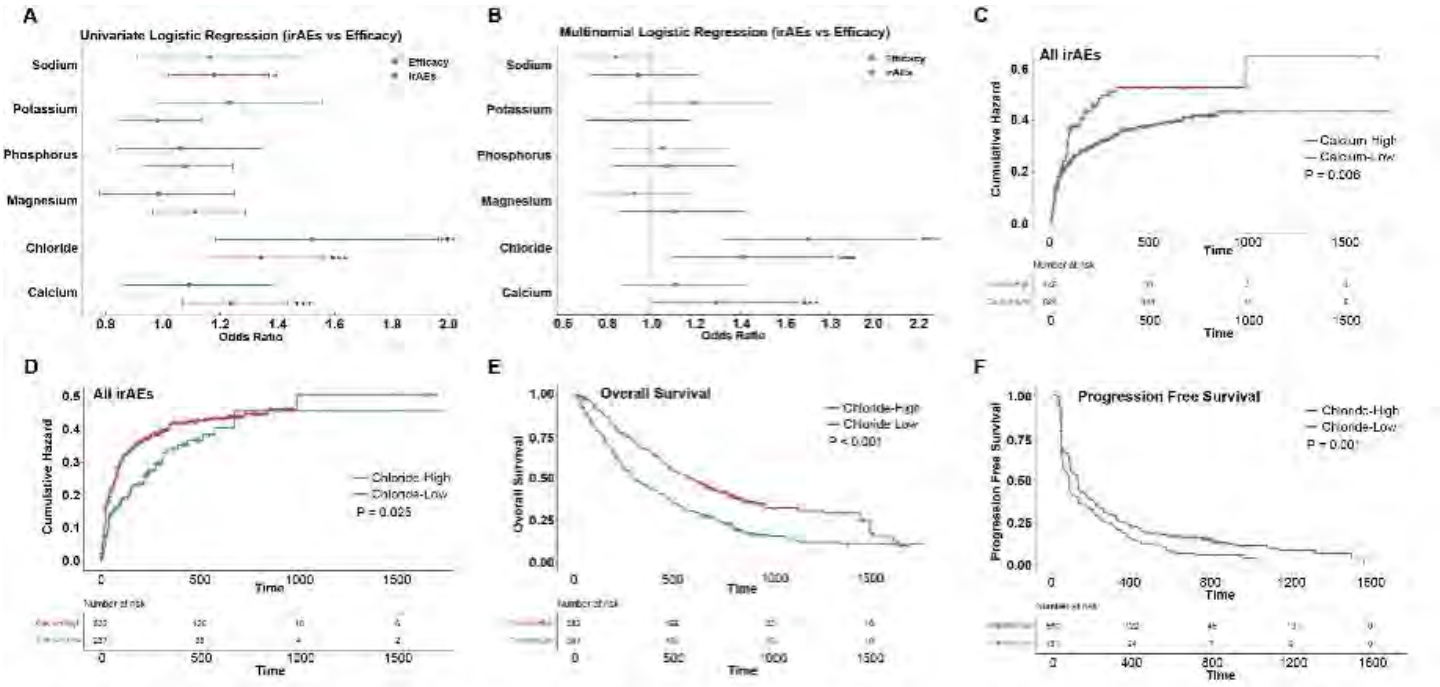

Fig1. Baseline levels of peripheral electrolyte ions captures the predictive value of irAEs and survival outcomes. (A-B)Univariate and multivariate logistic regression analysis of baseline peripheral ions associated with irAEs and immunotherapy response in advanced NSCLC. (C–D) Cumulative hazard curves of irAEs stratified by calcium and chloride levels. (E–F) Survival curves of overall survival and progression-free survival per chloride levels.

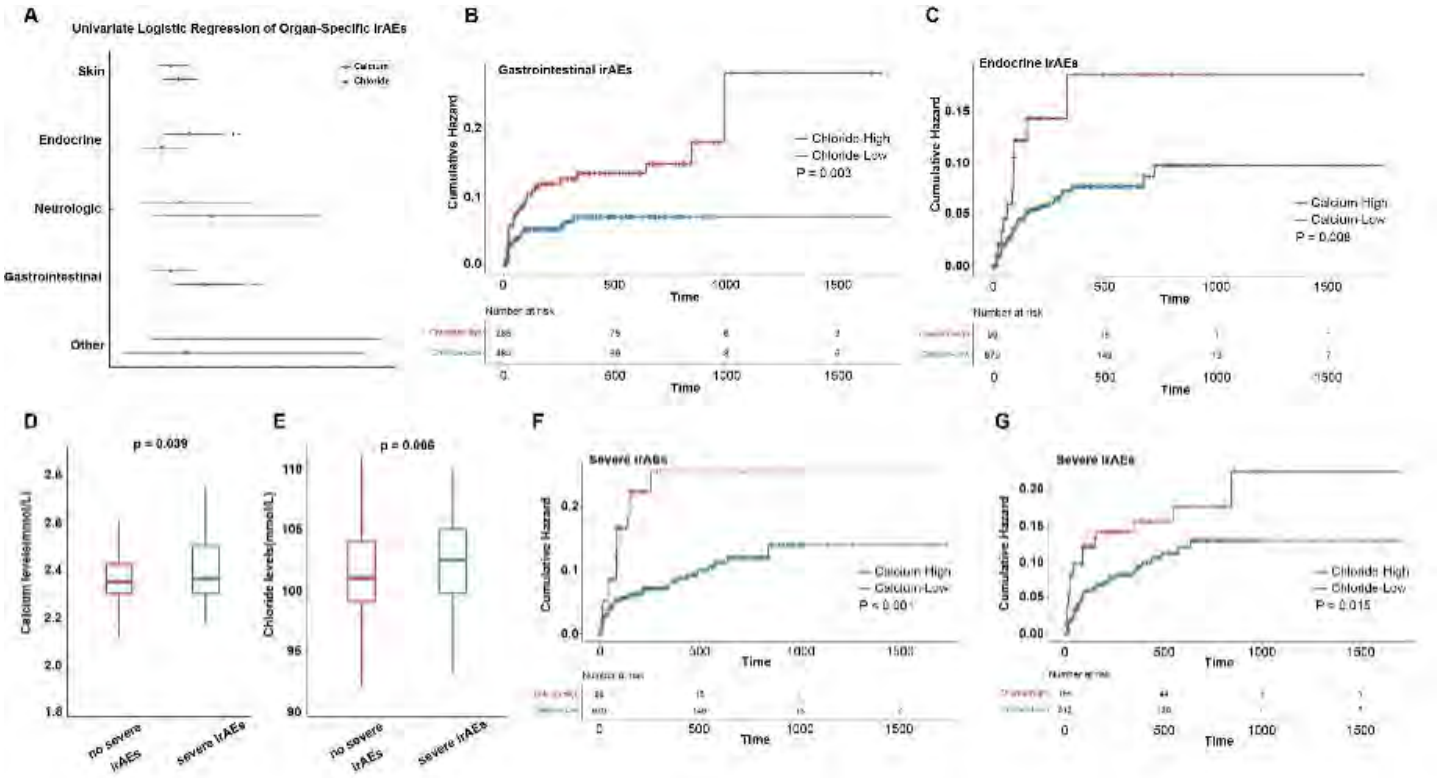

Fig. 2 Stratification of organ-specific and severe irAEs by baseline calcium and chloride levels. (A) Univariate logistic regression of baseline calcium and chloride levels across organ-specific irAEs (skin, endocrine, neurological, gastrointestinal, and others). (B–C) Cumulative hazard curves of gastrointestinal irAEs by chloride levels and endocrine irAEs by calcium levels. (D–E) Severe irAE status–based distribution of calcium and chloride levels. (F–G) Cumulative hazard curves of severe irAEs by calcium and chloride levels.

Keywords: immune-related adverse events (irAEs), electrolyte ions, non-small cell lung cancer (NSCLC)

P2.06.73 Cerebrospinal Fluid Biomarkers in Patients With Leptomeningeal Metastasis of Lung Cancer

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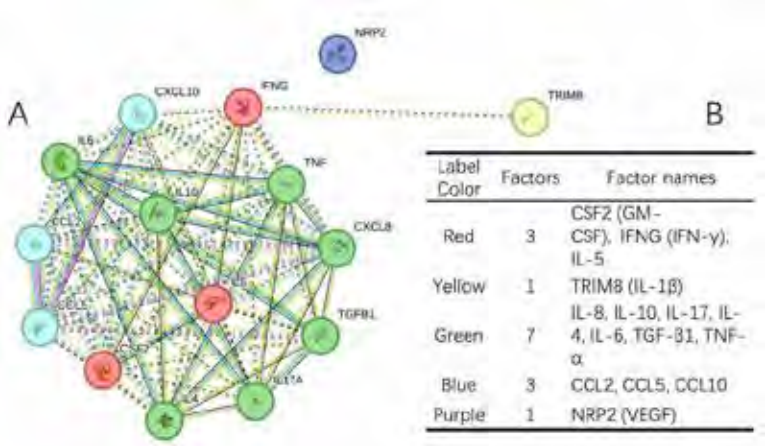
Introduction: Lung cancer is a most common malignancy to develop leptomeningeal metastasis (LM). Cerebrospinal fluid (CSF) serves as a unique tumor microenvironment for leptomeningeal metastatic tumor cells to grow. So far, limited research has investigated CSF inflammatory or tumor-related factors in LM patients. Here, we studied the levels of representative cytokines, chemokines, and growth factors in the CSF of patients with LM in lung cancer (LMLC) to identify potential biomarkers for LMLC and explore its unique fluid tumor microenvironment.

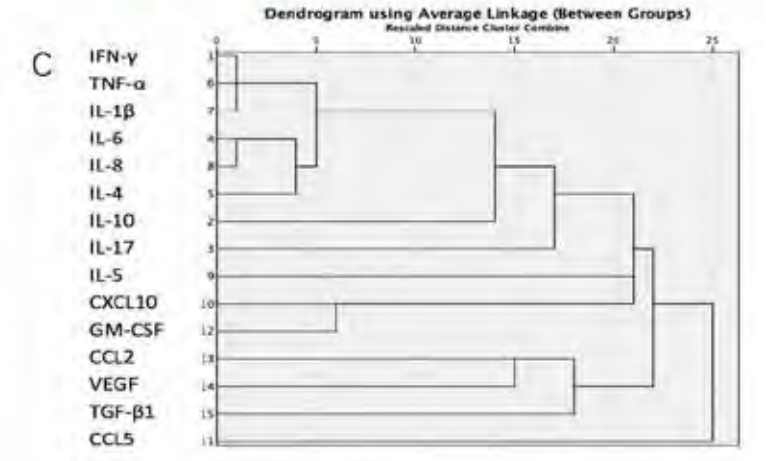
Methods: We enrolled 65 cases whose baseline CSF specimens were well-preserved upon diagnosis of LMLC at Peking Union Medical College Hospital between March 2014 and January 2022. Clinical information and long-term survival follow-up were obtained. Meanwhile 53 demographically balanced patients with benign central nervous system diseases were enrolled as a control group. High-throughput detection of factors (including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-γ, IFN-α, TGF-β1, CCL2, CCL5, CXCL10, VEGF and GM-CSF) in the CSF was performed using magnetic microflow immunofluorescence with the double antibody sandwich method. The LMLC diagnostic value was evaluated using receiver operating characteristic (ROC) curves. Univariate and Cox regression analyses were performed to analyze the prognostic risk factors. Cluster analysis and protein interaction network was used to explore potential interaction characteristics of the identified factors.

Results: 10 factors were identified to show significantly different levels in the CSF of patients with LMLC as with control group. The levels of TGF-β1, VEGF, CCL2, CXCL10, IL-4, IL-6, IL-8, IL-10, and IFN-γ were significantly greater while IFN-α levels were significantly lower ($p<0.05$). TGF-β1 had the greatest area under the ROC curve (AUC=0.856) for diagnosing LMLC. When cutoff value of TGF-β1 was 55.005 pg/mL, the sensitivity and specificity was 0.862 and 0.849,respectively. Patients with high IL-4 levels had a significantly greater mortality risk than those with low levels ($p = 0.0056$). Cluster analysis and protein interaction network(based on public database)revealed potential interaction characteristics of the identified factors.(see Figure 1).

Conclusions: This study provides an insight that LMLC patients demonstrated quite different spectrum of inflammatory and tumor-related factors in CSF than that with benign central nervous system diseases. The CSF levels of TGF-β1 and IL-4 may be used as diagnostic and prognostic biomarker for LMLC, respectively. Mechanism studies are still warranted.



Label Color	Factors	Factor names
Red	3	CSF2 (GM-CSF), IFNG (IFN-γ), IL-5
Yellow	1	TRIM8 (IL-1β)
Green	7	IL-8, IL-10, IL-17, IL-4, IL-6, TGF-β1, TNF-α
Blue	3	CCL2, CCL5, CCL10
Purple	1	NRP2 (VEGF)



Keywords: Leptomeningeal metastasis, cerebrospinal fluid, biomarker

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.74 Detection of Actionable Biomarkers in Liquid Biopsy From Non-Small Cell Lung Cancer Patients Using NGS-Based Assays

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Introduction: Analysis of cell-free DNA (cfDNA) by NGS has emerged as an opportunity for assessing actionable biomarkers in lung cancer patients with limited amount of tumor tissue. However, the availability of in-house liquid biopsy NGS assay options is limited. Many are expensive, require high cfDNA input, or involve complex workflows, limiting their clinical implementation. In this study, we have compared two NGS panels on different sequencing platforms, for the detection of actionable variants using cfDNA from late stage non-small cell lung cancer (NSCLC) patients.

Methods: cfDNA plasma samples from 49 metastatic NSCLC patients were used to prepare NGS libraries with the Oncomine Lung cfTNA Assay (Thermo Fisher, 12 genes), and the oncoReveal Core LBx panel (Pillar Biosciences, 104 genes). Libraries were sequenced with Ion S5 (Thermo Fisher) and NextSeq 550 (Illumina) sequencers, respectively. All lab workflows and sequencing configurations were strictly following the recommended procedure described in the manufacturer's user manuals. Sequencing data were analyzed using Thermo Fisher's Ion Reporter and Pillar's PiVAT softwares. Matched tumoural tissue sample was available in 20 out of the 49 patients.

Results: A total of 53 pathogenic variants were identified in 26 positive samples, detected using the Oncomine panel, of which 47 were also detected by the oncoReveal Core assay (PPA = 88.7%). At sample level, high concordance (47/49; 95.9%) was observed between the two panels (24 positive, 23 negative, and 2 positive samples detected only by oncoReveal Core). A high correlation among the VAFs of detected variants was observed between the two assays (r = 0.96). Further, 256 additional Tier I (drug response) and Tier II (pathogenic) variants were also detected by the oncoReveal Core panel that were not called by Oncomine. In 20 cases, tissue samples that had been previously tested were also available, with a total of 27 pathogenic variants detected in 17 positive tissue samples. 11 out of these 27 variants (40%) were not detected by either panels, 3 of them because they were not covered, and the other 8 likely due to insufficient tumor cfDNA present in the plasma sample. On the other hand, Oncomine and oncoReveal Core also detected 6 and 90 additional Tier I/II variants that were not detected by tissue testing.

Conclusions: Our study shows a high concordance among detected positive variants in NSCLC patient plasma cfDNA between two different liquid biopsy NGS assays. More importantly, the VAF of concordant variants detected were highly correlated, suggesting NGS testing as a dependable, non-invasive, alternative molecular testing for cancer biomarkers. Discrepancies were mainly attributed to low cfDNA levels in liquid biopsy samples and differences in panel coverage, highlighting key factors to consider when integrating NGS plasma testing into clinical practice.

Keywords: Liquid biopsy, Biomarkers, NGS

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.75 Liquid Biopsy NGS Accelerating Treatment Decision-Making in Non-Small Cell Lung Cancer

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Introduction: Recent breakthroughs in identifying molecular markers have transformed the treatment of non-small cell lung cancer (NSCLC), with therapies targeting specific mutations improving overall survival (OS). The use of Next Generation Sequencing (NGS) in clinical settings enables detailed analysis of tumor genetics to identify potential treatment targets. While traditional tissue biopsies remain the standard for tumor profiling, their invasive nature has made way for plasma-based biopsies, which offer a quicker, less invasive alternative to assess circulating tumor DNA. This advancement has shifted existing treatment approaches and enhanced patient outcomes, especially when used alongside tissue biopsy in a comprehensive testing strategy. This study explored a real-world community cohort of NSCLC patients who underwent both tissue and liquid biopsies to assess how these tests influence treatment decisions, time to start therapy, and overall outcomes.

Methods: This retrospective study analyzed adult patients with advanced NSCLC treated at Memorial Cancer Institute who underwent both tissue and liquid NGS testing between July 1, 2015, and February 25, 2025. We evaluated patient demographics, clinical characteristics, and biopsy-specific factors, including turnaround time (TAT), and time to treatment decision (TtT). Unpaired t-tests were used for statistical analysis of TAT and TtT, while descriptive outcome data were assessed using the Log Rank (Mantel-Cox) test. Treatment decisions were based on the available sample report, affected by insufficient quality or label alterations.

Results: The study analyzed 368 patients with NSCLC, most of whom were white (79.1%), non-Hispanic (63.6%), female (54.6%), and former smokers (63.3%), with adenocarcinoma as the predominant histology (89.7%). Liquid biopsy NGS had a significant reduction in TAT by 12 days compared to tissue biopsy, with median times of 8 days vs. 20 days, respectively ($p<0.0001$). Additionally, while 14.1% of tissue biopsy samples were non-reportable due to insufficient quality, all liquid biopsy samples successfully generated results. Liquid biopsy NGS guided treatment decisions in 81.9% of cases and was associated with a shorter TtT than tissue biopsy, with a median of 10 vs. 14 days for targeted therapy. Among treatment-naive patients, TtT was similar between biopsy methods, differing by only one day overall (13.5 vs. 12.5 days) and by two days for those receiving targeted therapy (7 vs. 9 days). In 190 patients with targetable genetic alterations, concordance between tissue and liquid biopsy ranged from 95.0% to 99.7%. PFS did not significantly differ between biopsy methods ($p\geq0.65$).

Conclusions: This study emphasizes the importance of liquid biopsy NGS in enhancing genomic profiling and supporting diagnostic and therapeutic decisions for advanced NSCLC patients. Liquid biopsy outperformed tissue biopsy in this study, offering faster TAT, reduced TtT, higher sample success rates with high concordance rates. These results demonstrate how liquid biopsy not only complements tissue biopsy but also can be used to decide front line therapy in metastatic NSCLC patients.

Keywords: Liquid biopsy, NGS, Targeted therapy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.76 Molecular Profiling of Lung Cancer Brain Metastases: Analysis Between Liquid Biopsy and Brain Metastasis Tissue Results

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Introduction: Molecular profiling is critical to the management of metastatic non-small cell lung cancer (NSCLC) patients in the modern era. While discordant mutational profiles between brain metastasis (BM) and primary tumors have been described, the correlations between peripheral liquid biopsies via circulating tumor (ctDNA) analyses and intracranial tumor tissue have not been well explored.

Methods: De-identified data were queried from metastatic NSCLC patients with both ctDNA and tissue-based assays from BM (Guardant360®, TissueNext). Up to 83 genes were analyzed to assess for differences in actionable genes and variants, defined as those that could be matched to available targeted therapies. Chi-squared tests were used to compare the groups.

Results: 115 patients met inclusion criteria with blood (peripheral) and tissue CNS samples analyzed contemporaneously in most (61% within 30 days). Among these patients, 92 patients demonstrated ≥1 actionable mutation, either on tissue or liquid biopsy analysis, thus constituting the study cohort. At the patient level, tissue analysis revealed alterations in actionable genes in 98% (n=90/92), whereas liquid biopsy identified alterations in actionable genes in only 53% (n=49/92). Therefore, 47% of patients (n=43/92) with altered and actionable genes were identified only by tissue; intriguingly, there were 2% (2/92) of patients identified only by liquid biopsy but not identified by tissue analysis. Of the 47 patients who had actionable genes identified in both tissue and liquid biopsy samples, 16 patients (34%) had concordant, 6 (13%) had partially concordant, and 25 patients (53%) had discordant results. At the variant level (n=1071 variants), 22% of tissue variants (n=162/729) were in actionable genes and 5% (n=36/729) were actionable variants; ctDNA results demonstrated a similar distribution (21% variants in actionable genes [n=73/342], 6% actionable variants [22/342]; p>0.05). Overall, 40 out of 115 patients had a total of 45 actionable variants: 5 were identified by ctDNA only, 22 were identified by tissue only, and all others (n=18) were identified by both ctDNA and tissue. The concordance rate between tissue and liquid biopsy for actionable variants was 37.5% (25 patients were discordant, 15 were concordant).

Conclusions: In this proof-of-concept study, tissue testing from NSCLC brain metastasis showed higher sensitivity than ctDNA for actionable genes and variants compared to blood assessment. This may be due to tumor-shed challenges of ctDNA relative to blood-brain barrier nuances for CNS-related disease. However, each assay identified unique variants. Therefore, integrating both methods may maximize diagnostic yield for brain metastasis patients to manage systemic and intracranial diseases.

Keywords: liquid biopsy, brain metastases, ctDNA

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.77 A Perioperative Circulating Tumor DNA Model for Landmark Detection in Non Small Cell Lung Cancer

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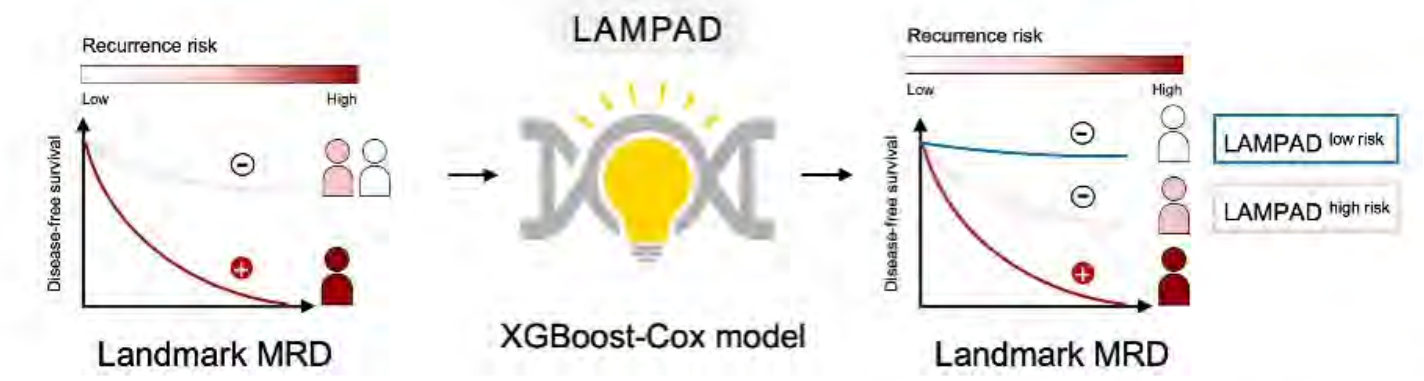
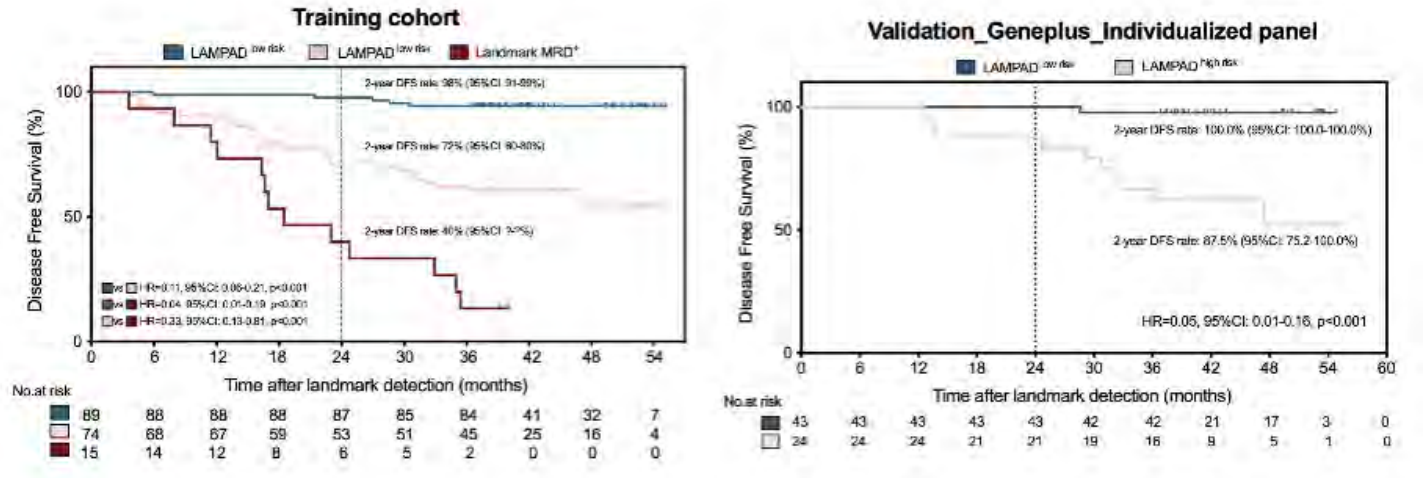
Introduction: Evaluation of molecular residual disease status in non-small cell lung cancer (NSCLC) patients after surgery primarily relies on circulating tumor DNA (ctDNA) analysis. However, the false-negative rate of single-timepoint ctDNA detection is approximately 40%, limiting its utility in guiding postoperative de-escalation therapy.

Methods: In this study, we present LAMPAD, an integrated approach that combines preoperative and postoperative ctDNA quantification parameters, capable of predicting disease-free survival (DFS) in patients with postoperative negative ctDNA.

Results: LAMPAD was trained on 163 stage I-III postoperative ctDNA-negative patients, further stratified into low-risk and high-risk groups, with the low-risk group achieving a 2-year DFS rate of 98.0%. The model is applicable to both fixed-panel and personalized ctDNA approaches, with the low-risk group achieving a 2-year DFS rate of 100%. Preoperative blood quantification features significantly contribute to the LAMPAD model, with methylation analysis revealing elevated cell-free DNA from bronchial and alveolar epithelial tissues (p = 0.007) and macrophages (p = 0.015) in the high-risk group.

Conclusions: Overall, the LAMPAD model outperforms single-timepoint postoperative ctDNA detection in predicting DFS, particularly in guiding de-escalation therapy for low-risk patients.





Keywords: Circulating tumor DNA, Molecular residual disease, Non-small cell lung cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.78 Using a Personalized, Tumor-Informed Circulating DNA (ctDNA) to Monitor Treatment Outcomes in Lung Cancer Patients

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Introduction: Lung cancer surveillance traditionally relies on advanced imaging techniques such as MRI brain, CT scans, and PET scans to detect disease progression or response. However, these modalities are associated with limitations including radiation exposure, high costs, and occasional inaccuracies. A personalized, tumor-informed circulating DNA (ctDNA) analysis, has emerged as a promising alternative, offering the potential to detect minimal residual disease (MRD) and early recurrence or response before radiographic evidence becomes apparent. While tumor-informed ctDNA has shown early clinical utility in cancers such as breast and colorectal cancers, its role in the active surveillance of lung cancer remains an area of active investigation. This study aims to evaluate the comparative effectiveness of tumor-informed ctDNA monitoring in lung cancer and explore its potential to complement or replace imaging techniques.

Methods: We did a retrospective study involving 88 patients with lung cancer. We use the Signatera test which is a personalized, tumor-informed assay designed to detect somatic and truncal variants prepared from whole exon sequencing (WES) from tumor and normal tissue. Surveillance results were considered concordant if there was evidence of disease progression (PD) or recurrence on imaging tests corresponding to a positive or increased ctDNA in plasma, while stable disease (SD), responses (CR, PR) or no evidence of disease aligned with a decrease or negative ctDNA result. Patient demographics, tumor characteristics, and genomic analysis were recorded. Concordance between ctDNA and imaging results was calculated to assess the correlation of both methods in detecting disease progression, and statistical analysis via Cohen's Kappa was conducted to determine the strength of the relationship between the two tests.

Results: Among the 88 patients, 52 (59%) were female predominantly White 71 (81%), non-Hispanic 46 (52%). 53 (60.2%) were former smokers, and 33 (37.5%) had never smoked. 85 (97%) patients had non-small cell lung carcinoma (NSCLC), primarily adenocarcinoma (89%). Disease stage at diagnosis: stage I 24 (27%), stage II 5 (6%), stage III 12 (14%), and stage IV 47 (53%). Twenty-six patients (29.5%) were excluded due to unavailable or outdated ctDNA results. CtDNA serum testing showed 94.3% (Cohen kappa (CK): 0.82) concordance with systemic imaging and 75% (CK: 0.25) concordance with brain imaging. Subgroup analysis for stage IV lung cancer revealed 89.7% (CK: 0.79) concordance with systemic imaging in patients treated with chemotherapy or immunotherapy, and 100% (CK: 1.00) in those receiving targeted therapy. In comparison, concordance with brain imaging was lower: 58% (kappa: 0) for chemotherapy/immunotherapy and 78% (kappa: 0.57) for targeted therapy. The patients with positive ctDNA results are significantly more likely to show progression or recurrence.

Conclusions: Personalized, tumor-informed ctDNA was able to accurately correlate with radiologic imaging in most of the NSCLC patients, particularly outside the CNS. There are challenges in making the test based on tissue availability that need to be considered. More and larger studies are needed to validate these results and longer follow up to evaluate survival.

Keywords: liquid biopsies, ctDNA, MRD

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.79 Deciphering Genomic and Transcriptomic Heterogeneity in Circulating Tumor Cells at Diagnosis in Small Cell Lung Cancer: CTC-CPC Study

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Introduction: Small cell lung cancer (SCLC) is an aggressive form of lung cancer with a high mortality rate, despite recent advances in therapeutics. Since 2019, a new classification has identified four subtypes based on the expression of transcription factors (ASCL1, NEUROD1, and POU2F3, or triple-negative), which could open new therapeutic opportunities. Solid biopsies are often non-informative in SCLC due to tumor necrosis and limited access to the primary tumor. Therefore, circulating tumor cells (CTCs) represent a valuable biological resource in clinical practice. The goal of the CTC-CPC study is to explore innovative circulating biomarkers in disseminated SCLC.

Methods: The CTC-CPC study is a monocentric, non-interventional study recruiting patients with newly diagnosed, treatment-naïve SCLC since April 2016. The first objective of the CTC-CPC study was to validate an EpCAM-independent CTC isolation method that allows the isolation of viable CTCs from SCLC (Ricordel et al., 2023). We performed whole exome sequencing (WES) on 22 CTC samples, as well as corresponding primary tumor (PT) biopsies from four patients. A Snakemake bioinformatics pipeline was built to perform alignment and variant calling. BioinfoMiner sofware was used to asses pathway enrichment analysis based on WES data from CTC and PT. We also developed a droplet digital PCR-based method to determine the transcriptomic subtype of CTCs.

Results: Among the 80 patients included in the study, WES was performed on CTC for 22 patients at diagnosis. The median age at diagnosis was 62.5 ± 9.5 years. Patients were predominantly male (63%), with disseminated stage SCLC (81%), smoking history (95%) and mainly ECOG PS 0-1. Mean number of CTC at diagnosis was 68.6 ± 136 cells/mL. First-line treatment consisted in platine-doublet plus immunotherapy for 31.8% of patients. Median PFS was 5.2 months and median OS 9 .3 months. CTCs exhibited a high mutational load and wide range of ploidy levels, ranging from tetraploid (4n) to septadecaploid (17n). Pathway enrichment analysis on both the CTC and primary tumor datasets identified specifically altered signaling pathways in CTCs. Filtering of pathways altered in more than 50% of samples revealed that extracellular matrix organization, sensory perception, and signaling by receptor tyrosine kinases were recurrently altered in CTCs but not in primary tumors. Copy number alterations (CNA) revealed two patient clusters: one with more deletions and the other with a more amplified copy number alteration profile. However, no correlation between CNA clusters and clinical characteristics or survival outcomes was found. In an experimental setting, the ASCL1 subtype was successfully detected in SCLC cells contaminating control blood, and we plan to evaluate this novel method on CTCs.

Conclusions: The CTC-CPC study supports the potential of CTCs as non-invasive biomarkers in SCLC. CTCs exhibited a high mutational load and distinct alterations in pathways like extracellular matrix organization and receptor tyrosine kinase signaling, not found in primary tumors. CNA analysis revealed two clusters of CTC with amplification-dominant or deletion-dominant genomic alterations. Additionally, the successful detection of the ASCL1 subtype in experimental settings suggests CTCs could be used to assess tumor subtypes and guide personalized treatment.

Keywords: small cell lung cancer, circulating tumor cells, genomics

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.80 Development of a Proteomics-Based Machine Learning Model for Diagnosing and Predicting Lung Cancer: Insights From the UK Biobank

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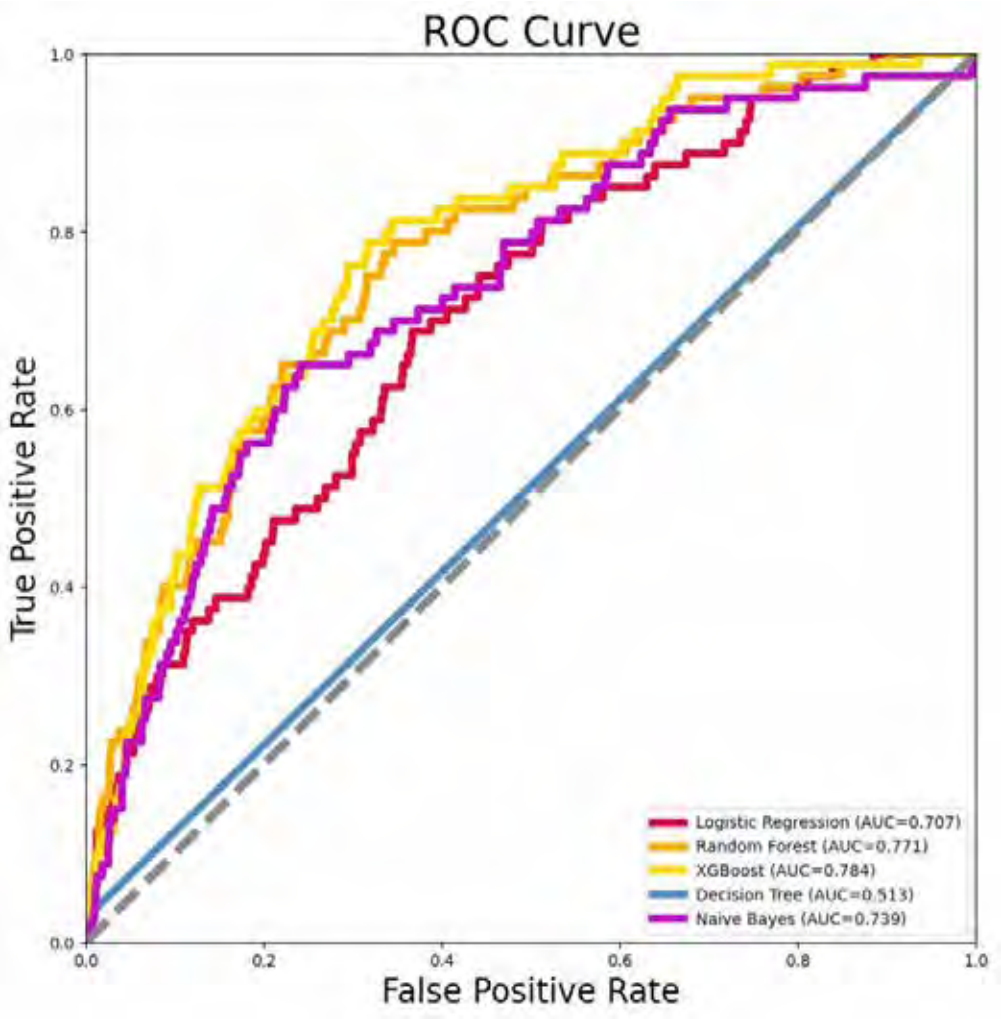
Introduction: Lung cancer ranks first in morbidity and mortality among malignancies in China. Early identification and treatment of lung cancer are critical for improving patient prognosis and quality of life. In-depth exploration of proteomics offers a foundation for elucidating molecular biological features of lung cancer and identifying novel biomarkers. This study aims to develop and validate a proteomics-based machine learning model for diagnosing lung cancer and evaluate its effectiveness in disease identification.

Methods: Using adult data from the UK Biobank, researchers conducted plasma proteomic analyses (2006-2010) on 2923 proteins from 52,580 healthy individuals and 431 lung cancer patients. Ten differentially expressed proteins between healthy and lung cancer cohorts were screened. Five machine learning models were constructed using protein-level data to predict lung cancer diagnosis, with their predictive performances compared. The SHAP (SHapley Additive exPlanations) framework was applied for interpretability analysis to quantify the contributions of variables to the model's predictions.

Results: Significant proteomic differences were observed between healthy and lung cancer populations. Peripheral blood levels of CD34, ITGAV, NUDT10, and other proteins were markedly elevated in lung cancer patients. Among the five machine learning models developed using the ten screened proteins, the random forest model demonstrated optimal diagnostic efficacy (AUC = 0.771). SHAP feature importance analysis identified CCN3, NUDT10, and APOA1 as the most discriminative proteins, corroborated by maximum SHAP bar plots.

Conclusions: This machine learning model leverages large-scale proteomic data to identify lung cancer patients effectively. The findings provide novel insights into the molecular characteristics of lung cancer and lay a scientific foundation for discovering diagnostic biomarkers and therapeutic targets.



Keywords: Proteomics, Machine learning, Biomarker

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.81 Circulating Tumour Cells, Spread Through Air Space and Lymph-Nodal Micrometastasis in Surgically Resected Early-Stage NSCLC

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Introduction: Lung cancer is one of the most lethal malignancies worldwide. In early-stage cases, surgery is considered the cornerstone of therapy; however, recurrence rates after radical resection remain as high as 20% in stage I. While several factors may contribute to treatment failure, many remain unknown.The aim of this project was to analyze the correlation between Circulating Tumor Cells (CTCs), Spread Through Air Spaces (STAS), and lymph node micrometastasis (<2 mm) in patients with clinical stage IA-IIA Non-Small Cell Lung Cancer (NSCLC) who underwent surgical resection.

Methods: This is a monocentric prospective study. From June 2023 patients with clinical stage IA-IIA NSCLC who were candidates for surgery were included. Patients who received neoadjuvant therapy or systemic treatment for other malignancies in the previous three years were excluded, as were those with severe pleural adhesions or who underwent wedge resection. Pathological features, including STAS and lymph node micrometastasis, were assessed on the surgical specimen. CTCs were evaluated through peripheral blood samples collected the day before surgery and 30 days postoperatively.

Results: Fifty-four patients were enrolled in the study; 49 met the inclusion criteria.

Twenty-seven were female (55.1%), with a mean age was 71.2 years (Standard Deviation, SD, ±7.9). Most patients were treated robotically (32, 65.7%) and underwent lobectomy (36, 73.5%). A vein-first approach was used in 32 cases (65.3%). Adenocarcinoma was the most common histology (40 cases, 81.6%). Lymph node micrometastasis was found in only 2 cases (4.0%); conversely, STAS was observed in 24 patients (49.0%). CTCs were detected in 26 patients (53.1%). Both pre- and postoperative CTCs were found in 4 patients (8.2%), while 12 patients (24.5%) had detectable CTCs only after surgery. The mean number of preoperative CTCs was 2.0 (±1.5), while the mean 30-day CTC count was 3.7 (±6.0). CTCs were more frequently found in non-adenocarcinoma histologies (p=0.061) and showed a borderline correlation with STAS (p=0.054); however, STAS was significantly associated with CTC counts >1 (p=0.011). Both CTCs and STAS were significantly more present in patients with a high grade (G3) adenocarcinoma pattern (p=0.003 for both) and in those with vascular invasion (CTCs p=0.002, STAS p=0.049).CTCs, but not STAS, were significantly associated with visceral pleural invasion (p<0.001 vs. p=0.076).Both factors were significantly associated with a higher pathological stage (CTCs p<0.001; STAS p=0.025). No significant correlation was found between lymph node involvement and either CTCs (p=0.288) or STAS (p=0.646). No statistically significant correlations were found between the presence and the number of postoperative CTCs and intraoperative variables, such as surgical technique (VATS versus RATS, p=0.620 and 0.423 respectively) and pulmonary vessel ligation (vein versus artery first, p=0.557 and p=0.188 respectively).

Conclusions: This study is among the first to highlight a significant correlation between CTCs and STAS. Both factors are more frequently associated with aggressive tumor behavior and features and may contribute to an increased risk of local or distant recurrence.Larger studies with longer follow-up are warranted to validate these findings and assess their prognostic impact.

Keywords: Circulating tumor cells, STAS, Non-Small Cell Lung Cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.82 Cell Free DNA Dynamics in Exhaled Breath Condensate to Predict Outcomes to Immune Checkpoint Inhibition in Advanced NSCLC

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Introduction: Dynamic changes in cell-free DNA (cfDNA) and/or circulating tumour DNA (ctDNA) may represent a biomarker of response to immune checkpoint inhibitor-based therapy (ICI) in non-small cell lung cancer (NSCLC). Exhaled breath condensate (EBC) is a novel liquid biopsy technique, which we have previously used to detect ctDNA in NSCLC. We sought to explore the hypothesis that dynamic changes in cf/ctDNA EBC may complement plasma ctDNA, in predicting outcomes.

Methods: Baseline EBC, plasma and buffy coat samples were collected from patient's pre-treatment, and 3 and 6 weeks following commencement of treatment. Following DNA extraction, absolute quantification of cfDNA (copies/mL) was performed with digital droplet PCR (ddPCR). Tumour sequencing was conducted as part of standard-of-care molecular testing. Plasma NGS was completed using the 484 gene Novogene PM 2.0 panel and subtraction of variants from buffy coat NGS was conducted using a dedicated bioinformatics pathway. Where variants were identified which could be targeted using ddPCR, custom ddPCR assays were designed based on tumour or plasma NGS and analysed in EBC and plasma using the BioRad QX100 system. The maximal change in cfDNA (Max cfDNA) at 3 and/or 6 weeks was defined as the maximum increase/decrease in cfDNA compared to baseline. Molecular Response (MR) was defined as ≥ 50% reduction in ctDNA variant allele fraction in EBC at 3 and/or 6 weeks following commencement of therapy. In our statistical analysis, we analysed outcomes with consideration of; Durable clinical benefit (DCB): Investigator-assessed radiological and clinical benefit for at least 6 months; Positive predictive value (PPV): Proportion of those with a MR amongst those with a DCB; Negative predictive value (NPV): Proportion of those without a MR amongst those without a DCB.

Results: Amongst 81 patients, the median age was 67 years, and 63% (51/80) of participants were male. The majority of enrolled patients received ICI + platinum doublet (50/81, 64%), as opposed to ICI monotherapy (31/80, 39%). All patient's samples were suitable for EBC cfDNA analysis and 58% (46/80) were suitable for EBC ctDNA analysis. EBC ctDNA MR was associated with a significantly improved PFS (PFS 13.6 mo vs 3.8 mo; HR 0.24, 95% CI 0.1-0.56), OS (OS NR vs 8.8 mo; HR 0.25, 95% CI 0.08 - 0.77; P <0.01) and durable clinical benefit (PPV = 59%; NPV 94%, Chi2 = 12.6, p < 0.01). When those with a MR in either plasma or EBC were combined, this improved the PPV over EBC ctDNA alone (PPV 80%, NPV 66%, Chi2 = 7.68, p < 0.01). Patients with a max cfDNA reduction ≥ 1% had a numerically improved PFS compared to those without with a trend towards significance (PFS 6.4 vs 3.8 mo; HR 0.60, 95% CI 0.36 - 1.01, p =0.06).

Conclusions: EBC-derived cfDNA and ctDNA dynamics are emerging as promising predictors of survival in NSCLC. Our findings suggest that integrating EBC with plasma ctDNA dynamics enhances positive predictive value beyond EBC ctDNA alone. This combined approach has the potential to significantly strengthen plasma-based assays and optimize response-adaptive ctDNA clinical trials in NSCLC.

Keywords: Non-small cell lung cancer, Circulating tumour DNA

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.83 Multimethod Circulating Tumor DNA Profiling for Minimal Residual Disease Monitoring in Early-Stage Non-Small Cell Lung Cancer

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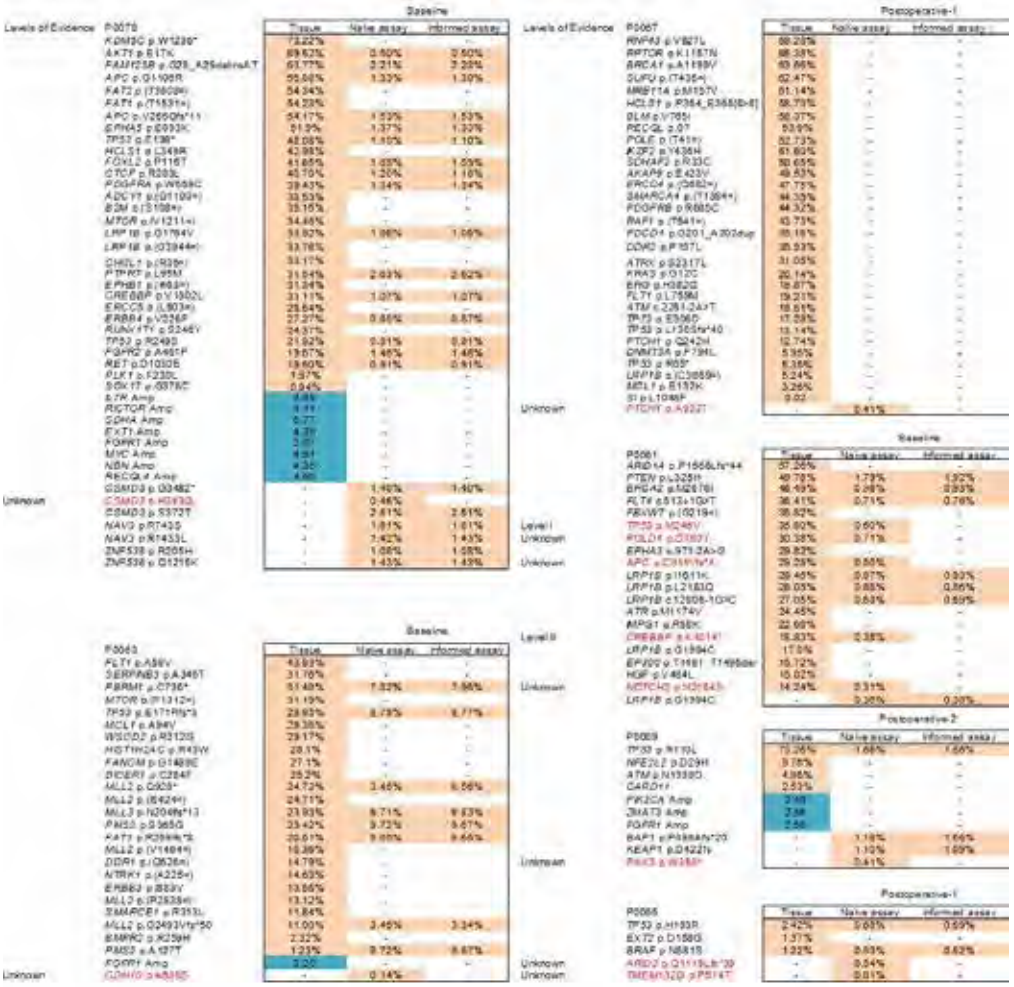
Introduction: Circulating tumor DNA (ctDNA) serves as a valuable biomarker for molecular residual disease (MRD) detection, enabling treatment optimization, recurrence risk assessment, and ultimately improved clinical outcomes. The technical strategies for ctDNA-MRD detection lack standardization, with ongoing debates regarding methodology selection. Tumor tissue samples are unavailable for a subset of cases in real-world practice. While tumor-naive ctDNA assays offer promising applications for MRD detection in tissue-limited NSCLC, their performance data remain scarce.

Methods: We conducted a head-to-head comparison of 417 serial samples from 84 patients using three ctDNA-MRD detection methodologies (tumor-naive, tumor-informed fixed panel and personalized assays) to comparatively assess their detection performance characteristics.

Results: Within our cohort, ctDNA was detected in 20.9% (87/417) of samples, while the remaining 79.1% (330/417) tested negative. Among the 87 ctDNA-positive samples, 74.7% (65/87) showed concordant results across all three methods. Notably, tumor-naive assays identified an additional 11 mutations in 6.9% (6/87) of samples that were not detected by tumor-informed assays. Personalized assays revealed 5 unique mutations in 3.4% (3/87) of samples that were not covered by fixed panel. Furthermore, high-depth personalized sequencing identified 7 low-frequency mutations in 8.0% (7/87) of ctDNA-positive samples that were undetectable by fixed assays. Intriguingly, longitudinal monitoring revealed 5 emerging resistance mutations in 4.6% (4/87) of cases within the 3-month pre-progression window, which were detectable by both tumor-naive and tumor-informed methods but missed by personalized profiling.

Conclusions: This study reveals the limitations and advantages of three ctDNA-MRD detection methodologies and these results serve as a reference for the optimization. Tumor-naive strategy is useful in postoperative MRD testing for NSCLC, and the techniques can be further improved and optimized detection accuracy, coverage, and detection depth, and fully integrated into routine clinical practice.



Keywords: Molecular residual disease, Tumor-naive, Non-small-cell lung cancer

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.84 Tracking Ctc Phenotypes in SCLC Liquid Biopsies as a Diagnostic and Therapy Response Assessment Tool

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Introduction: Liquid biopsies present a promising, minimally invasive procedure through which clinicians may be able to assess and monitor disease status by phenotyping circulating tumor cells (CTCs) at the single-cell proteomic level. However, liquid biopsies remain underutilized due to technical difficulties in detecting CTCs and studying their features in great depth. Phenotyping CTCs promises to help stratify patients and predict outcome and therapy response, facilitating treatment decision making. This can be particularly relevant in small-cell lung cancer (SCLC), an extremely aggressive lung cancer type with high CTC counts where tissue biopsies are scarce and targeted therapies are limited. In this study, we utilize CyTOF (Cytometry by Time-of-Flight), to interrogate phenotypic heterogeneity and biomarker expression in CTCs directly in SCLC patient liquid biopsies, providing a potential platform for subtyping and monitoring disease progression and therapeutic resistance at a personalized level.

Methods: We developed a 25-antibody CyTOF panel targeting SCLC markers such as SCLC subtype-specific transcription factors (TFs) NeuroD1, POU2F3, and ASCL1, therapeutic targets (e.g., DLL3), immune regulatory (e.g., PD-L1), and epithelial-mesenchymal transition (EMT) markers. Optimization was performed using SCLC cell lines (subtype controls), and blood samples from healthy donors (negative controls) and SCLC patients. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood, fixed, and processed for CyTOF. CTCs were initially identified by gating CD45 negative and CD56 positive cells (CD45-CD56+) with further validation based on TTF1 and SCLC subtype-specific TF expression. Whenever feasible, SCLC subtype was validated in matching primary tumor biopsies or CTC-derived xenograft models. Pleural effusions were analyzed in a subset of patients. Computational analysis was performed to assess intra- and inter-patient CTC heterogeneity, phenotypic differences between treatment-naïve and standard-of-care and Tarlatamab treated patients, and CTC dynamic changes in longitudinal specimens.

Results: We performed CyTOF on blood specimens from 12 healthy donors and 28 SCLC patients (treatment naïve, treated/relapsed and longitudinal specimens). Computational analysis revealed 3 clusters of CD45-CD56+ cells that were enriched in SCLC but not in healthy liquid biopsies. These cells were characterized by high expression of SCLC/CTC-associated markers such as CD24, DLL3, EpCAM and ALCAM. Further clustering analysis revealed the four established SCLC subtypes: 1) ASCL1+ (SCLC-A), 2) POU2F3+ (SCLC-P), 3) NeuroD1+ (SCLC-N), and 4) Inflamed (SCLC-I), and found that the most prominent SCLC CTC subtype in liquid biopsies was SCLC-I. We observed substantial CTC subtype and EMT heterogeneity within and across all specimens, with mesenchymal phenotypes increased in the relapsed setting. Notably, DLL3 expression was reduced in CTCs from patients that had undergone standard-of-care therapy compared to treatment-naïve patients. Two patients undergoing DLL3 targeted therapy (Tarlatamab) exhibited significant upregulation in CTC CD24 and MUC1 levels, revealing potential markers of resistance. Longitudinal tracking of CTCs in a subset of patients revealed subtype switching, specifically a gradual decline in NeuroD1 alongside an increase of POU2F3 levels.

Conclusions: Our approach can serve as a potential diagnostic and therapy response assessment tool where by utilizing CyTOF to longitudinally track CTCs directly in SCLC patient liquid biopsies can lead to tailoring SCLC therapy at a personalized level.

Keywords: Liquid Biopsies, CTCs, biomarkers, Phenotypic Heterogeneity, CyTOF

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.85 Clinical Utility of a "Plasma 1st Approach" for Molecular Diagnosis Using ctDNA in Advanced Lung Cancer, NHS England Pilot

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Introduction: ctDNA can be used for molecular profiling either as a "plasma 1st" before tissue, simultaneous with tissue or salvage on failure of tissue testing. The NHSE pilot has assessed the clinical utility and cost-effectiveness of a Plasma 1st approach in a national programme. We report selected outcomes as to TAT and clinical outcomes in patients enrolled in the pilot.

Methods: Patients within the UK were taken from a list generated by The Royal Marsden GLH who had received liquid biopsy samples through the pilot scheme from 2022 to December 2024. ctDNA testing was conducted using the Royal Marsden360Dx platform (a Tech transfer from Guardant). Patient information was collected from local records including tissue biopsy report date and results. Further information on therapy received and date of last visit or death was assessed from the same source. All data was analysed using R software.

Results: The data from North-East England is presented here with further data collection from other UK sites ongoing and to be presented at the conference. At present 306 patients were analysed. Turnaround time (TAT) was calculated from 223 patients with data available. Median TAT from sample dates for liquid and tissue biopsy were 13 and 15 days respectively (P = 0.01). IQRs respectively were 12 and 4 days. From date of CT scan liquid biopsy median TAT was 28 whilst tissue was 34 days (P = <0.001). IQRs were 23 and 33 days respectively. Tissue biopsy TAT based on histology demonstrated a significant difference (P = <0.001) between adenocarcinoma and squamous subtypes (42 and 31 days) from CT scan date. Survival data was available for 188 patients. Patients stratified to targeted treatment had an improved OS median 16 (CI 13 - NA) compared to 7 months (CI 6 - 10,P = <0.001). Comparing for the effect of biopsy time on survival demonstrated a significant difference between high, medium and low tertiles 15, 9 and 6 months (P = >0.001, HR 0.85 and 0.31).

Conclusions: We have demonstrated a plasma 1st approach decreased the IQR of sample TAT simultaneously decreasing TAT from CT scan leading to a more equitable service. There is space for improvement of TAT with earlier collection of blood samples. As of 1st April 2025, ctDNA will officially be commissioned on the NHS national testing directory.

Keywords: Tumour profiling, cfDNA

P2.06.86 Development and Validation of Peripheral Blood 5-Protein Signature Predicting the Efficacy of Immunotherapy in Advanced NSCLC

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Introduction: Immunotherapy has provided clinical benefit for some patients with advanced non-small cell lung cancer (NSCLC), but highly accurate efficacy predictive tools are still lacking in the clinical setting.

Methods: We performed deep proteomics (Proteograph) of plasma samples at baseline from 10 advanced NSCLC patients receiving 1L immunotherapy, and validated the candidate proteins with parallel reaction monitoring targeted proteome (n = 30). An efficacy prediction model was constructed by logistic regression and validated in an independent cohort (n = 30). Response was evaluated using RECIST 1.1 criteria. The PD-L1 tumor proportion score (TPS) was assessed by the PD-L1 immunohistochemistry E1L3N assays. Receiver operating characteristic curve analysis was applied to evaluate the performance of efficacy prediction.

Results: A total of 3216 proteins were detected, with 76% of the proteins identified at low concentrations (< 10 ng/mL) and 'new', and 222 protein levels were significantly different between the Res (CR/PR, n = 5) and non-Res (SD/PD, n = 5) groups ($p < 0.05$). A predictive model consisting of five plasma proteins (PGK1, CHGA, ELN, HNRNPH3, and SERBP1) was constructed with an AUC of 0.88 and treatment response was interpreted as a score >0.3029. Independent cohort validation yielded a specificity of 83.3% and a sensitivity of 88.9%, with a significantly better predictive performance than that of PD-L1 (TPS) ≥50% (AUC, 0.94 (5-protein model) vs. 0.56 (PD-L1)), identifying 83.3% (5/6) of patients with PD-L1 (TPS) <1% treatment response (Figure 1).

Conclusions: We constructed a predictive model of immunotherapy efficacy consisting of five plasma proteins with high accuracy and superior performance to PD-L1 expression.

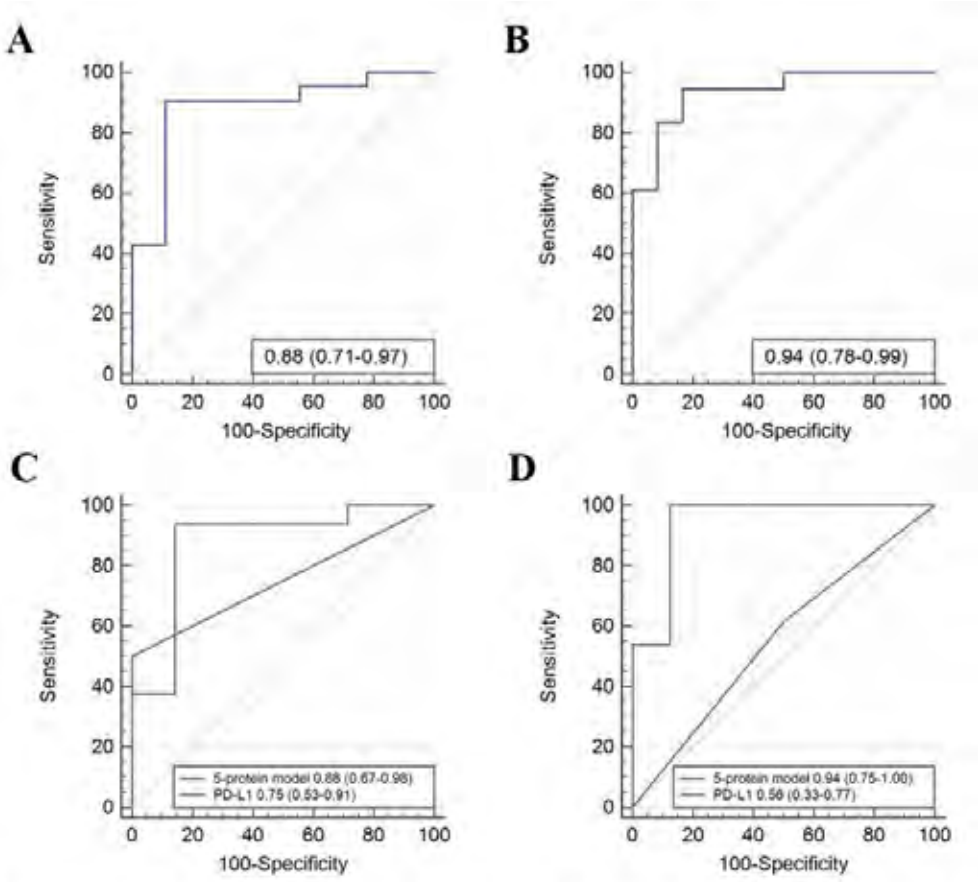

Figure 1. ROC curves and AUCs (95% CIs) for the 5-protein model (A, model development: Res, n=21; non-Res, n=9; B, model validation: Res, n=18; non-Res, n=12) and PD-L1 (C, model development: Res, n=16; non-Res, n=7; D, model validation: Res, n=13; non-Res, n=8). Res, CR/PR; non-Res, SD/PD.

Keywords: immunotherapy, efficacy biomarkers, peripheral blood

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.87 Reversible Smoking-Dependent Hpg80 Increase, a Path to Identifying NSCLC-Negative Individuals: An Incentive to Quit Smoking?

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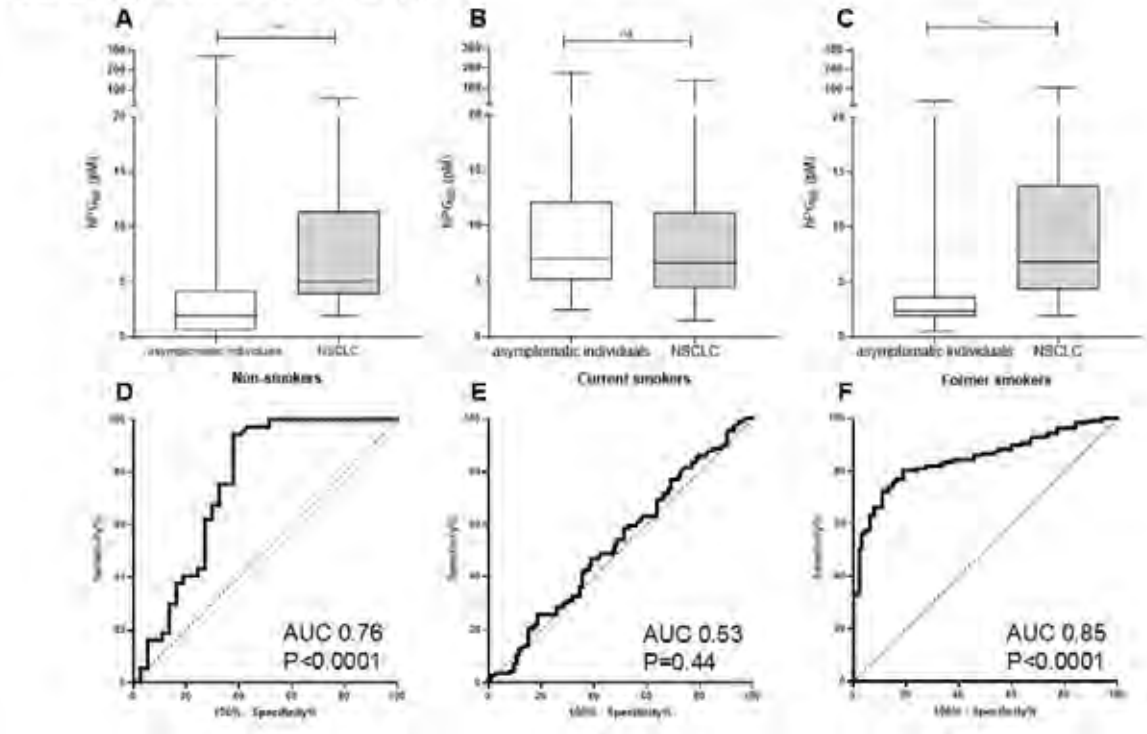
Introduction: Smoking is a major risk for lung cancer. While LDCT scan is used for early detection, blood-based biomarkers are needed to improve screening. The Wnt target and oncogenic blood biomarker hPG80 is linked to multiple cancers, including lung cancer. This study examines hPG80 in asymptomatic individuals and NSCLC patients, categorized by their smoking status. hPG80 was also evaluated in COPD patients, a comorbidity frequently associated with smoking.

Methods: Plasma hPG80 levels were measured using the ELISA DxPG80.lab kit (Biodena care, France) across five cohorts: 396 NSCLC patients, 200 lung cancer-negative COPD patients, 1199 individuals from the general population, 278 asymptomatic current smokers, and 228 asymptomatic former smokers. The entire cohorts were used for correlation analyses. ROC analyses assessed diagnostic accuracy with area under the curve (AUC) calculation.

Results: In asymptomatic current smokers, hPG80 levels were significantly higher than in the general population (median value 5.51 pM; IQR 3.97-8.00 vs 1.50 pM; IQR 0.32-3.55, respectively; p<0.0001). From 15 pack-years onward, hPG80 levels in asymptomatic current smokers were not statistically different from NSCLC patients whatever the smoking status (7.45 pM; IQR 5.60-10.5 vs 6.59 pM; IQR 4.39-12.08, respectively; p=ns). Similarly, asymptomatic COPD-positive individuals also exhibited significantly higher hPG80 levels than in the general population (6.07 pM; IQR 4.00-11.69; p<0.0001), but not significantly different from COPD-positive cancer patients (6.38 pM; IQR 4.45-13.69; p=ns), whatever the smoking status. In contrast, asymptomatic former smokers had levels of hPG80 similar to those in the general population (2.40 pM; IQR 1.8-3.65; p=ns). Finally, when comparing asymptomatic and cancer-diagnosed non- and former smokers, the AUC were 0.76 (n=37 in each group; 95% CI 0.64-0.88) and 0.85 (n=127 in each group; 95% CI 0.80-0.90) respectively (Figure 1D and 1F; p<0.0001). It was 0.53 (n=113 in each group; 95% CI 0.45-0.0) when compared with current smokers (Figure 1E; p=0.44).

Conclusions: These results show that smoking induces a reversible increase in hPG80 levels, highlighting that hPG80 is not only produced by cancer cells as already documented, but also in a situation increasing the risk of developing cancer, i.e. smoking. Current smokers have levels of hPG80 similar to those of NSCLC patients, whereas the majority of former smokers return to normal levels. Since over 90% of NSCLC in former smokers are hPG80-positive, hPG80 may help identify former smokers likely to be cancer-free, serving as an incentive to quit smoking.

Figure 1: hPG_{80} level in NSCLC patients compared to their respective age-matched controls: non- (**A**), current (**B**) and former smokers (**C**). ROC analyses of the comparison: non- (**D**), current (**E**) and former smokers (**F**).



Keywords: hPG80, NSCLC, screening

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.88 CfDNA and WBC DNA Sequencing Through MSK-ACCESS Powered With SOPHiA DDM to Delineate Tumor and Clonal Hematopoiesis TP53 Variants in Lung Cancer

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Introduction: Liquid biopsy (LBx) is a non-invasive approach enabling genomic profiling to identify treatment selection and resistance markers when access to tumor tissue is challenging such as in lung cancer. However, there is a risk of including variants derived from clonal hematopoiesis (CH) which constitute possible confounders in prognostically relevant genes such as TP53. SOPHiA GENETICS has developed a decentralized version of MSK-ACCESS® (Memorial Sloan Kettering Cancer Center - Analysis of Circulating cfDNA to Evaluate Somatic Status). The MSK-ACCESS® powered with SOPHiA DDM™ solution interrogates 147 cancer-associated genes for somatic variants and exhibits a high analytical concordance to the original single-site test. Importantly, through the inclusion of white blood cell (WBC) DNA sequencing, tumor variants are filtered to exclude CH and germline alterations.

Methods: The utility of MSK-ACCESS® powered with SOPHiA DDM™ in patients with lung cancer (small-cell and non-small-cell lung cancer) was investigated in a retrospective observational study. Sequencing libraries were generated from 3.5 - 20 ng of plasma cfDNA and 50 ng WBC DNA using the MSK-ACCESS® powered with SOPHiA DDM™ solution and sequenced on Illumina NovaSeq 6000. Variant detection was performed with the SOPHiA DDM™ Platform and calls without evidence of somatic origin were differentiated into germline and CH origin based on variant allele fraction (VAF). Concordance to orthogonally reported cfDNA variants was measured when available and used to investigate the benefit of matched WBC DNA sequencing.

Results: A total of 48 cfDNA + WBC DNA pairs were included in this study and successfully processed in the participating laboratories. Molecular profiling detected in 40/48 of all samples at least one somatic SNV/INDEL, with a median of 3 per patient (range 1-10). In total 161 variants were detected with a median VAF 0.82% (range 0.08-83%). Putative CH variants were observed at a similar frequency (sum 124, median 2, range 1-8) and distribution (median VAF 1.3%, range 0.07-35%) in cfDNA indicating the importance of matched WBC sequencing for their correct identification. Within all detected 25 TP53 SNV/INDELS, 4 were found at similar VAF in cfDNA and WBC DNA and assigned as CH variants. Importantly, 2/4 were reported by orthogonal liquid biopsy assays as tumor variants. All 4 CH TP53 mutations were classified as either "pathogenic" or "conflicting interpretations of pathogenicity" using the ClinVar catalog.

Conclusions: Combined cfDNA and WBC DNA sequencing by the MSK-ACCESS® powered with SOPHiA DDM™ solution improved the correct assignment of prognostic TP53 mutations in lung cancer by delineating CH from variants of somatic origin.

Keywords: cfDNA, lung cancer, clonal hematopoiesis

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.89 DYNAMALK: DYNAMic ct-DNA in ALK+ NSCLC Under the Australasian Thoracic Cancers Longitudinal Cohort Biobank Study (AURORA)

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Introduction: Dynamic ctDNA-profiling in advanced ALK+NSCLC enables personalised treatment. DYNAMALK assesses (1) ctDNA changes relative to prior therapies, PET and tissue biopsy, and (2) resistance patterns to evaluate ctDNA's real-time impact on treatment decisions beyond standard care.

Methods: DYNAMALK-(ACTRN12623000226606p) is a multi-centre, prospective study within AURORA-(ACTRN12625000038493), conducted by the Thoracic Oncology Group of Australasia (TOGA) with consumer co-design. ALK+ patients start first-line lorlatinib (Arm A), or subsequent-line of clinician choice (Arm B). Real-time ctDNA sequencing (Guardant360®USA) is performed baseline, first imaging, and disease progression, with Molecular Tumour Board recommendations. FDG-PET scans accompany ctDNA time-points, with optional tissue. Analysis is conducted after Arm B completed accrual.

Results: DYNAMALK opened August 2023 ,expected to complete enrolment July 2025. In March 2025, N=24/30 are enrolled in Arm A, N=20/20 in Arm B. Median age was 57; 22/44 (50%) Caucasian; 14/44 (32%) had brain metastases. All in Arm A and 4 (20%) in Arm B had a tissue biopsy at entry. In matched cases available, tissue had complete concordance with ctDNA genomic alterations reported in 6/27 (22%), with additional alterations detected in ctDNA in 15/27 (55%). Median turnaround time for results was 11 days (6-30), with 6/77 (8%) samples unanalysable. In Arm B, 15/20 (75%) received Lorlatinib, 5/20 (25%) Neladalkib. Median of prior lines was 1 (1-3). Arm A, 20/23 (87%) had detectable ctDNA at baseline: 1/23 (3%) with ALK-fusion only; 16/23 (70%) ALK-fusion with non-ALK co-mutations and 3/23 (13%) had non-ALK co-mutation(s) only. Arm B, 16/20 (80%) had detectable ctDNA at baseline: 2/20 (10%) with ALK-rearrangement; 7/20 (35%) with ALK-rearrangement and co-mutations (ALK and non-ALK) and 7/20 (35%) non-ALK co-mutations only. In Arm A TP53 was most frequent, followed by loss of tumour suppressors (ATM, PTEN and RB1), EGFR amplification in 2/23 (9%). MYC amplification occurred in both arms. In Arm B, ALK kinase domain mutation in 4/20 (20%). Of cases available, Arm A, 8/19 (42%) had complete plasma clearance at first time point 2-3 months and Arm B, 3/13 (23%). All patients had baseline FDG-PET. 15/18 (83%) Arm A , 13/14 (93%) Arm B had on treatment FDG-PET matched with ctDNA. All had metabolic response in Arm A, and all but one in Arm B. In both arms complete metabolic response did not correlate with ctDNA clearance. At interim analysis, median follow-up was 6 months (range 1-15) for Arm A and 9 months (range 2-17) for Arm B. Median time-on-treatment was not reached, with 90% (18/20) and 87% (13/15) remaining on treatment. In Arm B, 2 (10%) PD, one had co-occurring MYC-amplification and emergent MET-amplification. The second PD, ctDNA reported the ALK-rearrangement only.

Conclusions: DYNAMALK demonstrates the feasibility of a real-world national ctDNA study. This preliminary analysis confirms ctDNA can detect heterogeneous genomics associated with drug resistance. Despite complete metabolic responses on FDG-PET, ctDNA clearance did not directly correlate. Longer term follow up will provided information on molecular evolution of ALK-rearranged NSCLC, receiving next-generation and novel therapeutic sequencing and may help inform treatment personalisation.

Acknowledge-funders- LFA, TOGA, ALK+, RCA, Pfizer, G360

Keywords: ctDNA, ALK+, Liquid Biopsy

P2.06 PATHOLOGY AND BIOMARKERS
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P2.06.90 The Role of ctDNA Tumor Fraction in Advanced NSCLC and Its Impact on Patient Treatment Outcomes: A Prospective Real-World Study

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Introduction: Comprehensive genomic profiling (CGP) using targeted panel next-generation sequencing (TP-NGS) has become pivotal in the clinical management of locally advanced, unresectable, or metastatic NSCLC. Despite the limitations associated with tumor tissue sampling, ctDNA presents a promising alternative. This study aims to assess the prognostic value of ctDNA TF in advanced-stage NSCLC.

Methods: We conducted a multi-center prospective study in Hong Kong. Patients with advanced-stage NSCLC had blood samples collected within 31 days prior to the commencement of treatment, followed by CGP using FoundationOne® Liquid CDx (F1LCDx®).

Results: In our study of 438 patients, we demonstrated that the ctDNA TF serves as a robust prognostic and predictive biomarker. Treatment naïve patients with ctDNA TF high exhibited significantly poorer median progression-free survival (PFS) of 6.9 months and overall survival (OS) of 13.8 months compared to the TF group low ($p < 0.001$). CtDNA TF predicted OS over different time points with AUC ranges from 0.6-0.71 and was remarkable within the EGFR TKI subgroup, with an AUC of 0.77 for OS at 12 months. We validated a 2.3% cutoff for inferior overall survival, as the optimal disease-specific cutoff for ctDNA TF is unclear.

Conclusions: Our findings underscore the potential of ctDNA TF as a robust biomarker for risk stratification and treatment decision-making in advanced-stage NSCLC regardless of metastatic sites, treatment strategy, and lines of treatment, advocating for its incorporation into routine clinical practice.

Keywords: Next-generation sequencing, ctDNA Tumor Fraction, Biomarker

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.91 Plasma Proteomic Profiling Identifies DHX9 as a Predictive Biomarker for Chemoimmunotherapy Efficacy in Extensive-Stage Small Cell Lung Cancer

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Introduction: Although chemoimmunotherapy has improved outcomes in small-cell lung cancer (SCLC), reliable biomarkers for identifying the benefit patients from this treatment remain elusive. This study aims to investigate whether specific plasma protein biomarkers in extensive-stage SCLC (ES-SCLC) can predict the efficacy of chemoimmunotherapy.

Methods: Baseline plasma samples from 46 patients with ES-SCLC who received first-line chemoimmunotherapy at our hospital were analyzed. Patients were stratified into two groups based on their progression-free survival (PFS) following first-line chemoimmunotherapy: those designated as the primary resistance group (PriR; PFS ≤ 6 months) and the secondary resistance group (SecR; PFS > 6 months). A proteomics workflow incorporating liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based data-independent acquisition (DIA) was employed to profile plasma proteomes in the discovery cohort (DC; n=21). Protein biomarkers were screened using differentially expressed proteins (DEPs; defined as $P < 0.05$ with fold change >1.5 or <1/1.5) and elastic net regression. These biomarkers were subsequently validated through targeted parallel reaction monitoring (PRM) in an internal validation cohort (IVC; derived from the DC, n=19) and an external validation cohort (EVC; n=25). A multivariate Cox regression model was used to generate risk scores (RS), and receiver operating characteristic (ROC) analysis evaluated their predictive performance.

Results: A total of 413 DEPs were identified between the PriR and SecR groups. Functional enrichment analyses revealed significant upregulation of the cellular response to tumor necrosis factor ($P = 0.004$) and the chemokine signaling pathway ($P < 0.001$) in the SecR group. Rho GTPase-activating protein 4 (ARHGAP4) and ATP-dependent RNA helicase A (DHX9) were consistently validated in both IVC and EVC. A multivariate Cox regression model was established in the IVC: $RS = 0.21 \times ARHGAP4 - 1.45 \times DHX9$. DHX9 exhibited the highest AUC (0.976) compared to ARHGAP4 and RS in the ROC analysis. The IVC was divided into a DHX9-high (DHX9-H) group and a DHX9-low (DHX9-L) group based on the optimal threshold (0.551), with the DHX9-H group showing a longer mPFS than the DHX9-L group (7.4 months vs. 4.8 months, $P < 0.001$). In the EVC, DHX9 and the RS shared the same AUC (0.799), which was higher than that of ARHGAP4 (0.757). The EVC was also divided into two groups based on the same threshold (0.551) of DHX9 determined in the IVC, and the mPFS of the DHX9-H group was longer than that of the DHX9-L group (10.7 months vs. 2.7 months, $P < 0.001$).

Conclusions: Our study identified DHX9 as a potential biomarker for predicting the efficacy of chemoimmunotherapy in patients with ES-SCLC. Further studies are are required to establish the predictive threshold of DHX9 using ELISA assays and validate its clinical utility.

Keywords: Extensive-stage small cell lung cancer, Plasma proteomics, DHX9

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.92 Host-Derived Biomarkers of Inflammation and Body Composition Predict Immunotherapy Outcomes in Advanced NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) have improved outcomes in advanced non-small cell lung cancer (NSCLC), yet many patients experience resistance. Treatment selection is currently based on PD-L1 expression, which only partially predicts response. Host factors like body composition and systemic inflammation may also influence ICI efficacy. The prognostic value of circulating inflammatory/metabolic biomarkers, such as sRAGE, FGF21, GDF15, and cPLIN2, and body composition parameters has been scarcely explored in this setting. This integrative analysis was conducted in the framework of the SARC-LUNG study.

Methods: This monocentric prospective study enrolled 40 patients with stage IV NSCLC eligible for first-line ICI monotherapy or chemo-immunotherapy. Blood samples and CT-based body composition analyses were collected at baseline (T0) and after 3 months of treatment (T1). Plasma levels of the above-mentioned biomarkers were measured using ELISA/ELLA. Flow cytometry assessed peripheral leukocyte subsets. Skeletal muscle index (SMI) and fat compartments were measured at the L3 vertebral level from available CTs using semiautomatic segmentation (3D Slicer tool). Inflammation was characterized using derived neutrophil-to-lymphocyte ratio(dNLR), platelet-to-lymphocyte ratio (PLR), LDH, and lung-immune prognostic index (LIPI) as established prognostic indices. Associations with progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: Among the 40 patients, 67.5% were male and 87.5% had ECOG PS 0-1. SMI was below the gender-related threshold in 72.5% of cases. Adenocarcinoma was the predominant histology (82.5%); brain and liver metastases were found in 27.5% and 10% of patients, respectively. 70% received first-line chemo-immunotherapy. No imbalances were found in baseline metabolic biomarkers across clinical characteristics, except for sRAGE, which was higher in patients aged ≥70 years ($p < 0.001$). FGF21 was inversely correlated with muscle area ($r = -0.39$, $p = 0.027$) and SMI ($r = -0.44$, $p < 0.05$). FGF21 also correlated positively with PLR ($r = 0.34$, $p < 0.05$) and negatively with NK cells ($r = -0.59$, $p = 0.023$). Similarly, GDF15 showed a trend toward inverse correlation with muscle area and SMI. cPLIN2 showed a positive correlation with visceral ($r = 0.55$, $p = 0.00018$) and subcutaneous fat ($r = 0.45$, $p < 0.001$), and an inverse correlation with PLR ($r = -0.46$, $p < 0.0001$). sRAGE inversely correlated with LIPI ($r = -0.28$, $p = 0.01$) and dNLR ($r = -0.23$, $p < 0.05$). Patients with high baseline sRAGE (ROC-based cut-off) had longer PFS (10.0 vs 6.2 months, $p = 0.042$) and OS (not reached-NR- vs 16.1 months, $p = 0.024$). sRAGE increased significantly in responders compared to non-responders ($p = 0.04$) from T0 to T1. Low baseline SMI was significantly associated with shorter OS (NR vs 16.1 months,$p < 0.05$) and PFS (10.0 vs 6.1 months,$p < 0.05$). Additionally, an increase in SMI from T0 to T1 was associated with reduced mortality (HR =0.77, $p = 0.012$).

Conclusions: The SARC-LUNG study shows that integrating metabolic, inflammatory, and body composition biomarkers provides meaningful prognostic information in advanced NSCLC under upfront ICI. FGF21 and cPLIN2 reflect catabolic and inflammatory burdens, while sRAGE emerges as a promising early-response biomarker. Muscle loss remains a strong predictor of poor outcomes. These findings support incorporating host-related profiling into immunotherapy decision-making.

Keywords: immunotherapy, non-small cell lung cancer, sarcopenia

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.93 Distinct Clinical and Biological Features of Five SCLC Subtypes Identified by Plasma Proteomic Analysis

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Introduction: Small cell lung cancer (SCLC) is a heterogeneous disease with distinct subtypes defined by molecular profiles and neuroendocrine differentiation. Transcription factor-based classification divides SCLC into four major subtypes - SCLC-A, SCLC-N, SCLC-P, and SCLC-I - each with unique biological features and therapeutic vulnerabilities. The reliance on invasive tissue biopsies limits current SCLC subtyping. Here, we explore the potential of plasma proteomic profiling for SCLC subtyping.

Methods: Pre-treatment plasma samples were collected from 79 patients with extensive-stage SCLC treated with immune checkpoint inhibitors and chemotherapy. Proteomic profiling was performed using an aptamer-based assay that quantifies >7000 proteins per sample. Consensus clustering analysis was used to identify different plasma-proteomics-based subtypes. Bioinformatic analysis was performed to obtain biological and clinical insights per subtype. The study included statistical tests (ANOVA and Fisher exact tests) and examined known transcriptome-based biomarkers and an age predictor model.

Results: Five distinct SCLC subtypes were identified based on pre-treatment plasma proteomic patterns. Patients classified by subtype displayed differential overall survival (OS). The subtype-3 population displayed the lowest median OS (6 months), significantly lower than subtype-1 and subtype-2 populations (p-value 0.015 and 0.044, respectively; hazard ratio 0.417 and 0.438, respectively). The subtype-4 population displayed low median OS (10 months), though not significantly different from other subtype populations. Poor prognostic factors, such as high ECOG performance status and OS events, were significantly enriched among patients classified as subtype-3 (FDR<0.2). There were 469 differentially expressed proteins between the five subtypes, clustered into four main expression groups (ANOVA test, FDR<0.01). Enrichment analysis revealed multiple significantly enriched pathways for each protein cluster (Fisher's exact test, FDR<0.1). Specifically, the protein set associated with subtype-3 was enriched with processes such as cell cycle and splicing and included proteins related to inflammation. Subtype-3 exhibited high expression of multiple neuroendocrine biomarkers, including CHGA, NCAM1, and ENO2, and proteins associated with neuroendocrine-high subtypes, such as LDHA and BCL2. The latter was highly expressed in subtype-4 and VIP, a soluble marker previously suggested for monitoring neuroendocrine tumors. In contrast, subtypes 1 and 2 displayed the highest expression of NOTCH pathway proteins (NOTCH1-3) and HES1, a key transcription factor downstream of NOTCH signaling, both are associated with non-neuroendocrine subtypes. Last, the samples were analyzed using an age-prediction model previously developed on healthy subjects; the subtypes showed a differential age gap between the biological (modeled) age and the chronological age, with subtype-3 displaying the highest median age gap, followed by subtype-5.

Conclusions: Plasma proteomics-based SCLC subtyping represents a minimally invasive approach that overcomes biopsy limitations and enables easy monitoring of subtype shifts that may occur following treatment. The current study reveals novel patient clustering, with 2 subtypes displaying more neuroendocrine-related characteristics and poor prognostic outcomes and 2 subtypes displaying non-NE features. Our findings show an interplay with transcriptome-related subtyping, which can be further studied to develop new potential targets for intervention based on molecular subtyping and soluble markers.

Keywords: SCLC, Proteomics, Biomarkers

P2.06.94 "Integrating AI-Based Risk Stratification, LDCT, and Liquid Biopsy for Early Detection of Lung Cancer in High-Risk Individuals"

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Introduction: Early detection of lung cancer significantly improves patient outcomes, yet existing screening strategies are often limited by low participation and lack of targeted outreach. This study evaluates a layered approach incorporating an AI-based risk stratification tool, low-dose computed tomography (LDCT), and liquid biopsy (ctDNA) for identifying and monitoring early lung malignancies in high-risk populations.

Methods: An AI-driven questionnaire incorporating clinical, behavioural, and environmental risk factors was administered to 1,000 individuals. All participants categorized as high risk underwent LDCT screening. Those with radiological abnormalities (n=200) were further evaluated using plasma-based ctDNA analysis. Key mutations and methylation markers were assessed via targeted sequencing. Individuals with positive ctDNA findings (n=50) were advised structured follow-up with imaging at 3 and 12 months. Invasive diagnostic procedures were reserved for cases with progressive or persistent findings.

Results: Among the 1,000 high-risk individuals screened, 200 (20%) exhibited suspicious nodules on LDCT. Liquid biopsy performed on this subset revealed ctDNA positivity in 50 individuals (25%). These patients were enrolled in longitudinal follow-up, with ongoing monitoring to evaluate disease progression and refine the predictive accuracy of combined radiologic and molecular assessment. Histologic confirmation is currently pending based on follow-up scans and clinical evolution.

Conclusions: This interim analysis supports the feasibility of integrating AI-based risk assessment with imaging and liquid biopsy to enable early surveillance in lung cancer. The ctDNA assay added a valuable layer of specificity in triaging individuals for follow-up, potentially reducing unnecessary invasive procedures. This structured, non-invasive approach may enhance early detection efforts and provide a scalable model for population-level lung cancer screening programs.

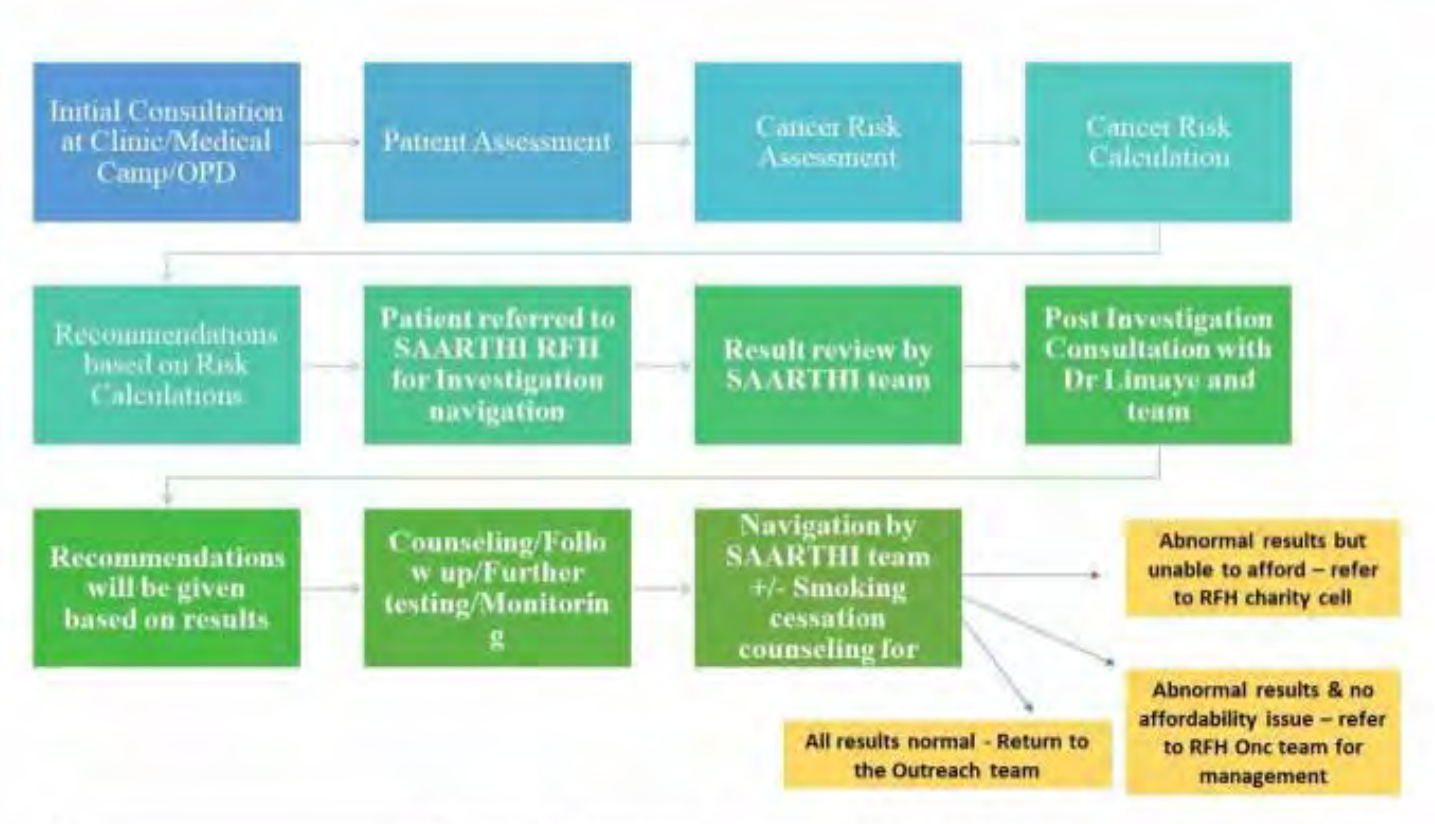

Figure 1: Strategy for Lung Screening

Keywords: Lung cancer screening, AI-based questionnaire, Liquid biopsy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.95 Deep Learning-Based Prediction of Immunotherapy Efficacy in Non-Small Cell Lung Cancer: Automated Tumor and Muscle Evaluation

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Introduction: The integration of imaging and clinical information through artificial intelligence (AI) offers a promising approach for accurately predicting the therapeutic efficacy of immune checkpoint inhibitors (ICIs) ± platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC). Muscle volume has been identified as a key predictor of ICI efficacy, but previous studies have not comprehensively assessed both tumor radiomic features and muscle volume. To enhance the predictive accuracy of treatment efficacy and prognosis, we developed a novel deep learning model for fully automated tumor segmentation and muscle volume quantification.

Methods: This study included patients with advanced NSCLC who received first-line ICI ± platinum-based chemotherapy between March 2017 and August 2023. We developed an ensemble model integrating a logistic regression model for clinical information analysis with a deep learning model for extracting tumor radiomic features and quantifying muscle volume. Tumor segmentation and psoas muscle volume were automatically extracted using a fully automated approach from pre-treatment chest-abdominal CT imaging and brain MRI. Each sub-model was independent, allowing flexibility in adjustments. The models were trained to predict 12-month overall survival (OS), 12-month progression-free survival (PFS), and treatment response using cross-entropy loss. Five-fold cross-validation was employed, with dataset splitting in a 5:3:2 ratio. The area under the curve (AUC) was calculated.

Results: A total of 232 patients were included, with 89 (38%) receiving ICI alone and 143 (62%) receiving ICI + platinum-based chemotherapy. The median OS was 24.5 months (95% confidence interval [CI]: 21.2-30.3), and the median PFS was 7.1 months (95% CI: 5.8-9.1). Our deep learning model demonstrated predictive accuracy with an AUC of 0.77 (95% CI: 0.57-0.97) for 12-month OS and 0.66 (95% CI: 0.53-0.79) for 12-month PFS. Deep learning-based stratification classified test set patients into high-group (N = 67) and low-risk group (N = 69). The high-risk group had a significantly shorter OS (20.3 vs. 30.7 months, $p < 0.05$) and a trend toward shorter PFS (7.2 vs. 8.9 months, $p = 0.06$).

Conclusions: Our deep learning model, integrating fully automated tumor segmentation and muscle evaluation with clinical information, demonstrated favorable predictive performance for survival outcomes in advanced NSCLC patients receiving first-line immunotherapy.

Keywords: Artificial intelligence, Immune checkpoint inhibitor, Non-small cell lung cancer

P2.06 PATHOLOGY AND BIOMARKER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.96 Exploration the Heterogeneity of HER2 Expression in Potential Candidates for Antibody-Drug Conjugate in Non-Small Cell Lung Cancer

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Introduction: Recently, T-DXd has been approved in patients with metastatic or unresectable non-small cell lung carcinoma (NSCLC) harboring HER2 mutations. Subsequently, FDA approved T-Dxd for adult patients with unresectable or metastatic HER2 immunohistochemistry (IHC) 3+ solid tumors. Therefore, the clinically more practical and convenient HER2 IHC has drawn increased attention for application in NSCLC. While, currently, there are no standard protocols for the selection of optimal specimen type for HER2 testing in NSCLC. The aim of our study is to investigate the concordance of HER2 status between biopsy and subsequent lobectomy specimens, as well as between primary and metastatic lesions.

Methods: We collected NSCLC cases at Peking University Cancer Hospital spanning the years 2017 to 2024 that underwent HER2 testing, possessed matched specimens, and exhibited at least one lesion with HER2 2+ or higher. All cases were independently re-evaluated by two pathologists.

Results: A total of 129 paired samples were included in our study. Eighty-eight paired surgical and biopsy samples, 102 matched primary and metastatic samples were included in the analysis. The concordance rates between biopsy and paired resection were 51.4% for HER2 2+ and 21.4% for HER2 3+, with significantly higher concordance observed in HER2 2+ compared to HER2 3+ (p=0.040). The concordance rates between primary tumor and metastasis were 39.4% for HER2 2+ and 35.4% for HER2 3+. No significant difference in concordance rates was observed between local regional lymph node metastasis and distant metastasis. Regardless of HER2 2+ or 3+, both biopsy and metastatic samples tended to underestimate HER2 expression. HER2 overexpression was more prevalent in adenocarcinoma (p=0.003), especially for HER2 2+. Additionally, HER2 3+ expression exhibited a significant positive correlation with a positive percentage greater than 30% (p=0.042) and an H-score greater than 65 (p=0.018).

Conclusions: Our results indicate that HER2 exhibits spatiotemporal heterogeneity in NSCLC, suggesting the need for sampling as extensively as possible to optimally identify the potential population that may benefit from T-DXd treatment.

Keywords: HER2, spatiotemporal heterogeneity, T-DXd

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.97 Monitoring the Risk of Second Primaries Through Blood miRNA Testing: Follow-Up of the BioMILD Lung Cancer Screening Trial

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Introduction: The BioMILD study, involving 4,119 participants, combined LDCT with a blood 24-miRNA classifier (MSC) and showed improved prediction of lung cancer incidence and mortality. Here we evaluated the ability of MSC to monitor the disease status in lung cancer patients of the BioMILD cohort after curative surgery. Modulation of MSC risk profile has been assessed to identify second primary tumors and deaths.

Methods: MSC profile has been assessed in plasma samples longitudinally collected after curative surgery for primary LC in 98 Stage I patients of the BioMILD study in over 10 years of follow-up. Overall, 776 MSC tests, 96 at first LC diagnosis and 680 post-surgery (median number of samples 7, IQR 5-11) were analysed by RT-qPCR using a 384-well microfluidic TaqMan cards (ThermoFisher), containing proper controls and probes for the 24 miRNAs of interest in duplicate.

Results: At the time of the first LC diagnosis, 77 patients (80%) had MSC+ and 19 (20%) had MSC- results. A second primary LC was observed in 17 (17%) patients and 11 (11%) died of any cause throughout the 10 years follow-up. Considering all 680 post-surgery MSC tests available, the percentage of MSC+ results decreased from 80% at diagnosis to 53.1% post-surgery. The sensitivity of MSC test for second primary LC was 70% within 6 months before diagnosis and remained high (65.9%, 66.1%, 66.3%) within 1, 2 and 3 years, respectively. Looking at the longitudinal modulation of MSC test over time, percentage of MSC+ gradually decreased in 87 patients who remained disease free (59% at 6mo, 48% at 2yrs, 37% at 5yrs, 33% at 7yrs) while an opposite trend was observed in the 17 who developed a second primary LC (59% at 6mo, 61% at 2yrs, 55% at 5yrs, 80% at 7yrs). When considering the percentage of post-surgery MSC+ test in individual patients, the relative risk was 2.8 (95%CI: 1.1-6.9) to develop a second primary LC in patients with ≥50% MSC+ test (p=0.021).

Conclusions: In BioMILD stage I LC patients, blood microRNA testing showed high sensitivity at pre-surgery and in longitudinal samples post-surgery to predict second primaries and deaths. Such a non-invasive blood test strategy might contribute to optimize the clinical management of LC patients after surgery.

Keywords: screening, blood biomarkers, microRNA

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.98 Deep Learning-Based 18F-FDG PET/CT Radiomics Model for Predicting Pathological Response to Chemoimmunotherapy in NSCLC

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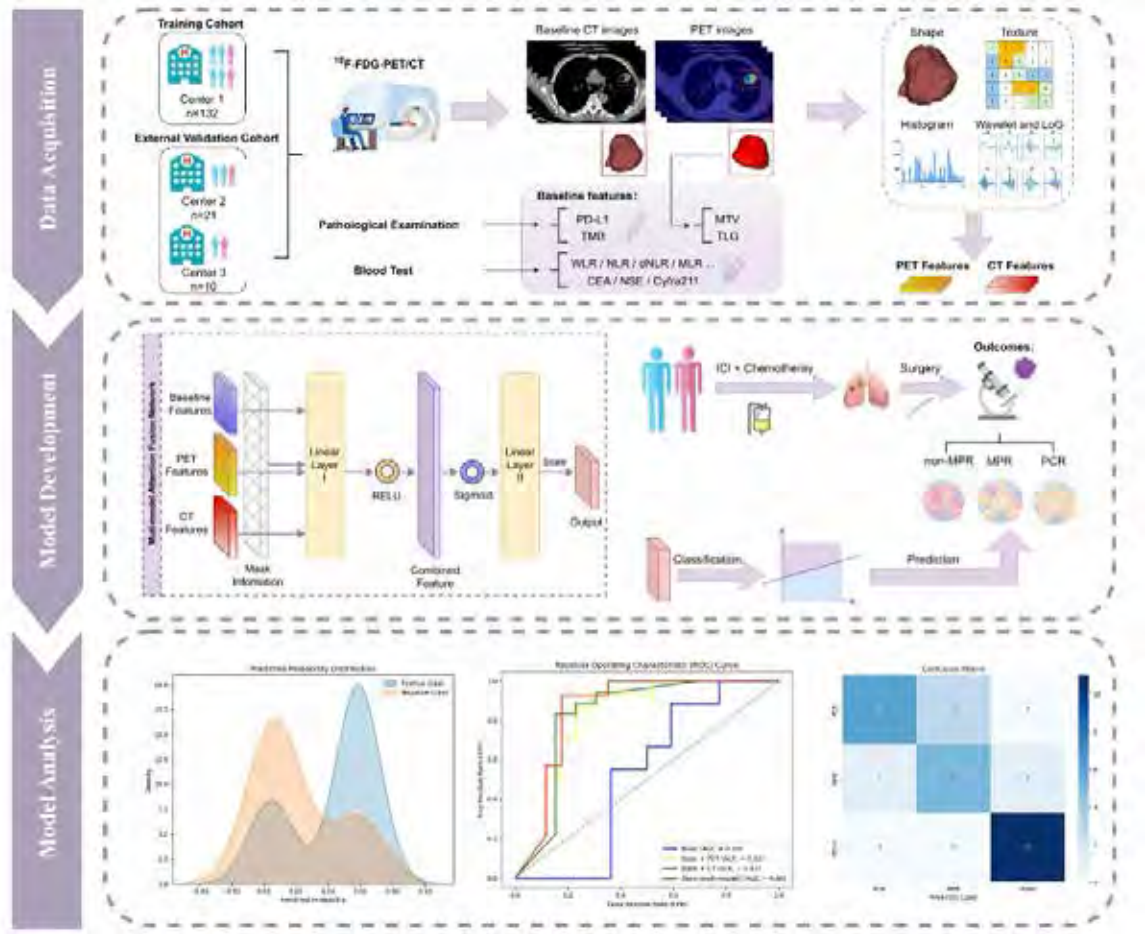
Introduction: In recent years, immune checkpoint inhibitors (ICIs), represented by PD-1/PD-L1, have made breakthrough progress in the treatment of lung cancer. However, the predictive efficacy of current biomarkers for ICIs remains insufficient. This study explores the predictive value of radiomics-based biomarkers for the treatment response to ICIs in NSCLC patients undergoing chemoimmunotherapy.

Methods: We retrospectively collected 18F-FDG PET/CT images from 132 NSCLC patients treated with chemoimmunotherapy between January 2023 and December 2024. A total of 1,834 radiomic features were extracted from CT images and 179 from PET images. A multimodal dataset was constructed by integrating PD-L1 expression, Tumor Mutational Burden (TMB), metabolic tumor characteristics (Metabolic Tumor Volume [MTV] and Total Lesion Glycolysis [TLG]), and peripheral blood biomarkers. The dataset was randomly divided into training and validation cohorts in an 8:2 ratio. We propose a Mask-MLP score model to compute patient-specific scores, which serve as the primary basis for evaluating the study endpoint (Pathological Complete Response, PCR). The model's accuracy was further validated in an external validation cohort consisting of 32 patients from two independent hospitals.

Results: Our study proposes a multi-model deep learning model which was constructed upon LDA feature engineering technique. Our model integrates diverse data sources including 10 clinical characteristics, 3 CT features, and 3 PET features. Our model achieved an AUC of 0.72 (95% CI: 0.39 to 0.8) in the training set. In the external independent validation cohort, the AUC was 0.86 (95% CI: 0.71 to 0.98), sensitivity of 92.86%, specificity of 82.35%. Compared to single-modality models based on clinical features (AUC: 0.53, 95% CI: 0.33 to 0.74) or individual CT (AUC: 0.83, 95% CI: 0.64 to 0.99)/PET features (AUC: 0.82, 95% CI: 0.65 to 0.97), the Mask-MLP score model significantly improved accuracy.

Conclusions: This study developed a deep-learning predictive model that integrates multimodal baseline data to evaluate pathological treatment responses to chemoimmunotherapy in NSCLC. The model allows for the accurate pre-therapeutic identification of potential treatment responders.



Keywords: Radiomics, Deep Learning, Treatment Response

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.99 Tumor-Associated Neutrophil Infiltration Predicts Benefit From Combination Chemoimmunotherapy in Non-Small Cell Lung Cancer

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Introduction: More than half of patients with advanced non-small cell lung carcinoma (NSCLC) do not respond to standard-of-care immune checkpoint blockade (ICB)-based treatment. Tumor-associated neutrophils (TANs) are emerging as potential mediators of resistance to anti-PD1 therapy. Prior studies have sought to indirectly assess TANs by surrogate markers readily accessible in peripheral blood, e.g., neutrophil-to-lymphocyte ratio and serum IL-8. We hypothesized that direct assessment of intratumoral neutrophils on routine H&E slides may improve the sensitivity and specificity of detecting patients unlikely to respond to ICB. The current study leverages data from a previously reported randomized phase 2 clinical trial of durvalumab + tremelimumab +/- platinum-doublet chemotherapy in patients with untreated metastatic NSCLC (CCTG BR34; Leighl et al. JTO 2022). The study aimed to: (1) assess the feasibility of direct scoring of TANs on H&E-stained pretreatment NSCLC biopsies and (2) test the association of intratumoral TANs with survival outcomes in patients receiving combination ICB (CIBC) with or without chemotherapy.

Methods: H&E-stained slides were previously collected from (N=301) patients with treatment-naive, metastatic NSCLC (without sensitizing EGFR or ALK alterations) enrolled in BR34. Inclusion required ≥10 high-power fields (HPFs) of intact, non-necrotic evaluable tumor tissue (at 40x magnification). TAN scoring was performed on n=225 pre-treatment NSCLC specimens from patients treated with chemotherapy + CICB (chemo+CICB, n=114) or CICB alone (n=111). For each slide, a maximum of 20 representative HPFs were visually evaluated for neutrophils by cellular morphology (e.g., segmented nuclei and bright pink cytoplasmic granules). Each HPF with ≥5 TANs located within the tumor epithelium or tumor stroma was scored as a TAN(+)HPF. Neutrophils associated with blood or necrosis were not counted. The proportion of TAN(+)HPFs was calculated. The percentage of necrotic tumor area was estimated. PD-L1 status was evaluated using the tumor proportion score.

Results: Among pre-treatment specimens with ≥1 TAN(+)HPF, the median proportion of TAN(+)HPFs was 5%. The proportion of TAN(+)HPFs did not correlate with percent necrosis (p=0.99) or PD-L1 tumor proportion score (p=0.10). All biopsy specimens with >5% TAN(+)HPFs were designated TAN(high). The prevalence of TAN(high) tumors (18.7%) did not significantly differ by treatment arm (p=0.76). TAN(high) tumors were associated with shortened median overall survival (OS) in the CICB alone arm (7.9 months TAN(high) versus 18.3 months TAN(low), p=0.004; HR: 2.39, 95% C.I.: 1.30-4.39). This association was absent in patients treated with chemo+CICB (HR: 1.00, p=0.99). The median OS for patients with TAN(high) tumors in the CICB alone arm was 7.9 months versus 15.3 months in the chemo+CICB arm (p=0.03). A multivariable adjusted test for interaction confirmed that TAN(high) predicted improved OS for patients receiving chemo+CICB versus CICB alone (HR: 0.39, 95%, C.I.: 0.17-0.93, p=0.03).

Conclusions: Our findings show that H&E-based classification of TAN(high) tumors is feasible and the TAN(high) phenotype is independent of tumor necrosis and PD-L1. TAN(high) NSCLC was associated with reduced OS in patients receiving CICB alone, but predicted OS benefit with the addition of platinum-doublet chemotherapy to CICB. These findings warrant further validation of TAN assessment as a biomarker to guide ICB-based therapy selection in NSCLC.

Keywords: Tumour-associated neutrophils, Non-small cell lung cancer, Immunotherapy

P2.06.100 Initial Biomarker Results From the Phase 2A Study of AFM24 With Atezolizumab in Patients With Advanced/Metastatic NSCLC

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Introduction: Despite significant progress in the treatment of non-small cell lung cancer (NSCLC) without actionable driver mutations, new therapies along with reliable response biomarkers are required for patients who progress after standard of care treatment. AFM24 is a tetravalent, bispecific innate cell engager (ICE) that binds CD16A on NK cells and macrophages and EGFR on solid tumors, redirecting and enhancing the innate and indirectly the adaptive immune response. This open-label, non-randomized Phase 1/2a study (NCT05109442) is evaluating the combination of AFM24 and atezolizumab for the treatment of EGFR-wildtype (EGFR-WT) NSCLC. The initial clinical and efficacy results of this study were submitted to ASCO 2025; here, we report additional correlative science analyses to identify correlative biomarkers in peripheral blood to complement the efficacy data.

Methods: AFM24 is given weekly at 480 mg intravenously (IV) in combination with 840 mg atezolizumab IV fortnightly, to patients with advanced/metastatic EGFR-WT NSCLC who progressed on ≥1 prior line of therapy, including at least a platinum doublet and a checkpoint inhibitor (CPI). Treatment is given in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. Longitudinal immunophenotyping of various immune cell types was conducted to identify potential biomarkers in peripheral blood and measure pharmacodynamic effects on immune effector cells during the first treatment cycle.

Results: As of 15 January 2025, 43 patients were treated with AFM24 and atezolizumab. All patients had discontinued their previous CPI treatment due to disease progression. As previously reported at ASCO 2025, the combination was well tolerated, with infusion-related reactions being the most common adverse event (AE), and a disease control rate (DCR) of 77% was observed in this study cohort. Immunophenotyping of peripheral blood mononuclear cells (PBMCs) was performed on 12 patients, with 11 patients passing quality thresholds. A correlation between the frequency of NK cells in PBMCs and DCR was observed, with a median NK cell frequency at baseline of 17.5% in patients with disease control (n=8) versus a median frequency of 1.5% in patients without disease control (n=3). After the first AFM24 dose in the safety lead-in phase, a decrease in the NK cell count was measured that remained below baseline levels throughout the first treatment cycle, thus suggesting a potential migration of NK cells to EGFR-expressing tumor cells. Further analysis of activation and exhaustion markers revealed pharmacodynamic effects of AFM24 and atezolizumab on the activation status of various immune cell types, indicating activation of both the innate and adaptive immune systems.

Conclusions: The combination of AFM24 and atezolizumab shows promising clinical efficacy in NSCLC patients who failed prior treatments, including platinum-based chemotherapy and a CPI, with a tolerable and well-managed safety profile. A DCR of 77%, along with some long, sustained responses, correlates with high numbers of NK cells in the peripheral blood, which potentially leave the periphery and migrate to the tumor upon AFM24 treatment. This combination immunotherapy approach could offer a promising chemotherapy-free alternative, with NK cell frequency as a potential minimally invasive predictive biomarker for treatment response.

Keywords: EGFR, Innate cell engager, NK cell

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.101 Neuroendocrine-Like Subtype or TMB-High Predicts Long-Term Survival Benefit From Sequential Thoracic Radiotherapy and ICI in ES-SCLC

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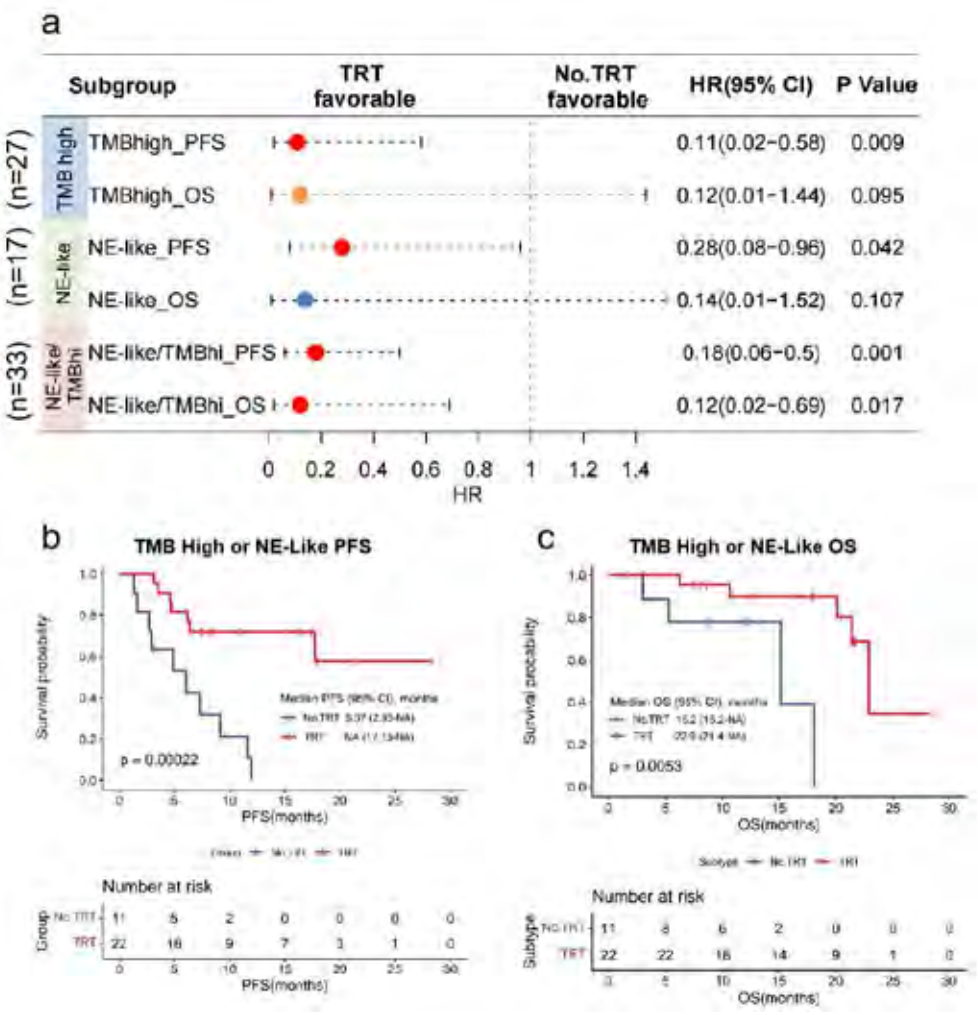
Introduction: The efficacy and safety of adebrelimab in combination with first-line chemotherapy followed by sequential thoracic radiotherapy (TRT) in ES-SCLC patients have been reported (NCT04562337). However, biomarkers to select patients who might benefit from TRT remain unidentified. This study integrates real-world data with the original Phase II trial to explore predictive biomarkers for TRT benefit.

Methods: In addition to 30 patients from initial Phase II trial, 27 ES-SCLC patients treated in real world practice were enrolled under similar criteria of phase II trial resulting in a total of 57 patients. 55 and 57 pre-treatment biopsies successfully underwent comprehensive genomic profiling (571-gene panel, AmoyDx master panel) and whole transcriptome sequencing, respectively.

Results: Among 57 patients who received an immunotherapy (with 30 Phase II trial patients treated with adebrelimab) plus etoposide/cisplatin regimen, 34 underwent sequential thoracic radiotherapy (TRT) based on treatment response, while 23 did not (non-TRT group). The TRT group exhibited a significantly longer median progression-free survival (mPFS: 11.3 vs. 6.1 months, p<0.001), although median overall survival (mOS: 22.9 vs. 18.0 months, p=0.68) was similar. Cox analysis revealed that in TMB-high patients (≥10 muts/mb), TRT was associated with a significant PFS benefit (n=27, HR=0.11, p=0.009) and a trend toward OS benefit (n=27, HR=0.12, p=0.095), while no significant differences were observed in the TMB-low group. Using non-negative matrix factorization, transcriptomic data classified patients into three subtypes; notably, in the NEUROD1/ASCL1-enriched NMF3 subgroup (NE-like), TRT conferred a significant PFS benefit (n=17, HR=0.28, p=0.042). Intriguingly, patients with either TMB-high or NE-like subtype features significant improvements in both PFS (n=33, HR=0.18, p=0.001) and OS (n=33, HR=0.12, p=0.017) with TRT.

Conclusions: This study integrates Phase II and real-world data to identify biomarkers predicting long-term survival benefit from TRT and immune checkpoint inhibitors in ES-SCLC patients after treatment of etoposide/cisplatin and immune checkpoint inhibitors.



Keywords: ES-SCLC, TMB, Radiotherapy

P2.06 PATHOLOGY AND BIOMARKERS
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.06.102 Prevalence and Concordance Analysis of MET Amplification/Overexpression in a Phase 1 Study of Davutamig (REGN5093) in a NSCLC

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Introduction: MET protein and genomic alterations are prevalent in NSCLC but the overlap of patients with alterations is not well established in later lines of therapy. Additionally, concordance between genomic alterations in tissue and blood has not been evaluated. Here, we report a centrally-confirmed prevalence analysis of MET overexpression (OE), MET exon 14 skipping (MET ex14) mutation, and MET amplification (Amp) alongside an assessment of the impact of biopsy age on MET OE in patients with advanced NSCLC (aNSCLC). We also present a concordance analysis of multiple MET Amp detection technologies using liquid and tissue matrices.

Methods: Patients with MET-altered aNSCLC (unresectable/metastatic) by local testing received davutamig intravenously Q3W (NCT04077099). MET protein expression was evaluated by immunohistochemistry (IHC) using the SP44 antibody (Roche Tissue Diagnostics). MET Amp and MET ex14 mutation status were performed on baseline tumor biopsies and plasma ctDNA (Guardant Health, Foundation Medicine, Inc.) samples using next generation sequencing (NGS) assays. Fluorescence in situ hybridization (FISH) with MET/CEP7 probes (Abbott Molecular) were used to assess MET Amp. Prevalence analysis was grouped by EGFR and MET ex14 mutation status. Concordance rate between methodologies was calculated by dividing the number of samples identically classified by both methods, by total number of overlapping samples.

Results: As of July 2024, of the enrolled patients (n=82), 70 had MET Amp data, and 59 were evaluable by IHC (54 patients had both results). Association analysis showed a significant relationship between MET OE and MET Amp (IHC 3+ ≥25%: 70% [38/54]; Amp: 48% [26/54]; Pearson's chi-square test: p=0.027). No significant difference in MET OE by IHC was observed between EGFR WT (IHC 3+ ≥25%: 75% [12/16]) and EGFR MUT (IHC 3+ ≥25%: 75% [15/20]) subgroups. Similar levels of MET Amp were reported between EGFR WT (67% [12/18]) and EGFR MUT (61% [14/23]) subgroups. Lower rates of MET OE and MET Amp were observed in patients with MET ex14 mutation (IHC 3+ ≥25%: 62% [8/13]; Amp: 23% [5/22]) compared with patients without MET ex14 mutation (IHC 3+ ≥25%: 75% [27/36]; Amp: 63% [26/41]). There were no significant differences in MET OE between fresh (IHC 3+ ≥25%: 70% [16/23]) and archival biopsies (IHC 3+ ≥25%: 85% [11/13]; p=0.299) and this was not impacted by acquisition timing (100-1000 days prior to enrolment) of archival biopsies (EGFR WT: p=0.87; EGFR MUT: p=0.26). Within tissue-based MET Amp detection technologies, high concordance (78%) was observed between FISH (Gene copy number [GCN] ≥5 or MET/CEP7 ≥1.8) and NGS (GCN ≥6). Liquid-based NGS testing for MET Amp was complementary (74% concordance) to tissue-based genotyping regardless of assay platform.

Conclusions: These findings identified that most patients with aNSCLC exhibited both MET OE and MET Amp, with age of archival tumor biopsy having no impact on MET expression. This supports the use of existing tissue samples and may reduce the need for fresh biopsies. Despite no consensus on technology assessing MET Amp, these results suggest reliable outcomes are achievable with specific cut-offs regardless of assay platform, warranting further sample analysis to validate these findings.

Keywords: Non-small cell lung cancer, Biomarker, Immunotherapy

P2.08 .01 Double Lung Transplantation in Patients With Recent History of Malignancy

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Introduction: Recent history of malignancy usually within five years is a contraindication for double lung transplantation (DLT). However, the relationship between a recent history of malignancy and lung transplantation outcomes is unclear.

Methods: Patients with respiratory failure and a history of cancer in the last five years treated with DLT were identified between 09/2021 and 11/2024. All patients had enrolled in the DLT registry aimed for lung-limited malignancies (DREAM) study cohort C (NCT05671887). Standard staging work-up confirmed the absence of any distant metastasis. All patients were followed up with computed tomography every 12 weeks.

Results: 14 consecutive patients who underwent DLT were included (age 58-75, 10 male, 4 female, and 13 former smokers). 10 patients had primary lung (stage IB-IIIB), two had prostate (stage I-IIc), one had bladder, and one had skin cancer. Among lung cancer patients, five patients had adenocarcinoma, four squamous cell carcinoma, and one poorly differentiated non-small cell carcinoma. Prior to DLT, patients received radioimmunotherapy (n=1), chemoradiotherapy (n=2), chemoradiotherapy plus immunotherapy (IO) (n=2), radiotherapy alone (n=2), and chemotherapy alone (n=3). The duration of IO was a median of 2 (2-18) months. The IO-free interval was 11, 27, and 44 months before DLT. All patients had high oxygen requirements before DLT. The indications for DLT were COPD (n=4), IO-related ILD (n=3), IPF (n=2), and COVID-related ILD (n=1). Transplant rejection did not occur, and there was no requirement for oxygen therapy for any patient. The median duration of follow-up for survival after transplant was 9 (7-17) months (Table 1).

Conclusions: 14 patients successfully underwent DLT for non-malignant indications of respiratory failure with less than a 5-year history of cancer without significant complications. Ongoing DREAM study cohort C will continue to investigate the role of DLT in patients with a recent history of malignancy.

Patients (n=10)	Reason for DLT	Smoking Status	Pretransplant cancer diagnosis	Definitive Treatment	Duration ofIO (month)	IO-free interval (month)	Duration of Waitlist (day)	Stage at DLT	OS after transplant (months)	Rejection
Case 1 (61y, White male)	COPD	Former	Stage IIIB (T3N2M0) Lung Mucinous AdenoCA	ImmunoRT	2	11	32	T0N0	12	No
Case 2 (69y, White male)	ILD-IO related	Former	Stage IIIB Lung SqCC	ChemoRT	N/A	N/A	12	y pT1aN0	9	No
Case 3 (58y, Black male)	ILD-Covid related	Former	Stage IB (T2aN0M0) Lung SqCC	Chemo Alone	N/A	N/A	61	pT2aN0M0	6	No
Case 4 (61y, White male)	COPD	Former	Stage IIIB Lung SqCC	ChemoRT + IO	18	27	20	T0N0	5	No
Case 5 (71y, White female)	ILD-IO related	Never	Stage 3B (cT4cN2cM0) poorly differentiated non-small cell lung carcinoma	ChemoRT + IO	2	44	66	T0N0	4	No
Case 6 (65y, White female)"	COPD	Former	Stage 1 (cT1b,cN0,cM0) Lung AdenoCA	RT Alone	N/A	N/A	78	T0N0	4	No
Case 7 (65y, female)	IPF	Former	Stage 2A (cT2b,cN0,cM0) Lung SqCC	Chemo Alone	N/A	N/A	13	Stage 2B	4	No
Case 8 (75y, White male)	IPF	Former	Stage 3 (pT4pN0) Lung AdenoCA	Chemo Alone	N/A	N/A	N/A	T0N0	4	No
Case 9 (63y, Female)	COPD	Former	Stage 1A (T1b 2.3cm pN0M0) Lung SqCC	RT Alone	N/A	N/A	8	T0N0	2	No
Case 10 (66, Hispanic male)	ILD-IO related	Former	Stage 3B (cT4cN2cM0) Lung Mucinous AdenoCA	ChemoRT	N/A	N/A	2	ypT3pN0	3	No

Keywords: double lung transplant, lung cancer, dream study

P2.08 .02 Long Term Prognosis Following Wedge Resection in Peripheral = cT1b Non-Small Cell Lung Cancer Patients Without Pulmonary Dysfunction

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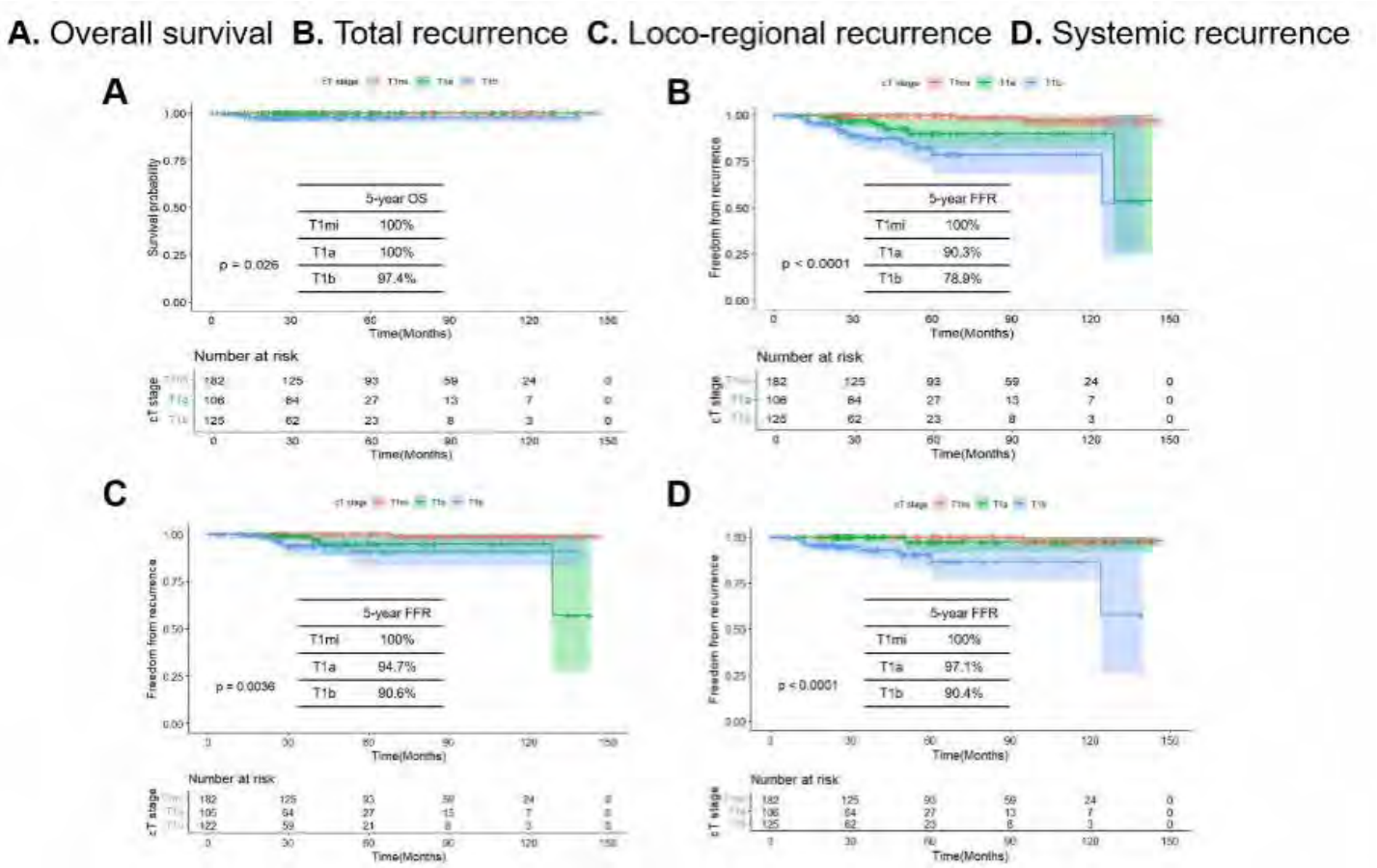
Introduction: This study is to investigate the long-term prognosis and pulmonary function change after wedge resection in patients with peripheral ≤ cT1b NSCLC and eligible for lobectomy.

Methods: We retrospectively reviewed data of 413 patients who underwent wedge resection for ≤ cT1b NSCLC between 2011 and 2022. Patients with previous history of lung cancer and FEV1 < 60% were excluded. Recurrences were classified as loco-regional recurrence (LRR; recurrences in the index lobe or at ipsilateral hilar/mediastinal nodes) and systemic recurrence (all other recurrences). Overall survival (OS) and freedom-from-recurrence (FFR) rates for all recurrence and LRR were analyzed. Pulmonary function changes at least postoperative 6 months were analyzed also.

Results: Clinical stages were cT1mi in 182 (44.1%), cT1a in 106 (25.7%), and cT1b in 125 (30.3%) patients. Histologic type was adenocarcinoma in 384 (93%) and non-adenocarcinoma in 29 (7%). The mean tumor size was 1.3 ± 0.7 cm and consolidation-to-tumor ratio (CTR) was 0.5 ± 0.5. The mean resection margin distance and margin-tumor ratio (MTR) were 1.2 ± 0.8 cm and was 1.1 ± 1.0, respectively. Lymph node sampling was done in 182 (44.1%) patients. (3.1 ± 5.3 nodes) After a median follow-up of 40 months, recurrences were diagnosed in 26 patients (local - 10; regional - 4; systemic - 12). There was 3 non-cancer-related death, and no patients died from NSCLC. OS rates were significantly different between cT1 stages. (5-year: cT1mi/ cT1a - 100%, cT1b - 97.4%, p = 0.026). FFR rates (5-year: cT1mi - 100%, cT1a - 90.3%, cT1b - 78.9%, p < 0.001) and FFR-LRR rates (5-year: cT1mi - 100%, cT1a - 94.7%, cT1b - 90.6%, p = 0.004) were significantly different between cT stages. In multivariate analysis, risk factors for all recurrence were age (HR=1.07, 95% CI=1.02-1.12, p = 0.003) and smoking (HR= 5.33, 95% CI=1.97-14.45, p = 0.001). However, no other risk factor was significant for LRR in multivariate analysis. After at least 6 months postoperatively, the mean reduction of FVC was -4.5 ± 8.7% and that of FEV1 was -4.5 ± 9.0%.

Conclusions: After wedge resection, overall survival of T1mi, T1a, and T1b were similar and excellent, and pulmonary functions were well preserved. Wedge resection can be an option in peripheral ≤ cT1b NSCLC.



Keywords: NSCLC, Wedge resection, Pulmonary function

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .03 Differentgrades of Visceral Pleura Invasion in Lung Adenocarcinomas Correlate With Aggressiveness and Poor Prognosis

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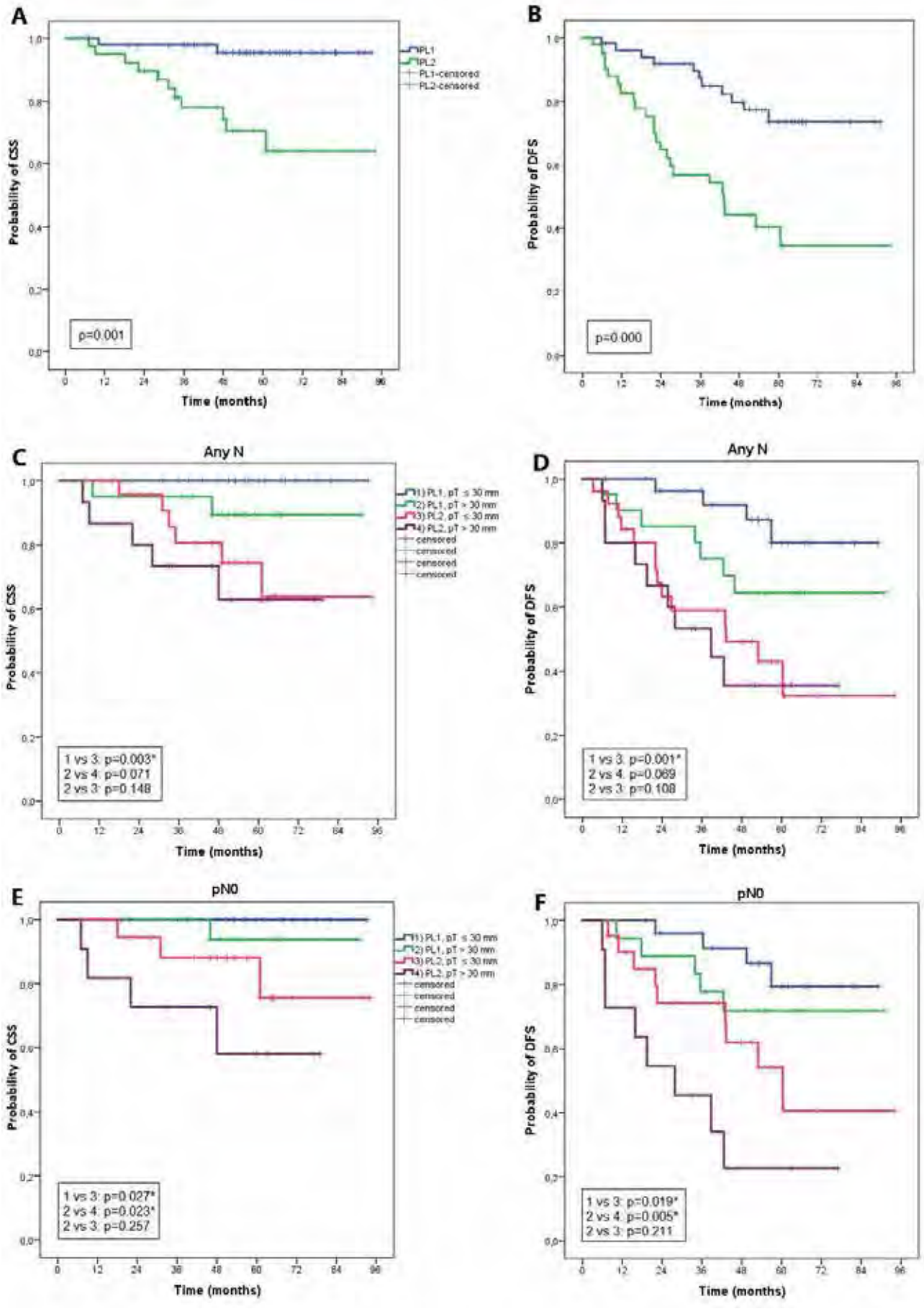
Introduction: Visceral pleura invasion (VPI) in lung adenocarcinoma (LUAD) is a negative prognostic factor. The prognostic impact of different grades of neoplastic VPI; PL1 (beyond the elastic layer but remaining below the pleural surface) and PL2 (emerging on the pleural surface), is still debated. This study evaluates the relationship between PL1/PL2, survival outcomes, and other histology-related risk factors in LUAD patients.

Methods: We retrospectively collected data from patients who underwent radical surgery for LUAD between 2017 and 2020. A multivariable analysis assessed predictors of Overall, Cancer-Specific (OS, CSS), and Disease-Free Survival (DFS). The relationship between VPI grade, other prognostic factors, and the site of recurrence (when it occurred) was also evaluated.

Results: Ninety-seven patients were included (PL1=55, PL2=42). The PL2 group had worse survival outcomes than PL1 ($p \leq 0.001$), independently of the pathologic stage ($p<0.05$). OS and CSS were significantly affected by PL2-VPI and high-grade histological patterns ($p<0.05$). PL2-VPI, with low differentiation grade (G3), also significantly affected DFS ($p<0.05$). Moreover, PL2-VPI was linked to high-grade patterns ($p=0.016$), lower differentiation grade ($p=0.005$), lymphovascular invasion ($p<0.001$), and higher distant recurrence incidence ($p=0.002$) than PL1-VPI.

Conclusions: PL2-LUADs showed worse survival outcomes and more frequent negative prognostic factors than PL1. These findings could help develop a scoring system to predict prognosis and determine the need for adjuvant therapy.



Keywords: lung adenocarcinoma, visceral pleura invasion, lung surgery

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .04 Open Versus Thoracoscopic Versus Robotic Sleeve Lobectomy for Central Non-Small Cell Lung Cancer: A Network Meta-Analysis

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Introduction: Sleeve lobectomy is the preferred surgical approach for central non-small cell lung cancer (NSCLC), but the comparative efficacy of open thoracotomy, video-assisted thoracoscopic surgery (VATS), and robotic-assisted thoracoscopic surgery (RATS) remains unclear. This network meta-analysis (NMA) aims to compare the perioperative and long-term outcomes among these three techniques.

Methods: We systematically searched PubMed, Embase, and Cochrane Library up to December 2024 (PROSPERO ID: CRD42025626437). Included studies compared at least two surgical approaches (thoracotomy, VATS, or RATS) for central NSCLC sleeve lobectomy. Data on perioperative outcomes (operative time, blood loss, lymph node dissection, hospital stay, complications, etc.), and long-term survival (recurrence-free survival [RFS], overall survival [OS]) were extracted. The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects NMA was performed using R and Stata.

Results: Thirteen retrospective cohort studies (1601 patients) were included: thoracotomy (65.3%, n=1045), VATS (27.9%, n=447), and RATS (6.8%, n=109). Eleven studies scored a 7 or 8 in NOS, whereas the other 2 studies scored a 6. As for the perioperative outcomes, RATS demonstrated the significantly reduced blood loss (51.4ml less than thoracotomy, 95% CI: -84.4 to -18.4ml; VATS vs. thoracotomy, -18.4 [-41.6, 4.8]), along with significantly reduced drainage volume (498.8ml less than thoracotomy, 95% CI: -784.3 to -213.3ml; VATS vs. thoracotomy, -381.0 [-512.0, -250.0]) and drainage duration (5.0 days less than thoracotomy, 95% CI: -5.1 to -2.5 days). RATS showed a trend toward shorter operative time (16.6min shorter than thoracotomy, 95% CI: -41.5 to 8.3min; VATS vs. thoracotomy, 40.0 [22.4, 57.7]), and hospital stay (1.1 days shorter than thoracotomy, 95% CI: -2.3 to 0.02 days; VATS vs. thoracotomy, -1.0 [-1.6, -0.4]). While lymph node dissection, positive surgical margins, complications, and mortality were observed comparable between RATS versus thoracotomy (p>0.05), and VATS was associated with the lowest complication rates (OR 0.67 vs thoracotomy, 95% CI: 0.48-0.94). Regarding long-term outcomes, RATS showed favorable trends in overall survival compared to both VATS (HR 0.73, 95% CI: 0.35-1.52) and thoracotomy (HR 0.53, 95% CI: 0.21-1.36), while recurrence-free survival showed no significant differences between approaches (RATS vs. VATS: HR 0.78, 95% CI: 0.36-1.68; VATS vs. thoracotomy: HR 0.83, 95% CI: 0.62-1.10).

Conclusions: Minimally invasive approaches (VATS/RATS) offer superior perioperative outcomes over open thoracotomy for central NSCLC sleeve lobectomy, with comparable long-term survival. RATS may further optimize intraoperative efficiency. Prospective trials are needed to validate these findings.

Keywords: non-small cell lung cancer, sleeve lobectomy, minimally invasive surgery

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .05 Robotic-Assisted Versus Video-Assisted Sleeve Lobectomy for Central Non-Small Cell Lung Cancer: A Multicenter Cohort Study

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Introduction: Sleeve lobectomy has emerged as the standard of care for centrally located non-small cell lung cancer (NSCLC), offering superior lung preservation compared to pneumonectomy. While both robotic-assisted (RATS) and video-assisted (VATS) approaches are widely adopted, their comparative efficacy remains uncertain. This multicenter study evaluates perioperative and long-term outcomes between RATS and VATS sleeve lobectomy in a large, propensity-matched cohort.

Methods: This retrospective study analyzed 339 consecutive patients with stage I-III NSCLC undergoing RATS or VATS sleeve lobectomy between January 2015 and September 2024 across three high-volume centers in China. The propensity score matched balanced baseline characteristics. Statistical analyses were performed to evaluate the perioperative outcomes and survival between the two groups (ClinicalTrials.gov ID: NCT06687408).

Results: The entire multicenter cohort enrolled 339 patients with NSCLC undergoing RATS (n=83, 24.5%) or VATS (n=256, 75.5%) sleeve lobectomy comprising predominantly males (n=308, 90.9%), with mean age 62.6±8.0 years and 69.6% smokers. The histological distribution included squamous cell carcinoma (75.2%), adenocarcinoma (9.5%), and others (15.3%), with 34.8% receiving neoadjuvant therapy and 55.5% adjuvant therapy (median follow-up: 30.1 months). The cohort comprised 31.0% in stage I (n=105), 33.9% in stage II (n=115), and 5.1% in stage III (n=119). A total of 154 VATS cases were matched with 76 RATS cases by propensity score. Perioperative outcomes demonstrated significantly shorter operative time for RATS (194.9±61.1 vs. 208.3±65.7 minutes, p<0.0001), less blood loss (123.0±171.5 vs. 163.6±219.1mL, p<0.0001), shorter hospitalization (11.7±6.8 vs. 13.1±6.7 days, p<0.0001), and superior lymph node dissection (stations: 7.7 vs. 7.3, p<0.0001; nodes: 19.4±10.8 vs. 18.0±9.7, p<0.0001). RATS showed similar conversion rates (3.95% vs. 11.04%, p=0.08), comparable R0 resection (88.0% vs. 86.7%, p=0.85), and equivalent complications (22.4% vs. 20.8%, p=0.86). Long-term survival analysis revealed comparable 3-year OS (80.9% vs. 88.4%, HR 1.78, 95%CI 0.67-4.74) and RFS (68.6% vs. 72.9%, HR 1.38, 95%CI 0.73-2.63), with no significant difference in perioperative mortality (5.26% vs. 3.16%, p=0.48).

Conclusions: RATS demonstrated comparable perioperative safety and oncologic outcomes to VATS, with potential advantages in lymph node dissection and postoperative recovery. Preliminary findings support RATS as a viable alternative for central NSCLC resection, warranting further prospective validation.

Keywords: non-small cell lung cancer, sleeve lobectomy, minimally invasive surgery

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .06 Clinical Significance of Tertiary Lymphoid Structures in Surgically Resected Stage II-III Lung Adenocarcinoma

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Introduction: Tertiary lymphoid structure (TLS) is lymphoid follicle-like aggregates observed within or around tumor tissues, playing a critical role in activating antitumor immunity in the tumor microenvironment. In several cancer types, TLS has been reported as prognostic marker and as predictive biomarker for the efficacy of immune checkpoint inhibitors. Although TLS was reported to be a potential prognostic marker in locally advanced non-small cell lung cancer, the subset analysis in terms of histologic type was not performed.. This study aimed to evaluate the association between the presence of TLS and postoperative prognosis in patients with locally advanced lung adenocarcinoma.

Methods: A total of 151 patients who received surgery at Tokyo Medical University Hospital between 2017 and 2020 and were histologically confirmed to be stage II-III adenocarcinoma were retrospectively analyzed. TLS was identified in hematoxylin and eosin stained specimens and defined by the presence of lymphoid follicle-like structures containing tingible body macrophage. The association between TLS and survival outcome was examined.

Results: Lobectomy was performed in 145 patients (96.0%) and segmentectomy in 6 (4.0%) respectively Lymph node metastasis was histologically confirmed in 101 patients (66.9%) and there were 79 stage II cases (52.3%) and 72 stage III cases (47.7%). TLS was detected in 42 patients (27.8%). The median recurrence-free survival (RFS) for the entire cohort was 40.0 months and median RFS was 30.4 months in the TLS-negative group and 47.9 months in the TLS-positive group (hazard ratio [HR]: 0.50; 95% confidence interval [CI]: 0.28-0.89; p = 0.015). The median overall survival (OS) for the entire cohort was 82.5 month and median OS was 65.7 months in the TLS-negative group and not reached in the TLS-positive group (HR: 0.61; 95% CI: 0.29-1.27; p = 0.181). In multivariate analysis for RFS, the presence of TLS (HR: 0.49; 95% CI: 0.280-0.872; p = 0.015) and absence of lymph node metastasis (HR: 0.52; 95% CI: 0.305-0.881; p = 0.015) showed favorable prognosis.

Conclusions: The presence of TLS was favorable prognostic marker in patients with resected stage II-III lung adenocarcinoma.

Keywords: Tertiary Lymphoid Structures, Lung cancer, locally advanced lung adenocarcinoma

P2.08 .07 Lymph Node Yield and Survival Among Lung Cancer Patients Treated With Neoadjuvant Systemic Therapy

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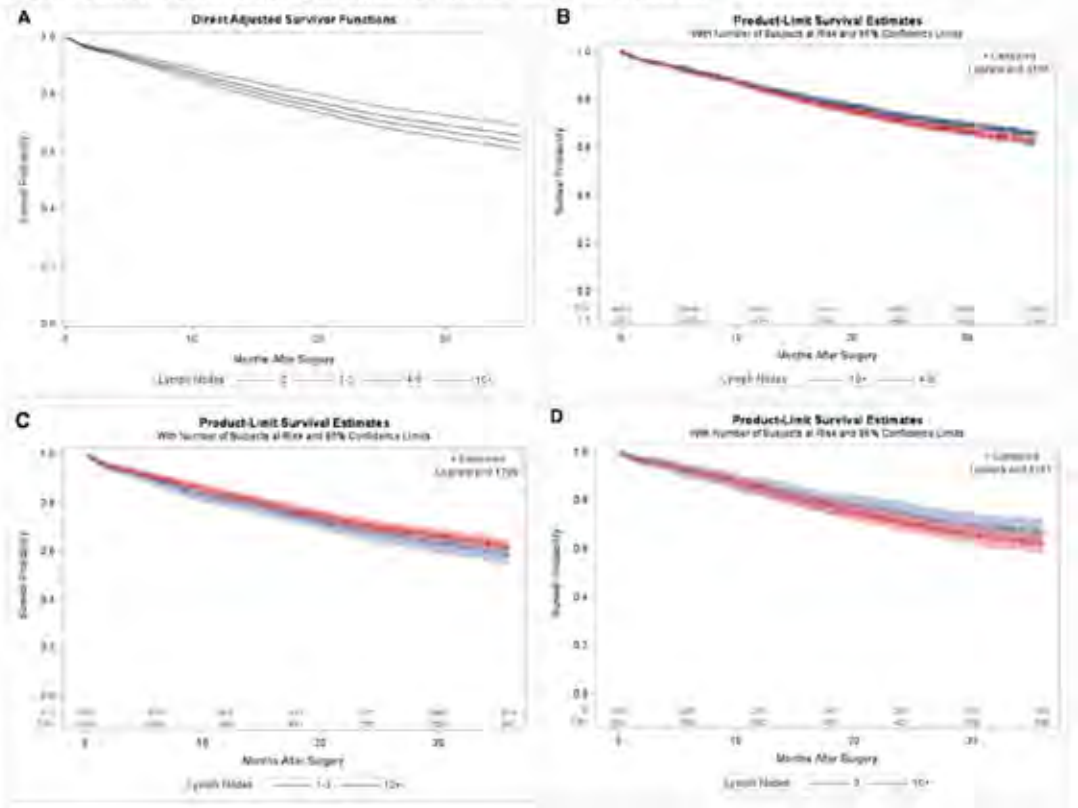
Introduction: Lymph node yield during resection of non-small cell lung cancer (NSCLC) has been positively associated with long-term survival, thus a current standard dictates that four nodal stations be sampled in surgically managed lung cancer patients. One rationale for accurate nodal staging has been to identify patients who may benefit from systemic therapy. Our objective was to determine the relationship between lymph node yield and survival among patients receiving pre-operative systemic therapy.

Methods: Adult patients diagnosed with clinical Stage II or III NSCLC between 2010 and 2021 in the National Cancer Database (NCDB) who received chemotherapy, chemoradiotherapy, or chemoimmunotherapy in the 20 weeks leading up to resection were included. Patients were stratified by nodal yield: 0 nodes, 1-3 nodes, 4-9 nodes, or 10 or more nodes. Three-year overall survival was assessed by the Kaplan-Meier method. Propensity-matching for survival curves and Cox proportional hazards models were adjusted for year of diagnosis, age, sex, race, ethnicity, Charlson-Deyo score, insurance, region, facility type, histology, neoadjuvant treatment type, extent of resection, and clinical T and N stage.

Results: Overall, 8631 patients were identified, including 2512 (29.1%) clinical stage II patients and 6119 (70.9%) stage III. The most common neoadjuvant treatment was chemoradiotherapy (4306, 49.9%), and 7228 (83.7%) underwent lobectomy. The median nodal yield was 12 (IQR 7-18), with 329 (3.8%) removing 0 nodes, (7.0%) removing 1-3 nodes, 2273 (26.3%) with 4-9 nodes, and 5422 (62.8%) with 10 or more nodes. Compared to 10 or more nodes in a Cox model, mortality risk was higher for 4-9 nodes (HR 1.09, 95% CI 1.00-1.19, p=0.04) and 1-3 nodes (HR 1.19, 95% CI 1.03-1.36, p=0.02), but similar for 0 nodes (HR 0.87, 95% CI 0.71-1.06, p=0.17, Figure 1A). Among propensity-matched patients, three-year survival following the removal of 10 or more nodes was superior to taking 4-9 nodes (65.7% vs. 62.2%, p=0.02, Figure 1B), but not significantly different to 1-3 nodes (61.9% vs. 58.5%, p=0.18, Figure 1C) or 0 nodes (61.8% vs. 67.4%, p=0.13, Figure 1D).

Conclusions: Lung cancer patients in whom greater than 10 nodes were removed demonstrated a modest survival advantage on multivariable analysis compared to those for whom only 1-3 or 4-9 nodes were removed. Further research is needed to clarify the importance of nodal yield after preoperative systemic therapy.

Figure 1: A) direct adjusted survival curves of Cox proportional hazards model comparing: 0 nodes vs. 1-3 nodes vs. 4-9 nodes vs. 10 or more nodes removed; B) propensity-matched 3-year overall survival curves comparing 10 or more nodes to 4-9 nodes; C) propensity-matched 3-year overall survival curves comparing 10 or more nodes to 1-3 nodes; D) propensity-matched 3-year overall survival curves comparing 10 or more nodes to 0 nodes.



Keywords: non-small cell lung cancer, surgery, lymph nodes

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .08 Treatment Options and Prognosis for Lung Cancer in Elderly Patients(?80 Years Old)

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Introduction: According to an official report, the average life expectancy in Japan in 2023 is 81.0 years for men and 87.14 years for women, with the percentage of patients who live to be 90 years old being 26.0% for men and 50.1% for women. Recently, the number of patients undergoing surgical treatment has been increasing; however, once complications occur, they can be serious. Even in the absence of complications, the actual prognosis may be shorter than the predicted life expectancy due to the after-effects of surgery. Other treatment options include cytotoxic chemotherapy, stereotactic radiotherapy, epidermal growth factor receptor-tyrosine kinase inhibitor(EGFR-TKI), and immune checkpoint inhibitors (ICI). Some patients opt for Best Supportive Care (BSC) due to the risk of death from other diseases.

Methods: We retrospectively reviewed the medical records of 244 patients aged 80 years or older, who were pathologically diagnosed with lung cancer between January 2012 and December 2023. We investigated the prognosis of surgical cases, non-operative cases, and BSC cases. For surgical cases, we considered the appropriate age, expected life expectancy, and the type of surgical procedure. Tumor size and lymph node metastasis, as described in the pathology reports, were reclassified according to the UICC 8th edition. We have evaluated EGFR gene mutations since 2014 and programmed cell death ligand-1(PD-L1) expression since 2017.

Results: A total of 244 patients (163 men and 81 women) were enrolled in this study. Of these, 79 underwent pulmonary resection, 80 received non-operative treatment, and 85 chose BSC. Lobectomy (n=51) was the most common surgical procedure, followed by segmentectomy (n=18), wedge resection (n=8), and pneumonectomy (n=2). Postoperative complications in the surgical group included two cases of empyema, one bronchial stump fistula, one cerebral infarction, and one pneumonia, all of which occurred after lobectomy. Non-operative treatments included 45 cases of cytotoxic chemotherapy, 21 cases of radical irradiation, 26 cases of EGFR-TKI, and 1 case of ICI. In stage I lung cancer, the 5-year survival rate was 65% for surgical treatment, 45% for non-operative therapy, and 0% for BSC, with the surgery group having the highest 5-year survival rate. The same trend was observed for stages II and III. Confined to women, the 5-year survival rate was high (>85%) for surgical treatment, regardless of stage. In contrast, for men, the 5-year survival rate was only 55%, even for stage I lung cancer. We further investigated surgical procedures in men and found that the 5-year survival rate was highest for segmentectomy, followed by lobectomy, wedge resection, and pneumonectomy. Lobectomy in elderly men may impose greater surgical stress than survival benefits.

Conclusions: The elderly women who underwent surgery had a high 5-year survival rates similarly to those of patients under 80 years old. In contrast, men who underwent lobectomy had only a 55% 5-year survival rate, suggesting that sublobar resection, rather than lobectomy, should be considered for elderly men based on life expectancy.

Keywords: Elderly Patients, Surgical Treatment, Life Expectancy

P2.08 .09 Surgical Resection After Induction Therapy in Initially Unresectable Driver Mutation-Negative Stage III Non-Small Cell Lung Cancer (NSCLC)

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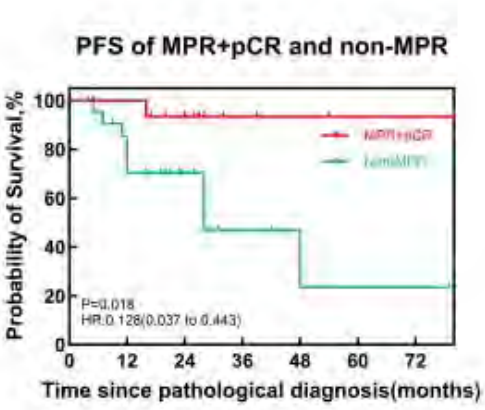
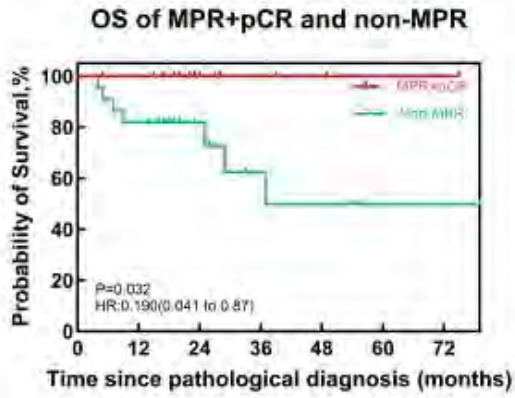
Introduction: With the significant improvement in the efficacy of drug therapy, some patients initially diagnosed with locally advanced unresectable non-small cell lung cancer (NSCLC) may become eligible for surgical resection after induction therapy. However, the survival benefit of this conversion therapy model (from unresectable to resectable) has not been conclusively established, particularly for patients who do not undergo systematic contralateral mediastinal and supraclavicular lymph node dissection during surgery, where the survival advantage remains controversial.

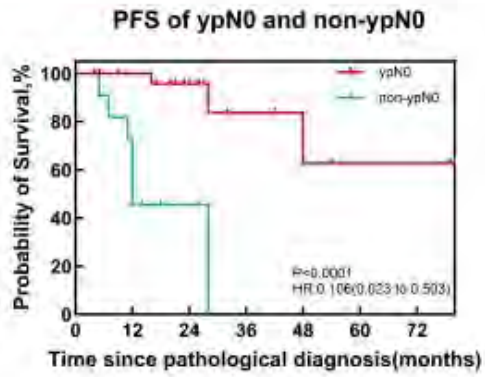
Methods: This study retrospectively enrolled 39 patients with stage III NSCLC who underwent surgical resection at Guangdong Provincial People's Hospital between January 2018 and April 2023 and met the study criteria. All included patients received at least two cycles of immune checkpoint inhibitor (ICI) monotherapy or combination chemotherapy as induction therapy, followed by surgical resection. The primary surgical approach involved resection of the primary lung lesion combined with ipsilateral systematic mediastinal lymph node dissection.

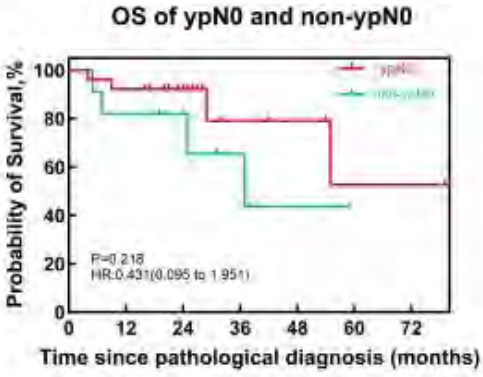
Results: Among the 39 patients ultimately included in the study, the objective response rate (ORR) to induction therapy was 64.1% (25/39). The major pathological response (MPR) and complete pathological response (pCR) rates in the primary lesion were 42.1% (16/38; 95% CI: 17.5%-48.7%) and 31.6% (12/38; 95% CI: 26.3%-59.2%), respectively. The median follow-up time for the entire cohort was 27.0 months (range: 6.0-80.6 months), with a median PFS of 42.0 months. The 2-year PFS and overall survival (OS) rates were 76.2% (95% CI: 54.9%-89.8%) and 89.3% (95% CI: 72.8%-96.8%), respectively.Patients who achieved a major pathological response (MPR) demonstrated significantly prolonged PFS and OS compared to those without MPR (PFS: Not reached vs. 28.0 months (18.5-35.2); HR: 0.128 (95% CI: 0.037-0.443); P = 0.018; OS: Not reached vs. 37.0 months (28.4-45.6); HR: 0.19 (95% CI: 0.041-0.87); P = 0.032). Additionally, patients who achieved ypN0 status on postoperative pathology demonstrated significantly superior PFS compared to non-ypN0 patients (median PFS: not reached vs. 12.0 months [8.4-15.6]; HR: 0.106 [95% CI: 0.023-0.503]; P<0.0001). Among patients with N3 disease, no statistically significant differences in PFS or OS were observed between those who received postoperative adjuvant radiotherapy and those who did not (median PFS: 30.0 vs. 28.0 months, HR: 0.808 [95% CI: 0.219-2.972], P=0.71; median OS: not reached vs. 59.0 months, HR: 0.728 [95% CI: 0.098-5.426], P=0.76).

Conclusions: The findings of this study suggest potential survival benefits from surgical resection in patients with stage N3 NSCLC who achieve both MPR and ypN0 status following induction therapy.









Keywords: Unresectable NSCLC, Conversion therapy, Induction therapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .10 Perioperative Outcomes of Extended Sleeve Resection at Our Institution

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Introduction: Following the results of the CheckMate816 and KEYNOTE671 trials, the use of neoadjuvant chemotherapy has increased. The benefits of preoperative treatment include improved surgical safety due to tumor shrinkage, higher rates of complete resection, and the possibility of preserving lung Volume. Given the inclusion of advanced lung cancer, there is an increasing opportunity for extended surgical procedures, leading to a reevaluation of surgical techniques. This study aims to retrospectively examine the perioperative outcomes of patients who underwent Extended Sleeve Resection at our hospital.

Methods: Between January 2010 and December 2024, 39 cases of extended sleeve resection were performed among 4,495 patients who underwent surgery for primary lung cancer. We retrospectively analyzed perioperative outcomes, including the frequency of postoperative complications. The Extended Sleeve Resections were classified as Type A (right upper and middle lobe ± S6 segment), Type B (left upper lobe + S6 segment), Type C (left lower lobe + lingular segment), Type D (right middle and lower lobe), and others based on previous reports.

Results: The study included 29 males (74%), with a median age of 70 years (range 42-85). 12 patients have history of diabetes (30%), and 33 patients (85%) had a smoking history. The clinical stages were as follows: Stage II/III/IV:12(31%) / 25(64%) /2(4%) patients. The median tumor size was 5.2 cm (range 1.2-12). The median %VC and FEV1.0% was 105% (range 67-128), and 68.5% (range 39.2-80.4). Induction chemotherapy was performed 10 cases, and preoperative radiation therapy was 1 case. All surgeries were performed by open thoracotomy and achievement R0 resection. The mean operative time was 261 minutes (range 166-442). The surgical types included Type A (9), Type B (8), Type C (16), and Type D (5) cases. 10 cases were received Pulmonary artery reconstruction at the same time. Pathological diagnoses included adenocarcinoma in 16 cases, squamous cell carcinoma in 17 cases. The pathological stages were Stage I/II/III :5(13%) /15(38%) /19(49%) patients. 14 patients received adjuvant chemotherapy. Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher perioperative complications occurred in 18 cases (46%), while respiratory complication including atelectasis and sputum retention in 8, pneumonia in 3, pneumothorax in 8, bronchial fistula in 1, pulmonary artery thrombosis in 1, chylothorax in 1, postoperative bleeding in 1, empyema in 3 cases. Among the complications, 4 cases required re-operation, of which 2 cases (5.1%) ultimately required completion pneumonectomy. There were 2 cases of postoperative death within 30 days (5.1%).In terms of frequency of complications by surgical technique, there were 4 cases (44%) in A, 5 (63%) in B, 6(38%) in C, and 2(40%) in D, with no statistically significant difference.

Conclusions: We retrospectively analyze the perioperative outcomes of Extended Sleeve Resection at our Hospital. Perioperative results in this study were comparable to previously reported results. While Grade III or higher anastomotic complications were limited to one case. The short-term perioperative outcomes were generally favorable, suggesting that Extended Sleeve Resection is a valuable technique for avoiding pneumonectomy.

Keywords: Extended Sleeve Resection, perioperative outcomes, postoperative complications

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .11 Management of High-Grade Endobronchial Pre-Invasive Lesion: To Treat or Not to Treat?

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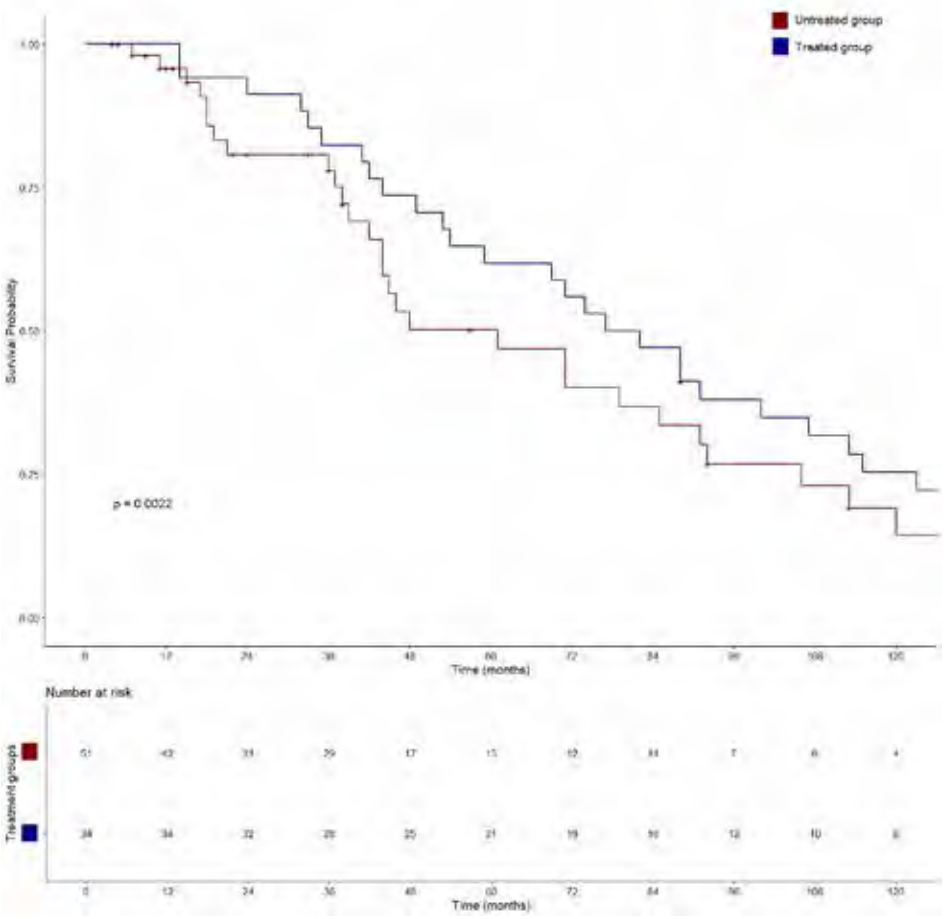
Introduction: High-grade pre-invasive endobronchial lesions have the potential to progress to squamous cell carcinoma (SCC), but their natural history varies considerably. As a result, the optimal management of these lesions is controversial, with treatment strategies varying across institutions due to lack of consensus. This study aims to compare the progression free survival (PFS) and overall survival (OS) outcomes between patients who received endobronchial treatment and those who were managed with surveillance alone.

Methods: We conducted a retrospective cohort study across two oncology centers: University College London Hospitals (UCLH, United Kingdom) and Amsterdam University Medical Center (AUMC, The Netherlands). Patients with high-grade pre-invasive lesions detected via autofluorescence bronchoscopy (AFB) underwent surveillance with repeat bronchoscopy and CT scans. At AUMC, patients routinely received endobronchial treatment (primarily diathermy), whereas at UCLH, treatment was reserved for cases that progressed to SCC. The primary outcome was PFS and the secondary outcome was OS. Survival was analyzed using Kaplan-Meier curves and Cox proportional hazards regression, adjusting for potential confounders.

Results: Between 1998 and 2007, a total of 85 patients were included in the study: 34 (40%) received endobronchial treatment, while 51 (60%) did not. There was a significant difference in histological distribution between the two groups: the untreated group had a higher proportion of carcinoma in situ (CIS) compared to the treated group (78.4% vs. 38.2%, p = 0.001). Additionally, patients in the untreated group were significantly younger than those who received treatment (median age: 67.0 vs. 77.0 years, p = 0.001). The overall median follow-up time was 46.2 months (IQR: 21.6-91.5). Endobronchial treatment was associated with a significantly reduced risk of disease progression (HR = 0.39, 95% CI: 0.21-0.73, p = 0.002). Median PFS was 71.0 months (IQR: 55.0-NA) in the treated group, compared to 38.0 months (IQR: 21.0-54.0) in the untreated group (p = 0.002). Treatment was also associated with improved OS, reducing the risk of mortality by 52.8% (HR = 0.47 95% CI 0.26-0.87, p = 0.015).

Conclusions: Our study demonstrated that endobronchial treatment significantly improved PFS and OS in patients with high-grade pre-invasive endobronchial lesions. However, the untreated cohort had a higher proportion of CIS compared to the treated group, raising the possibility that these patients were further along in their disease trajectory, which may have contributed to worse PFS outcomes. A randomized controlled trial is needed to further evaluate whether early intervention in this patient population can lead to improved survival.



Keywords: preinvasive, endobronchial, nsclc

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .12 Salvage Stereotactic Ablative Radiotherapy for Loco-Regional Recurrence After Initial Surgery According to the START NEW ERA Phase II Trial

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Introduction: Patients receiving salvage treatment for thoracic nodal recurrence (tnR) had similar survival to those with de novo stage III disease,so salvage therapy should ideally mimic that for de novo unresectable NSCLC.The objective of this trial was to assess local control (LC) and safety of salvage stereotactic ablative radiotherapy (SAbR) according to the START NEW ERA phase II trial (Clinical trials.gov NCT05291780) in tnR NSCLC patients after initial surgery (1).

Methods: Patients with tnR after previous surgery were enrolled. After PACICIF trial publication neoadjuvant chemotherapy (ChT) was prescribed in PD-L1 fit patients in order to offer immunotherapy (IO) consolidation. The tumor volume included any regionally positive node/s (N) based on PET-CT. Hepilor gel and kariosyte mouthwash were recommended in order to prevent dysphagia and esophagitis.The co-primary study endpoints were LC and safety.

Results: Between 2015 and 2024 32 patients with tnR from NSCLC after surgery were enrolled.Histology was adenocarcinoma and squamous cell carcinoma in 81% and 19%. 8(22%)received neoadjuvant ChT and 4(13%)IO consolidation. The median prescribed dose was 40Gy (35-50) in 5 daily fractions. After a median follow-up of 32 months (4-89), 3(10%) patients had experienced local recurrence (LR). The median LR-free survival (FS) was not reached (95% CI,- to not reached). The 1-,2-,and 3-year LR-FS was 92±5%,82±8%,and 74±11%,respectively. 11(34%)had out-field regional recurrence (outf-tnR) and were submitted to new SAbR on the out-field nodal recurrence site. The median outf-tnR-FS was not reached (95% CI, 28 to not reached). The 1-,2-,and 3-year outf-tnR-FS was 92±5%,82±8%,82±8%. 14(44%) developed distant progression (dP). The median dP-FS was not reached (95% CI,14- to not reached). The 1-,2-,and 3-y dP-FS was 88±6%,61±10%,and 55±11%. The median PFS was 33 months (95%CI,14 to 34). The 1-,2-,and 3-y PFS was 85±7%,54±10%,and 38±11%. At last follow-up, 23(72%) patients were alive. Median overall survival (OS) was 73 months (95% CI, 53-73 months). The 1-,2-,and 3-y OS was 88±6%,78±8%,and 73±9%. No patients experienced ≥ grade (G) 3 toxicity.

Conclusions: Patients with thoracic nodal recurrence from NSCLC after initial surgery and treated with salvage SAbR according to the START NEW ERA phase II trial had optimal LC and promising OS without ≥G3 toxicity. Our outcomes suggest the efficacy and safety of using this approach in thoracic nodal recurrence NSCLC patients in the place of concurrent ChT-RT. Prospective studies are warranted to investigate the association of SAbR with immunotherapy in this setting of patients.

1. Int J Radiat Oncol Biol Phys 2023 ;115(4):886-896. doi: 10.1016/j.ijrobp.2022.10.025.

Keywords: stereotactic ablative radiotherapy (SAbR), locally advanced non-small cell lung cancer, immunotherapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .13 Radiation Dose to the Heart and Cardiac Substructures Associated With Adverse Cardiac Events in Locally-Advanced Non-Small Cell Lung Cancer

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Introduction: Patients with locally-advanced non-small cell lung cancer (NSCLC) are at high risk of developing cardiac complications after concurrent chemoradiotherapy (ChT-RT). While mean heart dose is important, more recent studies have focused on dose to individual cardiac substructures. This study assessed the risk of major adverse cardiac events (MACE- unstable angina, coronary revascularization, myocardial infarction, congestive heart failure, or cardiac death), atrial fibrillation, and all cardiac arrhythmias based on extensive clinical and dosimetric variables.

Methods: All patients completing a course of ChT-RT for stage II-III NSCLC from 2007-2021 at Duke University Medical Center were included. Clinical data including baseline cardiac risk factors (e.g., hypertension [HTN], familial hypercholesterolemia [FH], diabetes mellitus [DM], tobacco use), co-morbid cardiac conditions, and post-treatment cardiac events were extracted. The heart and 15 cardiac substructures were contoured on contrast-enhanced planning CT scans. The cumulative incidence of cardiac events was estimated using the Fine-Gray subdistribution hazard model accounting for the competing risk of non-cardiac mortality. Multivariable Fine-Gray subdistribution hazards regression using a backward stepwise feature selection technique was performed to evaluate the association between clinical and dosimetry metrics and cardiac events. Progression-free (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: 320 patients evaluable. Median age: 66 (range, 33-87). M/F: 54%/46%. Baseline incidence of HTN, FH, DM, and tobacco use were 57%, 42%, 24%, and 50%, respectively. Baseline cardiac disease present in 99 patients (31%), most commonly coronary artery disease (n=59, 18%) and atrial fibrillation (n=29, 9%). RT technique: 3D- 47%; IMRT-53%. Median dose: 60 Gy (range, 58-74 Gy). Chemotherapy regimens: carboplatin/paclitaxel (n=143, 45%), cisplatin/etoposide (n=90, 28%), other (n=87, 27%). Adjuvant immunotherapy: 82 (26%). With a median follow-up of 46 months for surviving patients, cardiac events developed in 64 patients after ChT-RT. Accounting for the competing risk of mortality, the 5-year actuarial incidence was 18%. The 5-year risk of MACE, atrial fibrillation, and all cardiac arrhythmias was 8.4%, 6.9%, and 11.7%, respectively. The variables associated with MACE in multivariable regression were 3D RT technique (HR 3.93, 95% CI 1.96-7.90, p<0.001) and adjuvant immunotherapy (HR 2.73, 95% CI 1.39, 5.36, p=0.004). For atrial fibrillation, increasing pulmonary artery V25 (HR 1.02, 95% CI 1.01-1.04, p=0.003) was associated with a higher risk and cisplatin/etoposide (HR 0.25, 95% CI 0.07-0.91, p=0.036) was associated with a lower risk compared with carboplatin/paclitaxel. For all cardiac arrhythmias, increasing pulmonary artery V15 was the only factor associated with a higher risk (HR 1.02, 95% CI 1.01-1.04, p=0.002). PFS and OS at 5 years were 23% and 28%, respectively. All-cause mortality was higher with increasing mean heart dose (HR 1.02, 95% CI 1.01-1.04, p=0.002) and lower with adjuvant immunotherapy (HR 0.56, 95% CI 0.42-0.76, p<0.001).

Conclusions: This study demonstrates that treatment-related variables (chemotherapy regimen, utilization of immunotherapy, and radiation dosimetry to the heart and specific cardiac substructures) were more strongly associated with post-ChT-RT cardiac events than baseline cardiac risk factors in patients with locally-advanced NSCLC. Radiation dose to the pulmonary artery was most strongly associated with cardiac arrhythmias, including atrial fibrillation.

Keywords: Cardiac complications, Radiation therapy, dosimetry

P2.08 .14 Tumor Volume Changes During Stereotactic Body Radiotherapy for Lung Tumors Under Mri Guidance

C. Richlitzki[1], S. Hering[1], R. Gauß[2], J. Hofmaier[1], J. Hofmaier[1], N-S. Schmidt-Hegemann[1], C.K. Kurz[1], G.L. Landry[1], C.B. Belka[1,3,4,5], S. Corradini[1], C. Eze[1]

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Introduction: Gross tumor volume (GTV) changes during online MR-guided stereotactic body radiotherapy (oMRgSBRT) for lung tumors are poorly characterized. We investigated GTV changes during multifraction oMRgSBRT on a 0.35T MR-Linac.

Methods: GTV changes between simulation (SIM) and first fraction (F1) and all fractions were recorded. Paired Wilcoxon signed-rank tests were used for intra-patient comparisons. Logistic and linear regression models were used for feature-associated variables. The cumulative incidence of local failure (LF) and tumor progression were calculated using cumulative incidence functions (CIF). Area Under the Receiver Operating Characteristic Curve (AUROC) analysis was used to evaluate the performance of a binary classification model.

Results: 53 tumors were treated (215 fractions). The median SIM-F1 interval was 8 days (2 - 42 days). Median GTVs at SIM and F1 were 4.60 cc (range, 0.48 - 49.13 cc), and 4.81 cc (range, 0.70 - 50.57 cc) respectively ($p < 0.05$). Mean GTV ?SF1 (GTV difference between SIM and F1) was +7.25%. In total, 52.83% of GTVs decreased at the last fraction vs F1. Linear regression analysis revealed a significant association between the relative ?SF1 and baseline characteristics, age at initial diagnosis (Pearson correlation coefficient: -0.319, p-value: 0.02), former or current smoker (regression coefficient: -0.09, p-value: 0.012), and the ECOG PS (regression coefficient: -0.11, p-value: 0.047). GTV variations of ? 10%, and ? 20% occurred in 71.11%, and 37.77% between F1 and the final fraction. There was no significant difference in cumulative incidence of LF or progression after oMRgSBRT when stratified by treatment indication (primary lung cancer vs. lung metastases).

Conclusions: Inter-fractional GTV changes are common and may be predicted by baseline characteristics. Daily plan adaptation is pertinent for ensuring adequate target volume coverage and OAR sparing. A mean GTV increase of 7.25% between SIM-F1 indicates that short intervals are desirable.

Keywords: MR-guided radiotherapy, Lung Cancer, Gross tumor volume (GTV)

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .15 Cardiac Prioritized Planning in Locally Advanced Non-Small Cell Lung Cancer: Comparison of Modern RT Techniques

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Introduction: Our aim in this study is to perform cardiac-prioritized planning using modern radiotherapy (RT) techniques in the treatment of locally advanced non-small cell lung cancer (LA-NSCLC) and to compare these plans in terms of cardiac exposure, doses to other organs at risk, and target doses.

Methods: This retrospective study included 91 patients who received definitive RT for LA-NSCLC between 2022 and 2023. For each patient, three different planning techniques were implemented: IMRT, VMAT, and hybrid (a combination of IMRT and VMAT in a 1:1 ratio). During planning, the following dose constraints were used: heart mean dose (Dmean) <26 Gy, V30<50%; left anterior descending coronary artery (LAD) V15<10%; lung Dmean<20 Gy, V20<35%, V5<60%; esophagus Dmean<34 Gy; spinal cord Dmax<50 Gy.

Results: Tumor, target, and organ volumes are presented in Table 1. For each patient, 19 dosimetric parameters were calculated for IMRT, VMAT, and hybrid plans, and the statistical significance of comparisons among these values is summarized in Table 2. The IMRT technique provided the lowest dose exposure to critical organs such as the heart and LAD, while higher doses were observed with the VMAT technique. In terms of lung doses, IMRT also resulted in the lowest, and VMAT in the highest exposure. Additionally, IMRT and hybrid planning were found to be superior to VMAT in terms of target volume coverage (PTV V95) and plan conformity. All findings were statistically significant.

Conclusions: IMRT planning was found to deliver lower cardiac and lung doses compared to VMAT. In addition to the dose advantage, IMRT plans were also superior in terms of target parameters such as PTV V95 and conformity index. Therefore, we believe that IMRT planning can be prioritized in cardiac-focused planning for LA-NSCLC patients due to its dosimetric advantages.

Table 1. Patients' Tumor, Target, and Organ Volumes (cc)

	Mean±SD	Median (Min-Max)
GTV	135,3±108,8	101,0 (7,1–499,2)
CTV	333,8±190,9	280,0 (54,0-1109,9)
PTV	626,0±298,9	562,0 (136,4-1691,7)
LAD Volume	6,2±2,2	5,6 (3,1-13,8)
Heart Volume	713,2±142,6	701,4 (430,7-1134,6)
Lung Volume	3932,6±943,6	3842,6 (1884,0-6668,4)
(Lung-GTV) Volume	3905,9±944,5	3797,1 (1884,0-6612,2)
Heart and PTV Overlap Volume	19,8±20,9	14,2 (0,0-111,9)
LAD and PTV Overlap Volume	0,012±0,075	0,000 (0,000-0,700)

CTV: Clinical Target Volume; GTV: Gross Tumor Volume; LAD: Left Anterior Descending Coronary Artery; PTV: Planning Target Volume; SD: Standard Deviation

Table 2. Dosimetric Comparison of RT Techniques

	IMRT (IM)		VMAT (VM)		HYBRID (HI)			Post Hoc Analysis[c]		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	p	p (IM-VM)	p (IM-HI)	p (VM-HI)
LAD Dmax (Gy)	24,2 ± 15,9	21,1 (2,8-60,7)	25,2 ± 16,1	19,2 (3,2-58,3)	24,5 ± 15,6	20,0 (3,0-57,7)	0,002[a]	0,001	0,226	0,226
LAD Dmean (Gy)	4,3 ± 2,7	3,9 (0,8-14,0)	5,5 ± 3,9	4,8 (1,0-21,9)	4,9 ± 3,2	4,4 (0,9-17,6)	<0,001[a]	<0,001	<0,001	0,001
LAD V5 (%)	28,7 ± 23,6	26,3 (0,0-88,3)	35,2 ± 22,9	37,6 (0,0-100,0)	31,8 ± 23,3	34,0 (0,0-100,0)	<0,001[a]	<0,001	0,001	0,001
LAD V10 (%)	11,5 ± 14,2	3,9 (0,0-54,0)	14,1 ± 17,4	4,6 (0,0-73,8)	12,9 ± 15,8	3,8 (0,0-63,4)	<0,001[a]	<0,001	0,048	0,008
LAD V15 (%)	4,4 ± 7,1	0,3 (0,0-32,7)	7,8 ± 13,0	0,2 (0,0-55,9)	6,4 ± 10,4	0,2 (0,0-48,8)	<0,001[a]	0,004	0,445	0,226
Heart Dmean (Gy)	10,0 ± 4,9	9,8 (1,7-26,7)	11,4 ± 5,6	11,0 (1,7-24,7)	10,7 ± 5,2	10,7 (1,7-24,7)	<0,001[a]	<0,001	<0,001	<0,001
Heart V30 (%)	9,8 ± 6,6	8,1 (0,0-33,3)	11,4 ± 7,7	9,2 (0,0-30,7)	10,3 ± 6,8	8,6 (0,0-28,2)	<0,001[a]	<0,001	0,333	<0,001
Lung Dmean (Gy)	14,9 ± 3,1	15,1 (7,2-22,5)	15,7 ± 3,3	15,6 (7,9-23,1)	15,3 ± 3,2	15,3 (7,5-22,6)	<0,001[b]	<0,001	<0,001	<0,001
Lung V5 (%)	57,8 ± 11,8	57,5 (33,8-89,4)	64,3 ± 12,3	64,0 (37,1-99,1)	62,1 ± 12,0	62,1 (35,3-97,0)	<0,001[b]	<0,001	<0,001	<0,001
Lung V10 (%)	39,5 ± 9,6	39,0 (18,8-62,8)	44,9 ± 10,7	44,9 (25,5-71,2)	42,2 ± 10,1	42,9 (22,5-65,8)	<0,001[b]	<0,001	<0,001	<0,001
Lung V20 (%)	25,3 ± 6,3	25,9 (3,0-40,1)	27,0 ± 6,8	27,1 (4,9-43,7)	26,4 ± 6,7	26,3 (4,7-42,4)	<0,001[b]	<0,001	<0,001	<0,001
Esophagus Dmax (Gy)	60,5 ± 5,2	61,5 (29,4-65,6)	61,1 ± 5,5	62,5 (25,5-65,1)	60,3 ± 5,2	61,5 (27,3-63,7)	<0,001[a]	0,005	0,020	<0,001
Esophagus Dmean (Gy)	17,7 ± 5,8	17,1 (3,7-34,6)	20,6 ± 6,7	20,1 (5,0-36,9)	19,2 ± 6,1	19,1 (4,3-34,5)	<0,001[b]	<0,001	<0,001	<0,001
Spinal Cord Dmax (Gy)	33,3 ± 4,7	32,5 (18,3-50,1)	33,2 ± 5,5	32,1 (16,8-55,7)	32,8 ± 5,0	31,8 (17,5-52,8)	0,003[a]	0,104	0,003	0,664
PTV V95 (%)	97,7 ± 1,7	98,4 (94,0-100,0)	96,8 ± 1,7	96,3 (94,0-100,0)	97,6 ± 1,6	97,9 (91,5-99,9)	<0,001[a]	<0,001	1,000	<0,001
PTV Dmax (Gy)	64,8 ± 0,8	64,7 (62,5-67,1)	65,0 ± 0,7	64,9 (63,1-67,0)	64,1 ± 0,6	64,0 (62,9-65,8)	<0,001[a]	0,212	<0,001	<0,001
PTV Dmean (Gy)	61,0 ± 0,5	61,0 (59,6-62,0)	60,4 ± 0,3	60,4 (59,3-61,5)	60,7 ± 0,3	60,7 (59,9-61,4)	<0,001[a]	<0,001	<0,001	<0,001
Homogeneity Index	0,104 ± 0,034	0,095 (0,050-0,188)	0,108 ± 0,024	0,110 (0,060-0,180)	0,095 ± 0,026	0,092 (0,046-0,155)	<0,001[a]	0,020	<0,001	<0,001
Conformity Index	0,773 ± 0,071	0,787 (0,353-0,875)	0,656 ± 0,076	0,663 (0,308-0,816)	0,773 ± 0,064	0,789 (0,505-0,867)	<0,001[a]	<0,001	1,000	<0,001

Dmax: Maximum Dose (Gy); Dmean: Mean Dose (Gy); Hybrid (HI): Hybrid Radiotherapy Planning; IMRT (IM): Intensity-Modulated Radiotherapy; LAD: Left Anterior Descending Coronary Artery; PTV: Planned Target Volume; PTV V95: Percentage of the PTV Receiving 95% of the Prescribed Dose; RT: Radiotherapy; SD: Standard Deviation; V5/10/15/20/30: Percentage Volume of the Relevant Organ/Structure Receiving 5/10/15/20/30 Gy; VMAT (VM): Volumetric Modulated Arc Therapy.

Keywords: Lung Cancer, IMRT (Intensity-Modulated Radiation Therapy), VMAT (Volumetric Modulated Arc Therapy)

P2.08 .16 National Real-World Data on the Treatment of Locally Advanced NSCLC With Chemoradiotherapy and Adjuvant Durvalumab

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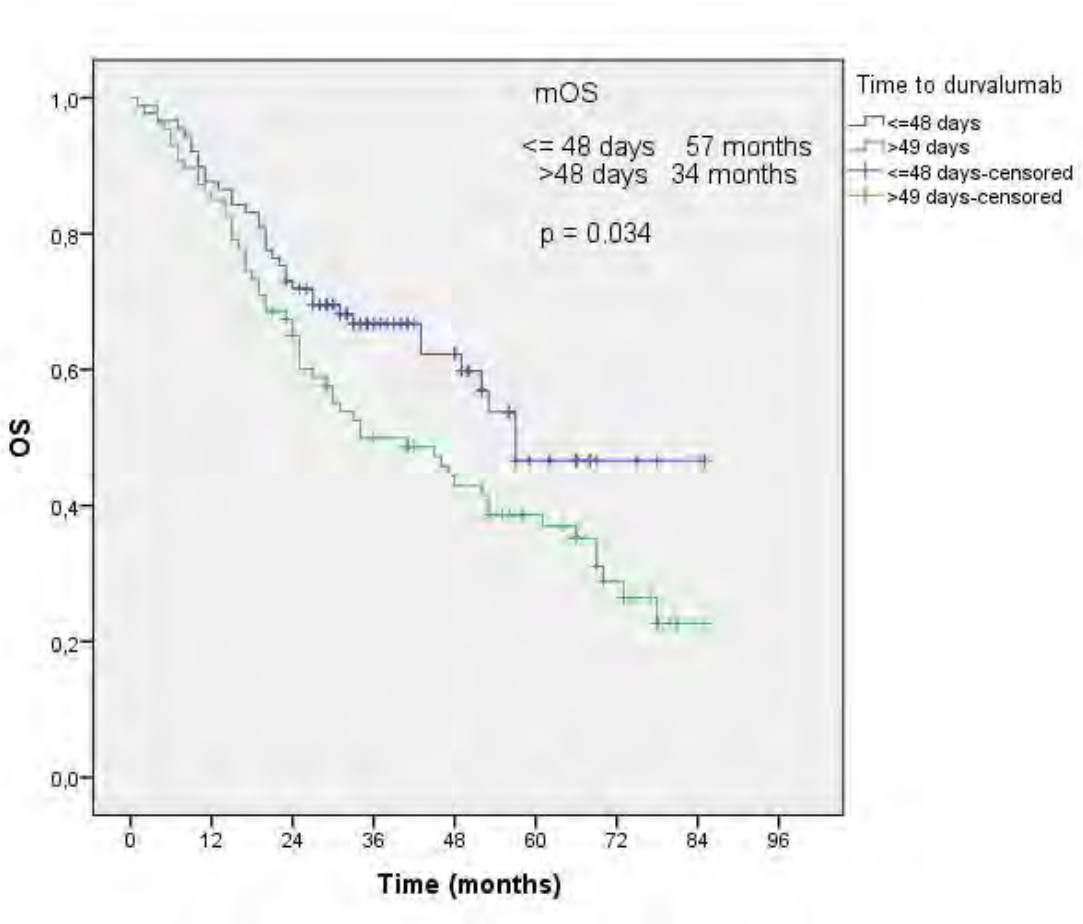
Introduction: Adjuvant durvalumab after chemoradiotherapy (ChRT) is the standard treatment for patients with locally advanced non-small cell lung cancer (LA-NSCLC) with PD-L1 positive tumours. We present national results of treatment of patients with LA-NSCLC in Slovenia.

Methods: We retrospectively reviewed the medical records of patients with LA-NSCLC treated with definitive ChRT and adjuvant durvalumab from December 2017 to December 2022 at the Institute of Oncology Ljubljana. We evaluated patient outcomes according to demographic factors and treatment characteristics. The survival outcomes were calculated using Kaplan - Meier actuarial survival methods. Overall survival (OS) was calculated from the start of durvalumab treatment until death from any cause or last follow-up on 13 March 2025.

Results: The majority of the 175 patients included (119 men, 56 women), with a median age of 64 (36-76) years, were current or former smokers (97.1%). Most patients (56%) had a squamous cell carcinoma. Only 7.4% of patients had unknown PD-L1 status and 44% of all patients had PD-L1 expression ≥ 50%. Most patients (68%) were treated with platinum-based induction chemotherapy with gemcitabine followed by concomitant etoposide/cisplatin and 17.1% were treated with pemetrexed/cisplatin. Concurrent chemotherapy was administered in 77.7% of patients and 88% of patients were irradiated with a dose ≥ 60 Gy. The median time from the end of RT to the start of durvalumab treatment was 48 days (range 4 - 130). Treatment with durvalumab completed 45.1% of patients and 25.7% discontinued treatment due to toxicity. Pneumonitis was the most common toxicity in 18.9% of patients. After a median follow-up time of 56 months, the median progression free survival was 23 months (CI 18.3-27.6). The median OS was 52 months, 2-year survival 68.5%, 3-year survival 57.5% and 5-year survival 42.2%. In univariate analysis, there were no differences in median OS according to gender, performance status, TNM stage, histology, PD-L1 expression, type and number of chemotherapy cycles, and radiation dose. Compared to older patients (median age), younger patients had significantly longer median OS, 69 months vs 34 months (p<0.000) and 5-year survival (47.8% vs 29.9%). We observed significantly longer median OS in patients that started durvalumab within 48 days compared to patients starting durvalumab 49 days or later after RT, 57 months vs 34 months (p=0.043), and 5-year survival (46.6% vs 37%).

Conclusions: Our survival data confirmed the results of the Pacific trial and validated the significant survival benefit of durvalumab consolidation treatment in unresectable LA-NSCLC patients,



Keywords: locally advanced non small-cell lung cancer, radiotherapy, durvalumab

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .17 Differential Cardiac Dose Evaluation and the Need of Planning Risk Volume (PRV) Margin for the Heart

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Introduction: The heart, a key organ at risk in thoracic radiotherapy, undergoes motion due to cardiac contractions and respiration. During expiration, it shifts upward, and during inspiration, it moves downward, leading to displacement and volume changes. These movements cause variations between planned and actual cardiac doses. While 4D CT captures respiratory motion, no standardised guidelines exist for measuring cardiac dose on a specific CT phase or dataset. This lack of standardization complicates accurate cardiac dose assessment and management, posing challenges in optimizing radiotherapy planning and minimizing cardiac exposure

Methods: A total of 54 lung cancer patients (all the patients had tumours in the upper lobe and hilar region) who underwent 3D and 4D CT simulation, all treated with VMAT plans, were analyzed using 3D CT, Maximum intensity projection (MIP 4D), inspiratory (INS 4D), and expiratory (EXP 4D) phases of 4D datasets for the heart dose variation and motion. The displacement of the center of the mass (COM) of the heart in all three directions (left-right (LR), superior-inferior (SI) and anterior and posterior (AP)), mean heart dose and cardiac substructure doses were calculated and correlated with tumour location across different lung lobes to understand dose variations.

Results: The atrium and great vessels' motion (in millimetres) in LR, SI, and AP directions were 2(1.2-4.8), 4.5(1.5-6), and 1.4(0.8-4.1) respectively. The ventricular motion was about 2.5(1.1-4.2), 4.5(1.5-6) and 1.4(0.8-4) in the LR, SI, and AP directions. The whole heart motion was about 1.7 (1.1-3.3), 3.8 (1.5-6), and 1 (0.7-1.8) in the LR, SI, and AP directions. For patients who had upper lobe tumour alone (22 patients), the mean heart dose varied (in ratio) between EXP vs 3D CT, EXP 4D vs MIP 4D and EXP 4D vs INS 4D was about 1.1(1.05-1.26), 1.09(1.06-1.13) and 1.26 (1.15-1.39) and the patients with both upper lobe and mediastinal lymphadenopathy (or) hilar tumour (32 patients), it was about 1.09(1-1.22), 1.08(0.97-1.1) and 1.08 (1.02-1.14) respectively. The mean dose differences (in ratio) between atrium and ventricle (in 3D CT) for upper lobe and upper lobe with mediastinal lymphadenopathy (or) hilar tumour patients were 4.15 (3.01-10.93) ($p>0.001$) and 4.16 (1.77-6.52) ($p>0.023$) respectively.

Conclusions: Respiratory motion significantly impacts cardiac dose variation in thoracic radiotherapy. To account for this, applying a planning risk volume (PRV) margin (LR-1.7mm, SI-3.8 mm and AP-1 mm) to the whole heart is essential, as each cardiac substructure contracts at different timings, but the net impact is collective. Additionally, lung lobe-specific heart dose evaluation is crucial. For upper lobe tumours, heart dose measured on expiration (EXP) 4D CT is more accurate, as it shows approximately 10% higher doses compared to conventional 3D CT. Conversely, for lower lobe tumours, inspiration (INS) 4D CT may be more appropriate. Moreover, tumour location greatly influences substructure doses; for example, in the upper lobe and hilar tumours, the atrium receives a significantly higher dose (median dose about 415%($p<0.001$) and 416%($p<0.023$)) as compared to the ventricle. Therefore, cardiac substructure-based dose constraints are likely more reliable than whole-heart volumetric constraints.

Keywords: cardiac sparing RT, PRV, cardiac motion

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .18 Evaluation of Target Volume Delineation Variability in NSCLC Radiotherapy

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Introduction: To evaluate inter-observer variability in target volume delineation for locally advanced non-small cell lung cancer (NSCLC) radiotherapy and examine the impact of available technological and multidisciplinary resources.

Methods: A combined survey and contouring exercise was performed among radiation oncologists from multiple centers in Brazil. Twenty-five radiation oncologists with expertise in lung cancer from 25 facilities and diverse regions participated in an online survey regarding epidemiology and technological resources and a subsequent contouring session during a conference. Participants received anonymized imaging datasets—including PET-CT, a 10-phase 4DCT study with average and maximum intensity projection reconstructions, and pre-contoured organs at risk—and delineated target volumes using Varian Eclipse v.16 according to their routine clinical practice. Sixteen groups were formed, and data from 12 groups were analyzed due to technical issues, with contour similarity assessed via the Dice similarity coefficient.

Results: Of the 16 groups formed, 4 were excluded because of technical problems, leaving 12 groups for analysis. The original planning target volume (PTV) measured 501 cm^3, while the mean delineated volume was 230.8 ± 88.2 cm^3, indicating a systematic underestimation of target volumes. The overall Dice similarity coefficient averaged 0.58 ± 0.14, with values ranging from 0.28 to 0.75, reflecting moderate agreement among observers. Variability was most pronounced in regions adjacent to organs at risk, suggesting that the proximity of critical structures may complicate accurate delineation. An observable trend indicated that increased clinical experience might be associated with higher contour accuracy, although this was not statistically verified.

Conclusions: The significant inter-observer variability in NSCLC target volume delineation underscores the need for standardized contouring protocols and enhanced training initiatives. Improved access to advanced imaging technologies and a more integrated multidisciplinary approach may mitigate these discrepancies, potentially leading to better treatment planning and patient outcomes. These findings have important implications for clinical practice and suggest that future policies should support the adoption of uniform delineation guidelines.

Keywords: lung cancer, target delineation, radiation oncology

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .19 Proton Beam Therapy for Lung Cancer in Patients With Interstitial Lung Disease: Initial Experience From the United Kingdom

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Introduction: Managing lung cancer in patients with interstitial lung disease (ILD) can be challenging due to the increased risk of treatment-related toxicities. Photon-based radiotherapy is of particular concern due to reports of severe or even fatal radiation pneumonitis. Due to the unique physical properties of protons, particularly the Bragg Peak, proton beam therapy (PBT) offers a promising alternative treatment option for this patient population. It allows for greater sparing of normal tissues, crucial in minimising lung dose, without compromising coverage of the target volume. This may reduce the risk of life-threatening pulmonary complications in patients with ILD. This study reports on the dosimetric outcomes and acute toxicities in patients with ILD following the initiation of the United Kingdom PBT service.

Methods: The first four patients with ILD treated with PBT were reviewed for this study. Dosimetric parameters, including target coverage, target volumes, doses to organs at risk (OARs) were analysed alongside acute toxicity outcomes. Toxicities were assessed weekly during treatment and one-week post-treatment using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Results: All patients were treated with 60 Gy in 30 fractions. Acceptable target coverage was achieved in all patients. The nominal median dose received by 95% of the clinical target volume (CTV) was 58.5 Gy (Nominal range: 58.2 Gy - 58.9 Gy; worst-case range: 55.7 Gy - 56.9 Gy). The median internal gross target volume (iGTV) was 64.3 cc (range: 30.2 cc - 197.7 cc) and median CTV volume was 162.3 cc (range: 30.2 cc - 197.7 cc). The median lung V20 was 19.8% (12.4% - 29.4%) while the median of the lungs minus iGTV mean dose (dmean) was 9.9 Gy (5.5 Gy - 14.4 Gy). The median dmean for other normal tissues included the heart 7.2 Gy (0.68 Gy -7.29 Gy), contralateral lung 0.1 Gy (0.0 Gy - 0.2 Gy), and the median oesophagus V35% was 12.5% (0.0% - 16.8%). All reported toxicities were grade 1-2, with no occurrences of severe (grade 3 or higher) toxicities.

Conclusions: These early findings are promising, indicating that PBT can be safely delivered to patients with lung cancer and ILD, achieving effective target coverage with no severe acute toxicities reported.

Keywords: Proton Beam Therapy, Interstitial Lung Disease, Lung Cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .20 VMAT vs IMRT Technique in Locally Advanced Lung Cancer Radiotherapy Treatment -Pulmonary Toxicity and Dosimetric Evaluation

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Introduction: Lung cancer patients on first presentation mostly belong to locally advanced group. Radiotherapy is an important treatment modality in this heterogenous group of patients Sophisticated radiotherapy techniques Intensity modulated radiation therapy- IMRT, Volumetric modulated arc therapy- VMAT have become standard of care in modern radiotherapy centers, still there is no consensus which of these two techniques is more effective. Aim of this study is to analyze and compare dose volume parameters for organ of risk-lungs, and evaluate pulmonary toxicity-acute and late side effects.

Methods: This study included 70 patients diagnosed and verified as locally advanced NSCLC with indication for radical radiotherapy treatment. IMRT treatment with radical dose 60Gy in 30 fraction was planned in first group (35 patients), and VMAT treatment was planned in second study group (35 patients). Dose volume constraints for organ of risk -lungs (V5, V20, MLD -Mean lung dose)were evaluated. Pulmonary toxicity was evaluated by RTOG scale and CTCA V 5.0, acute and late side effects for organ of risks lungs were evaluated.

Results: Based on this results there was statistically significant difference ($p<0.01$) between IMRT and VMAT group based on values V20 and MLD. IMRT group had significantly higher values. Also, based on this results there was no statistically significant difference ($p=0.155$) when comparison of values V5 between IMRT and VMAT group was done. There was no statistically significant difference when comparison of acute ($p=0,867$) and late ($p=0.654$) side effects for organs of risk lungs was done between IMRT and VMAT group.

Conclusions: This study presents dosimetric benefit of VMAT technique in terms of lower values of mean lung dose and V20,but this dosmetric evaluation benefit did not translate into a clinical benefit. There was no statistically significant difference between IMRT and VMAT group in terms of acute and late pulmonary side effect. Smaller number of monitor units, and shorter time for delivery radiation tretament can be factors atributed in favour of VMAT technique.Still, more studies should be done in order to determine optimal radiotherapy technique in tretment of locally advanced lung cancer. Key words- locally advanced,lung cancer. radiotherapy, IMRT, VMAT

Keywords: locally advanced, lung cancer, radiotherapy, IMRT, VMAT

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .21 Mapping Early Failure After CRT and Durvalumab in NSCLC: Insights From a Real-World Cohort

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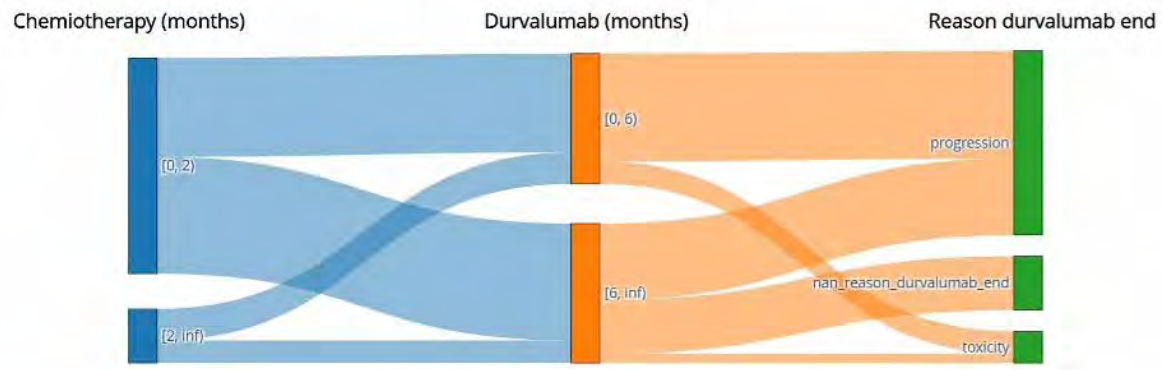
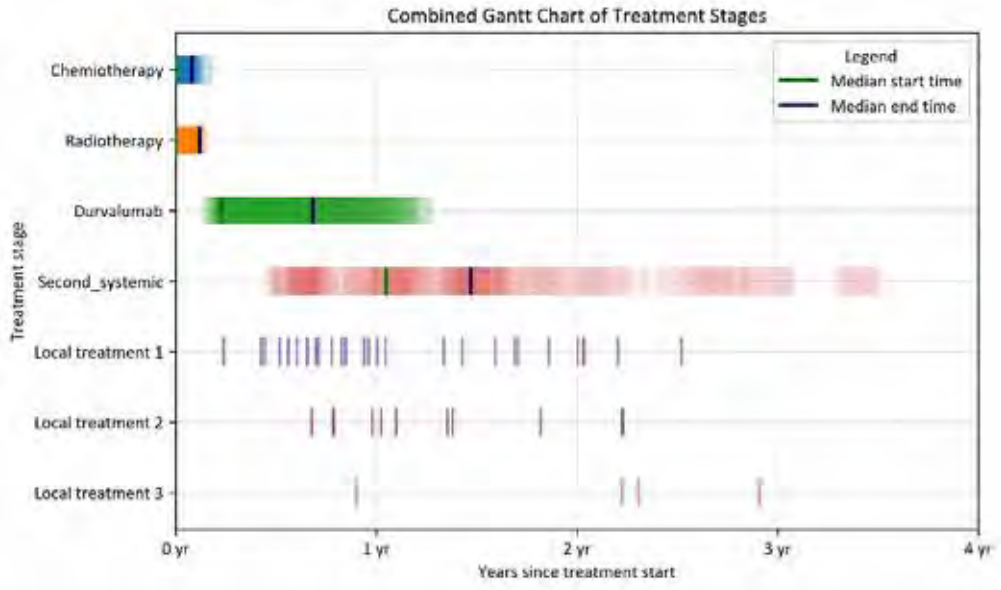
Introduction: Chemoradiotherapy followed by immunotherapy is the standard of care for unresectable stage III NSCLC, yet over 50% of patients progress within 24 months. This study analyzes early progression patterns in a real-world setting to guide future treatment strategies.

Methods: We retrospectively analyzed patients with confirmed NSCLC from five tertiary centers who completed CRT (≥54 Gy, platinum-based chemotherapy) and received ≥2 cycles of durvalumab within 2 months. Progression during or after durvalumab by January 31, 2024, was required. Data were analyzed using Python (pandas, scikit-learn, SciPy,plotly), with Gantt and Sankey plots generated for treatment visualization.

Results: Sixty patients were enrolled; 54 received subsequent systemic or local therapy. The median time to next treatment (TNT) and time to next systemic treatment (TNST) were 11.6 and 13.2 months, respectively. The median duration of chemoradiotherapy was 1.1 months, and durvalumab was 6.1 months. The treatment sequence for all patients is illustrated in a combined Gantt chart. A Sankey diagram displays the course of chemoradiotherapy (with/without induction chemotherapy), durvalumab duration, and reasons for durvalumab discontinuation. The most common progression region was lung (n=25), followed by brain (n=12), liver (n=7), lymph nodes (n=5), adrenal (n=4), bone (n=3), contrateral lung (n=2), other (n=2). Patients with local progression had a longer median TNT compared to those with distant or combined progression (17.1 vs. 9.9 months, p = 0.0088). Patients receiving radical local treatment for progression had longer TNST (29.1 vs. 12.6 months, p=0.016), with no similar effect seen for palliative radiotherapy.

Conclusions: The study suggests earlier distant progression than local, underscoring the role of early imaging and the potential benefit of radical local treatment in prolonging TNST.





Keywords: Real-World Cohort, Early Failure, CRT and durvalumab

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .22 In Field Progression Rates Following Concurrent Chemoradiotherapy for Stage III Non Small Cell Lung Cancer

S. Nesbit, M. Hammonds, T. Oughourlian, J. Goldman, E. Garon, A. Cummings, A. Lisberg, M. Velez, A. Gower, D. Gage, A. Lee, J. Deng, D. Moghanaki
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Introduction: A metric for measuring the efficacy of concurrent chemoradiotherapy (cCRT) for stage III non-small cell lung cancer (NSCLC) is in-field tumor control. However, evaluating in-field control rates from published studies is challenging, as many report progression-free survival rates that consider disease progression events occurring outside the RT treatment field. This hampers an understanding of the interactions between RT and consolidation immune checkpoint inhibitor (ICI) therapy, as well measurements of the benefit of surgical resection in lieu of cCRT for locally advanced NSCLC treated with similar systemic therapies. To address this issue, we examined how in-field progression rates are reported in the literature evaluating outcomes for stage III NSCLC treated with cCRT.

Methods: A systematic review was conducted using PubMed, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The search included all interventional, observational, prospective, or retrospective studies reporting outcomes in patients with stage III NSCLC who received cCRT ± ICI, published January 2000 to November 2024. Reference lists from retrieved articles were reviewed to identify missed studies. Statistical comparisons between published progression rates were deemed inappropriate for cross-study comparisons.

Results: Sixty articles met inclusion criteria, reporting outcomes from 63% prospective and 37% retrospective studies. Cohort sizes ranged from 10 to 713, totaling 7,350 patients. Median follow-up ranged from 14 to 132 months. Post-cCRT response assessments used criteria established by RECIST (46%), WHO (12%), and ECOG (2%), while 40% did not specify evaluation parameters. Of 60 publications, only 18 had sufficient information to evaluate in-field progression. This included 16 studies evaluating cCRT-alone and 2 studies with cCRT + ICI. Of these 18 studies, four included evaluations of progression within regional lymph nodes or the thorax (see Table). Median in-field progression rates were 30.8% [95% CI 23.1-37.9%] for cCRT, and 17.5% [95% CI 4.0-30.9%] for cCRT + ICI. Only one retrospective study (n=120) reported "in-field only" progression rates at 41% with cCRT and 11% with cCRT + ICI.

Conclusions: Most publications reporting outcomes following cCRT ± ICI do not specify in-field progression rates. Limited data exist to determine whether the benefits of ICI arise from improved tumor control in-field, out-of-field, or both. Future studies will have a greater impact if they clarify what the in-field progression rates are following cCRT ± systemic therapies.

Keywords: Non small cell lung cancer, Chemoradiotherapy, immunotherapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .23 Safety and Biomarker Analysis of Nrg-Lu004: Phase I Trial of Radiotherapy With Durvalumab in PD-L1 High LA-NSCLC

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Introduction: Patients with locally advanced non-small cell lung cancer (LA-NSCLC) and high PD-L1 (>50%) expression show improved outcomes with immune checkpoint inhibitors compared to chemotherapy. We hypothesized that concurrent durvalumab and radiotherapy (RT) would be safe and feasible in this population.

Methods: In the phase I study, NRG-LU004 (NCT03801902), stage II-III unresectable LA-NSCLC patients with PD-L1 >50% received durvalumab (1500 mg Q4 weeks) with either accelerated fractionated RT (ACRT, 60 Gy/15 fractions) or standard fractionated RT (SDRT, 60 Gy/30 fractions) for initial and expansion cohorts. Primary objective was safety assessed through dose-limiting toxicities (DLTs). Feasibility was defined as ≥80% of patients receiving ≥80% of planned durvalumab in the first eight weeks. Peripheral blood specimens were collected at baseline and throughout treatment for exploratory immune profiling analyses to evaluate biomarkers related to treatment and/or adverse events.

Results: Among 24 evaluable patients (enrolled 2019-2021), no DLTs occurred in ACRT. One DLT (bronchopulmonary hemorrhage, unrelated) occurred in SDRT. Both initial cohorts advanced to expansion. Most patients received RT per protocol (82.6%). At time of analysis, 24% had completed all durvalumab cycles. In ACRT, adverse events included four grade 3, one grade 4 (lymphopenia), and one grade 5 (lung infection, unrelated). In SDRT, there were eight grade 3 and one grade 5 (respiratory failure, unrelated) events reported. Durvalumab feasibility was 85% in ACRT and 75% in SDRT. Soluble proteomic analysis revealed significant immune changes, with increased Th1 signatures and homing markers in both arms (IFN-γ, IL15, CXCL11). The most extensive changes in circulating immune markers occurred in the durva+SDRT arm, while they were relatively limited in the durva+ACRT arm. Inflammatory and cytotoxicity soluble markers were consistently increased with the prolonged SDRT regimen, up to Day 90 (D90). Soluble markers associated with T-cell activation and cytotoxicity peaking at D90 in plasma were corroborated by CyTOF data where a rebound in T effector memory and TEMRA cell numbers was observed at D90 following an initial decrease. Finally, we also found immune biomarkers differentially associated with the occurrence of AEs, particularly presenting as decreased soluble protein measures at d15 upon durva+SDRT, but not upon durva+ACRT. Several of these markers appear related to tumor or endothelial cell expression (EGF, CAIX, ADA) and to cell death (CASP-8, granzymes A and H, FAS ligand), which implies that SDRT toxicity may reduce the capacity to mobilize effective anti-tumor responses. The most consistent biomarker significantly associated with AE occurrence regardless of arms, when measured either at baseline or early upon treatment (D15), was soluble CD5.

Conclusions: Chemotherapy-free thoracic RT (SDRT or ACRT) with concurrent durvalumab is safe in PD-L1 high LA-NSCLC. In addition, our work establishes the mechanistic basis for combination immunotherapy and radiation on circulating immune biomarkers.

Keywords: Radiation, non-small cell lung cancer, immunotherapy

P2.08 .24 Radiation Dose to the Circulating Blood Is Associated With Poor Overall Survival in Patients With Locally Advanced Non-Small Cell Lung Cancer

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Introduction: This study aimed to assess the radiation dose delivered to blood-bearing organs and circulating blood in patients with locally advanced non-small cell lung cancer (LA-NSCLC), and to evaluate their relationships with overall survival (OS).

Methods: The analyzed cohort included 155 LA-NSCLC patients treated with concurrent chemotherapy and intensity-modulated RT. Patients received a median prescription dose of 63 Gy in 1.8-2 Gy fractions. An in-house Artificial Intelligence auto-segmentation algorithm was used to contour 19 blood-bearing organs from planning CTs (Figure 1). Organ dose-volume histograms (DVHs) were generated, which were inputted into the Hematological Dose (HEDOS) framework to estimate blood DVHs for whole-body circulating blood and for blood within major contributing organs (lung, heart, aorta, and superior-vena-cava). Associations with OS were examined for the composite and per-organ mean blood dose. In addition, the mean dose to each organ, and pre-treatment hematologic parameters (lymphocyte, neutrophil, platelet, and hemoglobin, neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios) were assessed for their relationship to OS. For each parameter that reached statistical significance ($p<0.05$), the hazard ratio (HR) and its 95% confidence interval (95%CI) were reported.

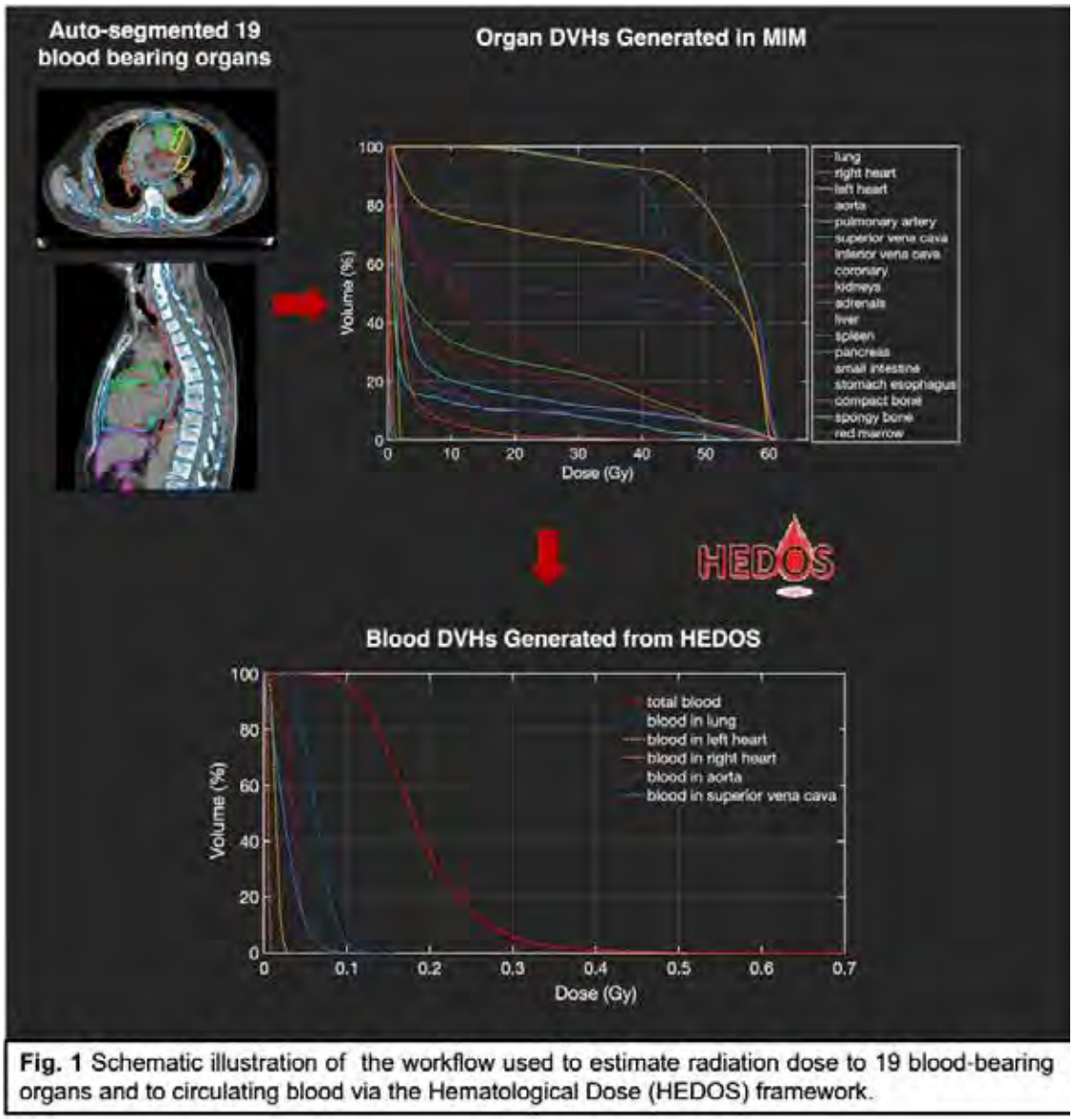
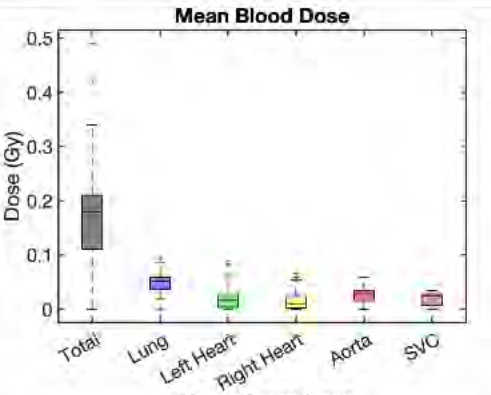
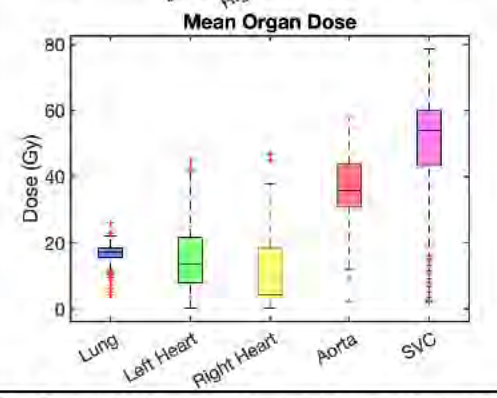


Fig. 1 Schematic illustration of the workflow used to estimate radiation dose to 19 blood-bearing organs and to circulating blood via the Hematological Dose (HEDOS) framework.

Results: Among the organ DVHs, increased mean dose to the lung, heart, aorta, pulmonary and coronary arteries were significantly predicting worse OS, with the largest HR of 1.2 observed for the mean lung dose (Figure 2). Additionally, higher pre-treatment NLR (HR=1.05 (1.01-1.10)), and lower lymphocytes (HR=0.6 (0.4-0.8)) were correlated with worse OS. Elevated composite blood dose, and the blood dose in lung, aorta, and heart were each correlated with worse OS. Notably, a wider 95% CI was observed for blood DVH metrics, reflecting greater uncertainty driven by the lower magnitude of blood dose.





Mean Dose Metric	HR (95% CI)	P-value
$bDVH_{Lung}$	$6.1x10^{15}$ ($1.3x10^{7}$-$2.2x10^{24}$)	0.0004
Lung	1.2 (1.1-1.3)	0.001
Pre-treatment lymphocytes	0.6 (0.4-0.8)	0.002
$bDVH_{Aorta}$	$1.2x10^{19}$ ($8.5x10^{6}$-$1.0x10^{31}$)	0.002
bDVH	23 (2.5-202)	0.01
$bDVH_{Left\ Heart}$	$1.2x10^{8}$ ($2.0x10^{2}$-$7.0x10^{13}$)	0.01
Left Heart	1.02 (1.00-1.04)	0.02
Pre-treatment NLR	1.05 (1.01-1.1)	0.02
Aorta	1.03 (1.00-1.05)	0.02
Pulmonary Artery	1.02 (1.00-1.04)	0.02
Right Heart	1.02 (1.00-1.04)	0.02
Coronary Artery	1.02 (1.00-1.04)	0.03
$bDVH_{Right\ Heart}$	$2.4x10^{6}$ (4.2-$1.4x10^{12}$)	0.03

Fig. 2. Left: Distribution of mean doses obtained from the total blood DVH (bDVH), the bDVH per organ, and the organ-specific non-bDVHs ; Note the order of magnitude difference in mean dose distributions (y-axis) between the mean blood dose (upper) and the organ dose (lower). Right: All identified significant overall survival associations ($p<0.05$) with mean doses from blood and organ DVHs, and pre-treatment blood analytes. Note: Mean dose metrics are organized in ascending p-value order (lowest p-value on the top).

Conclusions: Our results demonstrated that elevated mean doses to lungs, heart, major vessels, and circulating blood were significantly associated with worse OS, while higher pre-treatment lymphocytes correlated with improved OS.

Keywords: blood dose, locally advanced non-small cell lung canc

P2.08 .26 Randomized Phase II Trial of Adjuvant Radiochemotherapy, Concurrent Versus Sequential, in Resected pN2 NSCLC. ARCCS Trial

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Introduction: Postoperative radiotherapy (PORT) in non-small cell lung cancer (NSCLC) with mediastinal involvement has been a therapeutic option for a long time. However, recent randomized phase 3 trials (LungART and PORT-C) have shown no benefit in disease-free survival and increased toxicity with PORT. This randomized phase 2 study aimed to compare sequential and concomitant adjuvant chemoradiotherapy using a modern radiotherapy technique.

Methods: From 2020 to 2023, NSCLC patients were randomized after surgery to receive cisplatin-based chemotherapy for up to 4 cycles and sequential (Arm A) vs concurrent (Arm B) PORT (50 Gy/25 fractions). Intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) were mandatory. The study had 2 co-primary endpoints: G3+ acute esophageal toxicity and locoregional recurrence-free survival (LRFS).

Results: Twenty-four patients were enrolled, 11 in Arm A and 13 in Arm B. The study was closed due to low accrual, mainly due to the COVID-19 pandemic and negative data of LungART and PORT-C trials that discouraged continuation of the study. Patients and disease characteristics are shown in the table. All cases were adenocarcinomas and all patients underwent lobectomy. Nearly 30% of patients had R1 resection due to positive surgical margins or extracapsular nodal extension. In arm B, positive mediastinal nodes were higher and detected ones were lower than in arm A. Sixteen patients completed the planned 4 cycles of chemotherapy, 9 in arm A and 7 in B. One patient in arm A had regional progression after chemotherapy. After a median follow-up of 44 months, 1 local, 2 regional and 15 distant recurrences were recorded, while 17 patients were still alive. The 3-year LRFS was 82% and 91% in arms A and B, respectively. No severe acute esophageal toxicity was ever reported in either arm. Grade 1-2 esophageal toxicity occurred in 2 and 4 patients in arms A and B, respectively. Two patients in arm B reported pneumonitis.

Conclusions: The small sample size does not allow definitive conclusions to be drawn on the usefulness of postoperative concomitant radiochemotherapy. However, the use of modern radiotherapy resulted in a reduction of toxicities and an improvement in locoregional control. Recently, the management of pN2 NSCLC has radically changed with the advent of immunotherapy and targeted therapies, confining PORT to an extremely marginal role. Today, in extremely selected cases (high locoregional risk), PORT could still be proposed to reduce the risk of locoregional recurrence, but only by adopting the highest radiotherapy standards.

	Arm A Sequential CHT-RT	Arm B Concurrent CHT-RT
Age, mean	64	66
Gender, n (%)		
male	5 (45)	8 (62)
female	6 (55)	5 (38)
PS ECOG, n (%)		
0	8 (73)	12 (92)
1	3 (27)	1 (8)
Comorbidity Index, mean	4,7	3,8
Smoking status, n (%)		
current	5 (46)	2 (15)
former	3 (27)	3 (23)
never	3 (27)	8 (62)
TNM 8th Ed. , n (%)		
IIIA	7 (64)	9 (69)
IIIB	4 (36)	4 (31)
Mediastinal nodes detected, mean	6,7	5,5
Mediastinal nodes positive, mean	1,6	2,3
Quality of resection, n (%)		
R0	8 (73)	9 (69)
R1	3 (27)	4 (31)

Keywords: Postoperative radiotherapy, pN2, integrated treatment

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .27 Impact of CD73 on Immune Evasive Contexture and Clinical Outcomes in Lung Adenocarcinoma in Neoadjuvant Immunotherapy

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Introduction: The study aims to investigate the impact of CD73 expression on neoadjuvant immunotherapy in lung adenocarcinoma. We explored the expression of CD73, its dynamic changes during treatment, impact on the microenvironment, and their relationships with treatment efficacy in lung adenocarcinoma patients treated by neoadjuvant immunotherapy, in order to elucidate the CD73-related tumor microenvironmental changes.

Methods: In the first section, the study included 91 patients with treatment-naïve early-stage lung adenocarcinoma who underwent radical surgery at a provincial tertiary hospital in 2018. A prognostic prediction model was established based on clinical, pathological characteristics, and CD73 H-Score. A nomogram was developed based on the results of the Cox regression analysis. Additionally, 30 patients who underwent surgery after neoadjuvant immunochemotherapy between 2022 and 2023 were included in part 2 study. Multiplex immunofluorescence was done. The impact of CD73+ tumor cells on treatment efficacy and the immune microenvironment was analyzed through quantitative and spatial analysis.

Results: Univariate and multivariate Cox regression analyses revealed that tumor stage, pathological grade, and elevated CD73 H-Score were significant adverse prognostic factors for early-stage lung adenocarcinoma patients after radical surgery. Specimens from 30 lung adenocarcinoma patients were collected before or after neoadjuvant immunochemotherapy treatment. Differences in immune cell density were identified between major pathological response (MPR) and non-MPR patients. No significant correlation was found between CD73 expression on tumor cells and treatment efficacy or immune cell infiltration. In spatial analysis, in non-MPR patients, the distance between CD73+ tumor cells and CD8+ T cells was significantly longer than the distance between CD73- tumor cells and CD8+ T cells, which was not seen in the MPR group. After neoadjuvant treatment, the increase in immune cell density was greater in non-MPR patients than in MPR patients. In postoperative non-MPR patients, the distance between CD73+ tumor cells and CD8+ T cells was significantly longer than the distance between $CD73^-$ tumor cells and CD8+ T cells.

Conclusions: CD73 H-Score is an independent risk factor for poor prognosis in early-stage lung adenocarcinoma patients after radical surgery. In lung adenocarcinoma patients receiving neoadjuvant immunotherapy, the spatial distance between $CD73^+$ tumor cells and $CD8^+$ T cells may serve as a potential predictor for treatment efficacy.

Keywords: CD73, neoadjuvant immunotherapy, lung adenocarcinoma

P2.08 .28 Impact of Neoadjuvant Chemoimmunotherapy vs Chemotherapy in Stage III NSCLC: Real-World Analysis From Spanish ReSECT Database

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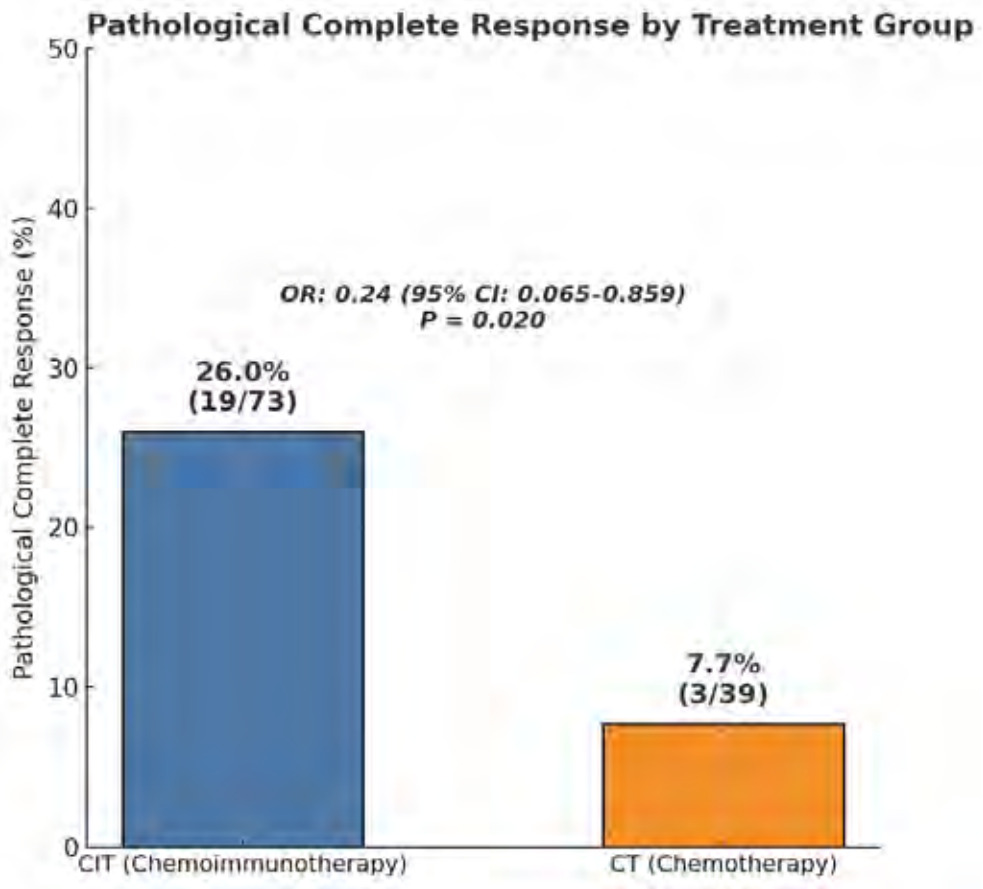
Introduction: Stage III non-small cell lung cancer (NSCLC) remains a therapeutic challenge despite multimodal treatment. Neoadjuvant chemoimmunotherapy (CIT) has shown promising results in clinical trials, but its real-world impact on oncologic and surgical outcomes requires further validation. This study compared CIT and chemotherapy (CT) in a multicenter cohort of resected patients. Primary endpoints were pathological complete response (pCR) and T/N downstaging. Secondary endpoints included resection complexity, quality, and perioperative outcomes.

Methods: A retrospective analysis was conducted using the Spanish National ReSECT prospective database. Patients with cIII NSCLC who received neoadjuvant CT or CIT followed by anatomical resection between January 2020 and February 2025 were included. Exclusion criteria comprised Pancoast tumors, N3 disease, alternative regimens, and non-systematic or non-lobe-specific lymphadenectomies. Oncologic variables included ypTNM, pCR, resection status (R0-un/R1-2), and number of resected nodes. Surgical variables included operative time, extended resections, complications, and readmissions. Quantitative variables were expressed as medians and IQRs and compared using the Mann-Whitney U test; categorical variables as frequencies using the chi-squared test.

Results: A total of 112 patients were analyzed (CIT: 73; CT: 39). Baseline characteristics were similar. pCR was significantly higher with CIT (26.0% vs. 7.7%, p=0.020; OR 0.237, 95% CI: 0.065-0.859), with a trend toward greater T downstaging (79.5% vs. 64.1%, p=0.077). Nodal downstaging was comparable (52.1% vs. 48.7%, p=0.736). R0-un resection was achieved in 80.8% (CIT) vs. 82.1% (CT, p=0.874), of which 41.1% and 33.3% were strictly R0 (p=0.421). Pneumonectomy was performed in 6.8% (CIT) and 10.3% (CT) and Minimally invasive approaches in 63.0% (CIT) and 66.7% (CT, p=0.701). Systematic lymphadenectomy was more frequent in CIT (75.3% vs. 59.0%, p=0.073). Dissection of ≥3 mediastinal nodes occurred in 64.0% vs. 66.7%, and ≥3 hilar nodes in 49.3% vs. 64.1%. Extended resections were more common in CIT (20.5% vs. 13.2%, p=0.336), with longer operative time (210 vs. 180 min). CIT showed higher complication (33.3% vs. 20.5%, p=0.155) and readmission rates (10.0% vs. 2.9%, p=0.199).

Conclusions: Neoadjuvant CIT was associated with significantly higher pCR and favorable trends in T downstaging and R0. Surgical complexity and perioperative morbidity were slightly higher without statistical significance. Further real-world studies are needed.



Keywords: Neoadjuvant Chemoimmunotherapy, Stage III NSCLC, Pathological Complete Response

P2.08 .29 Phase 2 Trial of Tislelizumab Plus Chemotherapy Induction Therapy for Newly Diagnosed Stage III Unresectable NSCLC

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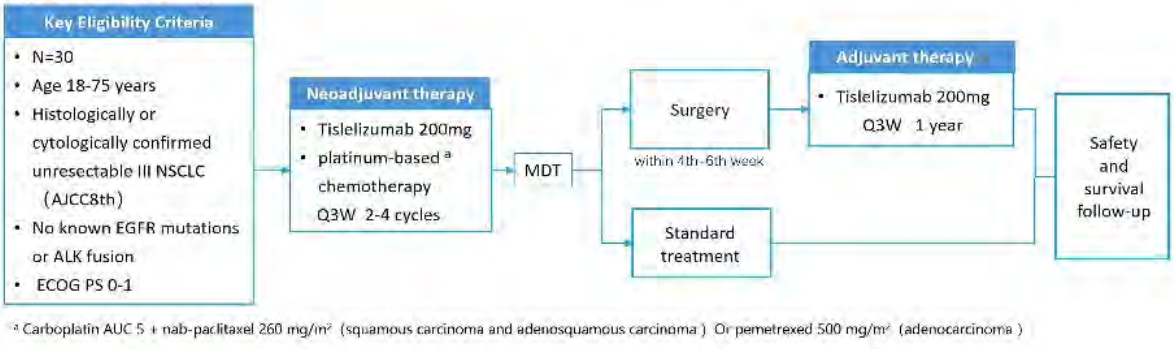
Introduction: Patients diagnosed with resectable stage III NSCLC will have a higher rate of pathologic complete response (pCR) and downstaging when treated with neoadjuvant therapy. However, for newly diagnosed unresectable stage III NSCLC, there is insufficient data to support immunotherapy combined with neoadjuvant chemotherapy followed by sequential surgery. Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody specifically designed to minimize binding to FcγR on macrophages. Our study aims to evaluate the efficacy and safety of Tislelizumab combined with chemotherapy in neoadjuvant treatment of newly diagnosed stage III unresectable NSCLC.

Methods: Study design: an open-label, single-arm prospective clinical study. (NCT06357598; Figure 1)The primary endpoint was R0 resection rate.The secondary endpoints included surgery rate, objective response rate (ORR), major pathological response (MPR), pCR, downstaging rate, disease-free survival (DFS), and safety.

Figure 1. Study Design



[a] Carboplatin AUC 5 + nab-paclitaxel 260 mg/m² (squamous carcinoma and adenosquamous carcinoma) Or pemetrexed 500 mg/m² (adenocarcinoma)

Results: As of March 28, 2025, 19 patients were enrolled, 12 patients have completed induction therapy. Among them, 10 patients were successfully converted, 1 patient had cancer progression, and 1 patient was unable to undergo radical resection due to tumor invasion of the aorta. The ORR for all patients was 66.7%. The rates of partial response (PR) and stable disease (SD) and progressive disease (PD) were 66.7 % and 25.0 % and 8.3 %, respectively. The surgical conversion rate was 83.3 %, and the R0 resection rate was 100 %. Among 10 surgically-treated patients, the pathological downstaging rate was 90%, the MPR rate was 50% and the pCR rate was 40%. Surgical details were shown in Table 1. The incidence of Grade ≥3 treatment-related adverse events (TRAEs) was 16.7%, all of which were leukopenia combined with neutropenia. The incidence of immune-related adverse events (irAEs) was 33.3%.

Table 1. Surgical Details

	Patients (n=10)
Interval between the neoadjuvant treatment (Last Dose) and surgery, d, median (range)	36.5 (32-115)
Extent of surgical resection	
Lobectomy	7 (70%)
Sleeve lobectomy	3 (30%)
Completeness of resection	
R0	10 (100%)
R1	0
Surgical approach	
Robotic-assisted surgery	10 (100%)
Thoracotomy	0
Duration of operation, minutes, median (range)	112.5 (70-270)
Intraoperative blood loss (mL) median (range)	20 (20-100)

Conclusions: The findings of this study suggest promising antitumor activity and manageable safety of Tislelizumab combined with chemotherapy in patients with newly diagnosed stage III unresectable NSCLC.

Keywords: Neoadjuvant Immunotherapy, Surgical Conversion, Unresectable NSCLC

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .30 Ia-Based Prediction in NSCLC Patients Undergoing Neoadjuvant Radiochemotherapy

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Introduction: Despite advances in therapies and diagnostics, the prognosis for patients with advanced-stage NSCLC remains poor, underscoring the importance of timely treatment for early-stage tumors. Therefore, our study proposes a non-invasive artificial intelligence (AI) method for predicting pathological complete response (pCR).

Methods: The features were extracted from simulation CT. Imaging analysis was conducted using two segmentation masks: the lung region of interest (ROI) and the planning target volume (PTV). Two techniques were employed: Gradual Learning (GL) and Explainable AI (XAI), integrated in the Doctor-in-the-Loop approach. The process consists of multiple phases: 1- Data Preprocessing: images were standardized and segmented into three levels. 2- Feature Extraction using CNN, a 3D DenseNet convolutional neural network. 3- XAI and Grad-CAM Heatmap: the model generates Grad-CAM heatmaps to highlight the regions influencing prediction. 4- XAI loss function penalizes the model if it focuses on irrelevant areas. 5- Final Classification: a fully connected layer processes the extracts features and assigns a probability of a positive or negative pathological response.

Results: From 2009 to 2020, 64 patients with a confirmed diagnosis of locally advanced NSCLC undergoing neoadjuvant radiochemotherapy and surgery were enrolled. With a median follow-up of 69.93 months, the median overall survival (OS) and progression-free survival (PFS) were 24.9 months and 20.03 months, respectively. Clinical outcome rates of overall population and the sub-analysis divided by treatment response (pCR/MPR vs. no pCR/MPR) are reported in Table 1. The Doctor-in-the-Loop approach showed progressive improvements throughout its learning phases (Table 1), achieving the best performance at Step 3 (focused on PTV). This step combines GL, which progressively guides network attention through segmentation masks (full CT, lung ROI, and PTV lesion), with XAI loss, which penalizes non-relevant areas identified using the Grad-CAM system, thereby enabling the model to focus on clinically relevant regions for feature extraction. In Step 3, the highest values were achieved for AUC (62.93%) and TPR (46.67%).

Conclusions: This study introduces an innovative approach where XAI models actively influence learning instead of being used only post hoc. Unlike conventional models, Doctor-in-the-Loop not only classifies pCR/no-pCR but also explains predictions, guiding the model toward clinically relevant areas.

Table 1

Clinical outcomes of the overall population

	Median (yrs)	1-year (%)	2-year (%)	3-year (%)	
OS	24.9 (12.1-37.6)	75%	62%	62%	
PFS	20.03	67%	41,60%	36.2%	
LC	NR	85.9%	63.4%	63.4%	
MFS	13.98 (12.92-67.74)	72.1%	56.6%	50.1%	
Analysis of clinical outcomes by pathological response (pCR/MPR vs no pCR/MPR)					
	Median (yrs)	1-year (%)	2-year (%)	3-year (%)	p value
OS pCR/MPR	46.56	70%	60%	55%	p =0.49
OS no pCR/MPR	22,36	77.3%	47.7%	38.6%	
PFS pCR/MPR	NR	81.3%	62.5%	62.5%	**p =0.026**
PFS nopCR/MPR	15.56	61.2%	33.2%	28.1%	
LC pCR/MPR	NR	92.9%	78.6%	78.6%	p =0.15
LC noPCR/MPR	NR	80.2%	56.7%	56.7%	
MFS pCR/MPR	NR	81.3%	74.5%	74.5%	**p= 0.02**
MFS nopCR/MPR	20.3	68.3%	49.4%	40.01%	
Performance metrics					
	AUC%	ACC%	TPR%	TNR%	
Doctor in the Loop	62.93	73.33	46.67	82.44	
XAI-guide	47.96	60.90	38.33	67.78	
Gradual Learning	48.44	65.77	16.67	82.67	
Segmentation	51.37	64.23	31.67	76.67	

AUC: Area under the curve; ACC: Accuracy; TPR: True positive rate; TNR: True negative rate

Keywords: lung cancer, IA, PCR

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .31 Clinical and Imaging Characteristics Associated With Pathologic Response After Neoadjuvant Chemoimmunotherapy in Stage II-III NSCLC

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Introduction: Neoadjuvant chemoimmunotherapy (NICT) has improved resectability and survival in non-small cell lung cancer (NSCLC), however accurate prediction of treatment response remains challenging. This study aimed to identify clinical and imaging biomarkers predictive of pathologic complete response (pCR) and major pathologic response (MPR) in stage II-III NSCLC patients receiving NICT.

Methods: We retrospectively analyzed 82 patients treated with NICT followed by elective surgery. Clinical and imaging data from sequential CT and PET/CT scans were collected. Univariable logistic regression was performed for pCR and MPR, and predictors with $p < 0.1$ in both analyses were advanced to multivariable modeling using backward elimination.

Results: Candidate predictors by univariable analysis included smoking history, histologically non-squamous cell carcinoma (non-SqCC), high PD-L1 expression (≥50%), N2 nodal involvement after chemoIO, tumor cavitation after chemoIO, Δ primary tumor size (representing percent decrease), and Δ SUVmax of primary tumor (also representing percent decrease). For pCR, the final model included N2 nodal involvement after chemoIO (OR, 0.20; 95% CI, 0.04-0.83; p = 0.034), tumor cavitation after chemoIO (OR, 6.96; 95% CI, 1.54-37.55; p = 0.015), and Δ SUVmax (OR, 201.81; 95% CI, 7.19-23,250.10; p = 0.009), with an AUC of 0.882 (95% CI, 0.775-0.989; p < 0.001). For MPR, the final model comprised non-SqCC (OR, 0.32; 95% CI, 0.08-1.18; p = 0.088), tumor cavitation after chemoIO (OR, 8.87; 95% CI, 1.23-134.54; p = 0.054), and Δ SUVmax (OR, 37.01; 95% CI, 4.05-728.01; p = 0.006), achieving an AUC of 0.878 (95% CI, 0.785-0.971; p < 0.001). Common significant predictors across both outcomes were tumor cavitation after chemoIO and Δ SUVmax; models constructed solely with these variables yielded AUCs of 0.856 for CR and 0.872 for MPR.

Conclusions: Our prediction model for NICT response in NSCLC demonstrate individualized risk stratification and guides treatment decisions in clinical practice.

Table 1. Univariable analysis of several clinical and imaging variables for major pathologic response (MPR) and pathologic complete response (pCR)

	MPR		pCR	
	OR (95% CI)	P value	OR (95% CI)	P value
Clinical and tumor characteristics				
Age	1.06 (1.01 – 1.13)	0.034	1.04 (0.99 – 1.11)	0.148
Sex | Male	1.53 (0.44 – 5.63)	0.502	Not Estimated*	0.992
Hypertension	0.86 (0.35 – 2.08)	0.732	0.69 (0.27 – 1.70)	0.438
DM	**0.18 (0.03 – 0.74)**	**0.034**	Not Estimated*	0.989
Previous history of cancer	1.33 (0.28 – 7.17)	0.719	0.28 (0.01 – 3.70)	0.246
Smoking history	**2.02 (1.07 – 3.99)**	**0.036**	**3.38 (1.56 – 8.29)**	**0.004**
Pack-year	**1.03 (1.01 – 1.05)**	**0.010**	**1.03 (1.01 – 1.06)**	**0.006**
Cycle	0.93 (0.42 – 2.03)	0.856	0.55 (0.23 – 1.24)	0.171
Completion of chemoIO	Not Estimated*	0.991	Not Estimated*	**0.992**
Histology		**0.001**		**0.001**
Non-SqCC	**0.19 (0.07 – 0.48)**		**0.17 (0.05 – 0.46)**	
SqCC	**Reference**		**Reference**	
EGFR mutant	0.29 (0.01 – 2.10)	0.282	Not Estimated*	0.993
PD-L1 (≥50%)	**2.78 (1.11 – 7.24)**	**0.032**	2.13 (0.80 – 6.31)	0.089
Imaging characteristics at baseline				
Size	1.42 (1.01 – 1.94)	0.067	1.62 (0.99 – 1.94)	0.171
SUVmax	**1.13 (1.03 – 1.25)**	**0.011**	1.09 (1.00 – 1.20)	0.056
Spiculated margin	**3.20 (0.10 – 0.83)**	**0.025**	0.67 (0.20 – 1.78)	0.407
Lobulated contour	1.97 (0.34 – 8.10)	0.314	0.92 (0.20 – 3.73)	0.896
Solid vs. subsolid | Solid	**5.48 (1.56 – 25.50)**	**0.014**	1.68 (0.53 – 6.42)	0.306
Abut to major vessel	0.97 (0.32 – 2.94)	0.955	2.67 (0.86 – 8.33)	0.086
Abut to main bronchus	0.75 (0.13 – 3.44)	0.668	1.70 (0.31 – 8.90)	0.515
Abut to pleura	1.30 (0.53 – 3.19)	0.565	0.67 (0.25 – 1.72)	0.410
Tumor necrosis	**2.91 (1.12 – 7.35)**	**0.030**	1.22 (0.47 – 3.15)	0.678
Tumor cavitation	5.08 (0.38 – 63.85)	0.239	2.25 (0.26 – 3.96)	0.431
Peritumoral GGO	2.06 (0.38 – 15.49)	0.432	2.30 (0.40 – 13.28)	0.328
Satellite nodule	0.46 (0.06 – 2.51)	0.387	0.41 (0.02 – 2.71)	0.421
Pleural effusion	0.36 (0.05 – 1.76)	0.237	0.28 (0.01 – 1.70)	0.246
N1 node involvement	0.93 (0.37 – 2.34)	0.883	0.65 (0.25 – 1.68)	0.369
Radiological ENE of N1 node	2.04 (0.82 – 5.21)	0.130	1.32 (0.50 – 3.42)	0.567
N2 node involvement	0.52 (0.19 – 1.33)	0.177	**0.37 (0.14 – 0.96)**	**0.042**
Radiological ENE of N2 node	0.69 (0.28 – 1.69)	0.418	**0.35 (0.13 – 0.89)**	**0.031**
Pulmonary fibrosis (vol, %)	**1.59 (1.15 – 2.45)**	**0.017**	1.15 (0.92 – 1.43)	0.218
Emphysema (vol, %)	1.04 (0.91 – 1.24)	0.558	1.10 (0.96 – 1.31)	0.214
Imaging characteristics after ChemoIO				
Size	0.99 (0.96 -1.02)	0.396	0.98 (0.95 – 1.01)	0.227
SUVmax	**0.82 (0.70 – 0.93)**	**0.005**	**0.77 (0.64 – 0.91)**	**0.004**
Tumor necrosis	1.44 (0.59 -3.53)	0.424	0.91 (0.35 – 2.32)	0.843
Tumor cavitation	8.32 (1.02 -10.60)	0.059	3.11 (0.98 – 10.41)	0.058
Peritumoral GGO	1.71 (0.39 – 8.87)	0.483	1.33 (0.26 – 5.90)	0.712
Satellite nodule	Not Estimated*	0.980	Not Estimated*	0.991
Pleural effusion	0.22 (0.01 – 1.01)	0.191	0.52 (0.03 – 3.74)	0.568
N1 node involvement	0.62 (0.25 – 1.51)	0.331	0.40 (0.15 – 1.10)	0.089
Radiological ENE of N1 node	1.37 (0.43 – 4.60)	0.592	0.53 (0.11 – 1.91)	0.370
N2 node involvement	0.46 (0.18 – 1.15)	0.092	**0.29 (0.10 – 0.75)**	**0.014**
Radiological ENE of N2 node	0.51 (0.21 – 1.25)	0.147	**0.26 (0.08 – 0.71)**	**0.012**
Dynamic imaging characteristics between baseline and post-ChemoIO				
Size decrease (%)	**184.85 (14.63 – 3806.56)**	**<.001**	**109.73 (8.96 – 2308.87)**	**0.001**
SUVmax decrease (%)	**127.57 (12.96 – 2461.30)**	**<.001**	**440.20 (19.18 – 33350.75)**	**0.001**
New tumor cavitation	**4.94 (1.38 – 23.47)**	**0.023**	**4.00 (1.22 – 13.90)**	**0.024**
New tumor necrosis	1.69 (0.44 – 6.52)	0.436	1.23 (0.28 – 4.80)	0.775
New pleural effusion	Not Estimated*	0.991	Not Estimated*	0.992
New peritumoral GGO	1.03 (0.12 – 6.98)	0.978	0.76 (0.08 – 6.50)	0.814
Disappearance of N1 involvement	1.96 (0.63 – 6.38)	0.251	2.67 (0.78 – 9.87)	0.129
Disappearance of N2 involvement	1.58 (0.65 – 5.74)	0.477	1.58 (0.61 – 10.10)	0.172
Disappearance of rENE (N1)	0.98 (0.22 – 4.27)	0.981	2.67 (0.58 – 15.02)	0.227
Disappearance of rENE (N2)	2.50 (0.85 – 17.13)	0.201	5.14 (0.93 – 59.23)	0.069

Note—ChemoIO (neoadjuvant chemoimmunotherapy), Diabetes mellitus (DM), Epidermal Growth Factor Receptor (EGFR), Programmed Death-Ligand 1 (PD-L1), SqCC (Squamous cell carcinoma), Tumor Proportion Score (TPS). All tests and chi-square tests were conducted by excluding any NA values to avoid potential distortion of the results.
* The OR could not be reliably estimated due to a wide confidence interval.

Table 2. Results of the multivariable analysis for selected clinical and imaging variables for major pathologic response (MPR) and pathologic complete response (pCR) using backward elimination with a p-value cutoff of 0.1, along with the model performance metrics for each individual model and for the model constructed using common predictors.

Outcome/Model	Variable	OR	95% CI	P value	Model AUC
pCR	**N2 node involvement after chemoIO**	0.20	0.04 – 0.83	0.034	0.882 (0.775 – 0.989)
	New tumor cavitation	6.96	1.54 – 37.55	0.015	
	SUVmax decrease (%)	201.81	1.79 – 23250.10	0.040	
MPR	**Histology (Non-SqCC)**	0.32	0.09 – 1.10	0.088	0.878 (0.785 – 0.971)
	New tumor cavitation	8.87	1.25 – 134.54	0.054	
	SUVmax decrease (%)	57.01	4.05 – 728.01	0.006	
Common predictor					pCR: 0.856 (0.749 – 0.963); MPR: 0.872 (0.775 – 0.969)
	SUVmax decrease (%)	-	-	-	
	New tumor cavitation				

Note—SqCC (Squamous cell carcinoma). All tests were conducted by excluding any NA values to avoid potential distortion of the results.

Keywords: Neoadjuvant Chemoimmunotherapy, Pathologic Response, Non-small cell lung cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .32 Single Cell Transcriptomic Analysis Reveals Tumor Immune Remodeling and Epithelial Cells Gene Signature After Neoadjuvant Immunotherapy

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Introduction: Although more and more phase III randomized clinical trials have confirmed that neoadjuvant immunotherapy and combination therapy can significantly improve the pathological response rate in patients with stage III NSCLC, the in-depth mechanism of benefit is not yet fully elucidated.

Methods: We used scRNA-seq to analyze the transcriptomes of 45,572 individual cells obtained from three lung squamous cell carcinoma (LUSC) patients before and after neoadjuvant immunotherapy, with major pathological response (MPR) in patient P01, and non-MPR in patients P02 and P03 (NCC2023C-892). A least absolute shrinkage and selection operator (LASSO) Cox proportional hazards regression analysis was executed to culminate in the selection of six most predictive genes for the risk prognostic model.

Results: The proportion of adaptive immune cells such as T cells, B cells increased after treatment, and the proportion of T cells in MPR patients increased significantly after treatment. Further, we found a significant increase in the proportion of CD8_CCL5 and CD4_TCF7 T cells in patients with MPR. We identified six genes (CCDC141, SNAL1, MME, CD226, DPP4, and HIGD1B) that distinguish malignant epithelial cells from non-malignant ones. Functional analysis revealed an enrichment of genes related to the EMT and TGF-β signaling pathway in the high-risk group (with highly expression of these six genes). Moreover, the high-risk group correlated with higher immune scores and T-cell receptor repertoire diversity, indicating a positive association with anti-tumor immune activity in the neoadjuvant immunotherapy.

Conclusions: Our study reveals that neoadjuvant immunotherapy remodels the tumor immune microenvironment (TME), and patients with different pathological response are observed with TME changes dissimilarly after treatment. We introduced the innovative risk score, differentiating malignant epithelial cells from non-malignant ones. High-risk groups were associated with the EMT and TGF-β pathway and provided insights into prognosis and immune activities in the neoadjuvant immunotherapy of LUSC.

Keywords: neoadjuvant immunotherapy, tumor immune microenvironment, epithelial-mesenchymal transition

P2.08 .33 Quantitative Pathological Analysis of the Surgical Specimens of NSCLC After Neoadjuvant Immunochemotherapy

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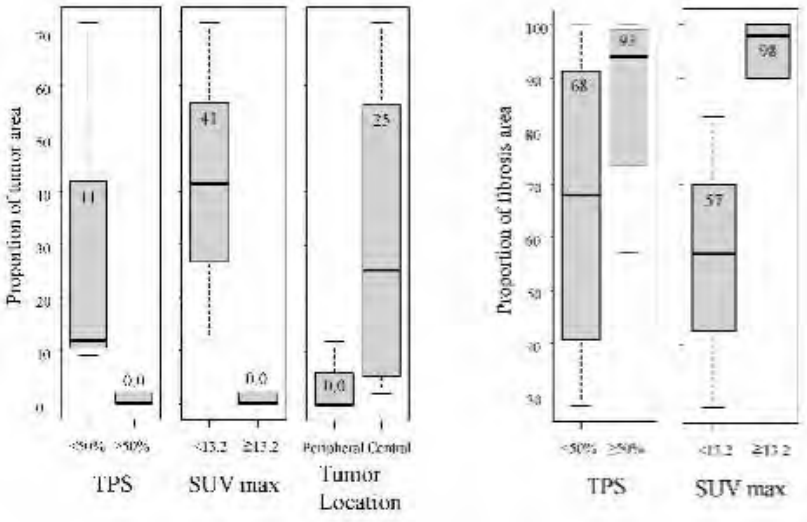
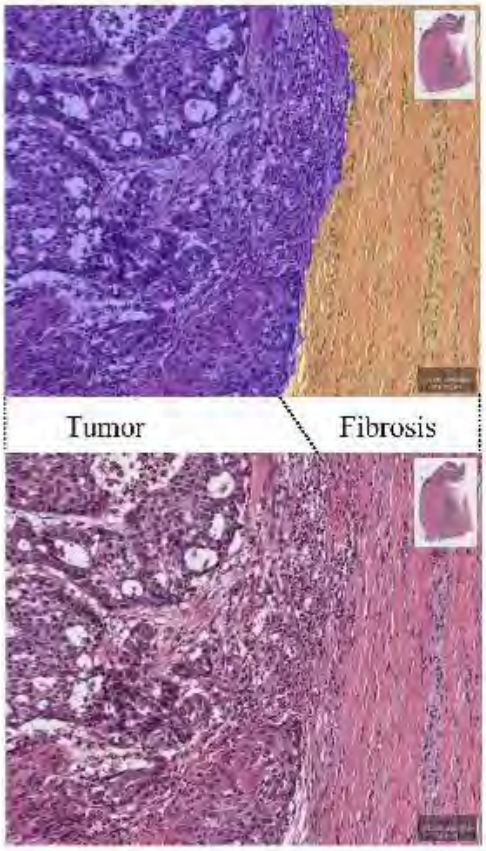
Introduction: Neoadjuvant immunochemotherapy has improved outcomes in non-small-cell lung cancer (NSCLC); however, the relationship between preoperative clinical factors and the histological characteristics of surgical specimens remains poorly understood.

Methods: This study conducted a retrospective analysis of eight patients with NSCLC, treated with curative surgery following neoadjuvant immunochemotherapy with the CheckMate 816 regimen (platinum-based chemotherapy plus nivolumab) between July 2023 and July 2024. For evaluating the distribution of fibrosis, residual tumor, and other components, histological mapping was performed on the largest cross-sectional area of the resected tumors. Quantification of the proportion of fibrosis and residual tumor area was performed using the image analysis software QuPath (Figure). The association between these areas and the following preoperative clinical factors was evaluated: PET SUVmax, tumor proportion score (TPS) from preoperative biopsy specimens, histological subtype, tumor location, and tumor size.

Results: The mean age and PET SUVmax of the eight cases were 64.6 years (47- 79) and 14.1 (5.5-22.7), respectively. The subjects included six males (75%) and three cases with SQ histology. Six patients (75%) had completed three courses of nivolumab + chemotherapy prior to surgery. The proportions of fibrosis, tumor, and other component areas were 76.1%, 17%, and 6.9%, respectively. The higher-SUVmax (≥13.2) group exhibited a lower proportion of tumor area compared with the lower-SUVmax group (median; 0.0% vs 41%). The high-TPS (≥50%) group and peripherally located tumors also exhibited lower proportions of tumor area compared with the lower-TPS group (0.0% vs 11%) and centrally located tumors (0.0% vs 25%). The proportion of fibrosis area was higher in the higher-SUVmax group compared with the lower-SUVmax group (98% vs 57%), and in the higher-TPS group compared with the lower-TPS group (93% vs 68%). No significant differences were observed in the other parameters.

Conclusions: Higher-SUVmax, higher-TPS, and peripherally located tumor were the factors associated with lower proportion of viable tumor cells. Additionally, this quantitative pathological analysis demonstrated an association between higher-TPS and increased fibrosis.





Tumors (Purple), fibrosis (Yellow), and other regions were identified, their areas measured using QuPath, and the percentage of each component within the tumor bed quantified.

Keywords: Neoadjuvant Chemoimunotherapy, Histological Patterns, Non-small cell lung cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .34 Serplulimab in Neoadjuvant Therapy for Locally Advanced Non-Small Cell Lung Cancer: A Prospective Single-Arm Study

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Introduction: Although a series of clinical trials, including CheckMate-816 and KEYNOTE-671, have demonstrated that patients with locally advanced non-small cell lung cancer (NSCLC) can benefit from neoadjuvant chemo-immunotherapy, the role of serplulimab in this setting remains unestablished. This study aims to evaluate the efficacy and safety of serplulimab in combination with chemotherapy as neoadjuvant treatment for locally advanced NSCLC.

Methods: This is a prospective, single-arm clinical study designed to enroll 80 patients with stage II-IIIB (T4N2) NSCLC based on the AJCC 8th edition, whose tumors are assessed as resectable or potentially resectable. Patients will receive 3 cycles of neoadjuvant therapy consisting of serplulimab (300 mg) combined with chemotherapy. Subsequently, patients will undergo curative-intent surgery or definitive chemoradiotherapy if re-assessed as inoperable. The primary endpoint is the major pathologic response (MPR) rate, and the secondary endpoints include pathologic complete response (pCR) rate, objective response rate (ORR), and adverse events (AEs).

Results: From October 1, 2023 to February 28, 2025, a total of 55 patients were enrolled, including 9 cases of adenocarcinoma, 45 cases of squamous cell carcinoma, and 1 case of undifferentiated carcinoma. In terms of clinical stage, 6 patients were stage IIA, 18 were stage IIB, 26 were stage IIIA, and 5 were stage IIIB. Three patients were still undergoing neoadjuvant therapy, and 10 patients withdrew from the study prematurely. Among the remaining 42 patients who completed neoadjuvant therapy and imaging evaluation, radiographic assessment showed complete response (CR) in 2 patients, partial response (PR) in 38, and stable disease (SD) in 2; the ORR was 95.2% (40/42). Except for 2 patients who received definitive radiotherapy due to ineligibility for surgery, 40 patients underwent curative-intent surgery. Among them, 35 (87.5%) underwent thoracopic resection, and the R0 resection rate was 100%. The MPR rate was 67.5% (27/40), and the pCR rate was 37.5% (15/40). During neoadjuvant therapy, 20 patients (36.4%, 20/55) experienced AEs, including 5 patients (9.1%, 5/55) with grade ≥3 AEs. Six patients discontinued treatment due to AEs, but no surgical was delayed due to treatment-related toxicity. One patient developed a serious perioperative complication (bronchopleural fistula), which resolved after stent placement and conservative management.

Conclusions: Interim results suggest that serplulimab in combination with chemotherapy demonstrates promising efficacy and manageable safety as neoadjuvant therapy for patients with locally advanced NSCLC. These findings warrant confirmation with continued patient enrollment and longer follow-up.

Keywords: Serplulimab, Neoadjuvant Therapy, NSCLC

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .35 PD-L1 as a Predictive Biomarker in EGFR-Mutated Non-Small Cell Lung Cancer With Neoadjuvant Immunochemotherapy

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Introduction: The role of PD-L1 in the prognosis and the efficacy of immunochemotherapy in perioperative EGFR-mutated (EGFR-M+) non-small cell lung cancer (NSCLC) is still unknown.

Methods: We retrospectively enrolled two cohorts of patients with EGFR-M+ NSCLC: 43 stage IB-IV patients receiving immunotherapy plus chemotherapy followed by surgery (NeoGroup), and 499 stage IB-III patients undergoing surgery without neoadjuvant therapy (AdjGroup). Radiological response, pathological assessment in the NeoGroup and genomic features, and clinicopathological factors in the AdjGroup associated with the PD-L1 tumor proportion score (TPS) were analyzed.

Results: In the NeoGroup, the objective response rate was 44.2%, with a pathological complete response (pCR) rate of 18.6% and a major pathological response (MPR) rate of 41.9%. A frequency of baseline PD-L1 TPS ≥ 1% correlated with better radiological responses (partial response (PR) 78.9% vs. stable disease (SD) 59.1% vs. progressive disease (PD) 0%; P = 0.05). Patients who achieved MPR showed a greater increase in PD-L1 TPS from baseline after therapy than patients without MPR (P = 0.0195). Baseline PD-L1 TPS ≥ 50% was related to more aggressive pathological features (AdjGroup, N = 499, P < 0.05). Patients with PD-L1 ≥ 1% more frequently harbored TP53 mutations, and more regularly appeared in patients achieving MPR than non-MPR(P > 0.05).

Conclusions: PD-L1 is a predictive biomarker for EGFR-M+ NSCLC with neoadjuvant immunochemotherapy. Higher baseline PD-L1 levels and a more significant increase in PD-L1 levels is associated with better efficacy.

Figure1

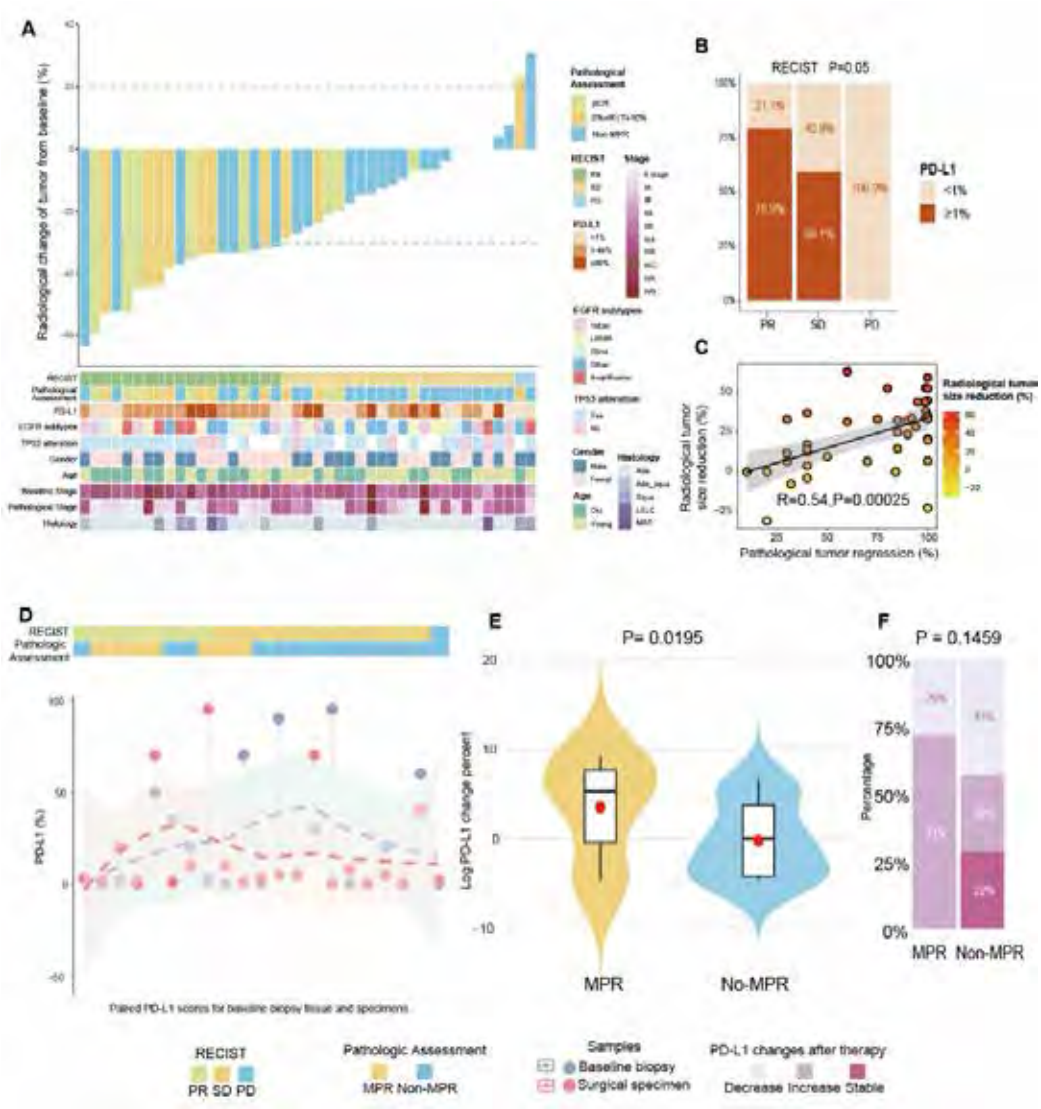
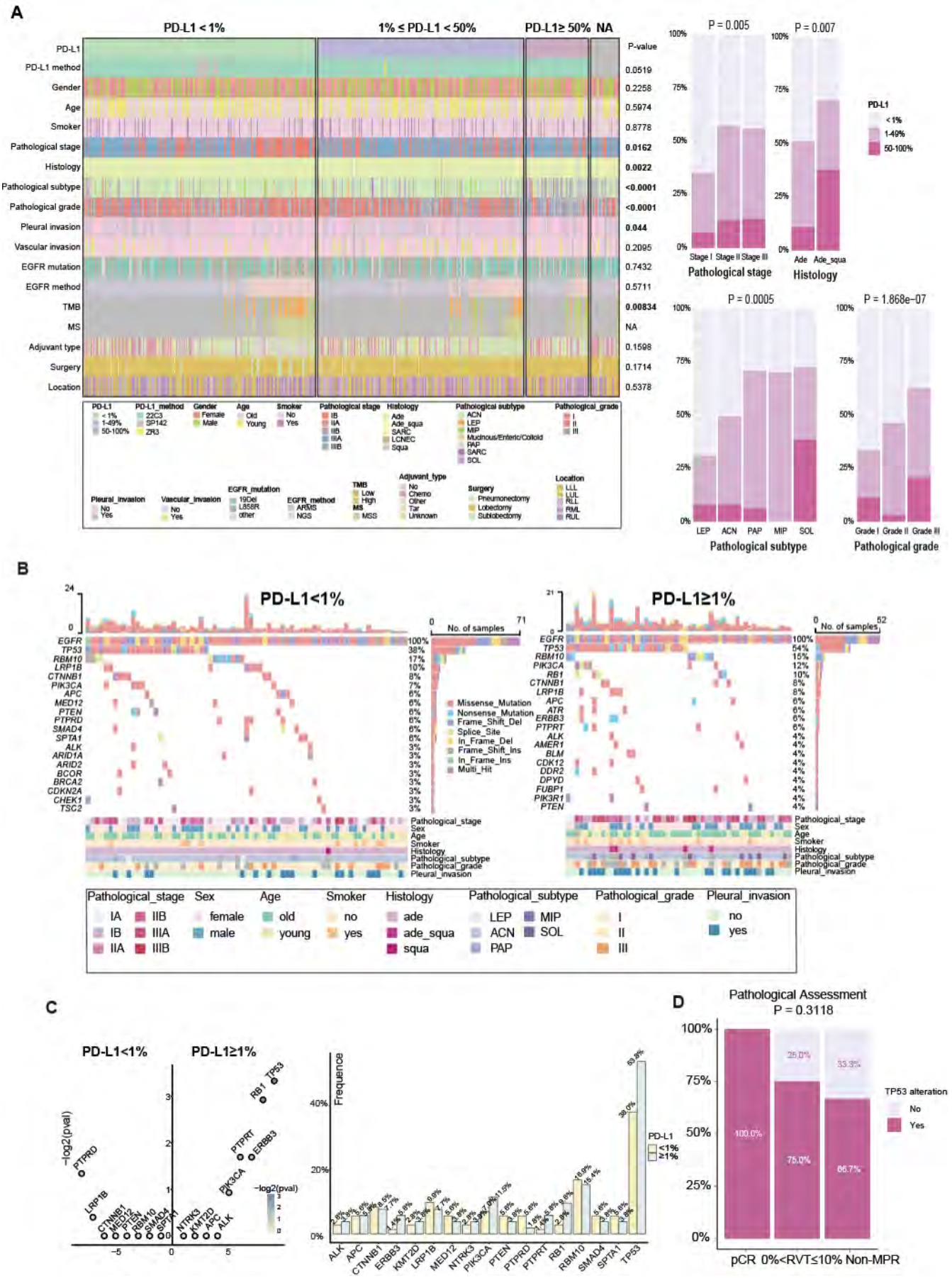


Figure2



Keywords: programmed death-ligand 1, epidermal growth factor receptor, neoadjuvant therapy

P2.08 .36 Survival Outcomes in Locally Advanced NSCLC Patients Converted to Resectable Disease by Neoadjuvant Therapy

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Introduction: Locally advanced non-small cell lung cancer (NSCLC) poses a significant therapeutic challenge due to its heterogeneity. Neoadjuvant therapy, while increasingly employed to convert inoperable disease to operable status, requires careful patient selection and assessment of response. This study evaluates the survival outcomes of patients with locally advanced NSCLC rendered resectable by neoadjuvant chemotherapy

Methods: We retrospectively reviewed data from adult patients with non-metastatic, initially inoperable locally advanced NSCLC who were treated at our tertiary center between January 2003 and December 2023, and who underwent R0 surgical resection after neoadjuvant therapy. Demographic, clinical, radiological, and pathological characteristics, treatment details, and survival outcomes were collected. Factors associated with event-free survival (EFS) and overall survival (OS) were analyzed.

Results: Thirty-five patients (86% male; mean age 67.6±8.0 years) were included. Staging at diagnosis was IIB (n=1), IIIA (n=11), IIIB (n=19), and IIIC (n=4). Histology was squamous cell carcinoma (80%) and adenocarcinoma (20%). Patients received a median of 3 (range 2-6) neoadjuvant therapy cycles (77% carboplatin and paclitaxel). Postoperative pathology revealed mediastinal lymph node involvement (37%), pleural contact/invasion (34.3%), angiolymphatic invasion (25.7%), and cartilage invasion (5.7%). Adjuvant treatment (56% carboplatin and paclitaxel) was administered to 51.4% of patients, with no factor significantly associated with this decision. During a median follow-up of 40.6 months (95% CI: 29-52.2), 13 (37.1%) patients experienced recurrence and 14 (40%) died. The 2-year EFS and OS rates were 53.9±8.9% and 66.3±8.4%, respectively. Median EFS was 15.7 months (95% CI: 0-56.1); median OS was not reached. Conversion to operable status after ≥3 neoadjuvant cycles, postoperative mediastinal lymph node involvement, and angiolymphatic invasion were associated with worse EFS and OS.

Conclusions: Neoadjuvant therapy offers long-term survival potential for select patients with locally advanced NSCLC. However, requiring ≥3 cycles for resectability, as well as the presence of postoperative mediastinal lymph node involvement and angiolymphatic invasion, are associated with poorer outcomes. These factors may help identify patients who could benefit from more aggressive treatment strategies or closer surveillance

Table 1. Factors associated with event-free and overall survival

Factors	2-year EFS	p	2-year OS	p
Neoadjuvant therapy cycles <3 *vs.* ≥3	85,7±13,2 *vs.* 43,8±10,2	**0,012**	100,0±0,0 *vs.* 55,7±10,1	**0,041**
Postoperative mediastinal lymph node involvement absent *vs.* present	67,6±10,1 *vs.* 27,1±14,8	**0,013**	81,6±8,3 *vs.* 36,3±15,4	**0,017**
Angiolymphatic invasion absent *vs.* present	65,4±9,3 *vs.* 15,6±14,2	**0,015**	76,7±8,3 *vs.* 31,1±17,9	0,071

* Survival rates are expressed as percentages with corresponding standard errors, and the P values were calculated using the Log-rank test.
Abbreviations: EFS, Event-free Survival; OS, Overall Survival.

Keywords: Locally advanced NSCLC, Neoadjuvant, outcome

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .37 Neoadjuvant Chemoimmunotherapy in Resectable NSCLC. Real-World Evidence From a Spanish Multicenter Cohort

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Introduction: Neoadjuvant chemoimmunotherapy (N-CT-IO) has become a standard approach for resectable non-small cell lung cancer (rNSCLC), showing significant improvements in pathological response and survival. The CheckMate 816 trial demonstrated that adding nivolumab to chemotherapy significantly improved pathological complete response (pCR) and event-free survival (EFS) over chemotherapy alone. NADIM I and II confirmed efficacy in stage IIIA NSCLC in the Spanish setting. More recently, KEYNOTE-671 supported perioperative pembrolizumab in stage II-IIIB rNSCLC. However, real-world (RW) data on clinical and molecular characteristics, treatment patterns, and outcomes remain limited.

Methods: We conducted a multicenter retrospective study of 82 patients with stage IB-IIIC rNSCLC treated with N-CT-IO across 9 Spanish centers. Clinical, pathological, and molecular features, including PD-L1 status and KRAS mutations, were collected. Pathological response and survival outcomes were assessed. EFS and overall survival (OS) were estimated using Kaplan-Meier curves, with subgroup analyses based on PD-L1 expression, molecular alterations, and baseline LIPI score.

Results: Median age was 64.7 years; 67% were male; 97.6% had ECOG 0-1. Most patients had stage IIIA (62.2%), with adenocarcinoma (54.9%) and squamous histology (41.5%). PD-L1 expression was <1% in 23.4%, 1-49% in 40.3%, and ≥50% in 36.4%. KRAS mutations were found in 45% of tested cases. The most common neoadjuvant regimen was carboplatin-paclitaxel-nivolumab (61%). Grade ≥3 toxicity occurred in one patient (1.2%). Surgery was performed in 85.4% (N=70), with a pCR rate of 32.9% (N=27). Among 42 patients with N2 disease, 83% underwent resection. pCR rates were similar across PD-L1 groups (<1%: 35.3%; 1-49%: 38.5%; ≥50%: 43.5%; p=0.865) and KRAS status (mutant vs wild-type: 33.3% vs 31.2%). pCR was 38.5% in patients with any molecular alteration vs 25% in those without. Favorable LIPI score was associated with higher pCR (41.3%) compared to intermediate/poor scores. No statistically significant differences in pCR were found across biomarker subgroups. At a median follow-up of 14.3 months, 1-year EFS and OS rates were 85.4% and 89.0%, respectively. Among resected patients, 7/70 relapsed. Median EFS was 12.9 months; median OS was not reached. Patients with PD-L1 ≥50% had the longest OS (42.1 months) with no deaths, while those with PD-L1 <1% had median OS of 28.3 months. Poor LIPI score was associated with shorter OS (19.3 months) compared to intermediate (43.9 months) or good (not reached) scores. There was a trend toward longer OS in patients without molecular alterations compared to those with at least one (p=0.23). None of these differences were statistically significant.

Conclusions: This multicenter RW analysis confirms the feasibility and efficacy of N-CT-IO in rNSCLC in routine clinical practice. Pathological and survival outcomes align with clinical trials, supporting its implementation as standard of care.

Keywords: Neoadjuvant

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .38 Identifying Risk Factors for Recurrence in Non-Small Cell Lung Cancer Patients With Pcr After Neoadjuvant Immunochemotherapy

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Introduction: In non-small cell lung cancer (NSCLC), achieving a pathologic complete response (pCR) following neoadjuvant immunochemotherapy is typically associated with a favorable prognosis. However, even patients with pCR remain at risk of recurrence after surgery. The factors contributing to recurrence in these patients have not yet been extensively investigated.

Methods: A retrospective analysis was conducted on 116 patients with NSCLC who achieved pCR after neoadjuvant chemoimmunotherapy. Among them, bulk RNA sequencing was performed on preoperative specimens, and multiplex immunofluorescence was conducted on postoperative specimens. Preoperative PET-CT scans and PD-L1 expression were also evaluated. The presence of treatment response in postoperative lymph nodes suggested lymph node metastasis before treatment.

Results: During the follow-up period, 12 patients experienced recurrence or died from tumor-related causes, while 1 patient died from a second primary cancer. RNA sequencing of preoperative specimens revealed that downregulation of ITGA8, NRG1, PLEKHG6, and PLA2G4C was significantly associated with recurrence (figure 1A). This association was further confirmed through univariate survival analysis (figure 1B). Although immune-related gene expression profile (GEP) scores were not related to recurrence (figure 1C), cancer-associated fibroblasts, neutrophils, and epithelial-mesenchymal transition were found to be significantly associated with recurrence (figure 1D). Higher standard uptake values (SUV) on preoperative PET-CT scans (cutoff = 12.9) (figure 2A) were associated with poorer survival ($p = 0.036$) (figure 2B). The presence of lymph node metastases before treatment was also significantly related to recurrence ($p < 0.001$). In contrast, PD-L1 expression levels were not associated with recurrence ($p = 0.704$). The immune microenvironment in postoperative specimens, including tertiary lymphoid structures, was not associated with prognosis.

Conclusions: Patients with high preoperative SUV values and lymph node metastasis, despite achieving pCR following neoadjuvant immunochemotherapy, remain at a significantly higher risk of recurrence.

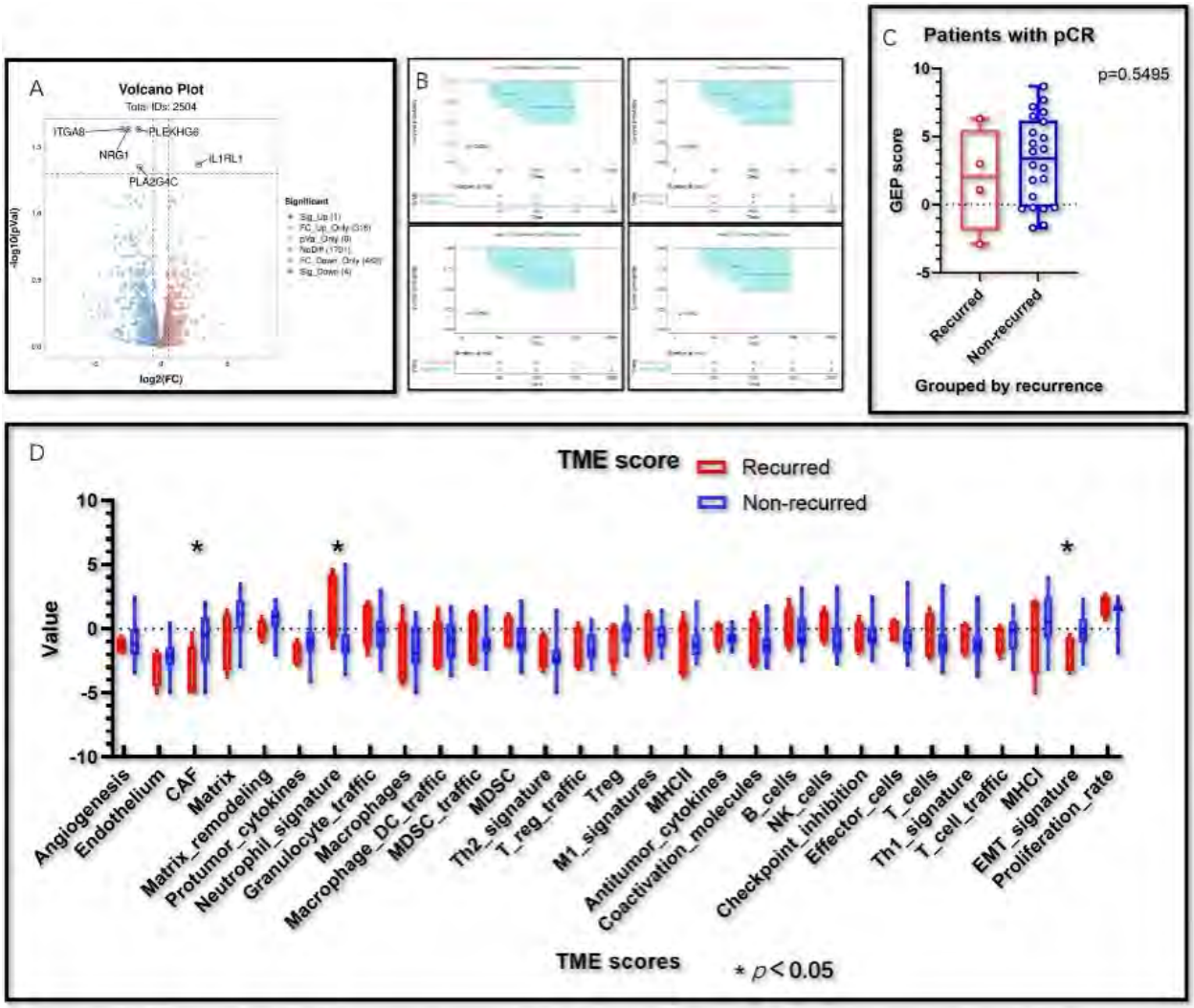

Figure 1. (A) Volcano plot of RNA sequencing revealed 5 differentially expressed genes between patients with recurrence and those without recurrence; (B) Four genes, namely ITGA8, NRG1, PLEKHG6, and PLA2G4C, were significantly associated with prognosis (univariate survival analysis); (C) Immune-related gene expression profile (GEP) scores were not associated with recurrence; (D) Tumor microenvironment (TME) scores indicated that cancer-associated fibroblasts, neutrophils, and epithelial-mesenchymal transition (EMT) were significantly associated with recurrence.

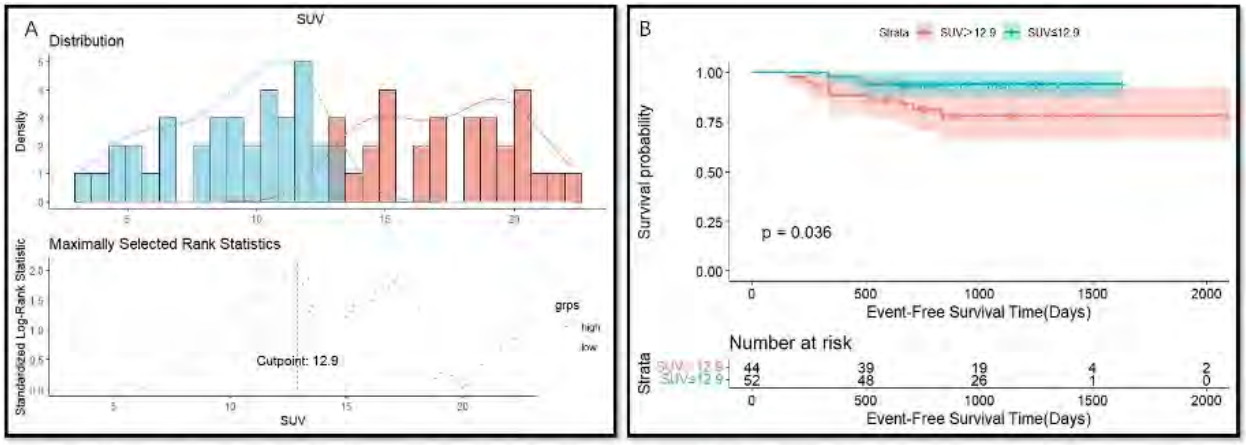

Figure 2. (A) The optimal cut-off value for survival analysis based on SUV from PET-CT scans, with the highest peak indicating the optimal cut-off point; (B) Kaplan–Meier survival curves stratified by the SUV cut-off value, demonstrating a significant difference between the two groups.

Keywords: Neoadjuvant Immunochemotherapy, pathologic complete response, Risk Factors for Recurrence

P2.08 .39 Targeting CHCHD3-cGAS to Remodel Immunosuppressive Microenvironment in Lung Adenocarcinoma: Mechanism and Clinical Translation

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Introduction: A significant proportion of treatment-naive lung adenocarcinoma (LUAD) patients exhibit intrinsic resistance to neoadjuvant chemoimmunotherapy (N=816 trial cohort), underscoring an unmet need for mechanism-driven therapeutic strategies.

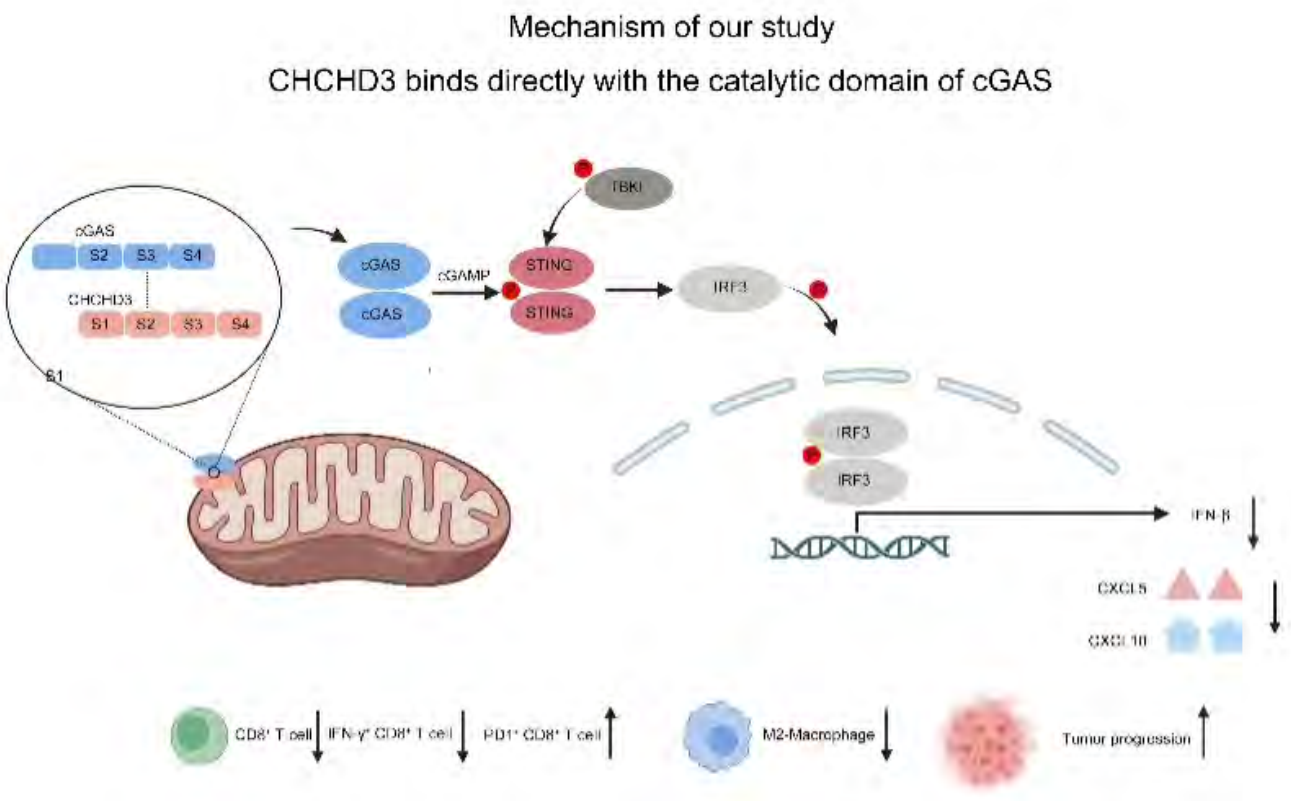
Methods: We conducted multi-omics profiling of 64 multicentric LUAD specimens from the CheckMate 816 trial cohort using single-cell RNA sequencing (scRNA-seq) and Visium spatial transcriptomics, enabling systematic identification of therapy-resistant subclones and spatially resolved immune-microenvironment dynamics. Experimental validation was performed through three complementary platforms:

1. Tet-op-hEGFR-TD/CC10rtTA bitransgenic mice for lineage tracing of EGFR-driven LUAD progression;
2. Humanized NSG mice (NOD.Cg-Prkdcscid IL2rgtm1Wjl/SzJ) with reconstituted human immune systems to model immunotherapy responses;
3. Patient-derived organoids (n=18) maintaining original tumor-stroma interactions for high-throughput drug screening.

Key techniques included: quantitative multiplex immunohistochemistry, luminescence-based cGAS-STING activity assays, high-content drug screening platforms integrating, CRISPR-Cas9 knockout validation, and PET-CT-guided pharmacodynamic monitoring with [18F]FDG to assess tumor metabolic response in real-time.

Results: Multi-omics profiling of 64 LUAD specimens (scRNA-seq, N=64; spatial transcriptomics, N=12) from CheckMate 816 clinical trials identified Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 3 (CHCHD3) as the top resistance driver. CHCHD3 overexpression induced immunosuppression in PDOs and EC mice ($p<0.01$). Mechanistically, the CHCHD3-S2 domain directly binds to the catalytic core of cGAS, reducing cytosolic cGAS by 68±5% ($p<0.001$) and inhibiting downstream chemokines production. CHCHD3 knockout upregulated CXCL5/CXCL10, enhancing CD8+T cells and macrophages infiltration, which sensitized immunotherapy. Drug screening identified TN4510 as a dual-target inhibitor binding CHCHD3-S2 and cGAS-S3 domains. Combining TN4510 with anti-PD-1 and chemotherapy synergistically inhibited tumor growth in humanized NSG mice (65% reduction vs. control, $p<0.001$).

Conclusions: CHCHD3 drives immunotherapy resistance by mitochondrial sequestration of cGAS and suppression of the cGAS-STING axis. Targeting CHCHD3 with TN4510 restores antitumor immunity and enhances neoadjuvant therapy efficacy in LUAD, providing a clinical strategy for treatment-refractory patients.



Keywords: lung adenocarcinoma, neoadjuvant immunotheraoy combined with chemothera, cGAS-STING pathway

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .41 The Influence of Perioperative Chemoimmunotherapy on Surgery for Resectable Non-Small Cell Lung Cancer:A Systematic Review and Meta-Analysis

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Introduction: Perioperative chemoimmunotherapy has demonstrated significant improvements in event-free survival (EFS) and pathological complete response (pCR) rates compared to chemotherapy in patients with early-stage or locally advanced resectable non-small cell lung cancer (NSCLC). However, its impact on surgical procedures and perioperative outcomes remains to be fully elucidated.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the comprehensive effects of perioperative chemoimmunotherapy on surgical outcomes. A systematic search was performed across PubMed, Web of Science, Cochrane Library, and Embase to identify published phase 2/3 RCTs investigating perioperative immunotherapy combined with chemotherapy (chemoimmunotherapy) versus chemotherapy alone in resectable NSCLC. Study outcomes included: rate of undergoing surgery, R0 resection rate, pathological downstaging, surgical approach and type, surgery cancellation or delay rate, operative duration, postoperative hospitalization duration, and surgical complications. Random-effects model were used for meta-analysis.

Results: Eight RCTs involving 3387 patients were included, two trials evaluated neoadjuvant therapy and six assessed neoadjuvant plus adjuvant regimens. Compared to chemotherapy, chemoimmunotherapy significantly improved the rate of undergoing surgery (RR = 1.05, 95% CI 1.01-1.10, P = 0.015) and R0 resection rate (RR = 1.04, 95% CI 1.02-1.07, P = 0.001), with no significant differences in R1 or R2 resection rate. Perioperative chemoimmunotherapy promoted pathological downstaging (RR = 1.37, 95% CI 1.10-1.69, P = 0.004), facilitating more definitive surgical interventions. Patients receiving chemoimmunotherapy were more likely to undergo minimally invasive procedures and limited resections (Table). No significant intergroup differences were observed in surgery cancellation/delay rates, operative time, or postoperative hospitalization duration (Table). Importantly, perioperative chemoimmunotherapy did not increase the risk of surgical complications, neither any grade nor grade ≥ 3 surgery-related adverse events (Table).

Conclusions: This meta-analysis demonstrates that integrating immunotherapy into perioperative treatment does not compromise surgical safety but enhances surgical feasibility through improved resection completeness and pathological downstaging. These findings support the dual role of perioperative immunotherapy in optimizing both efficacy and surgical outcomes for resectable NSCLC.

Table: Pooled results of meta-analysis

Outcomes	Pooled effect (95% CI)	*P* value
Rate of undergoing surgery	RR = 1.05 (1.01-1.10)	0.015
R0 resection rate	RR = 1.04 (1.02-1.07	0.001
Pathological downstaging	RR = 1.37 (1.10-1.69)	0.004
Surgical approach	Minimally invasive: RR = 1.11 (0.97-1.26)	0.131
	Thoracotomy: RR = 0.94 (0.84-1.05)	0.278
	Minimally invasive to Thoracotomy: RR = 0.73 (0.47-1.14)	0.165
Surgical type	Wedge resection: RR = 0.74 (0.17-3.31)	0.696
	Segmentectomy: RR = 1.91 (0.42-8.66)	0.401
	Sleeve lobectomy: RR = 0.74 (0.38-1.44)3	0.372
	Lobectomy: RR = 1.08 (1.02-1.15)	0.006
	Pneumonectomy: RR = 0.80 (0.65-0.98)	0.031
	Bilobectomy: RR = 0.71 (0.53-0.94)	0.018
	Lymph node dissection only: RR = 1.27 (0.10-16.49)	0.856
Surgery cancellation	Overall: RR = 0.68 (0.40-1.16)	0.155
	Due to PD: RR = 0.58 (0.32-1.08)	0.085
	Due to AEs: RR = 1.55 (0.74-3.28)	0.249
Surgery delay	Overall: RR = 1.18 (0.90-1.54)	0.244
	Due to AEs: RR = 1.44 (0.60-3.44)	0.412
Operative duration	WMD = -1.11 (-25.40-23.17)	0.928
Postoperative hospitalization duration	WMD = -0.01 (-0.97-0.95)	0.979
Surgical complications	Any grade AEs: RR = 1.00 (0.93-1.08)	0.948
	Grade ≥ 3 AEs: RR = 1.09 (0.87-1.37)	0.465

RR: Risk Ratios, AEs: Adverse Events, WMD: Weighted Mean Differences.

Keywords: perioperative chemoimmunotherapy, Resectable NSCLC, Influence on sugery

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .42 Impact of Delayed Initiation of Adjuvant Chemotherapy on Overall Survival Among Patients With Non-Small Cell Lung Cancer

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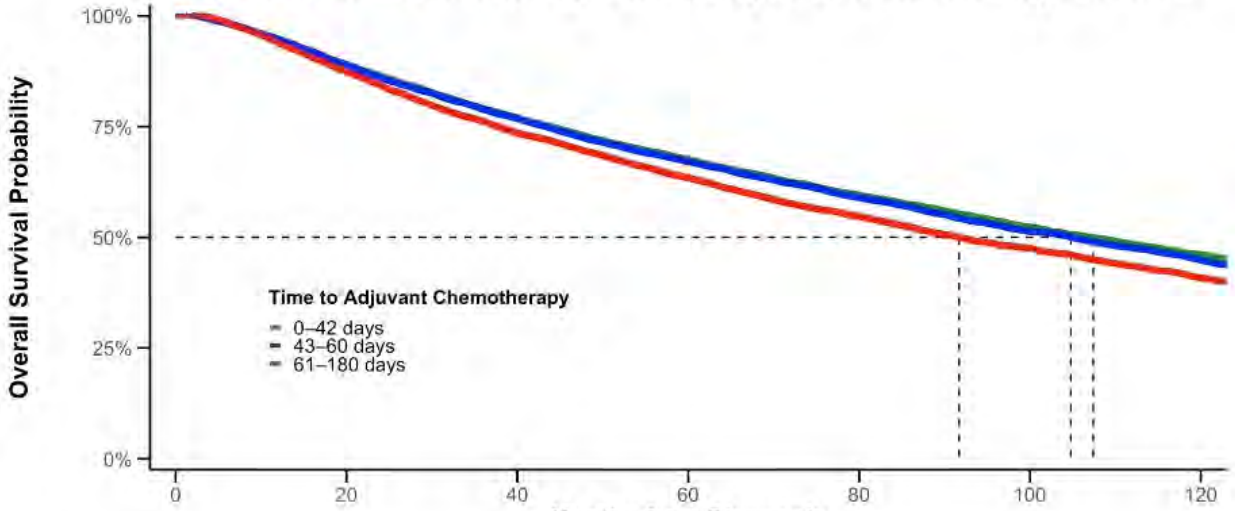
Introduction: Clinical trials included in the landmark LACE Bio analysis mandated adjuvant chemotherapy (AC) initiation 6-8 weeks after complete resection of non-small cell lung cancer (NSCLC); however, there are no data defining optimal AC timing in this population. This study aimed to evaluate whether delayed AC (initiation >60 days[d] after surgery) impacts overall survival in NSCLC.

Methods: We conducted a retrospective analysis of patients diagnosed with NSCLC between 2010-2021 in the National Cancer Database (NCDB). Inclusion criteria required complete resection by lobectomy or greater and receipt of AC 0-180d after surgery. Overall survival (OS) was evaluated using Kaplan-Meier (KM) method. Multivariate logistic regression was used to evaluate odds of 5-year mortality for patients with adequate follow up (diagnosed 2010-2017), adjusted for key sociodemographic and clinical characteristics.

Results: Of 28,581 patients who met inclusion criteria, 9,473 (33.0%) initiated AC 0-42d after surgery, 10,343 (36.0%) 43-60d, 8,765 (30.7%) 61-180d. KM curves for the entire cohort (n=28,581) showed significantly different survival among these groups (log-rank p<0.001); median OS for 0-42d was 107.4mo (95%CI:102.5-111.8), 43-60d was 104.8mo (95%CI:100.8-108.3), and 61-180d was 91.7mo (95%CI:88.3-95.6). Among patients with adequate 5 year follow up data (n=17,680) the adjusted odds of mortality at 5 years with delayed AC (60-180d) was 1.17 (95%CI:1.09-1.26, p<0.001). Higher stage, increasing Charlson comorbidity score, and treatment at a community center were also associated with higher 5-year mortality while female sex, Asian race and squamous cell histology associated with lower adjusted odds of mortality (Table 1).

Conclusions: Delayed AC >60d after NSCLC resection is associated with inferior OS and 17% higher odds of 5-year mortality. While some literature suggests that patients may still benefit from delayed AC compared to none, our data indicate that timely initiation of AC (≤60d postoperatively) is associated with improved OS.

Figure 1. Overall Survival by Time to Adjuvant Chemotherapy Initiation



at risk							
0–42 days	9473	8140	5956	4116	2689	1600	823
43–60 days	10343	8839	6425	4505	2951	1762	954
61–180 days	8765	7367	5218	3569	2270	1326	678

Table 1: Multivariate logistic regression of odds of mortality at 5 years post-diagnosis (n=17,434)

	n	(%)	aOR (CI)	*p* value
Age at diagnosis, median (IQR)	65	(13)	1.02 (1.01–1.02)	<0.001
Sex				
Male	8,775	(50.3)	Ref.	
Female	8,659	(49.7)	0.75 (0.70–0.80)	<0.001
Race				
White	14,672	(84.2)	Ref.	
Black	1,647	(9.4)	0.99 (0.88–1.10)	0.800
Hispanic	460	(2.6)	0.89 (0.72–1.09)	0.261
Asian	437	(2.5)	0.63 (0.50–0.79)	<0.001
Other/unknown	218	(1.3)	0.99 (0.74–1.32)	0.972
Insurance				
Private	6,503	(37.3)	Ref.	
Medicare	9,064	(52.0)	1.32 (1.22–1.44)	<0.001
Medicaid	1,110	(6.4)	1.40 (1.22–1.60)	<0.001
Other/unknown	757	(4.3)	1.17 (0.99–1.38)	0.061
Charlson Comorbidity Index				
0	9,346	(53.6)	Ref.	
1	5,471	(31.4)	1.14 (1.06–1.22)	<0.001
2	1,923	(11.0)	1.41 (1.27–1.56)	<0.001
3+	694	(4.0)	1.66 (1.41–1.94)	<0.001
Year of Diagnosis				
2010-2012	5,941	(34.1)	Ref.	
2013-2015	6,725	(38.6)	0.92 (0.85–0.99)	0.025
2016-2017	4,768	(27.3)	0.88 (0.81–0.96)	0.003
Facility Type				
Academic	5,945	(34.1)	Ref.	
Comprehensive community	6,748	(38.7)	1.10 (1.02–1.18)	0.016
Integrated network	3,751	(21.5)	1.02 (0.93–1.11)	0.702
Community	907	(5.2)	1.43 (1.24–1.66)	<0.001
Unknown	83	(0.5)	1.24 (0.72–2.06)	0.410
Histology				
Adenocarcinoma	10,901	(62.5)	Ref..	
Squamous cell	5,248	(30.1)	0.81 (0.75–0.87)	<0.001
Adenosquamous	473	(2.7)	1.39 (1.15–1.68)	<0.001
Other NSCLC	812	(4.7)	1.26 (1.08–1.46)	0.003
Clinical Stage‡				
IA1	168	(1.0)	Ref.	
IA2	1,674	(9.6)	1.11 (0.78–1.61)	0.569
IA3	1,941	(11.1)	1.39 (0.98–2.01)	0.071
IB	1,734	(9.9)	1.14 (0.80–1.65)	0.479
IIA	1,772	(10.2)	1.08 (0.76–1.56)	0.688
IIB	6,580	(37.7)	1.45 (1.03–2.07)	0.039
IIIA	2,956	(17.0)	1.84 (1.30–2.65)	<0.001
IIIB	565	(3.2)	2.21 (1.51–3.27)	<0.001
IIIC	44	(0.3)	2.30 (1.14–4.64)	0.019
Surgery Type				
Lobectomy	12,998	(74.6)	Ref.	
Bilobectomy	1,946	(11.2)	1.16 (1.05–1.29)	0.003
Pneumonectomy	1,601	(9.2)	1.40 (1.25–1.56)	<0.001
Extended Lobectomy δ	889	(5.1)	1.27 (1.10–1.46)	<0.001
Time to Adjuvant Chemotherapy				
0-60 days	12,094	(69.4)	Ref.	
61-180 days	5,340	(30.6)	1.16 (1.08–1.24)	<0.001

Ref. = Reference; aOR = adjusted odds ratio of mortality at 5 years post diagnosis; CI = 95% confidence interval. ‡AJCC 8th Edition clinical stage group. δLobe or bilobectomy extended with chest wall, pericardium, diaphragm or not otherwise specified.

Keywords: adjuvant chemotherapy, non-small cell lung cancer, survival

P2.08 .43 Perioperative Adebrelimab Plus Chemotherapy in Patients With Resectable Stage II-III NSCLC: 4-Year Update From a Phase 1b/3 Trial

Y-L. Wu[1], W. Yan[2], W-Z. Zhong[1], Y-H. Liu[1], Q. Chen[3], W. Xing[4], Q. Zhang[5], L. Liu[6], D. Ge[7], K. Chen[2], F. Yang[8], X. Lin[9], Y. Huang[9], L. Song[9], W. Shi[9]
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Introduction: In the phase 1b part of a phase 1b/3 trial (NCT04316364), neoadjuvant adebrelimab, a novel humanized IgG4 anti-PD-L1 monoclonal antibody, combined with chemotherapy has demonstrated favorable surgical outcomes, with high rates of major pathological response (55.9%) and pathological complete response (29.7%) in patients with resectable NSCLC. Here, we report 4-year updated outcomes following perioperative adebrelimab and chemotherapy.

Methods: In the phase 1b part, patients with previously untreated, resectable stage II and III (IIIA and T3N2M0 IIIB) NSCLC per AJCC 8th edition and without EGFR/ALK alterations, were enrolled. Patients received neoadjuvant treatment with 3 cycles of intravenous adebrelimab (20 mg/kg; day 1, Q3W), nab-paclitaxel (100 mg/m2; days 1, 8, and 15, Q3W), and carboplatin (area under the curve 5 mg/mL per min; day 1, Q3W), followed by surgical resection and 16 additional cycles of adjuvant adebrelimab (20 mg/kg; day 1, Q3W). Survival outcomes, including event-free survival (EFS), disease-free survival (DFS) and overall survival (OS), were secondary endpoints.

Results: 37 patients were enrolled and initiated study treatment; among them, 34 underwent surgery and 31 received adjuvant therapy. As of data cutoff (Jan.11, 2025), median follow-up was 47.0 mo (range 4.4-53.0). Sustained clinical benefits were observed overtime (Table 1), with 4-year EFS rate of 71.4% (95% CI 52.0-84.1), DFS rate of 72.1% (95% CI 53.0-84.5), and OS rate of 81.1% (95% CI 64.4-90.5). Across all treatment phases, 29 (78.4%) patients had grade ≥3 treatment-related adverse events (TRAEs) and 10 (27.0%) had treatment-related serious AEs. All grade ≥3 TRAEs occurring in ≥10% of patients were hematological toxicities. There were no treatment-related deaths.

Conclusions: With extended follow-up, perioperative adebrelimab and chemotherapy led to clinically meaningful survival benefits in patients with resectable stage II-III NSCLC. The safety profile remained consistent with previous reports, with no new safety signals identified. The randomized, double-blind, placebo-controlled phase 3 part of the trial is ongoing, with primary results expected soon.

Table 1. Survival outcomes

	Patients (n=37)		
	EFS*	DFS*,†	OS
Event, n (%)	10 (27.0)	10 (29.4)	8 (21.6)
Event rate (95% CI), %			
1-year	87.9 (70.9–95.3)	85.3 (68.2–93.6)	94.6 (80.1–98.6)
2-year	81.8 (63.9–91.4)	82.2 (64.7–91.6)	89.2 (73.7–95.8)
3-year	75.4 (56.7–86.9)	75.9 (57.5–87.2)	83.8 (67.4–92.4)
4-year	71.4 (52.0–84.1)	72.1 (53.0–84.5)	81.1 (64.4–90.5)

* Based on investigator assessment. † Assessed in patients who underwent surgery (n=34).

Keywords: Resectable NSCLC, Immunotherapy, Peri-operative

P2.08 .44 Adverse Cardiovascular Events Related to Immune Checkpoint Inhibitors in Staging IB-IIIb Non-Small Cell Lung Cancer: A Real-World Study

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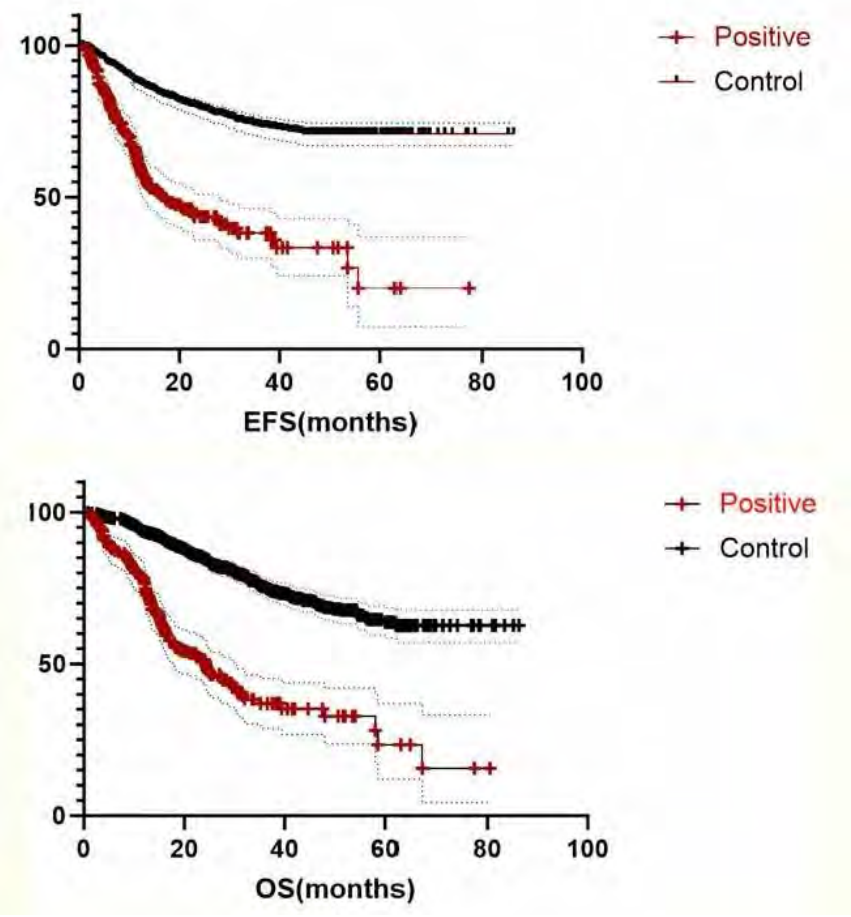
Introduction: The development of novel immune checkpoint inhibitors (ICIs) has improved early-stage or local-regional non-small cell lung cancer (NSCLC) outcomes but may result in cardiovascular toxicities. Traditional approaches to clinical trial safety evaluation have limitations in their ability to detect signals of cardiovascular risk. This study aims to evaluate immune-related adverse cardiovascular events in a real-world study.

Methods: This is a retrospective study of staging IB-IIIB NSCLC patients who were treated with immunotherapy as perioperative treatment or induction therapy or consolidation therapy at the Guangdong Provincial People's Hospital from 2018 to 2023. Cardiotoxicity was assessed using the CTCAE V5.0 criteria. We also explore the association between temporal elevations of cardiac biomarkers with disease trajectory and outcomes.

Results: In total, 1160 patients were included (85.7% male and 14.3% female), with a mean age of 61 years [23-92]. The percentage of patients with any grade cardiotoxicity was 16.5%; 87.5% of patients with previous heart disease (N=40) were diagnosed with cardiotoxicity, and 13.9% of those without previous heart disease (N=1120) were diagnosed with cardiotoxicity. Cardiac arrest and cardiac failure led to death in 45 cases. The median time from the initiation of treatment until the cardiac event was 45 days [14-96]. The most frequent toxicity was arrhythmias in 18.7% of patients, followed by coronary atherosclerotic heart disease in 15.9% of patients. The percentage of patients with myocarditis was 1.5%. Within 72 hours of admission, the increased cTnT, cTnI, and CK values compared with upper reference limits were associated with ICI myocarditis. Overall, ICI treatment increased the risk of cardiotoxicity compared with control groups (p-value<0.0001). Patients without adverse cardiovascular events had better event-free survival and overall survival.

Conclusions: These findings highlight that ICI-associated cardiovascular adverse events, particularly in patients with pre-existing heart disease, substantially impact NSCLC prognosis. Our results emphasize the critical need for enhanced cardiovascular monitoring protocols during ICI therapy. The identification of early biomarker signatures, as demonstrated in this study, may enable timely detection and intervention for cardiotoxicity. Future research should focus on validating sensitive predictive biomarkers and developing risk-stratified surveillance strategies.



Keywords: Adverse Cardiovascular Events, Immune Checkpoint Inhibitors, Non-small Cell Lung Cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .45 Immune Gene Guided Multi-Scale Pathomic Signature in H&E-Wsi Predict Neoadjuvant Immunotherapy Response in NSCLC

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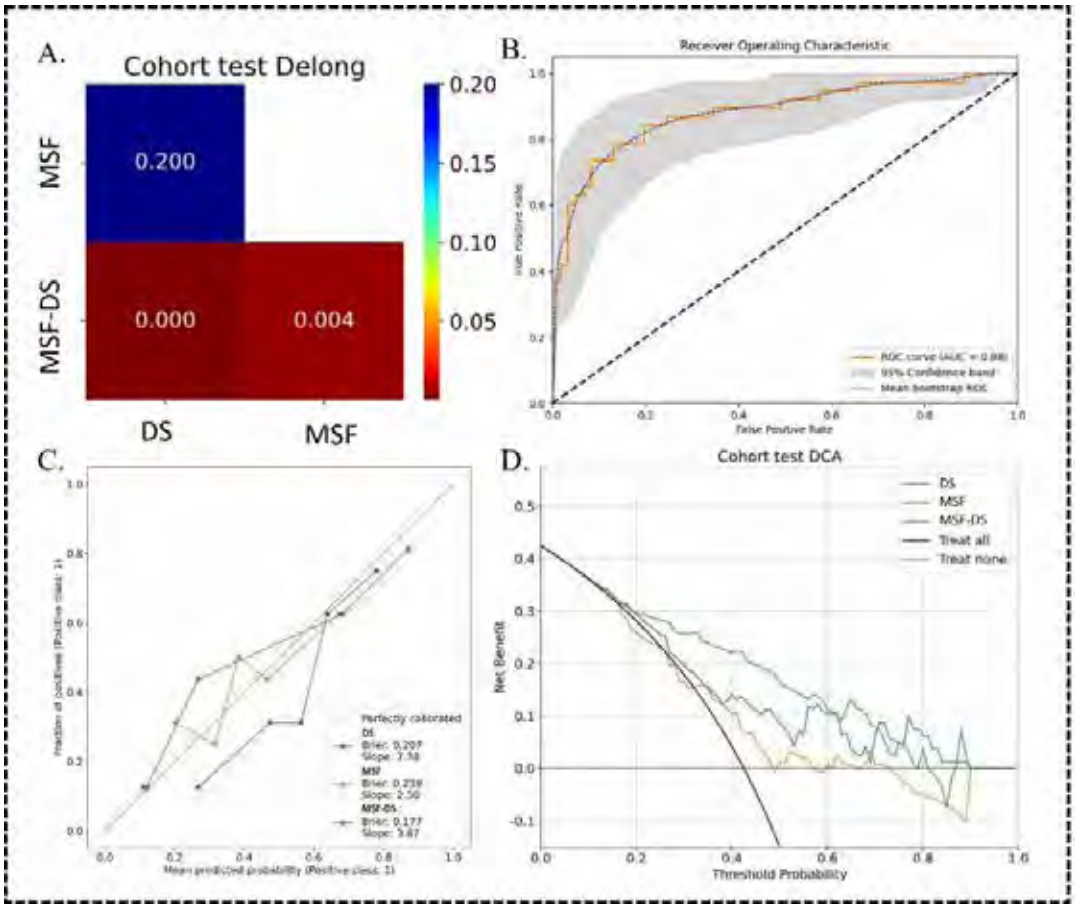
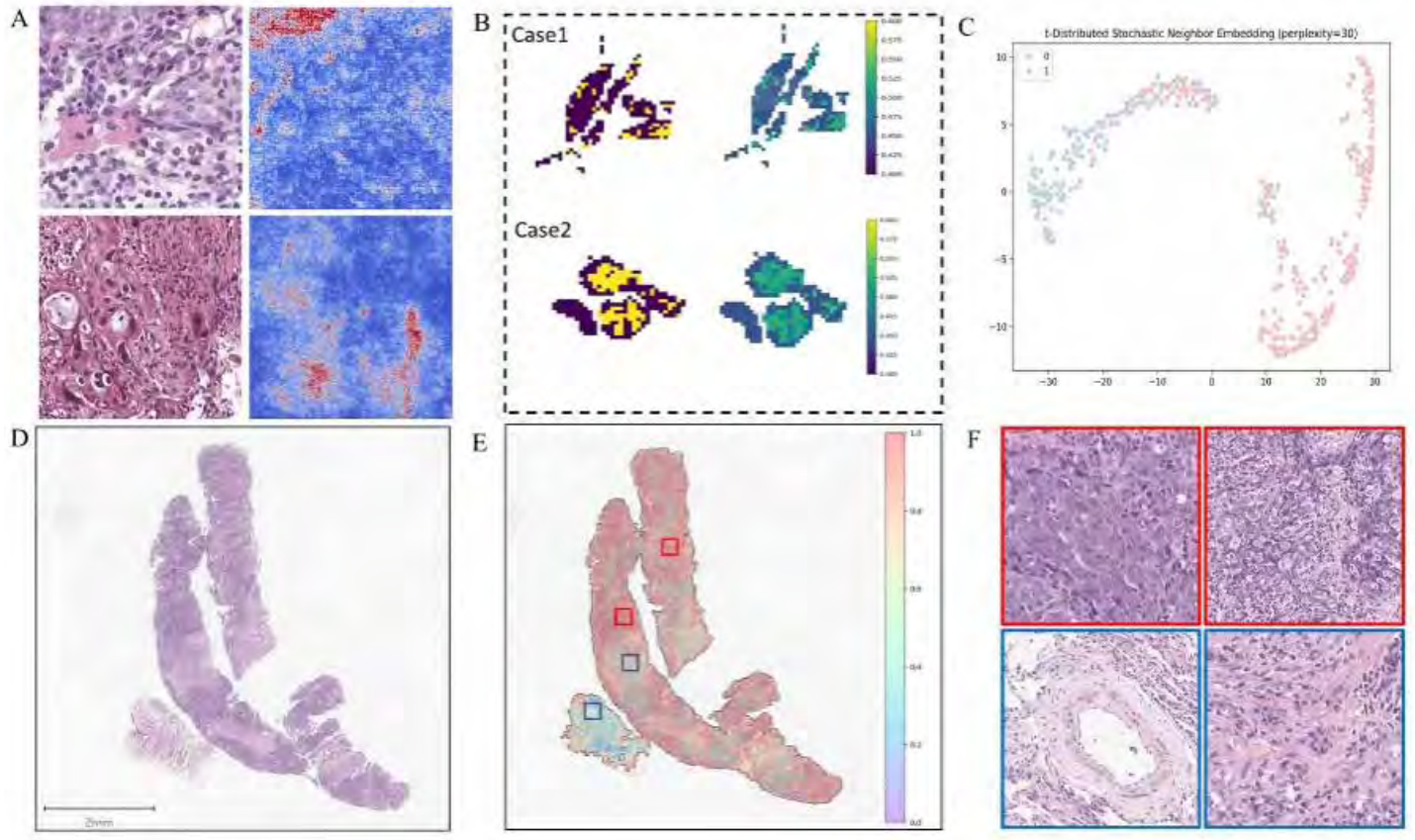
Introduction: Neoadjuvant immune-chemo therapy (NICT) has revolutionized resectable non-small cell lung cancer (NSCLC) treatment, yet heterogeneous pathological responses (18-83% MPR rates) and unresponsiveness in 30% of patients necessitate precise predictive tools. This study aims to develop a multi-scale deep learning model integrating H&E whole-slide image (WSI) features and immune-related gene expression profiles to predict pathological response to NICT.

Methods: A retrospective cohort of 260 stage I-III NSCLC patients (2019-2024) receiving NICT followed by resection and 465 patients from TCGA-LUAD was analyzed. The multi-scale fusion model (MSF-DS) combined: 1) WSI-derived morphological features via a Swin Transformer-based encoder pretrained on 15 million image tiles, 2) predicted expression of 135 immune dysfunction/exhaustion-related genes using ResNet50-autoencoder with attention mechanisms. Features were fused through a lightweight Transformer classifier. Model performance was evaluated using AUC, sensitivity, specificity, calibration curves, and decision curve analysis (DCA).

Results: The MSF-DS model achieved superior performance in the independent test set (n=65), with an AUC of 0.882 (95% CI:0.803-0.947), significantly outperforming MSF-only (AUC=0.776, P<0.001) and DS-only (AUC=0.629, P<0.001) models. Calibration curves demonstrated excellent agreement between predicted probabilities and observed frequencies (Brier score=0.177), outperforming single-modality models (MSF:0.241; DS:0.329). Key metrics included sensitivity=60.5%, specificity=96.7%, and PPV=92.0%. The model maintained robust prediction in PD-L1-negative subgroups (AUC=0.897). Saliency maps revealed decision-critical regions aligned with tumor nuclei atypia and lymphocyte infiltration patterns. Gene expression predictions correlated with T-cell activation markers (CXCL10, CD8B; Spearman ρ=0.41-0.58). DCA demonstrated clinical net benefit across 15-85% threshold probabilities.

Conclusions: This study establishes the first interpretable immune gene guided multi-scale model leveraging histomorphological patterns from pretreatment biopsies to predict NICT response in NSCLC. By bridging tissue architecture with transcriptic information, MSF-DS provides clinically actionable predictions (AUC>0.88) and visualizes biologically plausible decision drivers, offering a transformative tool for personalized neoadjuvant therapy stratification.





Keywords: Neo-adjuvant immunotherapy, Pathomics, Non-small cell lung cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .46 COPD Reshape the Tumor Microenvironments of NSCLC and Potentiate Antitumor Efficacy of Anti-PD-1 Therapy

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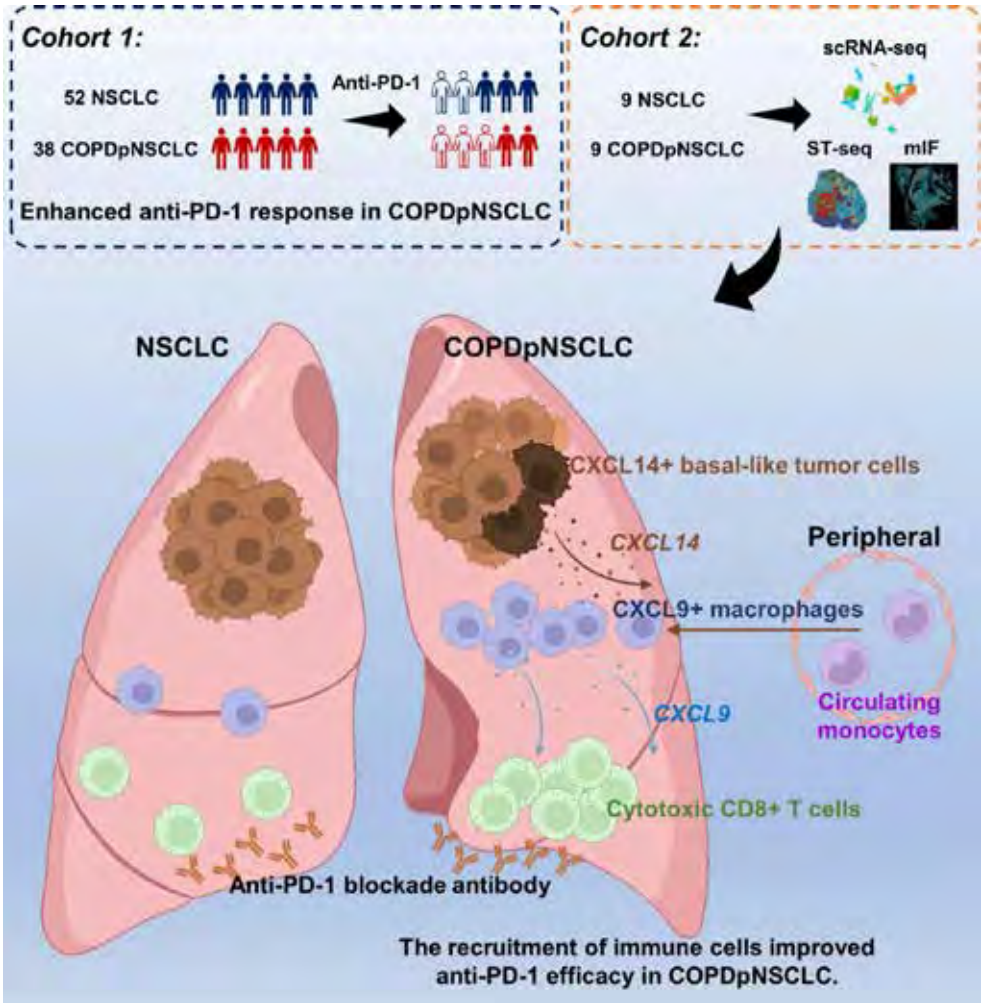
Introduction: Non-small cell lung cancer (NSCLC) patients with chronic obstructive pulmonary disease (COPD) have been reported to exhibit enhanced responses to anti-PD-1 therapy. However, the clinical association between COPD comorbidity and immunotherapy outcomes in NSCLC remains controversial, largely due to limitations in accurate COPD data collection. Furthermore, the underlying mechanisms driving these observations have not been fully elucidated.

Methods: We analyzed two independent cohorts of NSCLC patients receiving anti-PD-1 therapy. Cohort 1 consisted of 90 advanced NSCLC patients, rigorously stratified by COPD status based on comprehensive clinical evaluations including pulmonary function tests and imaging. Statistical analyses were performed to determine the impact of COPD on treatment response. In Cohort 2, we conducted integrated single-cell RNA sequencing and spatial transcriptomics on freshly resected tumor samples from 18 NSCLC patients with and without COPD to characterize the tumor microenvironment (TME) and identify key cellular drivers of immunotherapy efficacy.

Results: Our analysis of Cohort 1 demonstrated that NSCLC patients with COPD experienced significantly enhanced therapeutic responses to anti-PD-1 therapy, with COPD comorbidity emerging as a significant factor influencing treatment outcomes. In Cohort 2, multi-transcriptomic analyses revealed a distinct accumulation of CXCL14 basal-like tumor cells in NSCLC patients with COPD. These cells exhibited notable tumorigenic potential and were associated with the recruitment of CXCL9 macrophages within the TME. The presence of CXCL9 macrophages, known to enhance cytotoxic T cell activity, likely contributes to the improved response to anti-PD-1 therapy observed in this patient population.

Conclusions: Our findings identify the CXCL14-CXCL9 axis as a central mechanism driving the remodeling of the TME and enhancing the efficacy of anti-PD-1 therapy in NSCLC patients with COPD. These results underscore the critical need for accurate COPD data collection in cancer research and suggest that targeting this axis may provide novel therapeutic strategies to further optimize immunotherapy outcomes in this unique patient group.



Keywords: COPD, anti-PD-1, efficacy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .47 Lymphocyte Recovery and Risk for Immune Pneumonitis After Chemoradiation in Locally Advanced NSCLC

M. Satoskar, S. Zhao, K. Chian, N. Johns, A. Rudich, A. Khorasanchi, L. Wei, J. Gheeya, L. Roof, A. Alahmadi, R. Memmott, J. Kaufman, C. Presley, K. He, P. Shields, D. Carbone, M. Li, D. Owen
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Introduction: Consolidation durvalumab has played a pivotal role in the treatment of locally advanced non-small cell lung cancer (NSCLC) following concurrent chemoradiotherapy (CRT). Pneumonitis is a potentially severe adverse outcome of immunotherapy. In the landmark PACIFIC trial, one-third of patients who received durvalumab developed pneumonitis of any grade/etiology. There is limited evidence on biomarkers associated with pneumonitis risk especially after CRT. Lymphocytes play a role in the development of pneumonitis, and we hypothesized that fluctuations in absolute lymphocyte count (ALC) during CRT may be associated with immune checkpoint inhibitor (ICI) pneumonitis. In this study, we investigate the post-CRT lymphocyte recovery and its association with pneumonitis risk among patients receiving adjuvant durvalumab therapy.

Methods: This retrospective study included consecutive patients with unresectable Stage III NSCLC who underwent CRT followed by at least one dose of durvalumab at a single tertiary cancer center. Clinical data was extracted through review of electronic medical records. ALC was collected at nadir during CRT and approximately 30 days post-CRT. Lymphocytopenia was classified using the Common Terminology Criteria for Adverse Events V5. The diagnosis of pneumonitis was determined from review of radiology reports and medical oncology notes. Pneumonitis cases were further characterized as either certain ICI pneumonitis, or combined etiology of radiation and possible ICI pneumonitis. A competing risk model was used to evaluate the associations of post-CRT ALC, as well as the absolute change in ALC from nadir to post-CRT (absolute ALC recovery) with pneumonitis risk. Association between the presence of pneumonitis and overall survival (OS), calculated from durvalumab initiation to date of death or loss to follow-up, was also assessed using Cox proportional hazards model.

Results: This study included 117 patients with a mean age of 64.1 years, who received durvalumab within 12 weeks of completing CRT. The median ALC at nadir during CRT was 300 cells/uL (IQR: 200-450), increasing to 760 cells/uL (IQR: 510-1040) post-CRT. Among the 117 patients, 43 (37%) developed pneumonitis, including 13 cases of certain ICI pneumonitis (30%) and 30 cases of probable ICI pneumonitis (70%). Among the 43 patients with pneumonitis, the median time to onset of pneumonitis was 10.8 months. Post-CRT ALC was not associated with pneumonitis risk, however the absolute ALC recovery from nadir to post-CRT did show a positive trend towards significance. Every 10-unit increase in ALC was associated with a 0.8% higher risk of pneumonitis (HR=1.008; 95% CI: 1.000-1.017; p=0.05) after adjusting for age, ECOG performance status, histology, and PD-L1 expression. Median OS among patients with pneumonitis was 56.97 months and those without pneumonitis was 27.63 months; pneumonitis of any grade and cause was significantly associated with longer OS (p=0.018).

Conclusions: Absolute recovery in ALC from nadir during CRT to post-CRT (before durvalumab initiation) may be a predictor for pneumonitis risk in patients with advanced NSCLC receiving adjuvant durvalumab. The presence of pneumonitis was associated with longer OS. This may be related to lymphocyte count recovery resulting in improved immunotherapy response, although studies are warranted to understand the underlying mechanisms.

Keywords: pneumonitis, immunotherapy, lymphocyte recovery

P2.08 .48 Pacific Real-World Experience at Hospital Doce De Octubre

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Introduction: Historically, chemoradiotherapy (CRT) was the standard for treating unresectable stage III NSCLC, though outcomes were limited (median OS of 21.9 months). The PACIFIC trial significantly improved survival and progression-free survival (PFS), establishing a new standard of care. These findings have since been validated in real-world settings by the PACIFIC-R study. In line with this, a study was conducted to assess the experience with the PACIFIC regimen at our center.

Methods: This is a retrospective descriptive study that analyzed 24 patients with unresectable stage III NSCLC treated at Hospital 12 de Octubre between June 2018 and September 2024. All patients had ECOG 0-2 and any level of PD-L1 expression, receiving either concurrent or sequential chemoradiotherapy followed by durvalumab (10 mg/kg-every-2 weeks). The study evaluated treatment response (based on RECIST criteria), toxicity, progression patterns, and dosimetric variables such as V20 and mean lung dose. Statistical analysis was conducted using STATA version 18.

Results: Among the 24 patients analyzed (characteristics shown in Table 1), 67% received cCRT and 33% sCRT, with a median of 7.5 cycles of durvalumab (range: 1-26). The objective response rate was 54.2%. Median overall survival (OS) was 31.3 months (range: 3.1-66.5), and median progression-free survival (PFS) was 29.3 months (range: 2.2-66.5). Disease progression occurred in 11% of patients. At 5 years, OS and PFS rates were 45% and 29%, respectively. Pneumonitis was observed in 25% of patients—66% of which were grade 3—without correlation to lung dosimetric parameters. All patients received a mean lung dose below 20 Gy and a V20 <35%.

Conclusions: Our center's findings support the PACIFIC trial results, endorsing chemoradiotherapy followed by Durvalumab for unresectable NSCLC. Although OS was similar between concurrent and sequential CRT, the latter sowed poorer PSF (graph1). A high incidence of pneumonitis was observed, underscoring the importance of close patient monitoring.

Graph 1

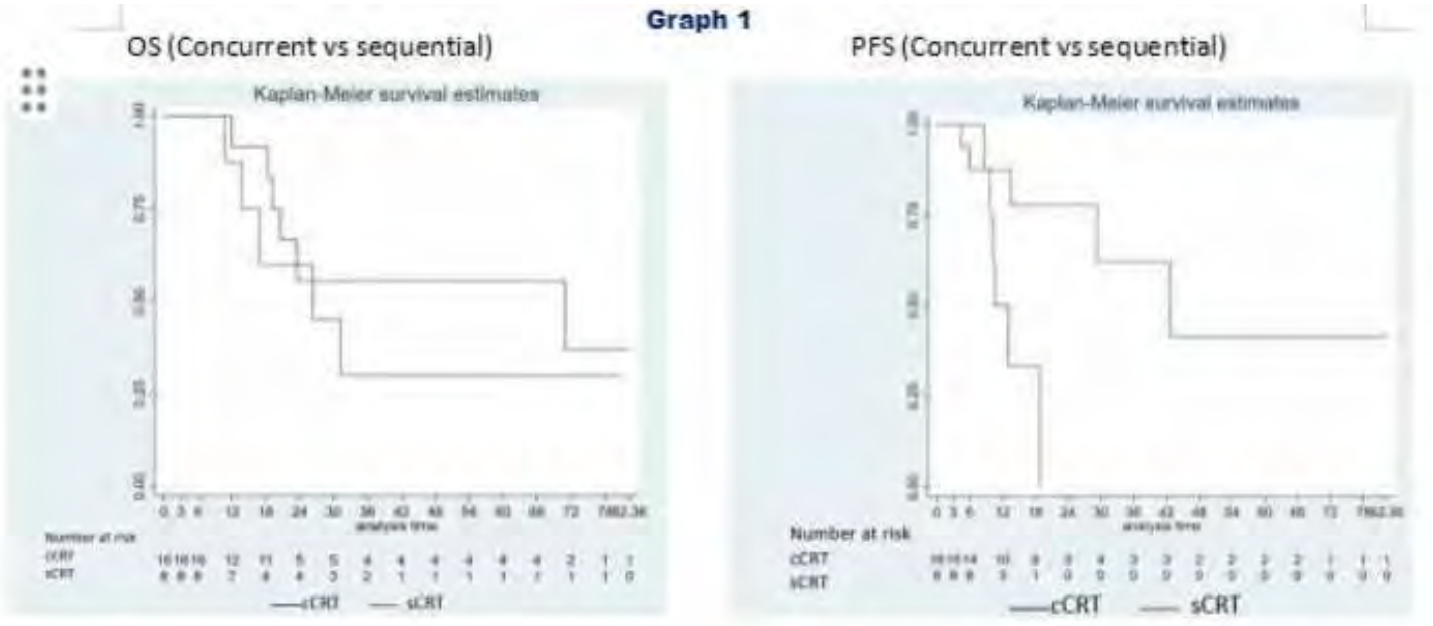

Table 1 : Clinical and Treatment Characteristics

Characteristic	Value
Sex, n (%)	
Female	7 (38.9%)
Male	11 (61.1%)
Age, median [IQR]	68 [60.0–74.0]
Age at diagnosis, median [IQR]	67.00 [61.0–72.0]
ECOG at diagnosis, n (%)	
0	3 (16.7%)
1	8 (44.4%)
2	7 (38.9%)
Initial T stage, n (%)	
T1	1 (5.6%)
T2	4 (22.2%)
T3	3 (16.7%)
T4	10 (55.6%)
Initial N stage, n (%)	
N1	1 (5.6%)
N2	13 (72.2%)
N3	4 (22.2%)
Type of therapy, n (%)	
Sequential	3 (16.7%)
Concurrent	15 (83.3%)
Lung doses, median [IQR]	
V20 Lungs (%)	23.4 [18.2–31.1]
MLD (Gy)	7.04 [5.02–10.52]
Number of durvalumab cycles, median [IQR]	7 [1–12]
RECIST 1.1 response at reassessment, n (%)	
CR (Complete Response)	1 (5.6%)
PR (Partial Response)	8 (44.4%)
SD (Stable Disease)	4 (22.2%)
PD (Progressive Disease)	5 (27.8%)
Progression, n (%)	10 (55.6%)
Systemic	8 (80%)
Local (tumor bed)	2 (20%)
Death (Exitus), n (%)	11 (61.1%)
Immune-related adverse events (irAEs), n (%)	9 (50%)
Most severe irAE grade, n (%)	
Grade 1	4 (22.2%)
Grade 2	3 (16.7%)
Grade 3	2 (11.1%)
Pneumonitis, n (%)	
Yes	3 (16.7%)
No	15 (83.3%)

Keywords: Unresectable stage III NSCLC, Pacific Trial, Real-world experience

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .49 Effect of the Immunological Circadian Rhythm on Treatment of Locally Advanced Non-Small Cell Cancer With Immunotherapy

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Introduction: Some studies, including a meta-analysis, observed that the circadian rhythm of immune cell's proliferation and destruction may influence progression-free and overall survival in metastatic cancer treated with immunotherapy (IO). This study aims to assess whether such differences persist in patients with locally advanced non-small-cell lung cancer (NSCLC) undergoing radical concurrent chemo/radiotherapy (CRT) and IO consolidation depending on the time of day of IO administration.

Methods: For this retrospective study, all the patients with histologically confirmed unresectable NSCLC PDL1 ≥1% treated with radical concurrent CRT and at least 1 cycle of IO consolidation (PACIFIC protocol) from 2018 to 2023 at three hospitals of the Institut Català d'Oncologia (ICO) were included. These patients were categorized depending on the most frequently time of IO administration in two groups: morning (receiving 50% or more doses before 3pm) or afternoon group (receiving less than 50% doses before 3 pm). Survival outcomes were estimated using Kaplan-Meier analysis and compared with the log-rank test. Progresion Free Surrvival (PFS) and Overall Survival (OS) were defined by RECIST criteria, and median follow-up was calculated using the Kaplan-Meier method.

Results: A total of 212 patients were identified. Median follow up 24 months. The mean age was 66.3 years (range 42-89) of which 165 (77.8%) were males, 113 (53.3%) were currently smokers and 116 (54.7%) presented squamous cell carcinoma histology. The morning group included 153 patients (72.2%), while the afternoon group included 59 patients (27.8%). Patients received a mean of 7.31 months (range 1-14) of consolidation IO after radical concurrent CRT wih a median follow up of 23 months. Progression-free survival (PFS) was significantly better in the morning group compared to the afternoon group. Median PFS was of 31 vs 19 months, Hazard Ratio 0.6294 (95% CI 0.4212-0.9404, p=0.0238). The 1-year and 3-year PFS rates were 70.2% vs. 60.2% and 48.7% vs. 32.8% respectively. Overall survival (OS) favoured the morning group but did not reach statistical significance. Median OS was 50 vs. 29 months, Hazard Ratio 0.6875 (95% CI 0.4585-1.031, p=0.070). The 1-year and 3-year OS rates were 80.4% vs. 72.9% and 57.6% vs. 33.0% respectively.

Conclusions: This is the first retrospective analysis in which has been observed that patients treated preferentially before 3pm exhibit a better disease control than those treated onwards in radical treatment with immunotherapy. Preferential treatment in the morning may enhance disease control and improve OS. These findings support the need for prospective clinical trials to further explore the impact of circadian timing on treatment outcomes.

Keywords: NSCLC, Immunotherapy, Circadian Rhythm

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .50 Tislelizumab With Chemotherapy as Neoadjuvant Therapy for Unresectable Stage III Lung Cancer: A Single-Arm, Phase II Trial

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Introduction: Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide. For patients with unresectable stage III NSCLC, traditional treatment methods have limited efficacy. Recently, the combination of immunotherapy and chemotherapy has shown potential benefits in conversion therapy of initial unresectable NSCLC. Tislelizumab has been approved for perioperative indications in resectable NSCLC in China, further highlighting its potential in conversion therapy. This study aims to evaluate the efficacy and safety of tislelizumab combined with chemotherapy as neoadjuvant therapy in patients with initial unresectable stage III NSCLC.

Methods: This prospective, single-arm, single-center clinical trial plans to enroll 30 patients with initial unresectable stage III NSCLC. Pts received neoadjuvant therapy of tislelizumab plus double platinum-based chemotherapy for 2-3 cycles (Q3W) followed by surgical resection. The primary endpoint was resectability rate. Secondary endpoints included pathology complete response (pCR), major pathological response rate (MPR), R0 resection rate and safety.

Results: As of February 28, 2025, eight pts with initial unresectable stage III NSCLC were enrolled. The median follow-up time was 19.2 months (range: 7.4-23.7). Among the 8 pts, 87.5% (7/8) completed 3 cycles of neoadjuvant therapy, and 12.5% (1/8) completed 2 cycles. All patients underwent surgery, achieving a surgical conversion rate of 100%. Preoperative imaging assessments revealed an objective response rate (ORR) of 75% and a disease control rate (DCR) of 100%. Postoperatively, three patients (37.5%) achieved complete pathological response (pCR), and all patients achieved major pathological response (MPR, 100%). 7 pts received sequential therapy with tislelizumab combined with chemotherapy following tislelizumab monotherapy, while 1 patient did not receive postoperative treatment. Three patients experienced recurrence or metastasis, and one of them died.

Conclusions: Tislelizumab combined with chemotherapy demonstrated significant efficacy and acceptable safety in patients with initial unresectable stage III NSCLC. This treatment regimen significantly improved surgical resection rates and pathological response rates, warranting further research and clinical application.

Keywords: Non-small cell lung cancer, Tislelizumab, Conversion therapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .51 Outcomes From a Phase II Study of Hypofractionated Chemoradiation and Consolidation Immunotherapy in Locally-Advanced NSCLC

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Introduction: Concurrent chemoradiation followed by immunotherapy for unresectable locally advanced non-small cell lung cancer (LA-NSCLC) results in suboptimal locoregional control (LRC) which is independently associated with worse overall survival. Standard radiation dose escalation has proven unsuccessful in improving outcomes and hypofractionation has been limited by increased toxicity risk. In this study, we use intermittent online adaptive Magnetic Resonance (MR)-guided radiotherapy to improve the therapeutic index of hypofractionated radiation with concurrent chemotherapy with the goal of improving LRC.

Methods: A single-institution, single arm prospective Phase II clinical trial with safety lead-in (NCT03916419) was conducted in individuals with inoperable AJCC 8th Ed. Stage IIB, IIIA, and select IIIB and IIIC NSCLC. Participants received 6000 cGy in 15 fractions with weekly carboplatin/paclitaxel and consolidation durvalumab for up to 12 months. Adaptive treatments occurred at fractions 6, 9, and 12. The primary endpoint was LRC with secondary endpoints including overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS). Acute and late toxicities were characterized per CTCAE v5 and dose limiting toxicity (DLT) defined as persistent non-hematologic grade 3 or any grade 4 toxicity within 6 months of chemoradiation. Survival outcomes were assessed with Kaplan-Meier analysis.

Results: Twenty-six individuals were enrolled (6 safety lead-in, 20 Phase II) between 8/2019 and 9/2023 with a median follow up of 20.7 months. Median age was 69 (range 58-81) with a majority male (54%), white (77%), ECOG performance status 0-1 (92%), clinical stage IIIA (54%) and adenocarcinoma histology (54%). All patients completed radiation and 25 patients (96%) received all 3 cycles of chemotherapy. Twelve months of consolidation durvalumab was completed in 6 patients (23%) with early discontinuation in the remaining from progression (42%) or immunotherapy toxicity (27%). No DLTs were observed in the safety lead-in. Grade 3 acute and late non-hematologic toxicity developed in 2 and 5 patients respectively including esophagitis (n=1), pneumonitis (n=2), and esophageal stricture (n=1). In addition to the grade 3 pneumonitis already noted, toxicities leading to durvalumab discontinuation included grade 1 (n=2) or 2 (n=1) pneumonitis, grade 2 arthralgia (n=1), or grade 2 colitis (n=1). No grade 4/5 toxicity was observed. Two deaths (respiratory failure and fatal hemoptysis) occurred 2-3 months after chemoradiation and were attributed to comorbidities or disease progression. Intermittent adaptation failed to consistently improve tumor coverage or organ-at-risk ideal constraint violation. Overall LRC was 77% (95% CI: 58-89%) with a median locoregional PFS of 38.8 months. Median OS and PFS were 29.6 months and 8.8 months respectively with a 3 yr OS of 44% (95% CI: 27-73%) and 3 yr PFS of 31% (95% CI: 16-60%). Overall distant control rate was 62% (95% CI: 43-78%) with a median DMFS of 23.6 months.

Conclusions: Hypofractionated chemoradiation and consolidation durvalumab is feasible with acceptable and anticipated toxicity and results in excellent LRC with OS comparable to other contemporary studies. With intermittent adaptation demonstrating no additional toxicity benefit, this hypofractionated regimen may effectively substitute for conventional chemoradiation and be more broadly applicable to non-MR and non-adaptive radiotherapy platforms.

Keywords: Chemoradiation, Hypofractionation, Locally Advanced NSCLC

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .52 Optimizing Lung Cancer Radiation Therapy: Integrating Immunotherapy and Targeted Therapy for Enhanced Clinical Outcomes

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Introduction: Lung cancer remains a leading cause of cancer-related mortality worldwide. Recent advancements suggest that integrating radiotherapy (RT) with immunotherapy (IO) and targeted therapy (TT) may enhance clinical outcomes. This study evaluates the impact of these combined modalities on overall survival (OS) in lung cancer patients, based on a comprehensive retrospective analysis of patient data and contextualized within recent findings from Europe and the USA.

Methods: A retrospective cohort study analyzed 198 lung cancer patients treated from 2020 to 2025, stratified into three groups: RT alone (45%), RT combined with IO (30%), and RT combined with TT (25%). The median age was 65.4 years (range: 29-90 years). Dosimetric parameters assessed included mean lung dose (MLD), lung volume receiving 5% (V5%), 20% (V20%), and 60% (V60%) of the prescribed dose. Kaplan-Meier survival analysis and Cox proportional hazards models were used to assess overall survival (OS), with significance set at $p<0.05$.

Results: The combination of radiation therapy (RT) with immunotherapy (IO) significantly improved overall survival (OS) compared to RT alone, with a median OS of 15.2 months versus 9.8 months ($p<0.05$). Although RT combined with targeted therapy (TT) showed a trend toward improved survival, the difference did not reach statistical significance. Dosimetric analysis confirmed that pulmonary toxicity remained within acceptable thresholds across all treatment groups. The mean lung dose (MLD) was 11.8 Gy (range: 8.5-15.2 Gy), remaining below established limits for radiation-induced lung injury. The lung volume receiving at least 5 Gy (V5%) had a mean value of 53.91%, aligning with international safety benchmarks to minimize pneumonitis risk. The lung volume receiving at least 20 Gy (V20%) averaged 21.5%, staying below the 30-35% threshold associated with symptomatic radiation pneumonitis. Additionally, the lung volume receiving at least 60 Gy (V60%) had a mean of 0.88%, indicating minimal exposure of lung tissue to high radiation doses. No significant increase in severe late toxicities, including long-term pulmonary fibrosis, was noted across the treatment groups. Furthermore, there was no significant rise in costal fractures among patients receiving combined therapies, reinforcing the feasibility and safety of integrating IO and TT with RT.

Conclusions: Our findings strongly support the integration of immunotherapy (IO) and targeted therapy (TT) with radiation therapy (RT) in lung cancer management, demonstrating significant improvements in survival and local control without increasing severe toxicity. The comprehensive dosimetric analysis confirms the safety of this multimodal approach, ensuring adherence to established pulmonary dose constraints. These results align with recent high-impact studies from Europe and the United States, reinforcing the growing consensus on the efficacy of combined modality treatments. Further prospective clinical trials are essential to refine patient selection criteria, optimize treatment sequencing, and maximize therapeutic benefit in clinical practice.

Keywords: Lung Cancer, Radiotherapy Integration, Multimodal approach

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .53 Safety Results of DEDALUS Trial: Sequential CT-IO, Hypofractionated RT and Consolidation IO in Unresectable Stage III NSCLC

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Introduction: The PACIFIC trial has established the standard of care for unresectable, stage III non-small cell lung cancer (NSCLC). The DEDALUS trial is a phase 2, single-arm, multicenter study aimed at patients who are not eligible for concurrent chemoradiotherapy (CRT) and are candidates for sequential CRT. This study evaluates safety and efficacy of an induction chemo-immunotherapy regimen followed by de-intensified, hypo-fractionated radiotherapy (RT) delivered concurrently with durvalumab, followed by durvalumab maintenance. This report presents the final safety analysis (primary endpoint).

Methods: Patients with unresectable stage IIIA-C NSCLC, regardless of PD-L1 expression levels and EGFR/ALK wild type, who were deemed unsuitable for standard concurrent CRT by a multidisciplinary evaluation, were considered eligible for this study. After three cycles of CT-durvalumab, responders received hypo-fractionated thoracic RT (45 Gy over three weeks) alongside durvalumab, followed by durvalumab maintenance for up to 12 months or until disease progression. The primary endpoint was safety, defined as the incidence of Grade 3 and Grade 4 possibly related adverse events (PRAEs) within the first six months from the initial durvalumab dose. Secondary endpoints were efficacy in terms of progression-free survival (PFS), overall survival (OS), and quality of life, using the EORTC QLQ-C30 and LC13 questionnaires administered at baseline, after chemo-immunotherapy, post-CRT and at the end of the study.Benchmark comparisons were conducted using the safety and efficacy data from the PACIFIC-6 study, applying identical inclusion and exclusion criteria. An estimated proportion of PRAEs within six months not exceeding 35% was considered acceptable; based on this estimate, the sample size was calculated to include 45 patients, with an expected rate of 20% for PRAEs, corresponding to an upper confidence interval (CI) limit of 34.6%. All data obtained from this study were recorded using an Electronic Data Capture system based on the RedCap platform with electronic case report forms.

Results: Between February 2022 and August 2024, 28 patients were screened, and 25 were enrolled across three Italian sites. Enrollment was halted earlier than anticipated due to a low accrual rate. The median age of participants was 70.4 years (ranging 51-84). Out of the 25 patients, 18 (72.0%) did not experience disease progression after induction chemo-durvalumab and received subsequent RT; 16 patients (64.0%) received at least one dose of durvalumab after RT.Adverse events (AEs) were distributed as follows: 79% Grade 1, 40% Grade 2, 15% Grade 3, and 1% Grade 4 toxicity. Twenty-four AEs were related to durvalumab, 46 to chemotherapy, and 5 to RT. The incidence of Grade 3-4 PRAEs was 11 (8.1%). The number of patients experiencing at least one Grade 3-4 PRAE was 7 (28.0%, 95% CI: 10.4-45.6, p = 0.35), with three patients experiencing more than one. Only one Grade 3-4 PRAE was immune-related, while 10 were related to chemotherapy and none to RT. No statistically significant changes were observed during the study treatment regarding quality of life.

Conclusions: Despite the reduction in the planned sample size, DEDALUS met its primary endpoint, showing acceptable safety and tolerability. Data concerning PFS and OS will be presented.

Keywords: Stage III unresectable NSCLC, Sequential CRT, Immunotherapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .54 Contemporary Treatment Patterns and Outcomes in Stage III NSCLC in the Immunotherapy Era

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Introduction: Background: Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease that requires complex, multimodal management. While recent advances—including neoadjuvant chemoimmunotherapy and consolidation immunotherapy post-chemoradiation—are gaining traction, real-world outcome data from leading academic centers remain limited. This study aims to describe contemporary treatment patterns and clinical outcomes in a cohort treated at a high-volume tertiary care institution.

Methods: This retrospective cohort included 213 patients with clinical stage III NSCLC treated between 2019 and 2023, all of whom received immunotherapy as part of their treatment. Immunotherapy (IO) indication included neoadjuvant IO followed by surgery (33%), adjuvant IO (15%), consolidation IO following definitive chemoradiation (31%), and palliative IO as part of a systemic treatment with or without a chemotherapy backbone (21%). Locoregional control (LRC), progression-free survival (PFS), and overall survival (OS) were estimated using Kaplan-Meier estimates.

Results: Median follow-up was 23.2 months (range, 1.2-65.5) and was similar across treatment groups. The median age was 64 years (range 38-86), with 59% of patients being male. Adenocarcinoma (65%) and squamous cell carcinoma (33%) were the predominant histologies. Actionable driver alterations were identified in 24% of patients, specifically KRAS (15.7%), EGFR (3.3%), BRAF (2.4%), and ROS1 (1.0%). PD-L1 tumor proportion score (TPS) was <1% in 37%, 1-49% in 31%, and ≥50% in 32% of patients, respectively. High PD-L1 expression (TPS ≥50%) was observed in 35% of patients receiving neoadjuvant therapy, 32% in the chemoradiation group, 29% in the upfront surgery group, and 30% among those treated with systemic palliative treatment. Stage distribution was 59% IIIA, 33% IIIB, and 8% IIIC. Notably, patients undergoing neoadjuvant therapy were primarily resectable stage IIIA (71.8%) and IIIB (23.9%), while those receiving chemoradiation included a higher proportion of stage IIIB (46.2%) and IIIC (12.3%). At 2 years, LRC was 66% in the neoadjuvant group, 60% in chemoradiation, 61% in surgery, and 34% in the palliative group. OS at 2 years was 71%, 73%, 58%, and 46%, respectively. PFS at 2 years was 48% in both the neoadjuvant and chemoradiation groups, compared to 23% in the palliative systemic therapy group.

Conclusions: In this real-world cohort, neoadjuvant immunotherapy followed by surgery and definitive chemoradiation yielded excellent outcomes, particularly in stage IIIA and IIIB disease. These findings highlight the importance of multidisciplinary management and appropriate patient selection in achieving high rates of cancer control.

Keywords: non small cell lung cancer, multimodality, stage III

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .55 Comprehensive Analysis of Baseline Genomic Features and Plasma ctDNA Dynamics in Unresectable Locally Advanced NSCLC

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Introduction: Locally advanced NSCLC (LA-NSCLC) is a highly heterogeneous group of tumors. With the continuous advancement of immune checkpoint inhibitors in clinical research, the treatment strategies for patients with unresectable LA-NSCLC have undergone significant changes. This study aims to characterize baseline tissue mutations, plasma circulating tumor DNA (ctDNA) dynamics, and their association with progression-free survival (PFS) in LA-NSCLC patients undergoing combined radiotherapy, chemotherapy or/and immunotherapy.

Methods: A total of 26 patients with unresectable LA-NSCLC were enrolled. Baseline tumor tissue mutations were identified using next-generation sequencing (NGS), and plasma ctDNA was longitudinally monitored through treatment and follow-up. Clinical outcomes, including PFS, were correlated with genomic alterations and ctDNA status.

Results: Baseline tissue analysis revealed frequent mutations in TTN, TP53, CSMD3, and MUC16, and frequent copy number variations in BDH1, MECOM, and PIK3CA. Significant associations were observed between specific mutations and PFS: SYNE1 (HR = -1.880, p = 0.001) and OTOP1 (HR = -2.030, p = 0.001) were associated with improved PFS, while KMT2D (HR = 2.118, p = 0.001) and NCOA1 (HR = 1.96, p = 0.006) were linked to worse PFS. DCHS1 copy number variation was associated with PFS (p = 0.039). Plasma ctDNA analysis showed that pre-radiotherapy ctDNA positivity was influenced by chemoimmunotherapy, with lower positivity rates in patients receiving induction chemoimmunotherapy (p < 0.05). Longitudinal ctDNA monitoring revealed that ctDNA-positive status at TP1 (at a radiation dose of 30Gy) and persistent ctDNA positivity were associated with worse PFS (p < 0.05). Furthermore, ctDNA dynamics demonstrated distinct patterns between treatment responders and non-responders, with early ctDNA clearance correlating with improved PFS. The ctDNA positivity rate at pre-radiotherapy baseline was 42%, decreasing to 23% at TP1 and 15% at TP2 (at a radiation dose of 60Gy). Patients with sustained ctDNA negativity after treatment had a median PFS of 18 months, compared to 8 months in those with persistent positivity.

Conclusions: This study highlights the prognostic value of baseline genomic mutations and ctDNA dynamics in LA-NSCLC. Specific mutations and ctDNA status can serve as biomarkers to guide personalized treatment strategies and predict patient outcomes. ctDNA monitoring provides real-time insights into treatment response and disease progression, offering a non-invasive approach to inform therapeutic decisions.

Keywords: Unresectable Locally Advanced NSCLC, Genomic Features, Plasma ctDNA Dynamics

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .56 Sequencing of Chemoimmunotherapy in Resectable Locally Advanced NSCLC: Single Center Experience

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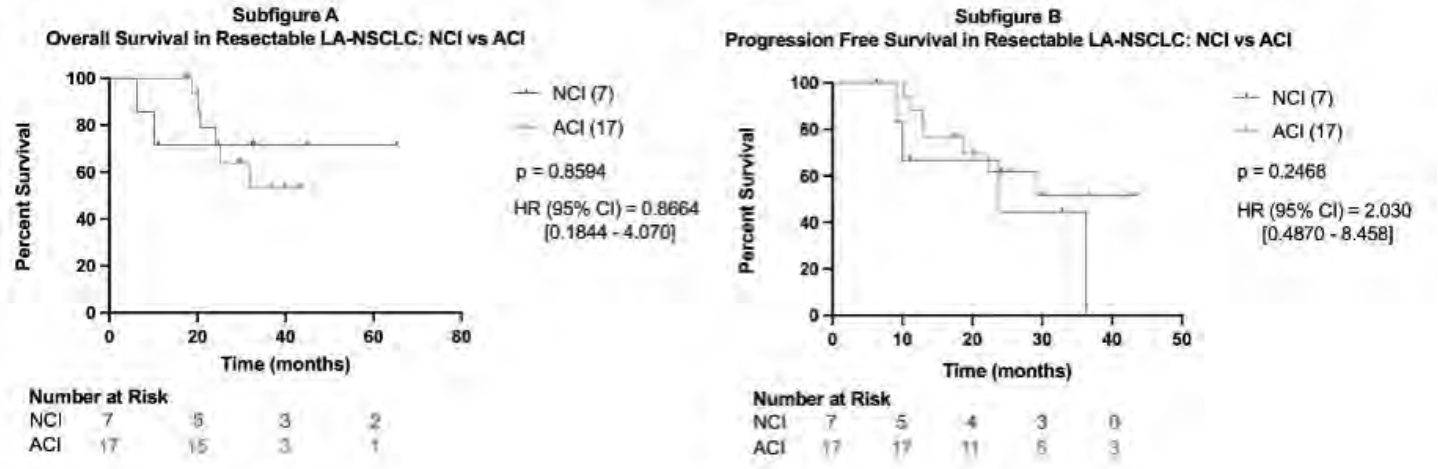
Introduction: Chemoimmunotherapy (chemo-IO) has become a standard treatment for resectable, locally advanced non-small cell lung cancer (NSCLC). Neoadjuvant chemo-IO (NCI) is gaining traction due to its biological rationale—exposing an intact tumor to immune checkpoint inhibitors (ICI) potentially triggering a more robust and lasting antitumor immune response. While this strategy has shown superiority over adjuvant chemo-IO (ACI) in melanoma, no prospective randomized comparison exists in NSCLC.

Methods: We conducted a retrospective review of patients with surgically resected stage II or higher NSCLC treated with either NCI or ACI from January 2018 to December 2023. Tumors were staged per AJCC 8th edition. Demographic, clinical, and survival data were collected and analyzed.

Results: Among 24 eligible patients, 79% were over 65, 50% male, and 75% European American. Alcohol and tobacco use were prevalent (83% and 100%, respectively). Most had government insurance (75%) and stage II disease (58%). Squamous histology was seen in 33%, and 46% had PD-L1 >50%. Carboplatin-based doublet therapy was used in 71% of regimens, with only one patient receiving concurrent radiation. Lobectomy was the primary surgical approach (92%). Of the cohort, 29% (7/24) received NCI and 71% (17/24) received ACI. More NCI patients presented with stage III disease (57%) compared to ACI (35%), but other baseline characteristics were similar. There was no significant difference in overall survival (OS) between NCI and ACI groups (median OS: undefined in both; HR 0.87, 95% CI 0.18-4.07; p = 0.86). Median follow-up among survivors was comparable: 32 months (NCI) vs 30 months (ACI; p = 0.41). Median progression-free survival (PFS) was 24 months in the NCI group and undefined in the ACI group (p = 0.25). Two-year OS rates were 71% (NCI) and 79% (ACI), while 3-year OS was higher in the NCI group (71% vs 53%). However, 2- and 3-year PFS rates favored ACI (62% and 51%) over NCI (44% and 0%).

Conclusions: In this small retrospective study, no survival differences were observed between NCI and ACI. A trend towards improved 3-year OS with NCI was noted, though ACI was associated with better PFS. Larger studies, including the ongoing PROSPECT-Lung trial (NCT06632327), are needed to clarify optimal sequencing of chemo-IO in resectable NSCLC.

Figure 1. Comparing neoadjuvant chemoimmunotherapy (NCI) versus adjuvant chemoimmunotherapy (ACI) in resectable, locally advanced non small cell lung cancer (LA-NSCLC) in terms of (A) overall survival and (B) progression free survival.



Keywords: Chemoimmunotherapy Sequencing, Non-small cell lung cancer

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .57 Small Volume Segmental Lung Autotransplantation for Treatment of Central Lung Cancer:One Case Report

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Introduction: Lung cancer, predominantly NSCLC, remains a global mortality leader, with central tumors posing unique surgical challenges due to proximity to critical bronchovascular structures. While sleeve resections preserve lung function, 15-20% of advanced central lesions still require pneumonectomy—a high-risk intervention with 6-8% 30-day mortality. Small-volume segmental autotransplantation addresses these limitations through precision resection of bronchovascular units (<30% lung volume), combining radical tumor excision with functional preservation. Our technique achieves 1.5cm resection margins—surpassing conventional sleeve limits (0.5-1cm)—via vascular anastomosis while mitigating ischemia-reperfusion risks. This innovation resolves two critical challenges: 1) balancing oncologic radicality and lung preservation in compromised patients, and 2) standardizing anastomotic techniques for broader applicability.

Methods: A 67-year-old male with a 30-pack-year smoking history and a family history of lung cancer (father) presented with paroxysmal cough and short of breathe for 6 months. PET/CT scan showed: (I) a hypermetabolic left hilar mass (12*10*9cm) invading left bronchus and left pulmonary artery trunk; hypermetabolic 3A lymph node (II) enlarged left hilar, carinal, and other mediastinal lymphnodes; (III) no sign of distant metastasis .Bronchoscopic biopsy confirmed squamous cell lung cancer. Endobronchial Ultrasound (EBUS) confirmed negative 7 and 4R lymph nodes (cT4N2M0,IIIB). PET/CT scan after 6 cycles of neo-adjuvant chemoimmunotherapy (cisplatin+paclitaxel+nivolumab) showed both the mass and mediastinal lymph nodes were slightly smaller and less hypermetabolic (Fig 1). Small volume lung autotransplantation was consideredto preserve the left 9+10 segments. After general anesthesia, the patient was placed on right lateral decubitus position. A 25 cm incision was made in the 5th left intercostal space. Left upper lobectomy with S6+7+8segmentectomy was performed. Frozen section of resection margins showed negative results. Wetherefore decided to perform left S9+10 segment autotransplantation in situ. After systemic heparinization (1 mg/kg), venous anastomosis was firstly completed between the pulmonary vein of the segmental graft and left upper pulmonary vein with 5-0 Prolene. Left A9+10 was anastomosed to left pulmonary artery stump with 5-0 Prolene. The anastomosis between B 9+10and left main bronchus was end to end style with 3-0 Prolene. The vessels and airway reconstruction procedures were diagrammatically demonstrated in Fig 2.

Results: Patient was extubated immediately after operation transferred to normal wards. Prophylactic antibiotic and analgesics were administered. Bronchoscopy was performed daily to evaluate the anastomosis and remove secretion. Chest tubes were removed on POD 5, and he was discharged on POD 12. CXR before discharge showed no pleural effusion or pneumothorax. Bronchoscopybefore discharge show no anastomotic ischemia or leakage. Tumor showed a 10.5 cm × 9.3cm×8.1 cm mass with hard texture, grey-white appearance. The Pathological diagnosis was bronchial squamous cell carcinoma. Patient underwent chest CT scan every 2 months and bronchoscopy every 3 months. Bronchoscopy showed no anastomotic stenosis or tumor recurrenceat 9-month follow-up.

Conclusions: While Di Rienzo's end-to-side tracheal anastomosis addresses diameter mismatches, our cases achieved tension-free bronchial reconnections via conventional end-to-end techniques. This simplification reduced operative complexity without compromising airway patency, as evidenced by absent anastomotic stenosis at 9-month follow-up.

Keywords: Small-volume segmental autotransplantation, lung cancer, bronchial reconnection

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .58 Advancing Care in NSCLC: Evaluating the Impact of New Treatment Modalities on Patient Outcome at the LTZ of the Comprehensive Cancer Center Zurich

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Introduction: Lung cancer remains one of the most diagnosed cancers worldwide and the leading cause of cancer-related deaths in Switzerland. Breakthroughs in detecting actionable genomic alterations (AGAs) permitting matched targeted therapies, immune checkpoint inhibitors (ICIs) and advanced locally ablative therapy (LAT) techniques have revolutionized cancer treatment for non-small cell lung cancer (NSCLC). The Lung and Thoracic Oncology Center (LTZ) at the Comprehensive Cancer Center Zürich (CCCZ) is at the forefront of these achievements, ensuring patients benefit from cutting-edge therapies. This study aimed to characterize treatment modalities and assess their impact on outcomes across all NSCLC stages, managed at the LTZ over the past decade.

Methods: Outcomes of patients with NSCLC of all stages diagnosed in 2018 ('modern cohort') were compared with patients treated before 2016 ('historic cohort') in a real-world setting. Patient and tumor characteristics, including age at diagnosis, gender, histological subtype, AGAs, PDL1 expression status, data on treatment types (e.g. locally ablative techniques for oligo-metastatic or oligo-progressive disease), and treatment lines. Patients were grouped into two cohorts by diagnosis date. Chi-square Test analyzed characteristics. Kaplan-Meier analysis was performed to assess overall survival, using capped survival data, with a maximum follow-up of 50 months. Log-rank test and Fisher's exact test evaluated survivor functions equality.

Results: 885 NSCLC cases were analyzed, with 698 cases assigned to the historic cohort and 187 cases to the modern cohort. In the historic cohort, 30.3%, 13.9%, 24.1% and 31.6% of patients were UICC Stage I, II, II and IV, respectively. This distribution was not significantly different from the modern cohort (P=0.98; 29.4%, 13.4%, 24.6%, 32.6%, respectively).There was a significantly higher 1-year survival rate in the modern cohort (84% versus 73%; p = 0.008), as well as a significantly higher 3-year survival rate (60% versus 49%; p = 0.015). In the stage-by-stage analysis, the 1-year- and 3-year survival rates were not different in Stage I. In Stage II, the 1-year survival rate was not different, but the 3-year survival rate showed a trend towards improved survival in the modern cohort (84.0% versus 59.8%; p=0.09). In Stage III, both the 1- and 3-year survival rates were significantly higher in the modern cohort (1y: 95.7% versus 74.1%; p=0.003. 3y: 67.4% versus 45.4%; p=0.02). Stage IV survival rates showed improvement trends in the modern cohort (1y: 62.3% versus 49.4%; p=0.08. 3y: 31.1% versus 23.9%; p=0.25). Overall survival trended higher in the modern cohort but was not significant, likely attributable to follow-up variations (p=0.027). In the stage-by-stage analysis, the survival was not different for Stage I, showed a trend towards improvement in Stages II and IV, as was significantly different for Stage III (p=0.019).

Conclusions: We observed improved survival rates and long-term survival in patients who were treated in 2018 compared to patients treated two or more years earlier. This might be attributed to increased use of new treatment modalities in patients with metastatic disease or relapses. We are expanding our database with retrospective data from 2019 onward and will present it at the meeting.

Keywords: NSCLC, Lung cancer, metastatic

P2.08 .59 SCGB1A1 Enhances Radioimmunotherapy Efficacy and Mitigates Pulmonary Toxicity via Dendritic Cell Functional Reprogramming

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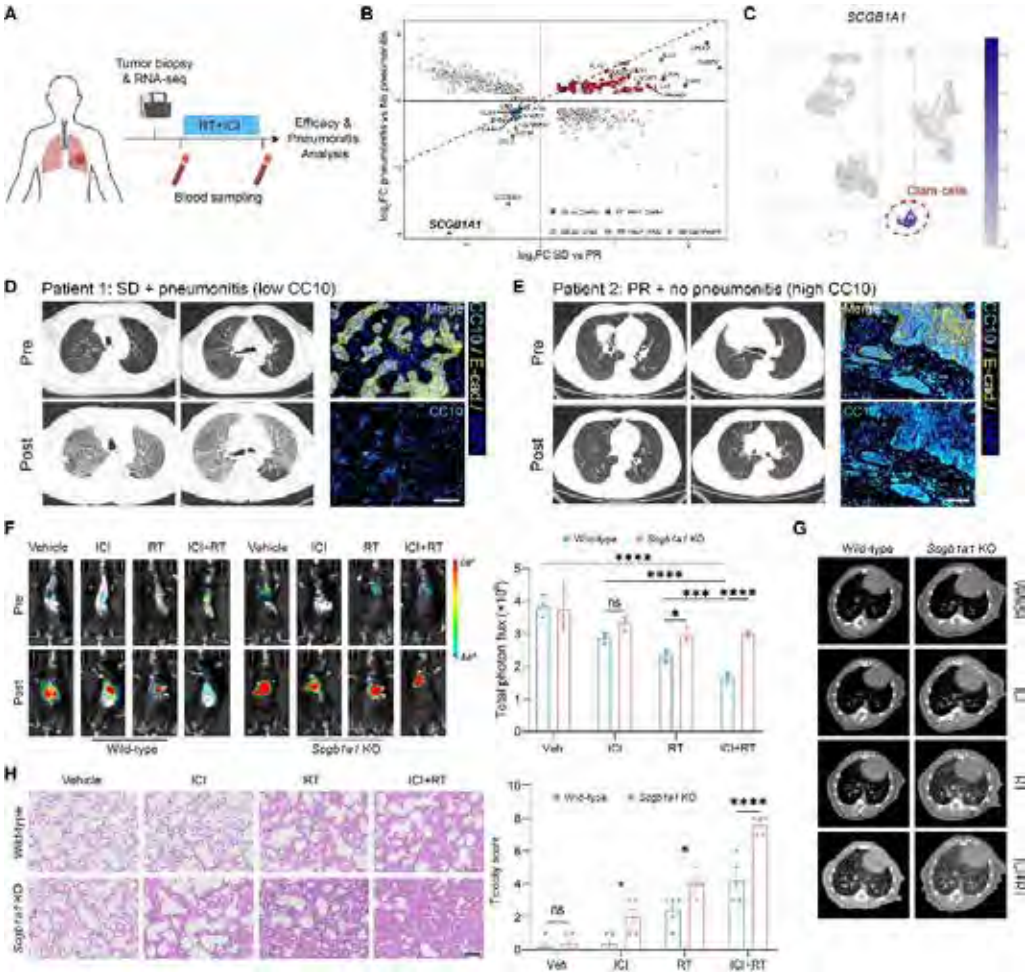
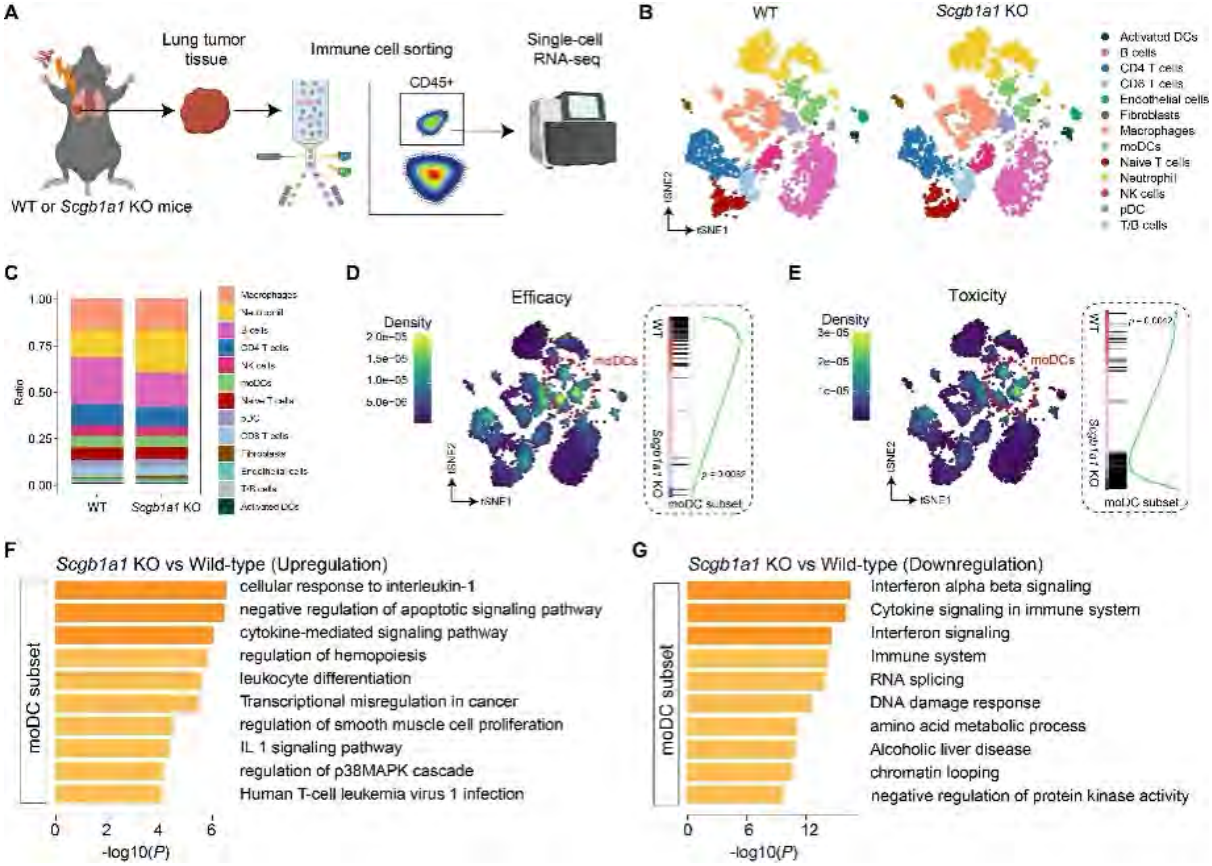
Introduction: Although radioimmunotherapy confers survival advantages in locally advanced NSCLC, tumor recurrence persists, with real-world data demonstrating elevated rates of grade 3-5 pneumonitis. Notably, attempts to enhance antitumor efficacy by including additional therapeutics have been largely discouraged due to concerns of exacerbating fatal pulmonary toxicity. Consequently, there remains a desperate need to develop effective strategies that concurrently optimize antitumor benefits and mitigate pneumonitis risks in radioimmunotherapy regimens.

Methods: Integrated transcriptomic-clinical analysis identified dual efficacy-pneumonitis regulatory molecules, validated through a radioimmunotherapy cohort and transgenic knockout murine models. Single-cell RNA sequencing of tumor-bearing Scgb1a1 KO mice characterized immune niche dynamics and critical cellular subpopulations, complemented by pathway enrichment studies elucidating mechanistic networks.

Results: Comparative transcriptomic profiling of efficacy versus pneumonitis in a lung cancer radioimmunotherapy cohort identified SCGB1A1 as a potential dual-regulatory molecule. SCGB1A1, which is specifically expressed in pulmonary club cells, encodes the secretory protein CC10. Increased expression of CC10 was associated with improved clinical outcomes and reduced pulmonary toxicity. In orthotopic lung tumor models, knockout of Scgb1a1 significantly diminished the efficacy of radioimmunotherapy and exacerbated pneumonitis. Single-cell analysis revealed enhanced neutrophil infiltration in tumors lacking Scgb1a1. Importantly, dendritic cell subsets demonstrated dual enrichment for both immune checkpoint inhibitor (ICI) efficacy and toxicity signatures, with wild-type groups exhibiting upregulation of ICI-efficacy markers, whereas knockout groups showed elevated ICI-toxicity markers. Mechanistically, the ablation of Scgb1a1 led to increased IL-1β signaling and suppression of DNA damage response pathways in dendritic cells.

Conclusions: SCGB1A1 enhances radioimmunotherapy efficacy while mitigating pulmonary toxicity through dendritic cell functional reprogramming. Intratracheal delivery of SCGB1A1 protein might be a promising strategy to improve patient survival and quality of life during radioimmunotherapy.





Keywords: SCGB1A1, Dendritic Cells, radioimmunotherapy

P2.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.08 .60 Telomere Length and Survival in Patients With Locally Advanced Unresectable Lung Cancer: Is There a Relationship?

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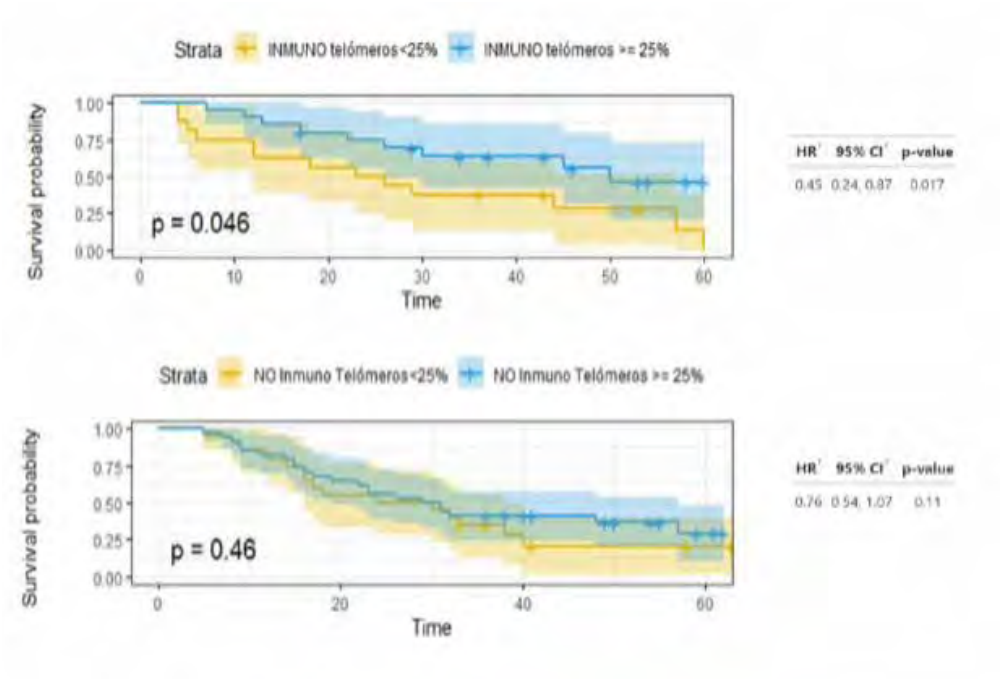
Introduction: Telomerase is overexpressed in 80-90% of tumors, preventing telomereshortening and providing "cellular immortality". Immunotherapy (IT) after concurrent chemoradiotherapy (CCRT) has demonstrated a benefit in overall survival (OS) in patients with non-small cell lung cancer (NSCLC) PDL-1 positive. The objective of this study is to analyze the relationship between telomere length (TL) and OS in patients with NSCLC PD-L1 positive treatedwith CCRT and IT.

Methods: Unicenter prospective study conducted between 2018-2021. Clinical, analyticaldata, tumor and treatments characteristics were collected. TL was obtained by buccal swab. Patients were classified into two groups based on z-score percentile used to measure TL: percentile <25 and >25. OS was analyzed during follow up until death/last visit using the Kaplan-Meier method

Results: Results: A total of 90 patients were included; 90% were men, mean age of 72 years (SD 6.3). 54% were squamous cells and 40% received IT. Regarding TL, 83% of patients showed lower length than the healthy population. No significant differences in OS were observed between the two study groups (HR 0.98, p=0.9). However, in subgroup analyisis, patients who received ITtreatment with TL percentile <25 had better OS than dose with TL percentile >25 (p=0.046). No differences on OS were observed in patients without IT treatment (Figure 1).



Conclusions: NSCLC patients have lower LT than healthy individuals. Those patients treatedwith IT with LT above the 25th percentile showed better OS. Further studies to validate these findings are required.

Keywords: Oncology, Pneumonitis, Telomere

P2.10.01 Maintenance Pemetrexed/Pembrolizumab vs Maintenance Pembrolizumab Alone in Advanced Non-Squamous Non-Small Cell Lung Cancer

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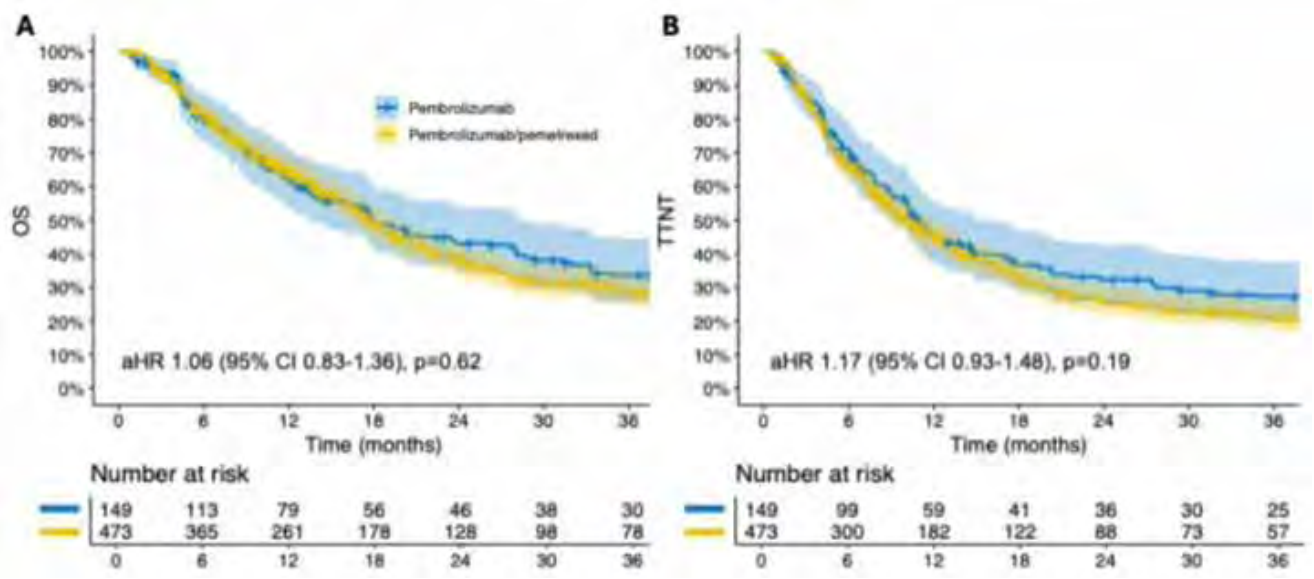
Introduction: KEYNOTE-189 demonstrated that adding pembrolizumab to both induction and maintenance chemotherapy improved progression-free and overall survival (OS) in patients with advanced/metastatic non-squamous NSCLC. Trial design limitations, however, leave unclear whether maintenance pemetrexed adds benefit to maintenance pembrolizumab alone. Maintenance pemetrexed remains a guideline-recommended standard of care in the immunotherapy era despite this ambiguity.

Methods: We identified Veterans with NSCLC who completed 4 cycles of carboplatin/pemetrexed/pembrolizumab (n=62) and then either maintenance pemetrexed/pembrolizumab ('pem/pembro', n=473) or pembrolizumab alone ('pembro', n=149). Survival estimates were generated by the Kaplan-Meier method. We performed propensity weighting to account for differences in baseline characteristics, including histology, PDL1, age, race, comorbidities, CNS disease, and response to induction chemoimmunotherapy. The primary outcome of the study was OS. Key secondary outcomes included time-to-next treatment (TTNT) and incidence of grade ≥ 3 adverse events of special interest. We estimated spending on the pemetrexed component of maintenance pemetrexed/pembrolizumab by US federal government payers (VA, Medicare Part B, and Medicaid) from 2017 to 2022.

Results: Baseline characteristics were well balanced. Unadjusted median OS was 18.1 months (95% CI 13.9-28.6) for pembro and 17.7 months (95% CI 16.4-19.9) for pem/pembro. After adjusting for baseline factors, treatment group was not associated with OS (adjusted hazard ratio [aHR] 1.06 for pem/pembro vs pembro, 95% CI 0.83-1.36, p=0.62) or TTNT (aHR 1.17 for pem/pembro vs pembro, 95% CI 0.93-1.48, p=0.19). Pem/pembro was associated with higher incidence of grade ≥ 3 neutropenia (aHR 2.86, 95% CI 1.44-3.05, p=0.004). Estimated cumulative US federal government payer spending on pemetrexed in the context of maintenance pembrolizumab from 2017 to 2022 amounted to $1.4 billion ($1.6 billion in 2024 USD).

Conclusions: In this retrospective cohort study, maintenance pemetrexed/pembrolizumab did not improve survival compared with pembrolizumab alone but was associated with increased toxicity and potentially unnecessary spending. Reassessment of legacy therapies in modern combination regimens and consideration of component contributions at the time of regulatory approval may be warranted.



P2.10.02 Developments in Treatment of Non-Small Cell Lung Cancer and Their Implications for National Practice.Registurk-Lung National Registry Study

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Introduction: The developments in the treatment of non-small cell lung cancer have rapidly emerged in the last decade by adding different targeted agents to the chemotherapy regimens we have been applying for the last 50 years. It seems important for our oncology practice to quickly transfer these treatment options, which have positive effects on quality of life and survival in the treatment of non-small cell lung cancer, to our daily practice and to ensure that our patients benefit from these treatment options. In this study, we investigated the reflections of newly developed treatments in our daily practice.

Methods: In our country, within the scope of the Registurk-Lung observational study (NCT05254119), a total of 5382 patients without driver mutation, metastatic non-small cell lung cancer were recorded between December 2021 and April 2024 in 41 centers representing the whole country. The demographic, histopathological, molecular and clinical data of the patients were recorded. The relationship between progression-free survival (PFS) time and overall survival (OS) time with these characteristics was investigated.

Results: 5382 patients were evaluated. The median age was 65 (25-91) years and 15.1% of the patients were female. The proportion of patients who never smoked was 9,6 %. Histopathologically, 39,7 % of the patients were diagnosed with squamous cell carcinoma. Unfortunately, subgroup determination could not be provided in 10,2 % of our patients. The other patients had non-squamous histology. 12,3 percent of patients received single agent immunotherapy or chemoimmunotherapy. Other patients had received only a combination of doublet chemotherapy. The PFS was 6.6, 7,7 and 9,6 months in only chemotherapy, chemoimmunotherapy and only immunotherapy groups respectively. Compared to the group that received chemotherapy alone, PFS and overall survival were longer in the group that received chemoimmunotherapy. This difference between the two groups was found to be statistically significant (p:0,001 for PFS and 0,041 for OS).

Conclusions: In clinical studies, the addition of immunotherapy to chemotherapy provides improvements in PFS and OS data. When we also consider the quality of life data, immunotherapy appears to be a development that increases both the quality of life and survival for patients in non-small cell lung cancer, as in other types of cancer.

Keywords: NSCLC, Immunotherapy, Registry

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.03 Long-Term Pemetrexed Administration Poses Risk of Renal Function Decline

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Introduction: Pemetrexed is a standard cytotoxic anticancer drug used for non-small cell non-squamous cell lung cancer and malignant pleural mesothelioma, and is increasingly administered long-term for non-small cell lung cancer in combination with immune checkpoint inhibitors or molecular targeted therapy. However, pemetrexed is a nephrotoxic drug, and there are reports that the cumulative dose correlates with nephrotoxicity.

Methods: Among patients treated with pemetrexed at our institution between November 2009 and March 2024, we conducted a retrospective study of patients who received at least 2 cycles of pemetrexed therapy.

Results: 461 pemetrexed-treated patients, 351 were included in the analysis, excluding patients who had received their first dose of pemetrexed outside of our hospital, patients who received pemetrexed again, patients who were started with an estimated creatinine clearance (eCCr) <45 mL/min, and patients in whom pemetrexed was discontinued after one course. Median age was 70 (36-90) years, 259 (73.8%) were male, 318 (90.6%) had non-small cell non-squamous lung cancer, 31 (8.8%) had malignant pleural mesothelioma, 2 (0.6%) had thymic carcinoma, median number of doses was 6 (2-83), median estimated eCCr at start was 72.3 (45.3-140 .2) mL/min. Concomitant medications included cisplatin in 152 patients (43.3%), carboplatin in 78 patients (22.2%), bevacizumab in 72 patients (20.5%), immune checkpoint inhibitors in 59 patients (16.8%), and EGFR-TKI in 4 patients (1.1%). Patients who had an eCCr <45 mL/min at pemetrexed discontinuation tended to have an older starting age, a smaller body surface area, and a lower starting eCCr. The results of propensity score matching using these background factors in 60 patients in each group showed that a higher frequency of administration was significantly correlated with a decrease in eCCr < 45 mL/min.

Conclusions: Long-term pemetrexed administration is associated with risk of renal failure.

Keywords: pemetrexed, renal function

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.04 Real-World Evidence on the Efficacy of TS1 in Patients With Advanced Non-Small Cell Lung Cancer

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Introduction: TS-1, an oral fluoropyrimidine derivative, has been used to treat advanced non-small cell lung cancer (NSCLC) following standard therapies. However, its real-world effectiveness across different lines of treatment, combination regimens, and clinically or molecularly defined subgroups remains inadequately characterized.

Methods: This retrospective study included 363 patients with advanced NSCLC who received TS-1 between 2012 and 2024. Primary endpoint was overall survival (OS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and time to treatment failure (TTF). Subgroup analyses were based on treatment line, dose, regimen, histology, metastatic sites, EGFR mutation status, and PD-L1 expression.

Results: TS-1-based regimens yielded an ORR of 19.0% and DCR of 86.2%, with median PFS, TTF, and OS of 2.4, 2.8, and 9.3 months, respectively. In multivariate analysis, patients who received TS-1 as first- or second-line therapy had significantly longer OS (p=0.028), PFS (p<0.001), and TTF (p=0.004) than later line use. Higher TS-1 dose (>40 mg) was associated with longer PFS (p=0.025), TTF (p=0.035), and higher response rate (p=0.029). Compared to TS-1 monotherapy, TS-1-based combination therapy was associated with improved OS (p=0.045). TS-1 combined with second-/third-generation EGFR-TKIs improved OS (p=0.019) and TTF (p=0.014), with additional TTF benefit observed in those receiving TS-1 combined with third-generation EGFR-TKIs (p=0.027). TS-1 combined with platinum-based chemotherapy significantly reduced progression risk (p=0.03) and improved ORR (44.4%) and DCR (88.9%) over monotherapy (ORR 17.7%, DCR 84.1%), although lower response rates were observed in patients with driver (p=0.023) and EGFR mutations (p=0.028) compared to TS-1 monotherapy. Absence of brain metastases was associated with higher odds of treatment response (p=0.048). Poorer OS was associated with non-adenocarcinoma histology (p=0.006), squamous subtype (p=0.002), ECOG PS of 2-4 (p=0.002), smoking (p=0.032), and the presence of bone (p=0.048), abdominal (p=0.033), or liver metastases (p=0.007). Additionally, abdominal (p=0.004) and liver metastases (p=0.007) were associated with shorter TTF. In patients with EGFR mutations, TS-1 combined with targeted therapy improved OS in univariate analysis (p=0.036), particularly when combined with second-/third-generation EGFR-TKIs (p=0.036) compared to TS-1 monotherapy, but not in multivariate analysis. Mutation status significantly impacted OS (p=0.04), with inferior outcomes in patients harboring ALK, ERBB2, or BRAF mutations compared to patients without identifiable driver mutations (p=0.005). Among patients tested for PD-L1, expression levels of 50-60% had worse OS than PD-L1-negative patients (p=0.004). Improved OS (p=0.01) was observed in patients with 30% PD-L1 expression; however, this association was not observed in neighboring PD-L1 expression ranges. In patients with PD-L1 ≥1%, TS-1 combined with either targeted (p=0.008) or immunotherapy-based therapies (p=0.012) improved treatment response, with both remaining significant in PD-L1 ≥30% subgroups (p<0.001 for both).

Conclusions: Earlier-line use of TS-1, higher dosing, and combination therapy, particularly with second-/third-generation EGFR-TKIs, were associated with improved OS. Better response rates were observed in PD-L1-positive patients receiving TS-1 in combination with targeted or immunotherapy-based regimens. Conversely, poorer OS was related to non-adenocarcinoma histology, ECOG PS of 2-4, smoking, and specific distant metastases. These findings underscore the potential value of developing biomarker- and phenotype-guided strategies to optimize TS-1-based treatment in NSCLC.

Keywords: Non-Small Cell Lung Cancer, TS-1 (Tegafur/Gimeracil/Oteracil), Real-World Evidence

P2.10.05 Real-World Efficacy of Second-Line Carboplatin Plus Pemetrexed in EGFR-Mutant NSCLC. an International, Multicentre Analysis

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Introduction: Osimertinib is the current standard of care as first-line (1L) treatment for patients with EGFR-mutant advanced non-small cell lung cancer (aNSCLC). Recently, the FLAURA-2 trial showed a longer progression-free survival (PFS) with 1L platinum-pemetrexed plus osimertinib vs osimertinib alone. These results raise questions about the optimal treatment strategy, osimertinib followed by chemotherapy or the combination upfront. Real-world (RW) evidence on the efficacy of second-line (2L) chemotherapy after osimertinib is scarce. Therefore, RW data could be very informative in the context of a changing landscape, with intensification regimens moved to the front-line.

Methods: We retrospectively identified patients with EGFR-mutant aNSCLC who received 2L carboplatin plus pemetrexed after 1L osimertinib between May 2018 and June 2023 in 11 European centres. Demographics and clinical data were collected and analysed. The primary endpoint was the overall response rate (ORR), while secondary endpoints included PFS and overall survival (OS) from the start of chemotherapy, as well as toxicity.

Results: We identified a total of 91 patients. Median age was 62.5 years (range 40 - 81), 56 patients (61.5%) were males, 58 patients (63.7%) were never smokers. Most patients (n = 81, 89.0%) had a common mutation, either exon 19 deletion (n = 48) or L858R (n = 33). The TP53 mutational status was available in 51 patients, among them a mutation was present in 19 patients (37.3%). ECOG performance status was ≥ 2 in 31 patients (35.3%). Baseline liver and brain metastases were present in 32 (35.2%) and 26 (28.6%) patients, respectively. Among 72 patients evaluable for response, the ORR was 33.3%. Median follow-up in right-censored patients was 20.5 months (95% CI 13.7 - 27.2). Median PFS was 5.3 months (95% CI 4.4 - 6.1) and median OS was 9.2 months (95% CI 7.5 - 10.8). In the multivariate Cox regression analysis, EGFR mutation subtype was not significantly associated with differences in PFS or OS (Table 1). Twenty-four (24.4%) patients experienced grade 3-4 chemotherapy-related adverse events. Dose reductions were required in 21 patients (23.1%), while treatment was stopped due to toxicity in 13 patients (14.3%).

Conclusions: This RW cohort of patients treated with carboplatin and pemetrexed after osimertinib showed an ORR and PFS comparable to previously published evidence, while the OS was notably shorter, reflecting the inclusion of patients with poorer PS in our cohort. Overall, outcomes with 2L carboplatin plus pemetrexed post-osimertinib remain poor and confirms the need to find more effective strategies.

Table 1. Multivariate Cox regression model of OS and PFS in EGFR-mutant NSCLC patients treated with second-line carboplatin plus pemetrexed after receiving first-line osimertinib.

	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
EGFR mutation (exon 19 deletion as reference)								
L858R	1.03 (0.63 - 1.67)	0.916	1.07 (0.62 - 1.86)	0.802	1.09 (0.64 - 1.84)	0.750	0.69 (0.38 - 1.24)	0.213
Uncommon	1.20 (0.58 - 2.48)	0.628	0.97 (0.43 - 2.23)	0.953	1.11 (0.51 - 2.42)	0.790	0.44 (0.18 - 1.07)	0.071
Age (per year increase	0.99 (0.97 - 1.01)	0.307	0.98 (0.96 - 1.01)	0.215	0.99 (0.97 - 1.02)	0.642	0.99 (0.97 - 1.02)	0.628
Gender (male vs female)	1.68 (1.05 - 2.69)	**0.030**	2.16 (1.25 - 3.71)	**0.006**	1.16 (0.71 - 1.90)	0.561	1.84 (1.05 - 3.24)	0.034
Smoking (ever vs never)	1.80 (1.10 - 2.94)	**0.019**	1.79 (1.06 - 3.05)	**0.031**	1.66 (1.00 - 2.75)	0.051	1.82 (1.05 - 3.16)	0.032
ECOG PS (≥2 vs 0-1)	1.39 (0.86 - 2.25)	0.352	1.99 (1.13 - 3.53)	**0.018**	2.54 (1.48 - 4.33)	**0.001**	3.73 (1.97 - 7.09)	**<0.001**
Liver metastases (Yes vs No)	1.62 (0.98 - 2.68)	0.058	1.31 (0.75 - 2.31)	0.346	1.49 (0.88 - 2.50)	0.135	1.58 (0.88 - 2.83)	0.126
Brain metastases (Yes vs No)	0.85 (0.53 - 1.37)	0.513	0.67 (0.38 - 1.19)	0.170	1.27 (0.76 - 2.13)	0.365	1.20 (0.68 - 2.09)	0.529

Keywords: EGFR, NSCLC, FLAURA-2

P2.10.06 Docetaxel in NSCLC: A Multi-Centre Real World Evidence Analysis in the Immunotherapy Era

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Introduction: Lung cancer screening (LCS) rates in the U.S. remain low despite endorsements from professional organizations and broad insurance coverage with no co-pay. Family physicians play an essential role in LCS, in having long-term relationships with their patients that emphasize preventive care, established screening protocols for other cancers, routinely screening for tobacco use, and providing cessation resources to their patients who smoke. Understanding what family physicians know about LCS, how they are implementing it their practices and their preferences for doing so, is critical to increasing the uptake of this life saving screening test.

Introduction: Docetaxel has been a standard of care in advanced non-small cell lung cancer (NSCLC) for over 2 decades, and numerous attempts to develop more efficacious options have failed. Docetaxel remains the 'final' line of approved therapy in most putative algorithms, but real-world evidence (RWE) outcomes have not been recently reported, particularly in the era of immune checkpoint inhibition (ICI).

Methods: With ethics board approval, we reviewed patients with advanced NSCLC who received docetaxel monotherapy over 10 years (January 2011 - December 2020) across 3 academic cancer centres in Ontario, Canada. We hypothesized that treatment outcomes in the RWE setting would be similar to those reported in clinical trials. RECIST response was not available. Eligibility included adult patients; histological confirmation of NSCLC; treatment with docetaxel monotherapy in the second line setting or beyond; and stage 3B or 4 at the time of treatment initiation.

Results: In total, 285 patients were included. Median age 62 years (17-85); 43% female; 68/22/9% ECOG PS 0-1/2-3/unknown; 65/27/7% adenocarcinoma/squamous cell/other. Metastatic sites: brain (28%), adrenal (16%), liver (35%), bone (63%), contralateral lung (52%) and pleura (57%). 16% had EGFR mutations. KRAS status was available in 64%, of whom 15% were mutation positive. PDL1 status was available in 66% (13% ≥50%, 17% 1-49%, 36% <1%). 48/35/17% were treated in 2nd / 3rd / 4th+ line with docetaxel. 112 (39%) of patients had received ICI therapy prior to docetaxel in previous curative and palliative intent. The median number of cycles received was 3 (range 2-9). Median OS in the whole population was 6.5 months (95% CI 5.9 - 7.3 months). OS in different populations is reported in the Table 1. In univariate analysis, factors associated with shorter survival included ECOG 2 vs 0 (HR 2.41, 95% CI 1.55-3.76, p<0.0001), ECOG 1 vs 0 (HR 1.82, 95% CI 1.23-2.69, p=0.0026), duration of prior line of therapy to docetaxel >6 months (HR 1.40, 95% CI 1.03-1.90, p=0.0311) and factors associated with a prolonged survival included KRAS mutation (HR 0.53, 95% CI 0.34-0.83, p=0.0054). In multi-variate analysis, KRAS (p=0.0268) and ECOG 2 vs 0 (p=0.0091)/ 1 vs 0 (p=0.0181) remained predictors of OS.

Conclusions: Docetaxel RWE OS is similar to early clinical trials, regardless of immunotherapy use. KRAS mutation, good ECOG PS (0/1) and a shorter duration of prior line of therapy to docetaxel were all associated with prolonged survival.

Table 1: Overall survival (OS) in different treatment populations

Patient group	Number	Median OS (months, 95% CI)	p-value
Overall	285	6.5 (5.9-7.3)	------
Prior ICI	112	6.6 (5.8-8.4)	0.58
No prior ICI	173	6.3 (5.4-7.3)	
2nd line	138	6.4 (5.3-7.6)	0.84
3rd line	99	6.3 (4.3-7.8)	
4th line +	48	7.2 (5.4-9.9)	
EGFR mutation	47	6.1 (3.7-7.5)	0.12
KRAS mutation	28	10.2 (3.8-17.2)	0.0047
ECOG PS 0	43	8.5 (5.8-14.0)	0.0012
ECOG PS 1	151	6.8 (6.0-7.9)	
ECOG PS 2	58	4.3 (3.1-6.2)	

Keywords: NSCLC, Docetaxel, Immunotherapy

P2.10.07 Combined Immunoscore for Predictive Stratification of Unresectable Non-Small Cell Lung Cancer

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Introduction: The identification of an immunoscore combining multiple components of the tumor microenvironment such as PD-L1 expression by tumor cells, CD8 and CD4 T lymphocyte infiltration, the presence of tumor-associated macrophages and neutrophils (TAMs and TANs), and the derived neutrophil-to-lymphocyte ratio (dNLR) appears highly promising in non-small cell lung cancer (NSCLC).

The primary objective of this study is to evaluate the predictive value of these biomarkers, particularly tumor PD-L1 expression, CD8 and CD4 T-cell infiltration, TAMs, TANs, and dNLR, in patients with unresectable NSCLC treated with a chemotherapy doublet.

In parallel, the secondary objective is to develop a combined immunoscore to optimize predictive stratification in these patients, thereby enabling better personalization of therapeutic approaches.

Methods: Between 2019 and 2023, we conducted a study on 56 patients with unresectable NSCLC. All patients were treated with a chemotherapy doublet at the Mohamed VI Cancer Treatment Center of Ibn Rochd University Hospital in Casablanca.

Immunohistochemistry was used to assess PD-L1 status (clone 22C3) and the density of CD8 (clone C8/144B), CD4 (clone 4B12), and TAMs (clone KP1). Additionally, the density of TANs was determined using H&E staining. Statistical analysis was performed using SPSS V21 software.

Results: The median age of the patients (N=56) was 67 years (range: 38-92 years), with a sex ratio of 5.22. A total of 80.35% of patients had a history of smoking, 80.14% were diagnosed at stage IV, and 33.93% had a performance status of 0.

Analysis of PD-L1 expression, as well as the density of CD8, CD4, TAMs, TANs, and dNLR, alongside chemotherapy response, revealed that patients with tumors poorly infiltrated by CD8 T lymphocytes had significantly better progression-free survival (PFS) and overall survival (OS) compared to those with highly CD8-infiltrated tumors (PFS: 6.63 vs. 3.01 months, p=0.012; OS: 14.07 vs. 5.06 months, p=0.005).

Furthermore, a low TAN density was associated with prolonged PFS (PFS: 7.04 vs. 3.26 months, p=0.020). Additionally, a dNLR < 0.12 was linked to improved PFS and OS compared to a dNLR ≥ 0.12 (PFS: 6.72 vs. 2.73 months, p=0.002; OS: 15.79 vs. 5.10 months, p=0.002).

Regarding the immunoscore, a combined score <9 was associated with significantly better PFS and OS compared to an immunoscore ≥9 (PFS: 6.60 vs. 3.13 months, p=0.002; OS: 12.26 vs. 7.05 months, p=0.009).

Multivariate analysis revealed that the presence of bone metastases and high-density CD8 infiltration were significantly associated with reduced PFS (p=0.004, p=0.005, respectively). Meanwhile, a performance status (PS 1-2) was significantly linked to poorer OS (p=0.043).

Conclusions: Our results suggest that tumor infiltration by CD8 T lymphocytes, TANs, and dNLR plays a significant role in predicting chemotherapy response. Additionally, the combined immunoscore appears to be a promising tool for stratifying patients based on their likelihood of responding to chemotherapy.

Keywords: Non-small cell lung cancer, Combined Immunoscore, Chemotherapy

P2.10.08 Antibody-Drug Conjugates Versus Docetaxel for Previously Treated Advanced NSCLC: Systematic Review and Meta-Analysis of RCTs

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Introduction: Docetaxel following progression on immunotherapy and platinum-based chemotherapy remains the standard of care for advanced non-small cell lung cancer (NSCLC), but offers limited efficacy. Antibody-drug conjugates (ADCs) may improve outcomes in this population. This meta-analysis evaluates the efficacy and safety of ADCs versus docetaxel in previously treated advanced NSCLC through a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: Databases [PubMed (MEDLINE), EMBASE and Cochrane Library], clinical trial registries, and proceedings of global oncology conferences from January 2015 to November 2024 were screened for phase II/III RCTs comparing ADC (e.g., sacituzumab govitecan, datopotamab deruxtecan, and tusamitamab ravtansine) versus docetaxel. Two researchers independently completed data retrieval and screening work using Covidence. The primary outcomes include progression-free survival (PFS) and overall survival (OS), while the secondary outcomes include objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). The pooled hazard ratios (HR) and odds ratios (OR) were meta-analyzed using the generic variance and Mantel-Haenszel methods as appropriate. Random-effect models were used to compute pooled estimates.

Results: Of the 212 records screened, 3 RCTs involving 1597 patients were included (Figure 1). ADCs did not significantly improve PFS (pooled HR: 0.91, 95% CI: 0.73-1.13). For OS, the pooled HR was 0.88 (95% CI: 0.78-1.00, p = 0.06), reflecting a borderline significant trend favoring ADCs, with negligible heterogeneity (I^2 = 0%). Furthermore, subgroup analysis demonstrated a significant OS benefit in the non-squamous cohort (HR: 0.85, 95% CI: 0.74-0.98, p = 0.03). Additionally, no difference was observed in terms of ORR (OR: 1.16, 95% CI: 0.54-2.51) and DCR (OR: 1.39, 95% CI: 0.75-2.57). Grade ≥ 3 treatment-related AEs were significantly lower (pooled OR: 0.49, 95% CI: 0.26-0.90, p = 0.02) with ADCs despite high heterogeneity (I^2 = 87%).

Conclusions: Our findings report a significant survival benefit in patients with non-squamous NSCLC treated with ADCs compared to docetaxel with a manageable safety profile. However, further research is needed to address heterogeneity, refine patient selection and obtain more mature survival data with predictive biomarkers.

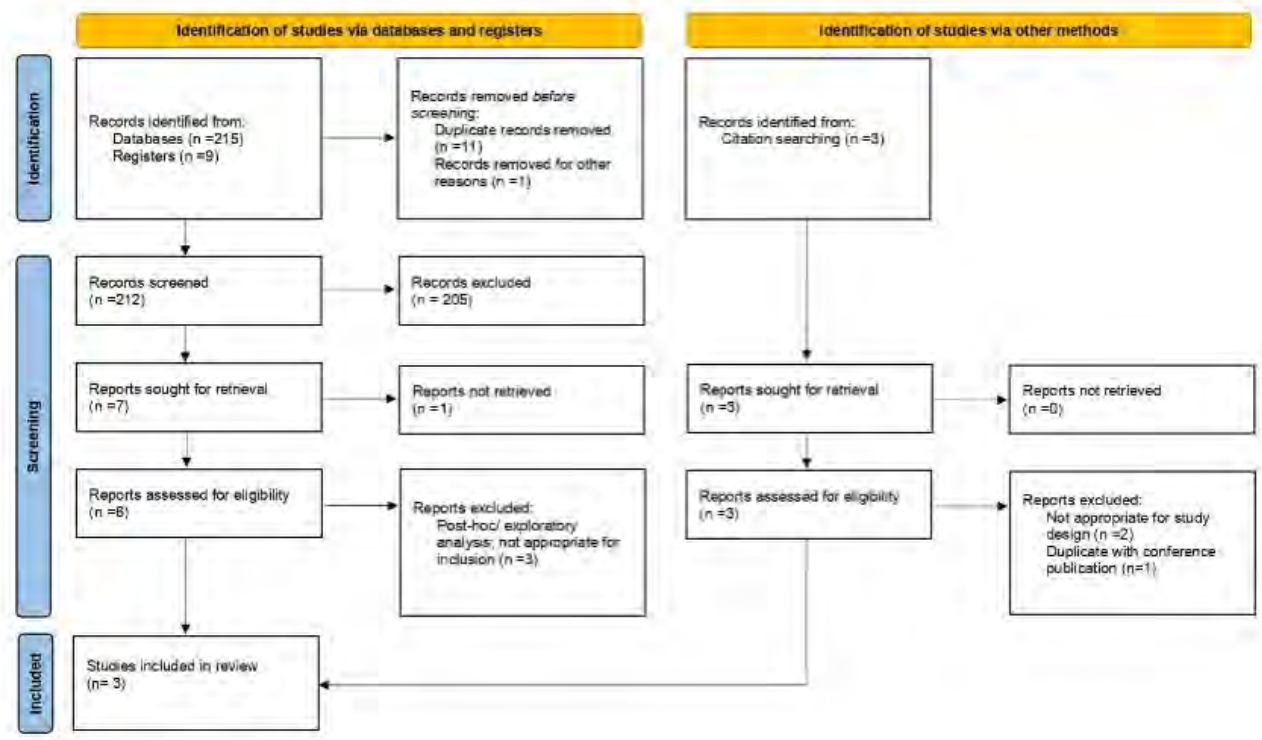

Figure 1: PRISMA 2020 flow diagram.

Keywords: Antibody-drug conjugates, chemotherapy, lung cancer

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.09 Single-Cell RNA Sequencing Reveals Subtype-Specific Resistance Mechanisms to TROP2-Targeted ADCs in Non-Small Cell Lung Cancer

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Introduction: Antibody-drug conjugates (ADCs) targeting TROP2 have demonstrated variable efficacy across non-small cell lung cancer (NSCLC) subtypes. The currently available TROP2-targeted ADCs, sacituzumab govitecan and datopotamab deruxtecan, have shown limited benefit in NSCLC overall, with relatively greater efficacy in lung adenocarcinoma (LUAD) compared to lung squamous cell carcinoma (LUSC), as seen in the TROPION-1 trial. In this study, we investigated the molecular basis underlying this differential response between LUAD and LUSC.

Methods: Single-cell RNA-seq datasets GSE131907, GSE148071, and GSE162498 were obtained from TISCH2.0, comprising a total of 361,000 cells from 97 patients after quality control. Data preprocessing involved merging datasets, normalization, scaling, and principal component analysis, followed by batch effect correction using Harmony. TROP2 expression was assessed across cell types and NSCLC subtypes using Seurat's FindMarkers function and pseudobulk differential expression analysis. Correlation analyses between TROP2 and markers of sensitivity or resistance to topoisomerase I (TOP1) inhibitors were conducted using the CSCORE algorithm.

Results: TROP2 was highly expressed on malignant epithelial cells in both LUAD and LUSC, with significantly higher levels in LUAD (fold change [FC] = 1.66, $P < 0.0001$). However, expression was not significantly different from that in normal lung epithelial cells in either subtype. In LUAD, TROP2 expression correlated positively with TOP1 ($r = 0.46$, $P < 0.0001$), suggesting potential sensitivity to TOP1 inhibitors. No such correlation was observed in LUSC. Instead, TROP2 expression in LUSC showed strong positive correlations with GCLM ($r = 0.85$), GCLC ($r = 0.40$), and GSR ($r = 0.33$), enzymes involved in glutathione metabolism and known mediators of resistance to TOP1 inhibitors. TROP2 in LUSC also correlated with ABCC2 ($r = 0.19$), a drug efflux transporter implicated in resistance to TOP1 inhibitors (all $P < 0.001$). Conversely, SLFN11, a gene associated with TOP1 inhibitor sensitivity, was negatively correlated with TROP2 in both LUAD ($r = -0.38$) and LUSC ($r = -0.36$) ($P < 0.0001$ for both).

Conclusions: Our study provides insight into the limited efficacy of TROP2-targeted ADCs in NSCLC, particularly in LUSC. While TROP2 remains a viable target, its expression in LUSC is associated with molecular signatures of resistance to TOP1 inhibitors, including upregulation of glutathione-related enzymes and drug efflux transporters. In LUAD, the correlation between TROP2 and both sensitivity and resistance markers suggest a more heterogeneous response. These findings highlight the need to optimize ADC payload selection for improved efficacy in NSCLC, especially in LUSC. Further translational studies are warranted to validate these findings.

Keywords: Antibody-drug conjugate, TROP2, Precision medicine

P2.10.10 Soluble Ceacam5 Resistant ADC for Effective Tumor Targeted Delivery With Clinically Validated Tumor Selective Linker Payl

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Introduction: Carcinoembryonic antigen cell adhesion molecule 5 (CEACAM5) is a cell surface glycoprotein prominently expressed in various cancers, particularly non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). LCB58A, a set of novel antibody-drug conjugate (ADC) targeting CEACAM5, utilizes a novel IgG1 antibody clone conjugated to LCB's proprietary ConjuAll technology. Key improvements over prior CEACAM5 ADCs include resistance to soluble CEACAM5 and use of LCB's clinically validated β-Glu cleavable linker with various payloads offering a promising therapeutic strategy.

Methods: The α-CEACAM5 monoclonal antibody was tested for binding affinity and internalization into cancer cells, in the presence of soluble CEACAM5 positive patient sera, using FACS and Incucyte systems. ADCs with various linker-toxin combinations were produced, and their cytotoxicity was evaluated across multiple cancer cell lines. For in vivo analysis, both cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models were employed alongside toxicity studies in human CEACAM5 transgenic (TG) mice. Toxicokinetic studies were also analyzed in TG mice using LC-MS/MS bioanalysis.

Results: The novel α-CEACAM5 antibody demonstrated efficient internalization, surpassing that of comparator antibody Tusamitamab in the presence of soluble CEACAM5. Binding specificity to CEACAM5 was validated via Retrogenix screening at therapeutically relevant doses. LCB58A ADCs exhibited significant cytotoxic effects in vitro and showed remarkable anti-tumor efficacy in CDX and PDX models tested. Toxicity studies showed that LCB58A ADC was well tolerated at efficacy dose with favorable toxicokinetic profile in TG mice.

Conclusions: LCB58A ADCs, leveraging the soluble CEACAM5-resistant antibody H81E6, demonstrate robust efficacy at tolerable doses. The ADCs' ability to specifically bind and efficiently internalize offers a significant therapeutic advantage, particularly in tumor environments with high levels of soluble CEACAM5. These findings highlight LCB58As' potential as highly effective treatment options for patients with CEACAM5-expressing solid tumors, representing a promising avenue in cancer therapy.

Keywords: CEACAM5, ADC, NSCLC

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.11 Single-Cell RNA Sequencing Identifies ALCAM and Gpnmb as Therapeutic Targets for ADC Development in Squamous Cell Carcinoma of the Lung

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Introduction: Antibody-drug conjugates (ADCs) combine the specificity of monoclonal antibodies with the cytotoxic potency of chemotherapeutic agents and have emerged as a promising treatment strategy in oncology. In non-small cell lung cancer (NSCLC), several ADCs have been investigated and showed better responses in lung adenocarcinoma (LUAD) compared to squamous cell carcinoma (LUSC). In this analysis, we leverage single-cell RNA sequencing to identify optimal targets and payloads for ADC development in LUSC.

Methods: The raw cell expression matrix, cellular annotations, and metadata for GSE131907, GSE148071, and GSE162498 were downloaded from TISCH2.0. Cells with less than 500 genes, 1000 counts, or more than 10 percent mitochondrial genes were excluded. A total of 361,000 cells from 97 patients were utilized. Preprocessing included merging the datasets, normalizing, scaling, and running principal component analysis. Integration of the datasets was then carried out using harmony, adjusting for batch effects. Differential expression of ADC targets between cell types and tissue subtypes was performed using the FindMarkers function in Seurat and a limma-based pseudobulk approach. Correlation analysis between ADC targets and sensitivity/resistance markers to topoisomerase 1 and microtubule inhibitors was conducted using the CSCORE algorithm.

Results: Transmembrane glycoprotein NMB (GPNMB) was significantly overexpressed in LUSC malignant cells versus normal epithelial cells (log2FC = 1.10, P = 0.012), while Activated leukocyte cell adhesion molecule (ALCAM) did not reach statistical significance. Both targets were also elevated in multiple cell types in the LUSC tumor microenvironment as compared to LUAD, including fibroblasts, macrophages, alveolar cells, and CD8+ T cells ($p < 0.0001$). In LUSC malignant epithelial cells, ALCAM negatively correlated with ABCC2 ($r = -0.41$, $P < 0.0001$) and ABCB1 ($r = -0.17$, $P < 0.0001$), two efflux transporters linked to resistance to maytansinoids and emtansine. ALCAM also positively correlated with CLTC ($r = 0.96$, $P < 0.0001$), which mediates clathrin-dependent ADC internalization. In contrast, GPNMB showed strong positive correlations with ABCG2, ABCC2, ABCB1, and SLC47A2 (all $p <0.0001$), which confer resistance to MMAE and camptothecins via drug efflux. Lastly, GPNMB ($r = -1$, $p < 0.0001$) and ALCAM ($r = -0.79$, $p < 0.0001$) were negatively correlated with NANS expression which can lead to increased ADC internalization and sensitivity by depleting sialic acid from the cell surface.

Conclusions: Our analysis highlights ALCAM and GPNMB as potential ADC targets in LUSC, with broad expression across malignant and stromal compartments. ALCAM's expression profile suggests susceptibility to maytansinoid-based ADCs such as Praluzatamab Ravtansine, due to its association with endocytosis and absence of efflux resistance signals. GPNMB, while a promising target, is associated with expression of multiple efflux transporters, raising concerns about resistance to ADCs like Glembatumumab Vedotin. These findings support a tailored approach to ADC design based on tumor subtype and resistance landscape.

Keywords: Antibody-drug conjugates, ADC targets, Resistance

P2.10.12 Trastuzumab Deruxtecan in Patients From China With Pretreated HER2-Mutant NSCLC: Final Results From the DESTINY-Lung05 Study

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Introduction: In October 2024, trastuzumab deruxtecan (T-DXd) became the first HER2-directed therapy to receive conditional approval in China for previously treated HER2-mutant (ERBB2; HER2m) unresectable/metastatic NSCLC. Approval was supported by primary results from both DESTINY-Lung02 (confirmed objective response rate [ORR], 49%; median progression-free survival [PFS], 9.9 months; median overall survival [OS], 19.5 months) and DESTINY-Lung05 (confirmed ORR, 58.3%; median PFS by independent central review [ICR], not evaluable [NE]). Here, we report the DESTINY-Lung05 (NCT05246514) final analysis.

Methods: This open-label, single-arm, Phase 2 study evaluated T-DXd (5.4 mg/kg intravenously every 3 weeks) in patients from China with HER2m (locally or centrally confirmed activating HER2 exon 19/20 mutation) metastatic NSCLC with disease progression on or after ≥1 prior anticancer therapy. Confirmed ORRs by ICR (primary endpoint) and by investigator (secondary endpoint) were per RECIST 1.1. Other secondary endpoints included duration of response (DOR), disease control rate (DCR), and PFS by both ICR and investigator per RECIST 1.1; OS, and safety.

Results: At data cutoff (November 4, 2024), 72 patients with HER2m NSCLC had received T-DXd 5.4 mg/kg; median age was 57.0 years (range 34-76), 56.9% were female, and 69.4% were non-smokers. Patients had received a median of 2.0 (range 1-7) prior systemic therapies. Median T-DXd treatment duration was 8.6 months (range 0.7-26.9), and median duration of follow up was 20.2 months (range 2-27). Confirmed ORR was 56.9% by ICR (95% confidence interval [CI] 44.7, 68.6), and 59.7% by investigator (95% CI 47.5, 71.1). By ICR, median DOR was 11.6 months (95% CI 5.8, NE), DCR was 91.7% (95% CI 82.7, 96.9), and median PFS was 9.9 months (95% CI 7.1, 16.5). Median OS was 21.0 months (95% CI 17.5, NE). Additional efficacy data are reported in the table. Grade ≥3 drug-related adverse events (AEs), drug-related serious AEs, and drug-related AEs leading to discontinuation occurred in 40 (55.6%), 23 (31.9%), and four (5.6%) patients, respectively. Overall, the most common drug-related AEs were platelet count decreased (66.7%) and white blood cell count decreased (66.7%). No drug-related deaths occurred. Adjudicated drug-related interstitial lung disease / pneumonitis occurred in nine (12.5%) patients (n=1 Grade 1; n=7 Grade 2; n=1 Grade 3).

Conclusions: Building on the primary DESTINY-Lung05 data, these results with longer follow up further demonstrate that T-DXd 5.4 mg/kg provides durable responses and survival benefit in patients from China with pretreated HER2m metastatic NSCLC. No new safety signals were reported.

	N=72	
	ICR	INV
Confirmed ORR, % (n)	56.9 (41)	59.7 (43)
95% CI	44.7, 68.6	47.5, 71.1
Best OR, n (%)		
Complete response	1 (1.4)	0
Partial response	40 (55.6)	43 (59.7)
Stable disease	25 (34.7)	24 (33.3)
Disease progression	5 (6.9)	4 (5.6)
NE	1 (1.4)	1 (1.4)
Median DOR, months (95% CI)	11.6 (5.8, NE)	9.4 (7.2, 13.5)
DCR, % (95% CI)	91.7 (82.7, 96.9)	93.1 (84.5, 97.7)
Median PFS, months (95% CI)	9.9 (7.1, 16.5)	9.7 (8.1, 13.4)
12-month PFS rate, % (95% CI)	46.1 (33.7, 57.6)	44.1 (32.2, 55.3)
18-month PFS rate, % (95% CI)	31.2 (19.6, 43.6)	22.8 (13.6, 33.4)
Median OS, months (95% CI)	21.0 (17.5, NE)	
12-month OS rate, % (95% CI)	75.0 (63.3, 83.4)	
18-month OS rate, % (95% CI)	59.7 (47.5, 70.0)	
24-month OS rate, % (95% CI)	39.7 (27.5, 51.7)	

CI, confidence interval; DCR, disease control rate; DOR, duration of response; ICR, independent central review; INV, investigator; NE, not evaluable; OR(R), objective response (rate); OS, overall survival; PFS, progression-free survival

Keywords: Trastuzumab deruxtecan, HER2-directed therapy, Metastatic non-small cell lung cancer

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.13 Sunvozertinib Combined With Bevacizumab in Previously Treated Advanced NSCLC With EGFR Exon 20 Insertion Mutations

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Introduction: Sunvozertinib is a rationally designed, oral, and potent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). A pivotal clinical study (NCT05712902) has demonstrated the significant antitumor efficacy of sunvozertinib monotherapy for previously treated advanced non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations (exon20ins), leading to its conditional approval in China in this disease indication. With the positive results of EGFR TKI combined with bevacizumab in NSCLC with EGFR sensitizing mutations (ARTEMIS-CTONG1509), it is hypothesized that sunvozertinib combined with bevacizumab could further enhance the antitumor effect in NSCLC with EGFR exon20ins. Here we report the preclinical and clinical data on this combination therapy.

Methods: The preclinical effect of sunvozertinib with bevacizumab was tested in patient-derived xenograft (PDX) animal models carrying EGFR exon20ins, and potential mechanism-related biomarkers were evaluated before and after treatment by immunohistochemistry. WU-KONG29 (NCT06276283) is an ongoing phase 2 multicenter dose escalation and expansion study to investigate the safety and efficacy of this combination therapy in patients with EGFR mutant (EGFRm) NSCLC, with a focus on EGFR exon20ins. In the dose escalation part, previously treated patients with EGFRm NSCLC received sunvozertinib 200 mg or 300 mg once daily (QD) with bevacizumab 15 mg/kg once every 3 weeks. In the dose expansion part, previously treated patients with EGFR exon20ins received sunvozertinib 300 mg QD with bevacizumab. Safety and efficacy were assessed by investigators per CTCAE5.0 and RECIST1.1, respectively.

Results: Sunvozertinib with bevacizumab led to greater tumor shrinkage in PDX models, as well as a greater decrease in tumor microvessel density and downstream signaling (pS6) than single drugs. As of January 3, 2025, a total of 19 previously treated patients were enrolled in the WU-KONG29 study, and 14 patients who had EGFR exon20ins were treated with sunvozertinib 300 mg QD and bevacizumab. The median age was 56 years, and 92.9% had an ECOG score of 1. All patients had metastatic disease, and 42.9% had baseline brain metastasis. All patients received prior chemotherapy. Per investigator assessment, 8 out of 14 patients achieved partial response, with an objective response rate (ORR) of 57.1% (50% confirmed) and a disease control rate of 100%. With a median follow-up of 9.8 months, the median duration of response (DoR) was not reached, and the 12-month durable response rate was 71.4%. With a median follow-up of 12.4 months, the estimated median progression free survival (PFS) was 16.4 months. In patients with baseline brain metastasis, the confirmed ORR was 50%, and the median PFS was 11.0 months. Treatment-related adverse events of grade ≥3 and serious adverse events were reported in 52.6% and 10.5% of patients, respectively. No new safety risks were noted compared to individual drugs.

Conclusions: Our results demonstrated notable combination effect of sunvozertinib with bevacizumab in pretreated NSCLC with EGFR exon20ins.

Keywords: Advanced non-small cell lung cancer, EGFR exon 20 insertion mutation, Sunvozertinib combined with bevacizumab

P2.10.14 Individualized Neoantigen Therapy With Unusual Radiotherapy Enhancement (iNATURE) a Phase II Randomized Study

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Introduction: Personalized neoantigen-based vaccines targeting tumor-specific neoantigens are emerging as a promising immunotherapy, with recent publication in Nature reporting 9 cases showing no relapse 40 months after surgery. However, in refractory solid tumors, the effect is limited due to significant tumor burden. We hypothesized that neoantigen peptide vaccines combined with immune modulating precision Critical Lesion Radiotherapy (CLERT) can improve local and distant tumor control. This study aimed to evaluate the safety, feasibility, and early efficacy of this approach in metastatic cancer patients who failed systemic therapy.

Methods: This is a phase II randomized study (NCT06314087) focusing on refractory metastatic cancers. Eligibilities included metastatic solid tumors with progression after systemic therapy and “targetable” lesions for CLERT. Neoantigens were selected using an AI-powered immunogenicity prediction platform based on whole exosome sequencing by three independent teams. There were two arms: the control arm with placebo, and the vaccine arm receiving fully personalized peptides, BXP-001. All patients received CLERT one week before vaccine injection, with 5 prime immunizations and four monthly boosters. Control patients crossed over to the vaccine arm upon disease progression. Immune responses were assessed through T cell and antibody testing.

Results: This is a pre-planned interim report. A total of 46 patients have been screened with WES genomic testing of over 20000 genes. On average, 2.626 (95% CI: 2.111-3.142) tumor mutation burden were tested. All patients had immunogenic mutations, with tumor neoantigen burden ranged from 0.756-1.099 (median 0.928), 60% patients were found to have 5+ high-ranking immunogentic neoantigens, confirmed by all 3 teams. Upto March 31, 2025, 11 of these NSCLC patients were enrolled and successfully randomized. Two patients died from tumor progression accociated complication before protocol treatment start. Seven patients are currently undergoing treatment or have already completed it, while others are awaiting treatment initiation. Among the 7 treated patients treated per protocol, 3 and 4 patients were assigned to the neoantigen and control arms, respectively. 3 of 4 control patients had disease progression on placebo arm and were subsequently crossed over to the vaccine arm. All 7 patients received vaccine had disease controlled with a median follow-up of 2.73 months (95% CI 1.16-6.39). The median PFS for the placebo group was 1.4 months (95% CI 1.13-NR), while the median PFS for the neoantigen group has not yet been reached. Immunogenicity analysis of PBMC and plasma samples revealed neoantigen-specific immune response in T cell and antibody in all tested patients. There was no grade 2 above toxicity in either of the arms, 14.3% received vaccine had grade 1 injection site bruise and 14.3% fatigue.

Conclusions: This study at the first time demonstrated iRT of fully personalized neoantigen peptide vaccine (BXP-001) and CLERT was feasible, safe, and capable of eliciting neoantigen-specific immune responses in all analyzed patients with refractory solid tumors. The preliminary results in PFS between vaccine and placebo groups appears to be promising. Further study with larger sample size in multicenter setting is beining kicked off to confirm this promising strategy.

Keywords: Neoantigen Vaccine, Critical Lesion Radiotherapy, Randomized Study

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.15 Mechanistic Study of Osimertinib Combined With Sitravatinibto Overcome Acquired Osimertinib Resistance in Non-Small Cell Lung Cancer

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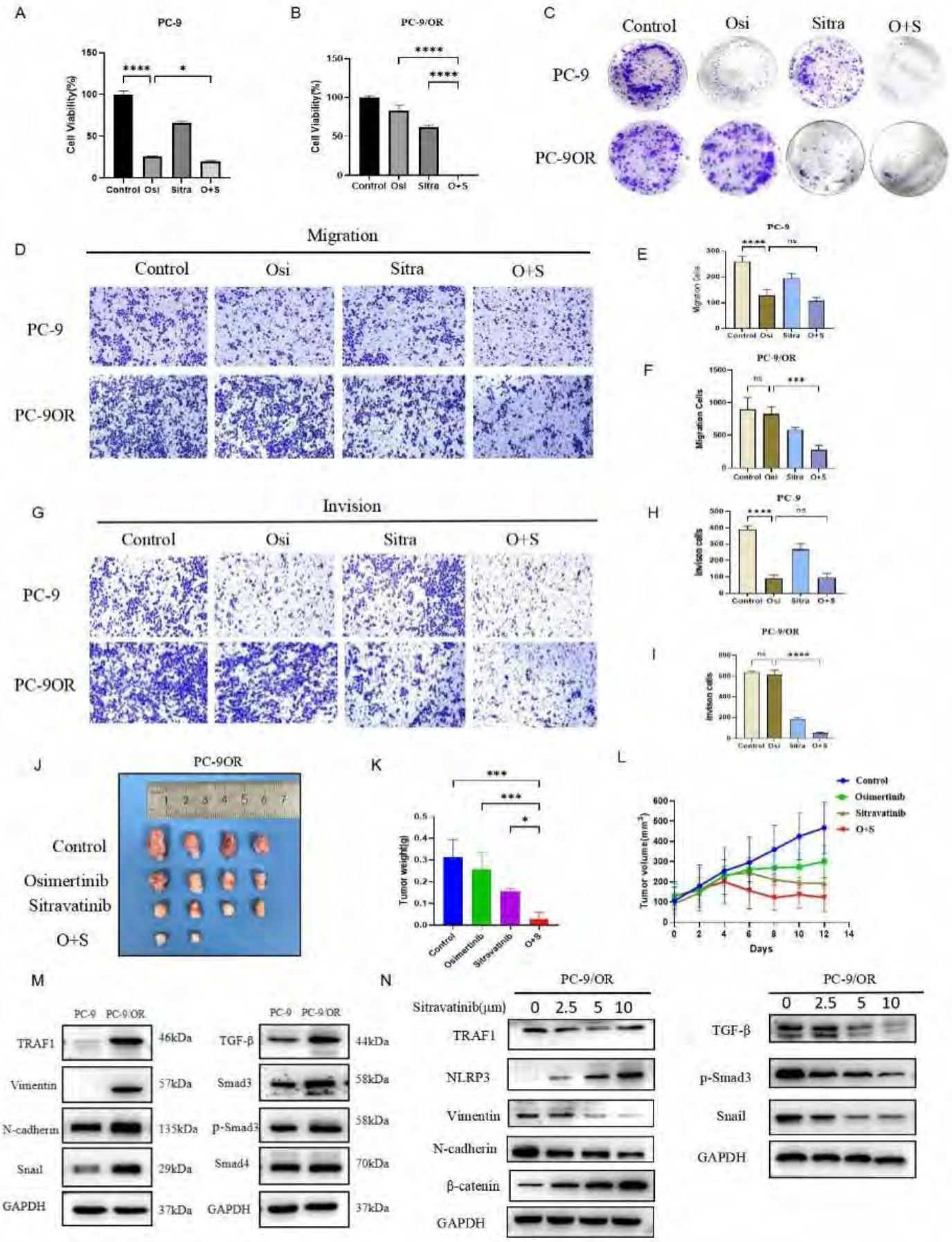
Introduction: Osimertinib,a third-generation EGFR inhibitor, has become the standard treatment for EGFR-mutant non-small cell lung cancer (NSCLC). However, acquired resistance remains a major challenge for most patients after prolonged therapy.Sitravatinib a multi-target tyrosine kinase inhibitor, has shown promise in overcoming immune resistance and chemotherapy resistance in the treatment of various solid tumors. Its potential to overcome targeted therapy resistance in NSCLC, however, remains unclear.

Methods: A NSCLC osimertinib-resistant cell line (PC-9/OR) was established to mimic clinical resistance. In vitro experiments were then conducted to evaluate the effects of combining osimertinib with sitravatinib on cell proliferation, migration, and invasion, while also investigating the underlying molecular mechanisms. Furthermore, a NSCLC osimertinib-resistant mouse model was developed to assess the in vivo anti-tumor activity of the combined therapy.

Results: Compared with osimertinib monotherapy, the combination of osimertinib and sitravatinib significantly inhibited the proliferation, migration, and invasion of drug-resistant cells. However, this combinational treatment did not exhibit a markedly enhanced inhibitory effect on the parental cells. Moreover, in a mouse model of osimertinib-resistant non-small cell lung cancer (NSCLC), the combination therapy significantly suppressed subcutaneous tumor growth compared to osimertinib alone.Transcriptomic and proteomic analyses revealed that in the osimertinib-resistant cell line, several differentially expressed genes were identified, among which the anti-apoptotic protein TRAF1 and mesenchymal markers associated with epithelial-mesenchymal transition (EMT), including Vimentin and N-cadherin, were markedly upregulated. Upon treatment with varying concentrations of sitravatinib, the expression levels of TRAF1, Vimentin, N-cadherin, and proteins related to the TGF-β signaling pathway, which regulates EMT, were reduced in a dose-dependent manner. In contrast, the expression of the epithelial marker β-catenin increased in a dose-dependent fashion. Additionally, the expression of the pyroptosis-associated protein NLRP3 was elevated in a dose-dependent manner.

Conclusions: This study found that the combination of sitravatinib and osimertinib significantly inhibits the proliferation, migration, and invasion of osimertinib-resistant non-small cell lung cancer (NSCLC) cells, and markedly suppresses tumor growth in vivo. Mechanistic investigations revealed that TRAF1 and EMT-related signaling pathways are notably activated in osimertinib-resistant cells. The combined therapy may overcome resistance by simultaneously inhibiting anti-apoptotic mechanisms, inducing pyroptosis, and targeting the TGF-β/SMAD/SNAIL axis to suppress the EMT process. These findings provide novel insights and potential therapeutic strategies for the treatment of NSCLC after the development of resistance to osimertinib.



Keywords: Non-Small Cell Lung Cancer, Acquired Resistance to Osimertinib, Drug Combination

P2.10.16 Paclitaxel Liposome Combined With Immunotherapy in the First-Line Treatment of Advanced NSCLC: Updated Results of a Real-World Study

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Introduction: Paclitaxel liposome is a formulation in which paclitaxel is encapsulated within liposomes composed of lecithin and cholesterol. Unlike conventional solvent-based paclitaxel, this formulation eliminates the need for polyethoxylated castor oil, thereby reducing the incidence of drug-induced toxicity, particularly hypersensitivity reactions. This study aimed to evaluate the real-world effectiveness and safety of paclitaxel liposome-based chemotherapy plus immunotherapy as first-line treatment among Chinese patients with advanced non-small cell lung cancer (NSCLC).

Methods: Data were extracted from the "Efficacy and Safety of Immunotherapy in NSCLC Patients: A Multi-Center Observational Study" project ,part of a real-world lung cancer database initiative launched by the Lung Cancer Special Committee of the China Medical Education Association.This analysis specifically focused on paclitaxel liposome plus immunotherapy regimens. Patient records were obtained from an online hospital platform. Non-laboratory adverse events were based on analyses of patient-reported outcome(PRO) data.The study evaluated advanced NSCLC patients who underwent first-line treatment with paclitaxel liposome-based chemotherapy and immunotherapy in eight Chinese hospitals between April 2020 and January 2025. The primary outcome was progression-free survival (PFS), while secondary outcomes included objective response rate (ORR), overall survival(OS) and safety.

Results: Among 336 eligible patients, 320 were male, with a median age of 68.5 years (range: 61.0 -73.0). 240 (71.4%) were squamous cell carcinoma, 27(8.0%) were adenocarcinoma. 31.0% of the patients were at stages IIIB-IIIC, and 69.0% were at stage IV. The median treatment cycles for first-line paclitaxel liposome-based chemotherapy and immunotherapy were 4. Immunotherapy agents included tislelizumab (n=192), pembrolizumab (n=51), sintilimab (n=38) and others. All patients were co-administered platinum with 91.1% receiving carboplatin. As of March 2025,the median duration of follow-up was 14.9 months. The median PFS was 13.07 months (95% CI: 11.4-14.0),with 1-year and 2-year PFS rates were 53.1% (95% CI: 46.3-58.5) and 28.6%(95%CI:20.4-35.0),respectively. The 1-year and 2-year OS rates were 90.7% (95% CI: 86.6-93.6) and 73.7%(95%CI:65.4-79.1),respectively. Multivariate analysis identified treatment cycles (>3) of paclitaxel liposome and achieved ORR as independent predictors of prolonged PFS(P<0.05) Among all patients,24 achieved a complete response, 188 demonstrated a partial response, 106 had stable disease, and 18 experienced progressive disease. The overall ORR was 63.1%, and the DCR was 94.6%. Adverse events of all grades were recorded in 94.6% of the patients,with 63.4% were of grade 3 or higher. All observed adverse events were consistent with those described in the product prescribing information. The most common adverse events included bone marrow suppression, gastrointestinal reactions, and liver function abnormalities. The adverse events observed in >20% of the patients were anaemia, leucopenia, neutropenia, increased r-glutamyltransferase, increased alanine aminotransferase, thrombocytopenia, hypoproteinemia, increased alkaline phosphatase and increased aspartate aminotransferase.

Conclusions: In this real-world study, paclitaxel liposome-based chemotherapy plus immunotherapy demonstrated robust efficacy and a manageable safety profile in advanced NSCLC, without an increased risk of unexpected toxicity. These findings support its use as a viable first-line treatment option in this population.

Keywords: Paclitaxel liposome, Immunotherapy, Non-small cell lung cancer

P2.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.10.17 Dual PARG-TOP1 Inhibition Exacerbates Dna-Protein Crosslinks and Replication Stress: A Promising Strategy for Enhancing Top1i-ADC Efficacy

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Introduction: Antibody-drug conjugates with topoisomerase I inhibitor payloads (TOP1i-ADCs) are having a significant impact as cancer therapies in select tumor types. However, a persistent challenge facing broad development of TOP1i-ADCs across solid tumors is optimization of tumor-specific payload delivery required for meaningful anti-tumor activity given low or heterogeneous tumor-selective antigen expression. Recent findings indicate an essential role for the poly ADP-ribose glycohydrolase, PARG, in the repair of TOP1-DNA cleavage complexes (Top1ccs), a type of enzymatic DNA-protein crosslink (DPC) that can promote lethal DNA damage when sufficiently induced by TOP1i. Here we evaluated the potential for PARG inhibition to selectively amplify TOP1i-induced DNA damage and to promote the therapeutic effects of TOP1i-ADCs in multiple preclinical models. We find that the clinical-stage PARG inhibitor, IDE161, significantly enhances TOP1i-dependent accumulation of Top1ccs and associated replication fork failure in cell line models. Notably, IDE161 promotes the efficacy of multiple TOP1i-ADCs in lung cancer models, establishing IDE161 as a promising partner for TOP1i-based ADC therapies to enhance efficacy and durability and improve patient outcomes.

Methods: Mechanistic PARGi sensitivity and PARG gene dependency associations were assessed by multiomic profiling across cancer cell line panels. Single-agent and combination effects of PARG and TOP1 inhibitors on cell viability were evaluated via high-throughput multiplexed screens and synergistic effects were validated in select cell lines. Mechanism of action was established by quantifying drug effects on replication stress markers including replication fork progression (DNA fiber assay), PAR chain accumulation (MSD), and Top1cc/γH2AX levels (immunofluorescence). In vivo tumor growth inhibition was measured in tumor cell-derived xenografts (CDX) treated with IDE161 and TOP1i-ADCs.

Results: Evaluation of IDE161 antiproliferative activity across a panel of molecularly characterized cancer cell lines highlighted significant associations of PARG sensitivity with molecular signatures of chronic replication stress. Consistent with this, IDE161 induced PAR chain accumulation, extensive replication fork stalling, increased transcription-replication conflicts, activation of the ATR-mediated cell cycle checkpoint, and γH2AX signatures associated with pan-genomic replication fork collapse. Notably, pan-cancer drug assessments indicated a strong correlation between PARGi and several TOP1 inhibitors. Multiplexed viability screens with combination treatment of IDE161 and topotecan revealed enhanced cellular proliferation defects in multiple tumor models compared to single agent treatment. Mechanistically, the combination of TOP1 and PARG inhibition showed increased Top1cc levels and enhanced replication fork slowing, suggesting that the IDE161/TOP1i combination induces DNA lesions that interfere with DNA replication. In addition, TOP1 inhibition synergistically increased the accumulation of cellular PAR levels and γH2AX caused by IDE161 treatment, suggesting hyper-PARylation of Top1ccs and failure of DPC resolution, demonstrating that IDE161 amplifies TOP1 inhibitor-induced DNA damage and replication catastrophe. Importantly, deep, durable, and complete responses were observed with IDE161 in combination with multiple TOP1i-ADCs in lung cancer CDX models, that were not achievable with monotherapy.

Conclusions: These findings deliver a strong mechanistic rationale for the use of systemic PARG inhibition to enhance the efficacy and durability of TOP1i-ADC therapies in solid tumors, particularly in the setting of lung cancer.

Keywords: PARG, Topoisomerase I, ADCs

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .01 Expedited Diagnostics Coordination Leads to Expedited Care in Advanced Stage Lung Cancer

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Introduction: To design a patient-centric treatment plan for advanced stage non-small cell lung cancer, evaluation of actionable genetic variants is essential. Genetic mutations can be evaluated via tissue analysis and serum analysis. Such tests typically take time to process which can lead to delayed initiation of systemic treatment if there is not a symptomatic presentation necessitating urgent initiation of chemotherapy. These delays not only burden oncology practices but are also a source of significant anxiety for patients awaiting a conclusive treatment proposal and subsequent initiation of therapy.

Methods: The purpose of this work was to expedite genetic variant analysis and to reduce testing delay-related anxiety for newly diagnosed patients with advanced stage NSCLC. The intervention was two pronged: First, serum genetic variant testing was ordered at the time of diagnosis/staging by the lung nodule clinic within the pulmonary department as part of the preparation for upcoming oncology consultation. If the patient is local, the testing was obtained at the treatment facility. If the patient lived a distance from the treatment facility, a draw local to the patient was coordinated in collaboration with the serum genetic variant testing vendor; there was no additional charge to the patient for this service. Standard practice was to have such testing obtained at the time of oncology consult. Second, within 48 hours of the pulmonary provider delivering the diagnosis to the patient, the lung cancer nurse navigator conducted a virtual visit with the patient to provide an overview of the oncology process at the treatment facility. A discussion of consultation visit expectations, processing time of genetic variant testing and the necessity of those results prior to treatment planning, and general overview of management of advanced stage NSCLC was provided. The patient was provided an opportunity to ask questions of the nurse navigator.

Results: Over a period of 6 months, data abstraction from the patient record comparing the intervention group (patients sent from pulmonary department) versus the control group (patients triaged direct to oncology from non-pulmonary provider) was completed. At the time of oncology consult, 51% of intervention patients had serum genetic variant analysis resulted while only 11% had resulted in the control group. Therefore, treatment decisions were finalized in 71% of intervention patients as compared to 26% from the control group. Patients who were referred from pulmonary medicine who received the post-diagnosis oncology introductory phone call expressed appreciation in timely contact, education, and resource access when applicable.

Conclusions: Coordination of genetic variant analysis serum testing at the time of diagnosis increases the likelihood that test results will be available at the time of oncology consult to therefore allow for treatment decisions at the first consult visit. Additionally, by drawing variant testing earlier systemic treatment can be initiated earlier. This in combination with a nurse navigator-initiated oncology introduction call can reduce patient anxiety, set clear patient expectations, and illustrate to the patient that the team is actively working on their case all leading to an improved patient experience.

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .02 Communication Needs of Patients With Advanced Lung Cancer Receiving Immunotherapy: Results of a Qualitative Study

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Introduction: The demand for information and participation in decision-making among cancer patients is steadily increasing but often remains unmet. The rapid advancements in lung cancer treatments over recent years have resulted in greater complexity, which can be overwhelming for patients. For a predominantly elderly and frail population, shared decision-making is particularly challenging. Recent studies indicate that lung cancer patients receiving immunotherapy frequently have an inadequate understanding of treatment goals and prognosis hazarding the timely integration of palliative care. Our study aims to explore patients' knowledge about immunotherapy, the information and decision-making process, and their awareness of palliative care topics in order to inform the development of a digital decision-support tool.

Methods: Semi-structured, in-depth interviews were conducted with 20 patients with advanced lung cancer receiving immunotherapy at the Department of Thoracic Oncology (Heidelberg University Hospital), Germany. Qualitative content analysis was performed using MAXQDA.

Results: We identified the following themes: decision-making preferences, information provision and processing, prognostic awareness, perceptions of palliative care, and utilization of digital tools. Overall, patients showed limited and often inaccurate knowledge about immunotherapy. They recalled the informed consent process, but participation in decision-making with physicians was minimal, leading in most cases to uncritical acceptance of the medical treatment recommendations. The primary information source was the medical staff, while web-based information and digital sources were generally viewed negatively. Although patients were mostly aware of the goals of palliative care in general, there was significant variability in their prognostic awareness and perceptions of personal palliative care needs.

Conclusions: The substantial gaps in knowledge regarding the effects and risks of immunotherapy, along with limited awareness of opportunities to integrate personal preferences into decision-making, highlight the need for enhanced patient empowerment strategies. The rapid pace and complexity of advancements in cancer treatment options require flexible approaches to information delivery and decision-making. Digital solutions could play a key role in supporting this process. The negative attitude towards the use of digital devices in our study may be age-related, underscoring the importance of involving elderly patients in the development of digital tools. These tools should be designed to empower patients in a way that addresses their unique information needs and decision-making strategies.

Keywords: communication, decision-making, immunotherapy

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .03 Predictive Value of LIPI Score in the Response to Immunotherapy in Very Elderly Patients With Advanced Non-Small Cell Cancer

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Introduction: The Lung Immune Prognostic Index (LIPI) score is a tool for predicting response to immunotherapy in non-small-cell lung cancer (NSCLC). However, its use in very elderly populations is unknown, although the use of immunotherapy is increasing in this group. In addition, there is an increasing incidence of NSCLC in very elderly (≥80 years, geriatric guidelines definition). Objective: study the value of LIPI in predicting response to immunotherapy in very elderly patients "pts" with advanced NSCLC.

Methods: Prospective study of pts over 80 years with a diagnosis of advanced NSCLC who had received immunotherapy. The LIPI score was calculated using LDH and dNLR values collected 30 days prior to the start of treatment (dNLR>3, LDH >ULN). Molecular study (TruSight Panel) and PD-L1 were performed in all pts. SPSS software and Kaplan-Meier test were used to compare survival in months "m" (statistical significance p<0.05) between prognostic groups according the LIPI score.

Results: Thirty pts with a median age of 83 years [80-95] were studied. Males were 80% and females 20%. The most frequent histology was adenocarcinoma (18 pts, 60%) followed by squamous (10 pts, 33.3%). The PD-L1 was ≥50% in 13 pts (43.3%) and <50% in 17 pts (56.7%). 26.7% of pts had driver mutations, the most frequent were KRAS G12C (10%), METex14 skipping (10%) and ERRB2 (Ex20Ins 3.3% and G660D 3.3%). The most frequently altered gene was KRAS (20%). 80% (24 pts) received first-line treatment (62.5% monotherapy 'ICI' and 9 chemo-immunotherapy 'CT-ICI') and 20% in second-line (100% monotherapy). According to LIPI score, 7 pts (23.3%) belonged to the good prognostic group, 15 pts to the intermediate group (50%) and 8 pts to the poor prognostic group (26.7%). Median overall survival (OS) was 14m in good prognosis group, 6m in intermediate and 1m in poor prognosis group (p=0.062). Median progression-free survival (PFS) was not reached 'NR' in the good prognosis group, 5m in intermediate group and 1m in poor prognosis group (p=0.035). The disease control rate was 85.7% in good prognosis group, 60% in intermediate and 25% in poor prognosis group (p=0.057). Statistically significant differences were maintained in OS and PFS irrespective of the use of chemo-immunotherapy or immunotherapy and the use in first-line treatment. In the CT-ICI group OS was 8m versus 7m versus 1m (p=0.18) and PFS was 6m versus 7m versus 1m (p=0.018). In the ICI group the OS was 14m versus 5m versus 1m (p=0.133) and the PFS was NR versus 2m versus 1m (p=0.110). In first-line treatment the OS was NR versus 6m versus 1m (p=0.038) and PFS was NR versus 5m versus 1m (p=0.007). In second-line treatment was not possible calculate differences due to the sample size.

Conclusions: The prognostic groups established according to the LIPI score correlated with efficacy to immunotherapy in very elderly pts with advanced NSCLC. The LIPI score is a valid tool that may allow personalisation and individualisation of the treatment of NSCLC in very elderly pts that present an increasing incidence.

Keywords: Very Elderly Patients, Immunotherapy, LIPI score

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .04 End-Of-Life Systemic Therapy and Survival in Metastatic Lung Cancer: A Territory-Wide Real-World Studyof 24,608 Patients

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Introduction: The role of systemic anticancer therapy (SACT) at the end of life (EOL) remains controversial. While concerns exist regarding overtreatment and diminished quality of life, recent advances in targeted therapies and immunotherapies may provide clinical benefits even in the terminal phase of lung cancer patients. However, limited real-world evidence exists on the impact of EOL SACT, particularly in Asian populations.

Methods: This cohort study with prospective follow-up utilized a territory-wide electronic healthcare database covering over 90% of Hong Kong's population. Patients diagnosed with metastatic lung cancer with minimum follow-up of 2 years were eligible. Hospitals were stratified into quartiles based on the National Quality Forum 0210 measures (NQF 0210) which was designed to evaluate the proportion of cancer patients receiving SACT within 14 days of death, aiming to reduce potential overtreatment at the end of life. The primary outcome was overall survival (OS), while SACT and hospice care utilization were tested as independent variables. Overlap weighting was applied to balance covariates, and survival analyses were performed across NQF 0210 quartiles.

Results: A total of 24,608 patients with stage IV lung cancer were enrolled between January 1, 2010, and December 31, 2022. The median survival was 8.3 months (95% confidence interval (CI), 8.1-8.4) in all patients, and 12.7 months (95% CI, 12.5-12.9) in 16.544 patients (67%) received SACT 67.2%.. The median survival was 7.1 months (95% CI, 6.9-7.3) in 4,067 patients (57.1%) received hospice care. In 8050 patients (32.7% received both SACT and hospice care, the median OS was 12.0 months (95% CI, 11.7-12.4). Interestingly, higher NQF 0210 rates were associated with significantly longer OS (Q4 versus Q1: hazard ratio (HR), 0.620; 95% CI, 0.570-0.674; P < 0.001). Median OS was 4.2 months in Q1 versus 10.4 months in Q4. Improved OS in higher NQF 0210 quartiles persisted across subgroup analyses by diagnosis year and hospice use. Notably, hospice care alone in patients without SACT showed no significant survival improvement (2.7 vs. 2.5 months; HR, 0.894; 95% CI, 0.778-1.028; P = 0.115), whereas combining hospice with aggressive SACT was associated with significant survival gains (Q4 versus Q1, HR, 0.575; 95%CI, 0.514-0.643).

Conclusions: Higher hospital-level SACT use at EOL is associated with improved OS in advanced lung cancer patients, either alone or with use of hospice service. Medial survival difference is remarkable for these patients with end stage of life. Value of EOL SACT deserves further study. Refinement of EOL quality measures is needed to balance minimizing ineffective treatment while preserving survival benefits.

Keywords: Metastatic lung cancer, End-of-life care, Systemic anticancer therapy

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .05 A Shared Decision Aid for First-Line Treatments of ALK+ Advanced Non-Small Cell Lung Cancer: A Patient-Centered Approach

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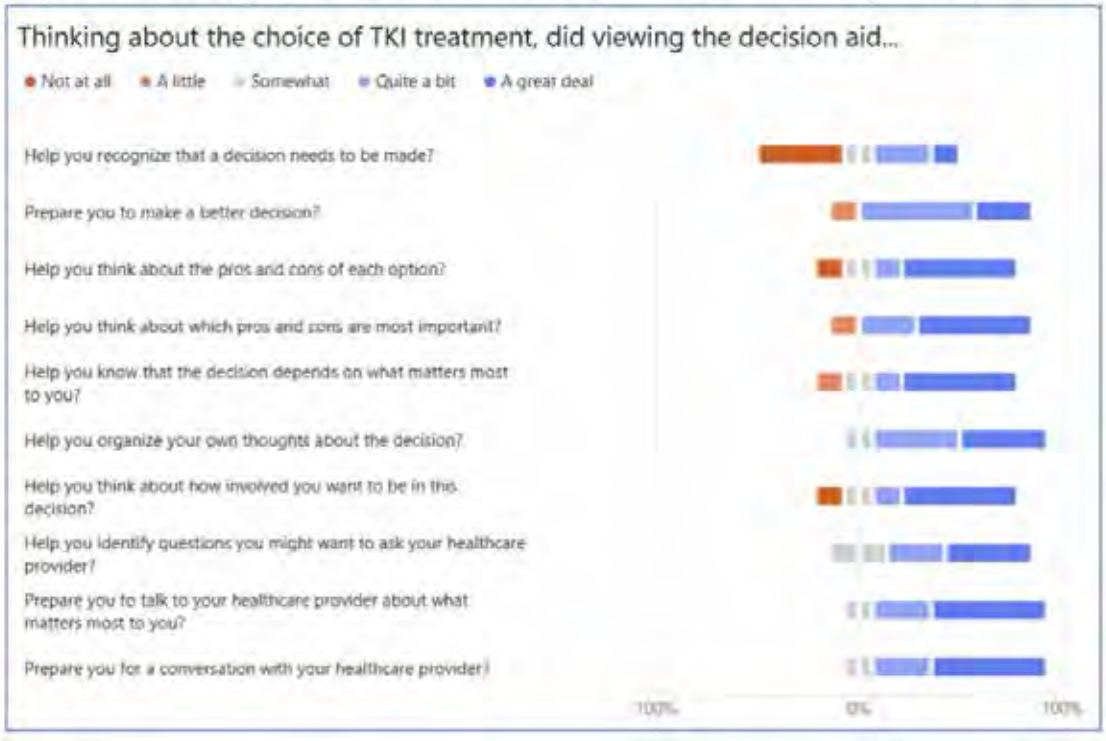
Introduction: Choosing first-line (1L) anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) for ALK+ advanced non-small cell lung cancer (aNSCLC) is challenging due to varied treatment risk/benefit profiles, lack of head-to-head trials, and patient preferences. Patient decision aids (DAs) can improve knowledge, reduce decisional conflict, and support values-concordant decisions. A team of oncologists, patient advocacy group (PAG) representatives, DA and preference experts, industry scientists, and web developers created the first digital DA with a values clarification activity (VCA) for newly diagnosed ALK+ aNSCLC patients to support shared decision-making with oncologists.

Methods: The study included 25 participants. Concept interviews with 11 patients informed content and user interface development, followed by 3 oncologist interviews and beta testing with 7 patients (interviews and surveys) to refine the DA. Transcripts were analyzed using an Excel-based matrix. Four patient advisors provided feedback throughout development. The DA comprises: Introduction/patient journey, TKI education, resources, a quantitative VCA (Best Worst Scaling [BWS]), an individualized report with a treatment attribute priority list, and other features.

Results: Patients (n=18, age range: 33-76; time since diagnosis: 2-20 months; all using 1L TKIs) expressed the value of the DA for newly diagnosed patients seeking information about treatment options. Many indicated that having this DA upon diagnosis would have been informative and empowered them to engage in shared decision-making with their providers. Patients endorsed the teaching approach, aggregating treatment "similarities" and "differences" to highlight differentiators and reduce information overload. Findings indicated balanced treatment presentation, attention to cognitively/psychologically challenging concepts, question features, and use of the VCA. Patients confirmed the importance of individualized reports and pre-generated questions. Beta testing demonstrated the desired deliberation during the VCA; participants discussed multiple attributes as important, and selecting the most and least important features was challenging yet meaningful in determining their priorities. Beta participants demonstrated positive responses on the preparation of the decision-making measure (Figure 1). Oncologists (n=3; 1 community health and 2 academic centers; currently caring for patients with ALK+aNSCLC; range: 2-10) supported the DA's value in helping patients understand treatment options and identify preferences. Suggestions were made to refine content further (e.g., addition of a new similarity item).

Conclusions: The DA was well received. Participants discussed the value of centralized, patient-friendly information about 1L TKIs that helps patients understand their priorities and supports shared decision-making. The DA will be disseminated by ALK Positive (United States) and Go2Lung PAGs via their websites in the second half of 2025.

Figure 1. Results from preparation of the decision-making measure (beta user testing interview)



Keywords: ALK+ aNSCLC, shared decision making, first line

P2.15 .06 Best Practices and Process Variations of Lung Cancer Multi-Disciplinary Teams: Insights From Europe and Israel

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Introduction: Multidisciplinary teams (MDTs) are key in the Lung Cancer care pathway. They leverage diverse disciplines involved in patient treatment decisions to achieve better patient outcomes than single-discipline decisions. MDTs drive earlier treatment initiation and improved guideline-concordant care, positively impacting survival outcomes. Although they share a common goal, there are significant differences in how Lung Cancer MDTs operate across hospitals in Europe and Israel, with each hospital employing varied best practices to achieve high-performing MDTs.

Methods: Over 150 semi-structured interviews were conducted with MDT members from 28 hospitals across 20 countries in Europe and 3 hospitals in Israel. MDT members also completed an MDT self-assessment to demonstrate MDT maturity and a questionnaire to assess perceived impact of Lung Cancer MDTs on: MDT status quo (team composition, process), patient pathway (scale, time), and qualitative impact (patient outcomes, cost). Best practices and process variations were then pressure tested with 31 working groups within respective hospitals.

Results: We obtained 3 sets of results: First, a clear overview of the existing MDT organisational processes within Europe and Israel, including variations, advantages, and disadvantages in processes, as well as the maturity level of participating MDTs. The MDT self-assessment results demonstrate a high MDT maturity across participating hospitals, especially in domains of MDT process (average score 3.2/4.0) and culture (average score 3.3/4.0); conversely, a lower score in Technology (average score 2.2/4.0). The lower score in technology likely reflects a lack of integrated systems, digital tools to aid MDT preparation and decision making, and a few hospitals still using a paper-based system. Second, 50+ best practices encompassing patient access, MDT operations, technology utilisation, medical practice quality, and team capabilities were identified. Third, insights on common gaps and challenges across European countries and Israel requiring process organisation, institutional, or policy-level action were identified. Examples mentioned by participating hospitals range from a lack of structure to registering patients for MDT discussion, to the need for an MDT coordinator or Nurse Navigator role to follow patient journeys, as well as the MDT preparation, discussion, and follow-ups. Although 40% of participating centres indicated a Nurse Navigator or MDT coordinator present, this was usually in the form of a secretary providing strictly administrative support. Another common insight was the lack of funding from national health services or hospitals on resources, time and effort required by all disciplines to participate in MDTs. Organisational and institutional level gaps were identified and matched to actionable best practices, including quick-wins ready for implementation (e.g., creation of a standardised patient registration template and reporting structure) and long-term initiatives requiring further efforts.

Conclusions: This study provides insights into specific Lung Cancer MDTs' ways of working, process variations, best practices, and recommended actions for improvement. This can improve how MDTs are organized and managed Europe-wide, ultimately improving patient outcomes. The description of typical challenges and gaps encountered by MDTs throughout Europe and Israel can serve as a guide for hospitals on the essential collaboration needed to effect change on both national and global scales.

Keywords: Multi-disciplinary Team, MDT, Lung Cancer

P2.15 .07 Effect of Message Framing in a Digital Lung Cancer Screening Decision Navigation Intervention: A Three-Arm Randomized Controlled Trial

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Introduction: The risks and benefits of low-dose CT (LDCT) screening necessitate informed decision-making among high-risk individuals. Patient decision aids (PDAs) help align screening choices with personal values. Research suggests message framing influences health decisions, but its impact on lung cancer screening (LCS) uptake remains unclear. To address this, we developed China's first LCS PDA, the LCS Loss-Gain Balance (LCS-LG-B), integrating gain-framed (emphasizing benefits) and loss-framed (highlighting consequences) messaging. This study aims to develop a digital decision navigation intervention tailored for high-risk individuals in China and evaluates its effectiveness in promoting LCS uptake by leveraging gain-framed and loss-framed messaging through the LCS-LG-B.

Methods: Using a systematic review, qualitative interviews, and expert consultation, we developed a digital LCS decision navigation intervention incorporating shared decision-making, patient navigation, and framing effects. From March 2024 to March 2025, participants were recruited and randomly assigned (1:1:1) into three groups (63 per group). Details of the intervention are shown in Figure 1. Primary and secondary outcomes—including LDCT uptake, decision conflict, self-efficacy, decision preparation, LCS knowledge, and health beliefs—were assessed at baseline (T1), post-intervention (T2), and at 1-month (T3), 3-month (T4), and 6-month (T5) follow-ups, with data analyzed using generalized linear mixed models and Chi-square tests.

Results: A total of 53, 54, and 56 participants remained in the loss-framed, gain-framed, and control groups, respectively. Both intervention groups showed significant improvements over the control group in decision conflict (F=4.232, p=0.015), decision self-efficacy (F=8.392, p<0.001), decision preparation (F=7.430, p<0.001), and health beliefs-perceived risk (F=4.347, p<0.001). Decision preparation was higher in the gain-framed group at T2 (D=3.757, p=0.005), T3 (D=2.814, p=0.016), and T4 (D=3.300, p=0.004). Health beliefs-perceived barrier was higher in the loss-framed group at T3 (D=3.157, p=0.009). Health beliefs (D=6.700, p=0.001), perceived benefit (D=1.286, p=0.031), and self-efficacy (D=2.743, p=0.001) were higher in the loss-framed group at T2. About 29 (53.7%) in the loss-framed, 23 (42.6%) in the gain-framed, and 9 (16.1%) in the control group underwent LDCT ($\chi 2$=14.60, p=0.001).

Conclusions: This study preliminarily applies cognitive framing in LCS decision-making using China's first LCS PDA. Both gain- and loss-framed interventions significantly improved LCS knowledge, health beliefs, decision quality, and LDCT uptake. Message framing effectively motivates high-risk individuals to undergo screening, supporting early lung cancer detection and improved outcomes. This structured, personalized approach to secondary prevention offers a new strategy for increasing voluntary LCS participation and reducing lung cancer mortality. Future research should explore long-term effects and scalability across diverse populations.

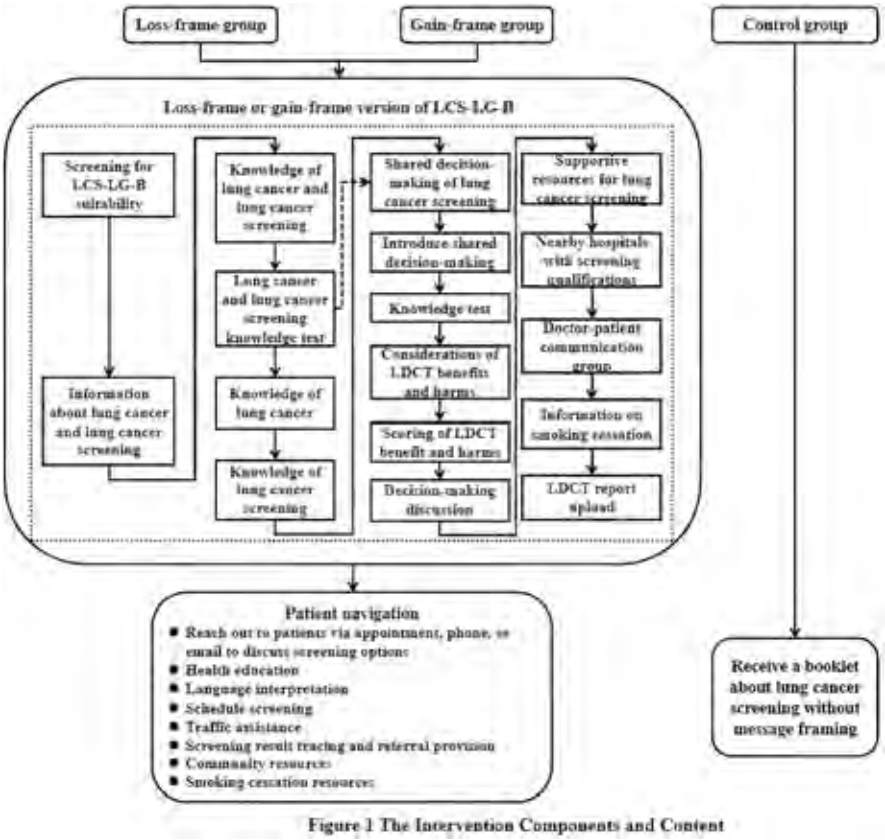

Figure 1 The Intervention Components and Content

Keywords: Lung cancer screening, Decision aid, Frame effects

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .08 Effects of a Decision Support Intervention for Patients With Advanced Lung Cancer: RCT-Results and Document Analysis

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Introduction: The therapeutic algorithms in lung cancer are rapidly evolving due to the continuous approval of new drugs, resulting in steadily improving survival rates. However, recent studies show that the increasing complexity has had a negative impact on prognostic awareness and patient-physician communication. In a population primarily composed of elderly and frail patients, this uncertainty threatens goal-concordant care. As a result, the importance of guideline recommendations emphasizing patient-empowerment and shared decision-making has never been greater. Yet, there is still al lack of evidence-based tools that are comprehensively implemented to support these practices.

Methods: Randomized controlled, open, mono-center trial (n=138) with two arms: A) use of a decision aid incl. clarification of personal values accompanied by a decision-coaching session vs. B) usual care; primary endpoint: clarity of personal values (Value Clarity Subscale of the Decisional Conflict Scale). Secondary outcomes: patients' self-efficacy (DSES), decisional conflict (DCS), perceived preparation for and involvement in decision-making (PDMS and PICS), general health and emotional state (EQ-5D-5L and HADS). We performed an additional document analysis for information needs, participation preferences, and personal values (decision aids and decision coaching; n=40).

Results: The evaluation showed high values for decisional conflict in both groups (total mean score arm A 41,25 and arm B 38,65), exposing relevant conflict in 57,6% of patients, highest in the subscale for information (64,4%) and uncertainty (58,9%). PDMS showed that most patients considered the intervention helpful. All other outcomes showed no significant differences with equally high DCS scores in both arms' follow-up. The document analysis showed the highest information needs in regard to treatment options (67,5%), general information about the disease (65%), its course/prognosis (60%), supportive care (52,5%), and side-effects (50%). For participation preferences 27,5% wished the physician to decide, 55% shared decision-making and 17,5% to decide alone. The most important personal values patients indicated were quality of life (65%), honesty (47,5%), hope (40%), and trust (35%).

Conclusions: Patients with advanced lung cancer experience significant decisional conflict. While the intervention successfully enhanced their perceived preparation for decision-making, it was not sufficient to substantially reduce the measured conflict. Given the considerable uncertainty faced by these patients, it is crucial to identify their specific information needs, personal values, and preferences for participation. These factors should guide the development of future decision support interventions and go together with a pro-active attitude by physicians in addressing them. In a landscape of rapidly evolving oncological information and increasing prognostic uncertainty, there is an urgent need for tailored support that can adapt flexibly to the individual needs of patients in their decision-making process.

Keywords: communication, decision-making, decision-coaching

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .09 Long-Term Survival in Malignant Pleural Effusion: Validation of the LENT and PROMISE Scores

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Introduction: Malignant pleural effusion (MPE) is a common manifestation of advanced cancer, associated with poor prognosis. The LENT and PROMISE scores are prognostic scoring systems for MPE, developed to predict short-term mortality and aid in clinical management decisions. This study aims to identify long-term survivors (LTS) among patients with MPE and to evaluate whether the LENT and PROMISE scores are useful in predicting LTS.

Methods: We conducted a retrospective cohort study of adults with cytologically confirmed MPE at a tertiary academic center in South Korea between January 2003 and December 2023. The prognostic performance of the LENT and PROMISE scores was assessed using Kaplan-Meier survival analysis. LTS were defined as patients who survived ≥5 years after MPE diagnosis. Clinical characteristics and independent predictors of LTS were evaluated using multivariable logistic regression.

Results: Among 2,614 patients with MPE, the mean age was 61.4±13.0 years, and 58.5% were female. The most common primary malignancies were lung (50.5%), gastrointestinal (18.2%), and breast cancers (17.9%). Both the LENT and PROMISE scores effectively stratified survival (log-rank $p<0.01$). A total of 166 patients (6.4%) were LTS. Lung cancer was more common among LTS (63.9%), while gastrointestinal cancers were less frequent (7.8%). In multivariable analysis, both the LENT and PROMISE scores were independently associated with LTS. The use of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) also showed significant associations with long-term survival.

Conclusions: Among patients with MPE, 6.4% survived for more than five years. Both the LENT and PROMISE scores were validated as independent predictors of LTS, and the use of TKIs or ICIs was also significantly associated with LTS.

Keywords: malignant pleural effusion, LENT score, PROMISE score

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .10 Improving Patient-Reported Outcome Symptom Monitoring Using Bayesian Networks

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Introduction: The SYMPRO-Lung study showed that patient-reported outcome (PRO) symptom monitoring linked to an alert system significantly improves health-related quality of life in patients with lung cancer. However, to implement PRO-symptom monitoring on a larger scale, it is critical to decrease the number of unnecessary alerts. We aimed to optimize the SYMPRO-Lung alert algorithm using Bayesian networks to 1) lower the number of unnecessary alerts and 2) explain determinants of reported symptoms.

Methods: Within the SYMPRO-Lung study, patients with lung cancer starting new treatment reported their symptoms weekly during one year via an online questionnaire (based on the PRO-CTCAE). When symptoms reached a pre-defined threshold, an alert was triggered indicating contact with a healthcare professional was necessary. Patients could indicate if they felt contact was unnecessary. To decrease these unnecessary alerts, we used a Noisy-OR network, a causal independency model in which each cause-node influences the effect-node independent of other cause-nodes. Subsequently, a Bayesian network was created to explore determinants of alarming situations (triggering a necessary alert) compared to non-alarming situations (triggering an alert labeled as unnecessary or triggering no alert), corrected for baseline characteristics (age, treatment and cancer stage and histology). Determinants included receiving treatment, progression of disease, emotional functioning, comorbidities and other reasons.

Results: We included 7185 symptom reports from 244 patients. 1325 (18%) symptoms triggered an alert, of which 799 (60%) were classified as necessary alerts. The Noisy-OR model predicted 979 necessary alerts (74%), of which 628 (64%) were correctly predicted as a necessary alert. None of the alerts missed by the Noisy-OR model concerned severe symptoms. The Bayesian network indicated that undergoing treatment was the most apparent determinant of reported symptoms (probability 0.68), followed by impaired emotional functioning (probability 0.42). Patients who reported alarming situations were more likely to have comorbidities, disease progression, or impaired emotional functioning compared to patients reporting non-alarming situations (Table 1).

Conclusions: The Noisy-OR network for alert prediction was able to reduce the number of alerts with 26% by better predicting if contact with healthcare is necessary compared to the original SYMPRO-Lung algorithm, without missing severe symptoms. Based on the Bayesian network we gained insights in the relation between symptoms and their determinants. This optimized alert algorithm will advance the further implementation of PRO-symptom monitoring on a larger scale.

Table 1. Mean probability (standard deviation) of underlying reasons in alarming and non-alarming situations, given the symptoms and patient characteristics.

Underlying reason	Alarming situation	Non-alarming situation
Receiving treatment	0.89 (0.31)	0.78 (0.42)
Progression of disease	0.07 (0.16)	0.06 (0.14)
Impaired emotional functioning	0.57 (0.36)	0.29 (0.29)
Two or more comorbidities	0.37 (0.37)	0.17 (0.25)
Other reasons	0.03 (0.14)	0.13 (0.31)

Alarming situation: a situation triggering an alert that is indicated as necessary. Non-alarming situation: a situation triggering an alert that is indicated as unnecessary or a situation not triggering an alert.

Keywords: non-small cell lung cancer, symptom monitoring, Bayesian Network

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .11 Non-Cancer-Related Mortality in Lung Cancer Patients: The Role of Comorbidities in a 7-Year Retrospective Case-Control Study

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Introduction: Lung cancer remains one of the leading causes of mortality worldwide, prompting continuous efforts to develop therapies that improve survival outcomes. However, these patients frequently present with multiple comorbidities, whose exacerbations may negatively influence prognosis and, in some cases, constitute the direct cause of death.

Methods: We conducted a retrospective, observational, and analytical case-control study including patients diagnosed with lung cancer and treated at Fundación Santa Fe de Bogotá between 2016 and 2023. The primary objective was to evaluate the association between comorbidities and all-cause mortality. We collected sociodemographic and clinical variables, comorbid conditions, and causes of death (cancer-related or not). The main outcome was all-cause mortality at two years of follow-up. A descriptive analysis of the population was conducted, followed by bivariate analysis using the Chi-squared test, and subsequently a multivariate analysis to adjust for potential confounding variables.

Results: A total of 503 patients were included, of whom 53.7% were women. The mean age was 69 years (range: 28-97). The most prevalent comorbidities were smoking history (55%), arterial hypertension (45.5%), chronic obstructive pulmonary disease (COPD) (17.2%), and diabetes mellitus (15.6%). Overall mortality was 59.4% (n = 299), with non-oncologic, comorbidity-related deaths accounting for 24% of all deaths. The most frequent non-oncologic causes of death were septic shock (32%), heart failure (10%), and chronic kidney disease (7.5%). Bivariate analysis revealed statistically significant associations between mortality and tumor stage, history of COPD, and pulmonary embolism (PE). Detailed findings are presented in Table 1. In the multivariate analysis, adjusted for tumor stage, age, sex, and treatment type, COPD (OR: 2.43; 95% CI: 1.31-4.55; p = 0.00) and PE (OR: 2.12; 95% CI: 1.01-4.79; p = 0.04) were associated with increased risk of death. Interestingly, heart failure was associated with lower mortality risk (OR: 0.43; 95% CI: 0.21-0.92; p = 0.02); however, 92% of these patients had a left ventricular ejection fraction (LVEF) >40%, with a mean LVEF of 56%.

Conclusions: Comorbidity exacerbations significantly contribute to mortality in lung cancer patients. Notably, COPD and PE were associated with increased risk of death, highlighting the importance of early identification and management of these conditions to potentially improve patient outcomes.

Table 1. Bivariate Analysis of Clinical and Comorbidity Variables Associated with All-Cause Mortality in Lung Cancer Patients

Characteristic	Category	Alive (n = 204)	Deceased (n = 299)	p-value (Chi²)
Stage	I (n=80)	75%	25%	<0.001
	II (n=31)	71%	29%	
	III (n=58)	45%	55%	
	IV (n=300)	27%	73%	
Sex	Female (n=270)	45%	55%	0.03
	Male (n=233)	36%	64%	
Smoker	Yes (n=280)	40%	60%	0.50
	No (n=222)	40%	60%	
Hypertension	Yes (n=228)	43%	57%	0.37
	No (n=275)	38%	62%	
COPD	Yes (n=86)	28%	72%	0.01
	No (n=417)	43%	57%	
Diabetes	Yes (n=80)	44%	56%	0.57
	No (n=423)	40%	60%	
Tachyarrhythmia	Yes (n=57)	44%	56%	0.66
	No (n=446)	40%	60%	
Pulmonary embolism (PE)	Yes (n=51)	26%	74%	0.02
	No (n=452)	42%	58%	
Heart failure	Yes (n=45)	53%	47%	0.07
	No (n=458)	39%	61%	
Deep vein thrombosis (DVT)	Yes (n=40)	28%	72%	0.08
	No (n=463)	42%	58%	
Myocardial infarction	Yes (n=39)	33%	67%	0.38
	No (n=464)	41%	59%	
Autoimmune disease	Yes (n=36)	42%	58%	0.98
	No (n=467)	40%	60%	
Stroke	Yes (n=33)	24%	76%	0.06
	No (n=470)	42%	58%	
CKD without dialysis	Yes (n=33)	33%	67%	0.45
	No (n=470)	41%	59%	
GI bleeding	Yes (n=14)	50%	50%	0.61
	No (n=489)	40%	60%	
Interstitial lung disease	Yes (n=10)	40%	60%	0.99
	No (n=493)	40%	60%	

Keywords: Survival Analysis, Comorbidities, All-Cause Mortality

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .12 Non-Pharmacological Dermatologic Care for the Prevention and Management of Immune-Related Skin Toxicities in Patients With Lung Cancer

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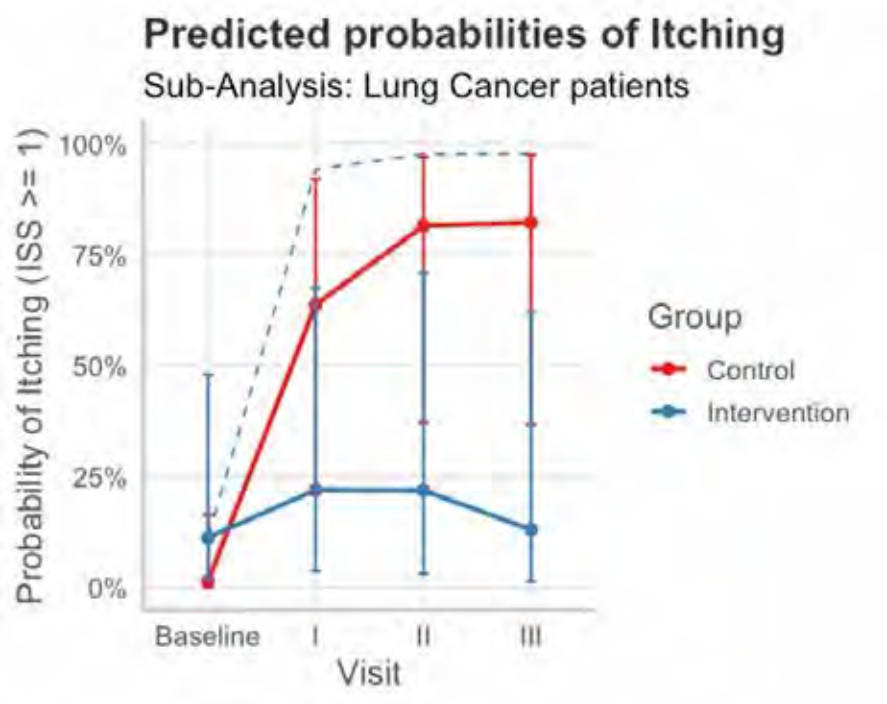
Introduction: Checkpoints are one of the main pillars of cancer treatment. However, despite their overall favorable profile, their use has been associated with specific toxicities called immune-related adverse events (irAEs). Dermatologic irAEs are among the most common (40%), especially pruritus and dryness.Although these skin toxicities are usually mild, diagnosis and early management are crucial for maintaining an acceptable quality of life for patientsThis is an analysis of the subgroup of lung cancer patients included in this study in patients with different types of cancer receiving immunotherapy. The aim of the study was to determine whether Niacinamide and Shea Butter provide better control of immune-related skin toxicities.

Methods: This is a single-center, phase IV 2-arms single-blinded, randomized trial. In the intervention arm, participants received cleansing and moisturizing products containing the active ingredients niacinamide and shea butter, and in the active control arm, cleansing and moisturizing products containing the active ingredients argan oil and coconut butter.For data collection, an initial (baseline) visit was conducted, followed by three additional visits every 8 weeks. The data collection instruments included two validated scales: the itching intensity scale and the Dermatology Life Quality Index questionnaire.Additionally, participants answered a questionnaire about soap and cream use frequency, sunscreen application, skin changes, and the need for medication due to skin toxicity.

Results: From May 30th, 2022, to December 21st, 2023, 130 patients with different tumor types were enrolled. This analysis includes data from 58 patients with lung cancer, 27 control and 31 intervention group, with similar baseline characteristics baseline characteristicsThe intervention reduced the probability of pruritus in lung cancer patients. In the control group, pruritus increased from nearly 0% at baseline to ~80% by visit III. In contrast, the intervention group started slightly above 10% and never exceeded ~25%. The gap between the intervention's actual effect and the expected 'no intervention' scenario suggests that the treatment prevented the worsening of pruritus over time (Figure 1). This plot is based on R models using a Mixed-Effects Logistic Regression schema.

Conclusions: The intervention arm effectively reduced pruritus in lung cancer patients, preventing its worsening over time. These findings highlight its potential in managing immune-related skin toxicity.



Keywords: Skin Toxicity, Immunotherapy, Hygiene and hydration

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .13 Patient Self Management Education and Cancer Treatment Adherence in Low Middle Income Africa a Systematic Scoping Review

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Introduction: Cancer mortality is disproportionately higher in low-middle-income Africa than in high-income countries. Lung cancer is the leading cause of cancer death worldwide and, in Africa, lung cancer related morbidity is concerning as mortality rates continue to steadily increase. Currently, lung cancer is one of the top three leading cancers, ranked by deaths, in Africa. High mortality is, in part, due to poor cancer treatment adherence. Patient self-management is a critical driver of treatment adherence, but the most appropriate self-management education for the African population is unclear. To improve cancer treatment adherence in countries like Ethiopia, it is imperative to first understand the evidence base on factors that influence treatment adherence at the local level and, in so doing, gain an understanding of what might constitute appropriate and effective patient self-management education. This presentation showcases phase 1 of a 3-phase PhD co-design research program that aims to reduce unnecessary premature disability and death with improved cancer treatment adherence in Ethiopia. The paper aimed to systematically review the literature on patient self-management education and cancer treatment adherence discrete to low-middle income countries in Africa.

Methods: MethodsUtilising Joanna Briggs methodology, CINAHL, MEDLINE (PubMed), HINARI, Web of Science, the Cochrane Register of Controlled Trials, and Google Scholar databases were searched, with no date limits. Peer-reviewed, primary studies focusing on patient self-management education and cancer treatment adherence in adults (≥18 years) in low- or middle-income countries in Africa were included. No limits were set on cancer type and stage, clinical or education setting; education type or delivery mode; health professional role that delivered the education. Qualitative and quantitative studies could be included. Synthesis took a narrative analytical approach using the Template for Intervention Description and Replication (TIDieR) checklist.

Results:

ResultsAn initial 3,785 studies were identified. After duplicate removal and title and abstract screening, 251 studies underwent full text review, with 12 studies included. Three key themes were generated to describe mediators of cancer treatment adherence and, in turn, inform patient self-management education and delivery mode (phase 2 of the PhD program): 1. Safe, “meaningful” education, 2. Challenge of social structures, and 3. The power of interpersonal interactions between nurse, patient and family. Financical implications, health care access, cultural and religious beliefs, and health literacy affect cancer treatment adherence. Attitudes of health professionals towards cancer treatment also affect patient adherence to treatment. Quality interactions among nurses, patients, and caregivers represent a crucial role in influencing adherence.

Conclusions: ConclusionAppropriate self-management education delivered by knowledgeable, skilled health care clinicians has the potential to facilitate cancer patient treatment adherence in low-middle income Africa. However, empiric high quality evidence on strategies to address mediators of adherence is limited, heterogenous and often not evaluated with validated approaches. Notwithstanding that this gap in knowledge represents immediacy in terms of poor health outcomes in real world low-middle income Africa, it emphasises the urgent need for this grassroots, cross-border collaborative research between Ethiopia and Australia.

Keywords: cancer, adherence, treatment

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .14 Improving Access and Recruitment to Clinical Trials for Lung Cancer Using the Lung I-Act Tool: A Mixed Methods Uk Wide Pilot Study

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Introduction: Globally, lung cancer is the leading cause of cancer related death. Clinical trial participation can lead to better patient outcomes by providing access to new and innovative treatments and making a contribution to the development of treatments for future generations. Despite reported widespread enthusiasm for clinical trial participation, less than 10% of cancer patients take part. Reasons for this include sub-optimal communication, with less than half of lung cancer patients stating that clinical trial opportunities were discussed between themselves and a healthcare professional. Lung cancer nurses often feel ill-equipped to talk about clinical trial opportunities with patients. Lung I-ACT is a tool that has been developed to support lung cancer nurses to talk to patients about clinical trial opportunities. It has been piloted across the UK to test its acceptability to lung cancer nurses and patients in practice-based settings. The pilot study findings can inform approaches to effectively improving discussions about clinical trials between nurses and patients.

Methods: The development of Lung I-ACT was informed by findings from a systematic literature review and qualitative focus groups exploring barriers and facilitators to clinical trial participation for lung cancer patients. A subsequent co-production workshop conducted with lung cancer nurses and patients helped researchers shape tool development further. Lung I-ACT comprises a complementary patient-facing leaflet with a nurse-facing poster, each designed to promote a drip feed approach to discussions about trials so that patients can make informed choices about participation. A six-month pilot, consisting of longitudinal surveys for nurses and interviews with nurses and patients was conducted at seven UK-wide NHS Trusts. Four intervention and three control sites were selected to compare differences in clinical trial knowledge, confidence and awareness between nurses using the Lung I-ACT tool and nurses who were not.

Results: Interview findings identified that specific elements of the Lung I-AT tool acted to encourage nurses to discuss clinical trials with more patients, increasing their perceived knowledge, confidence and awareness of trials. Benefits of the tool in terms of its content, presentation and utility in practice were highlighted, with the tool's content cited as facilitating effective discussions about trial participation. The survey data (n=29) demonstrated no significant differences in knowledge, confidence and awareness between intervention and control sites, but participant numbers were small.

Conclusions: Our findings demonstrate that with effective, targeted support, lung cancer nurses can be empowered to have more conversations about clinical trial opportunities with patients. This has the potential to lead to more patients being able to make informed choices about enrolment. The findings have international applicability across a range of healthcare settings.

Keywords: Lung cancer, Clinical trials, Nurses

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .15 Impact of Palliative Care in Patients With Non-Small Cell Lung Cancer and Brain Metastases: A Retrospective Quality Analysis

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Introduction: Brain metastases (BMETs) represent a common and devastating complication of non-small-cell lung cancer (NSCLC). Several factors, including functional status and extracranial disease presence, significantly affect prognosis in these patients. The updated Recursive Partitioning Analysis (U-RPA) classification can aid in guiding prognosis, with U-RPA classes 2b and 3 indicating survival of likely less than 1 year. Early utilization of palliative care (PC) is recommended in the multidisciplinary care of patients with BMETs. This study assessed PC utilization and its relationship with survival, hospice referrals, emergency care, and advance care planning in this population.

Methods: We conducted a retrospective review of NSCLC patients diagnosed with BMETs at the University of Vermont between January 1, 2017, and December 31, 2022. Inclusion criteria were age ≥18 years, diagnosis of NSCLC with BMETs, and follow-up ≥ 3 months. Patients were stratified into U-RPA Class 1/2a (> 1-year survival) vs. Class 2b/3 (< 1-year survival). Outcomes were compared between those who received PC and those who did not. Kaplan-Meier analysis assessed survival, while chi-squared and regression analyses evaluated associations between PC involvement and hospice use, emergency visits/readmissions, and completion of advance directives (ADs).

Results: Among 222 patients, 114 (51%) received PC consultations. PC utilization was higher in patients with poor prognosis (U-RPA 2b/3: 74% of PC group). Median survival was shorter in the PC group (114 vs. 432 days, p = 0.00007); however, among U-RPA 2b/3 patients, survival did not differ significantly (146 vs. 160 days, p = 0.07). PC involvement was associated with higher hospice enrollment in both U-RPA groups, particularly in U-RPA 2b/3 (71% vs. 49%, p = 0.012). AD completion was more frequent among PC patients overall (82% vs. 63%, p = 0.003), although not statistically significant in the U-RPA 2b/3 subgroup (82% vs. 70%, p = 0.14). Emergency visits/readmissions were more common in PC patients with poor performance status (33% vs. 11%, p = 0.01). Adjusted analyses showed that PC was not independently associated with survival (p = 0.39) but correlated with greater hospice and AD uptake.

Conclusions: Palliative care remains underutilized in NSCLC patients with BMETs, particularly among those with poor performance status and despite guidelines recommending early integration. Although PC did not confer a survival advantage, its association with improved hospice utilization and advance care planning highlights its value in enhancing quality care at end-of-life care. Increased systemic efforts are needed to promote early PC referral for this population.

Measure		Palliative Care	No Palliative Care	P-value
Number of Patients		114	108	p = 0.0019
	U-RPA 2b/3	84	57	
	U-RPA 1/2a	30	51	
Median Survival (Days)		177	432	p=0.00007
	U-RPA 2b/3	146	160	p =0.07
	U-RPA 1/2a	462	1282	p = 0.02
Hospice Utilization		69%	35%	p = 0.0000007
	U-RPA 2b/3	71%	49%	p = 0.012
	U-RPA 1/2a	63%	20%	p = 0.00019
Advance Directives Completed		82%	63%	p = 0.003
	U-RPA 2b/3	82%	70%	p = 0.14
	U-RPA 1/2a	80%	55%	p = 0.04
Emergency Visit/Readmission		33%	17%	p= 0.0068
	U-RPA 2b/3	33%	11%	p = 0.01
	U-RPA 1/2a	33%	24%	p = 0.48

Keywords: Palliative, Brain Metastases, Non Small Cell Lung Cancer

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .16 ECMO as a Procedural Bridge for Malignant Airway Obstruction in Lung Cancer

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Introduction: Malignant central airway obstruction (MCAO) is a potentially fatal complication in advanced lung cancer requiring urgent airway intervention. Rigid bronchoscopy remains the standard approach forrestoring airway patency, but the procedure necessitates advanced anesthetic support, which may not be readily available in low-volume centers. In such settings, extracorporeal membrane oxygenation (ECMO) may serve as a physiologic bridge to maintain oxygenation and procedural stability, especially when anesthesiology teams lack experience with complex airway management. We report a case series of patients with lung cancer-related MCAO who underwent ECMO-assisted rigid bronchoscopy at a center performing fewer than eight such procedures annually.

Methods: We retrospectively reviewed four patients with lung cancer and MCAO who underwent rigid bronchoscopy under veno-venous ECMO support at our centre . All patients were assessed by a multidisciplinary team. ECMO cannulation was performed in the operating room immediately prior to the intervention, and ECMO decannulation was performed on postoperative day (POD) 1. Clinical variables including histologic subtype, ECOG performance status, tumor stage, procedural time, and stent placement were analyzed.

Results: Four patients (2 males, 2 females; median age 65.5 years) with lung cancer-related MCAO underwent ECMO-assisted rigid bronchoscopy. Histologic subtypes included adenocarcinoma (n=1), squamous cell carcinoma (n=2), and adenoid cystic carcinoma (n=1); stages ranged from IIIB to IV. ECOG performance status was 2 in three patients and 3 in one. All procedures were completed successfully under VV-ECMO support. Airway stents were placed in three patients (2 Song's, 1 Dumon); one patient underwent tumor debulking without stenting. Mean procedure time was 2 hours 14 minutes (ECMO insertion time 13-25 minutes). Oxygenation was stable throughout, and all patients were weaned from ECMO on postoperative day 1 without complications.

Conclusions: ECMO-assisted rigid bronchoscopy was safe and feasible for managing lung cancer-related MCAO, even in a low-volume center. ECMO support facilitated procedural stability, particularly where anesthetic experience was limited.

Keywords: Central Airway, Bronchoscopy, Palliative treatment

P2.15 .17 Preliminary Results on Feasibility of Virtual Delivery of Exercise Therapy for Mitigation of Lung Cancer Decline

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Introduction: Exercise may mitigate declines in physical and psychosocial function in patients living with advanced lung cancer. However, low patient recruitment and retention limit the development and uptake of evidence-based exercise programs. To overcome these potential barriers, MoVE Phase 2 is a virtual exercise program for patients living with advanced lung cancer in British Columbia, Canada, that builds upon patient feedback that Phase 1 did not reach all people who could benefit due to the travel requirements. Our primary objective is to assess the feasibility of a virtual 12-week exercise intervention amongst patients with advanced lung cancer. Our secondary objective is to assess the efficacy of resistance training delivered virtually to mitigate declines in physical and psychosocial function associated with lung cancer treatment.

Methods: This prospective, single-arm study is currently ongoing with a planned recruitment of 4 consecutive cohorts of 12 patients each. Eligible participants are patients on systemic therapy for advanced lung cancer willing to participate in a twice weekly, one-hour, supervised virtual group exercise program for 12 weeks. Feasibility measures include uptake (attendance and retention ≥80%), adherence (meeting self-reported target exercise intensity over 24 sessions, ≥80%), and safety. Efficacy measures, including patient-reported outcomes and physical function, will be reported with availability of additional data from subsequent cohorts.

Results: Preliminary feasibility data from cohort 1 are presented in Table 1. Twelve of 15 participants screened were enrolled (80% recruitment). Eleven participants completed baseline assessments (one withdrew prior due to symptom burden) and 10 participants completed the supervised exercise program (83% retention). One participant withdrew during the program due to an unrelated adverse event. Average attendance was 75%, with treatment-related symptoms (39%) and conflicting appointments (37%) accounting for most missed sessions. One participant missed 15 of 24 sessions (38% attendance) due to high symptom burden; attendance excluding this individual was 81%. Exercise adherence was 99%. There were no related safety events.

Conclusions: Our preliminary results show that a virtual exercise program for patients being treated for advanced lung cancer is mostly feasible to deliver; however, intervention attendance did not meet the target for cohort 1 (<80%) due to one participant's poor attendance of 38%. With this outlier removed, attendance met feasibility at 81%. An exercise intervention that leverages the emerging acceptance of virtual healthcare delivery may address a critical gap in health equity in older adults with lung cancer in British Columbia.

Table 1

Participant Characteristics at Baseline	n=11
Age (average, range, in years)	65 (51-77)
Gender (F:M)	6 (55%): 5 (45%)
Time since diagnosis (average, range, in months)	22.3 (2-67)
Type of anti-cancer treatment	
Chemotherapy alone	2 (18%)
Targeted therapy alone	4 (36%)
Chemotherapy + targeted therapy	2 (18%)
Immunotherapy	2 (18%)
Chemoradiation	1 (9%)
Feasibility Measures	
Recruitment: # pts enrolled / # pts referred (%)	12/15 (80%)
Retention: # pts completed / # pts enrolled (%)	10/12 (83%)
Attendance: # sessions attended / 24 sessions (%)	18/24 (75%)
Reasons for not attending sessions (%)	
Treatment-related symptoms	21/54 (39%)
Conflicting appointment	20/54 (37%)
Travel	5/54 (9%)
Non-intervention-related injury	4/54 (7%)
Non-treatment-related illness	2/54 (4%)
Family obligation	1/54 (2%)
Other	1/54 (2%)
Adherence: # sessions where RPE target was met/24 sessions (%)	23.76/24 (99%)
Safety: # events related to intervention (%)	0 (0%)

Pts: participants; RPE: rating of perceived exertion

Keywords: virtual exercise, non-small cell lung cancer, small cell lung cancer

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .18 Quality of Life for Lung Cancer Survivors

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Introduction: Lung cancer is the leading cause of cancer-related deaths in the United States, with 87% of diagnoses being non-small cell lung cancer (NSCLC).1 Medical innovations have contributed significantly to improved outcomes for lung cancer survivors (LCS). However, more research is needed to understand the quality of life (QOL) for patients as they live longer with this diagnosis.

Methods: Patients who were alive at least one year after diagnosis with NSCLC were designated as survivors. Survivors who were treated at Johns Hopkins between 2020-2024 completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 as part of a larger survey battery. Demographic information, types of therapy, and the intent of therapy (curative or palliative) were gathered via chart review. Clinical and sociodemographic factors associated with the EORTC QLQ-C30 Global health status/QoL scale were examined using Wilcoxon rank sum and Kruskal Wallis tests. This analysis focused on patients who were ever versus never on OTT. Additionally, a subgroup analysis excluded curative intent patients, and another analysis examined demographic and clinical characteristics associated with QOL among ever OTT patients only. The results of this abstract focused on QOL overall and did not differentiate between ever versus never on OTT.

Results: Of the 428 patients invited to complete the survey, 307 were included in this analysis. The median age of the cohort was 68, and predominantly female (59.9%) and Caucasian (73.9%). 38.4% of patients had Stage I-II NSCLC, 18.6% had Stage III and 43% had Stage IV; yet 60% received palliative-intent therapy. LCS who had received 3 or more lines of therapy reported higher QOL (83 vs. 66.7 for 1-2 and 66.7 for 0, p=0.006). Retired LCS reported the highest QOL at 75, compared to 58.33 for employed patients and 66.67 for those who were unemployed or did not respond (p= 0.015). Notably, household income, level of education, and living arrangements did not meet statistical significance.

Conclusions: As the LCS population grows, it is important to understand their needs and QOL in the survivorship period. Our study shows that retirement and more lines of therapy were significantly associated with higher QOL. Further evaluation of targeted interventions towards LCS at high risk of impaired QOL related to sociodemographic factors is warranted. References 1. American Cancer Society. Key Statistics for Lung Cancer. Published online January 16, 2025. Accessed April 3, 2025. https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html

P2.15 .19 Assessment of NSCLC Treatments and Correlation With Hypogonadism in Male Patients With NSCLC

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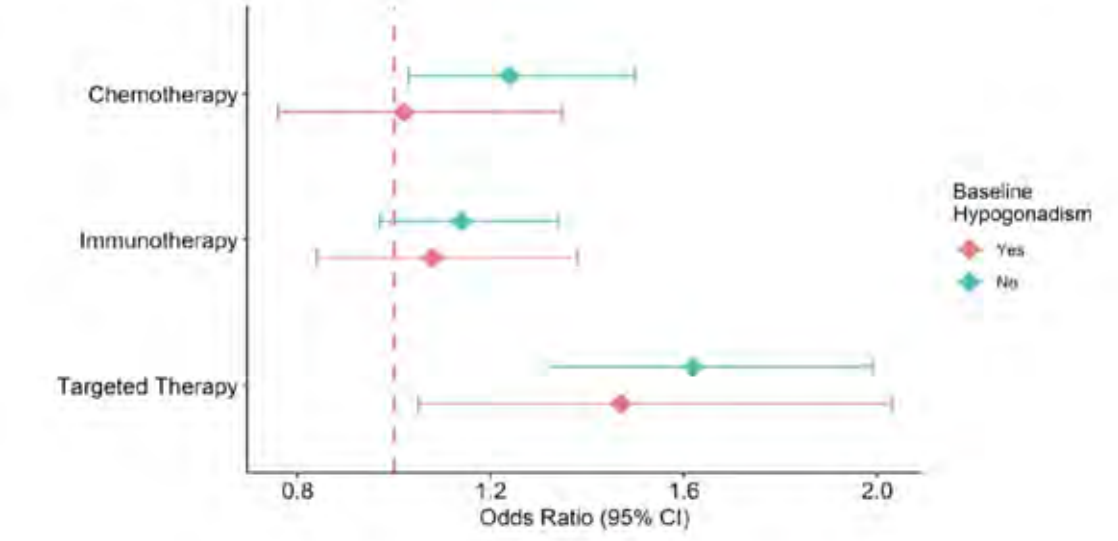
Introduction: Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer, with treatment advancements significantly improving patient survival. However, systemic therapies including chemotherapy, immunotherapy, and targeted therapy may contribute to endocrine dysfunction, including hypogonadism, which remains an underexplored aspect of NSCLC management. This study evaluates the prevalence of hypogonadism in male patients with NSCLC and assesses its correlation with different treatment modalities.

Methods: A retrospective analysis was conducted on 4,428 male patients with NSCLC, stratified by baseline hypogonadism status utilizing the TriNetX database. Patient characteristics, treatment types, and testosterone levels pre- and post-therapy initiation were analyzed. Paired t-tests assessed changes in testosterone levels, and logistic regression models evaluated associations between therapy types and hypogonadism outcomes.

Results: At baseline, 1,507 patients (34.1%) had hypogonadism, with affected individuals being older (mean age: 67.3 vs. 64.1 years, $p < 0.001$) and having a higher BMI (28.5 vs. 26.6, $p < 0.001$) compared to those without baseline hypogonadism. Comorbidities, including diabetes ($p < 0.001$) and hyperlipidemia ($p < 0.001$), were more prevalent in the hypogonadal group. Post-treatment testosterone levels of the whole cohort significantly declined from baseline assessment (mean difference: -67.32 ng/dL, $p < 0.001$) over a mean of 338 days from cancer treatment initiation. For patients without baseline hypogonadism, logistic regression indicated that targeted therapy was significantly associated with increased odds of developing hypogonadism (OR=1.62, 95%CI: 1.32-1.99, p<0.001), while chemotherapy was also significantly associated with increased odds of developing hypogonadism, but to a lesser degree (OR=1.24, 95 CI: 1.03-1.50, p=0.025). Immunotherapy did not show a statistically significant correlation with developing hypogonadism. For patients with baseline hypogonadism, only targeted therapy was significantly associated with odds of worsening hypogonadal status (OR=1.47, 95%CI: 1.05-2.03, p=0.022).

Conclusions: Hypogonadism is prevalent in male NSCLC patients and is worsened by systemic therapies, particularly targeted treatments. These findings underscore the need for routine endocrine evaluation and potential testosterone monitoring in NSCLC management. Future research should explore the risk of hypogonadism with individual targeted therapies and strategies to mitigate treatment-induced hypogonadism and its impact on patient quality of life.

Graph 1. Forest plot on the outcome of hypogonadism in relation to treatment with different types of systemic therapy.



Keywords: Hypogonadism, Therapy, NSCLC

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .20 Influence of Preoperative Mental Health on the Postoperative Outcome and Quality of Life After Anatomic Lung Resection

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Introduction: In addition to functional and technical aspects, mental health plays a crucial role in the recovery and quality of life after surgical procedures. Systematic analysis on the influence of factors such as anxiety, stress, and depression on the postoperative outcome in oncologic thoracic surgery are yet lacking.

Methods: This is a prospective cohort study. We included all patients who underwent anatomic lung resection between April 2023 and June 2024 without complicating factors according to inclusion and exclusion criteria. Anxiety, depression, stress, and quality of life were assessed preoperatively, at discharge, and at 3, 6, and 12 months postoperatively using questionnaires (PSS-10, HADS, and EORTC QLQ-C30 and LC13).

Results: A total of 98 patients were included in this study. In a preliminary analysis of the first 53 patients, elevated preoperative stress (PSS-10 >23) and anxiety scores (HADS >7) were observed in 28 (53%) and 19 (36%) patients, respectively, while elevated depression scores (HADS >7) were seen in 8 patients (15%). Elevated preoperative anxiety scores correlated with higher depression (p=0.004) and stress scores (p<0.0001). Additionally, we observed a quantitative association between higher preoperative anxiety scores and postoperative complications (Ottawa Classification ≥IIIa; p=0.3). Preoperative stress did not correlate with postoperative complications (p=0.5). In the overall cohort, the Global Health Score declined postoperatively but returned to baseline after 6 months. Patients with elevated preoperative depression scores showed a significantly lower Global Health Score immediately postoperatively compared to patients with normal depression scores (p=0.03) as well as persistently lower Global Health Scores throughout the follow-up period. Elevated preoperative anxiety and stress levels appeared to have no impact on long-term quality of life.

Conclusions: A significant proportion of patients undergoing anatomic lung resection show signs of impaired mental health preoperatively, which negatively affects the postoperative outcome and quality of life. These findings highlight the importance of early psycho-oncological interventions, for example in the context of prehabilitation programs.

Keywords: Quality of Life, Mental Health, Anatomic Lung Resection

P2.15 .21 Feasibility and Preliminary Efficacy of Multimodal Prehabilitation in Patients With NSCLC Receiving Neoadjuvant Therapy

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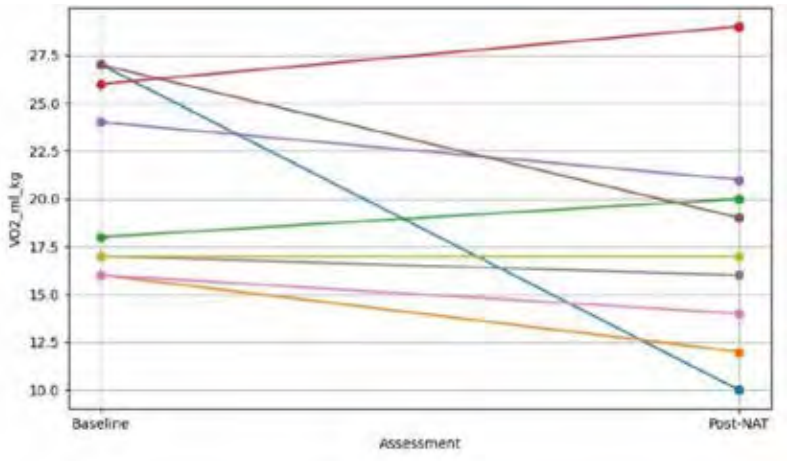
Introduction: Patients with non-small cell lung cancer (NSCLC) who receive neoadjuvant therapy (NAT) can experience a decline in cardiopulmonary fitness (CRF) and pulmonary function during treatment. In this study we aimed to explore the feasilibity of a supervised multimodal prehabilitation program in patients with NSCLC receiving NAT and its preliminary efficacy to prevent potential declines in the aforementioned parameters.

Methods: This pilot prospective study recruited patients with NSCLC who were scheduled for NAT followed by surgical resection. Patients were invited to participate in a multimodal prehabilitation program during treatment and prior to surgery (9-12 weeks), including nutritional and psychological support plus supervised exercise training twice weekly. Our main objective was to assess the feasibility (recruitment rates, retention rates, adherence), safety, and preliminary efficacy to maintain CRF and pulmonary function during NAT

Results: Between June 2023 and March 2025, a total of 24 patients were screened for eligibility and 20 were approached after inclusion and exclusion criteria were applied. Of those, six patients refused participation (recruiting rate 70%). Attendance to supervised exercise training ranged from 1 to 20 sessions (median 8.5, Q1 - Q3 6.25 - 14.5) resulting in a median adherence of 63.5% (Q1 - Q3 37.4 - 73.6). Three patients discontinued exercise training during NAT (retention rate 79.6%). One patient was hospitalized twice due to side effects during treatment. No adverse events were reported related to prehabilitation. Changes in CRF and pulmonary function are shown in Table 1. We observed a non-significant decline in CRF during treatment, with most individuals showing mild reductions or even slight improvements in CRF (Figure 1) with age being the only factor positively correlated with mean change in VO2peak (r=.667, p=.050).

Conclusions: Multimodal prehabilitation during NAT appears feasible, safe and might prevent deterioration of cardiorespiratory fitness and pulmonary function.



VARIABLE	BASELINE	POST-NAT	P value
FEV1 (liters/min)	2.67 (0.7)	2.67 (0.6)	.374
FEV1 (% predicted)	91.8 (11.4)	89.9 (13.4)	.208
FVC (liters/min)	3.9 (1.1)	3.9 (1)	.406
FVC (% predicted)	101.7 (12.2)	101.1 (17.8)	.441
DLCO (% predicted)	78.7 (21.6)	73.5 (16.3)	.141
VO2peak (mL/min)	1430.4 (511)	1252.2 (536.8)	.214
VO2peak (ml/min/kg)	20.4 (4.9)	17.5 (5.6)	.123
VO2peak (% predicted)	81.7 (18.3)	69.6 (16.7)	.110
RER	1.22 (0.2)	1.2 (0.1)	.678
HR (% predicted)	98.5 (9.9)	94.1 (9)	**.025**

Keywords: Prehabilitation, Neoadjuvant Therapy, Cardiorespiratory Fitness

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .22 A Nutritional Strategy to Mitigate Toxicities and Optimize Dose Intensity in Patients With Lung Cancer: The Nutricare Study

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Introduction: Patients diagnosed with lung cancer are often among the most malnourished of all patients with solid tumors and have a significant risk of developing treatment-related toxicities. Providing nutritional support with medically tailored meals and nutritional counseling may reduce both the prevalence and severity of treatment-related toxicities and improve relative dose intensity (RDI) of lung cancer treatment leading to better outcomes.

Methods: The NutriCare study (NCT04986670), a “Food is Medicine” intervention, was a national, multisite, randomized trial evaluating the impact of medically tailored meals plus weekly nutritional counseling (NutriCare) vs. informational control (NutriTool) on the outcomes of vulnerable patients with newly diagnosed lung cancer initiating treatment. Vulnerability was defined as: ≥65 years of age, underrepresented minority, rural resident, no health insurance, and/or income ≤130% of the federal poverty line. Participants completed a 90-minute baseline assessment within 8 weeks of study consent. Demographics, dietary intake, cancer stage, income, healthcare utilization, and adverse events, were collected via electronic medical records; patient surveys were performed at baseline, 3-months, and 8-months. Relative dose intensity, measured as a ratio of delivered dose intensity to scheduled dose intensity, was calculated by collecting treatment regimen information as well as associated treatment delays and dose changes. Descriptive statistics, inferential statistics and mixed effects regression models accounting for repeated measures were used for data analysis.

Results: Across four oncology centers in the US, 127 participants were randomized to the intervention arm (NutriCare n=70) or control arm (NutriTool n=57) from 11/2020-08/2022. After accounting for lung cancer type, staging, and systemic therapy indication, both study arms demonstrated similar treatment intensity (mean RDI of NutriCare = 0.868, mean RDI of NutriTool = 0.886). However, those randomized to the NutriCare group treated for limited stage SCLC (n = 5, mean RDI = 0.9) or stage IV NSCLC (n = 15, mean RDI = 0.923) as well as those receiving sequential radiation treatment (n = 2, mean RDI = 0.94) were found to have a greater RDI. In contrast, those randomized to the NutriTool group treated for limited stage SCLC (n =2, mean RDI = 1.0) or stage II NSCLC (n = 4, mean RDI = 0.942) or receiving sequential radiation (n = 1, mean RDI = 1.0) were found to have a greater RDI. Notably, those randomized to the NutriCare group had a greater risk of experiencing a grade 3 or higher adverse event than those randomized to the NutriTool arm (Risk Ratio = 1.8, 95%CI: 1.3-2.6), p=0.001) with the most prevalent adverse events among both arms being GI-related.

Conclusions: We found nutritional counseling and medically tailored meals improved RDI among patients with stage IV NSCLC as compared to nutritional information alone. While there are significant improvements in systemic therapies to treat lung cancer, further research is needed to identify nutritional strategies to ensure patients can experience the full benefits of lung cancer treatment.

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .23 Uncertainty in Illness, Symptom Severity and Hope in Advanced Lung Cancer Patients Undergoing Immunotherapy

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Introduction: Immunotherapy is a relatively new treatment options for advanced lung cancer (LC) patients. However, in the treatment process, uncertainty in illness remains a concern for patients. However, limited investigations have been reported. The purpose of this study is to explore the perceived uncertainty in illness, symptom severity, hope and their relationship in advanced LC patients undergoing immunotherapy.

Methods: We conducted a cross-sectional study with consecutive sampling to recruit advanced LC patients who had received at least one cycle of immunotherapy from two centers in Northern Taiwan. Patients were assessed of their perceived uncertainty (by Mishel's Uncertainty in Illness Scale), symptom severity and level of hope (by Herth's Hope Index). The descriptive statistics and Spearman's correlation were applied to analyze the data. Institute Review Board approval and patients' consents were obtained before patients' assessments.

Results: There were 140 patients recruited. The overall results showed that advanced LC patients perceived moderate to high levels of uncertainty, moderate levels of hope and mild to moderate levels of symptom severity. The top five symptoms included fatigue, weakness, appearance change, itchiness, and shortness of breath listed as the order of mean scores. The correlation analysis revealed that patients with higher symptoms level reported to have higher uncertainty and lower hope. Patients with higher uncertainty in illness reported to have lower perceived hope.

Conclusions: This study supported our assumptions that advanced LC patients undergoing immunotherapy had relatively higher uncertainty. Higher uncertainty and severer symptoms are associated with lower hope. Taken together, in order to increase LC patients' hope level, health care professional should assess and intervene more on patients' symptom management and their uncertainty concerns. Interventions and care model to decrease their illness uncertainty and symptoms to increase perceived hope are strongly suggested.

Keywords: uncertainty in illness, symptom severity, hope

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .24 A National Survey of Lung Cancer Survivorship Care at United States Cancer Centers From the American Cancer Society

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Introduction: Advances in lung cancer early detection and treatment have increased the number of people living with lung cancer. Yet, there are no standards or guidelines specific to lung cancer survivorship, and how survivorship care is delivered for people with lung cancer in the United States (US) is unknown. We conducted a cross-sectional survey to characterize survivorship care delivery at US cancer centers, focusing on care available to lung cancer survivors, to inform future research, policy, and organizational efforts to improve survivorship care.

Methods: An interdisciplinary working group of the American Cancer Society National Lung Cancer Roundtable Survivorship Task Group, comprised of clinicians, patient advocates, and researchers with lung cancer expertise, and representatives from the Association of Cancer Care Centers (ACCC) and the Cancer Survivorship and Supportive Care Professionals Network, developed a 20-item survey about survivorship care delivery based on literature review and prior surveys. The sample included all National Cancer Institute (NCI)-designated Cancer Centers that serve adults and a subset of community cancer centers in the ACCC network. Using REDCap, an electronic survey was administered to site representatives using used a four-wave mailing approach (i.e., modified Dillman method): an introductory email and four reminders, sent every two weeks, to complete the survey. We conducted an interim analysis of responses from NCI-designated Cancer Centers; results from community cancer centers will be reported separately.

Results: The completion rate from NCI-designated Cancer Centers was 73% (47/64), of which 41 (87%) reported having a clinic or program to provide survivorship care. Nineteen survivorship programs (46%) defined a survivor as "a patient who has completed curative-intent treatment for cancer and is on surveillance or maintenance therapy" and the remaining 22 (54%) of programs used the definition, "any patient with a diagnosis of cancer or history of cancer." One-third (34%) of programs offer services specifically tailored to patients living with advanced cancer. Lung cancer survivors have access to a survivorship program at 73% of facilities, with 9 (22%) offering a lung cancer-specific survivorship clinic and 21 (51%) offering a general survivorship program that serves lung cancer survivors. Lung cancer-specific services include pulmonary rehabilitation and lung cancer support groups at 27% and 20% of programs, respectively. Advanced practice providers are the most common clinician providing survivorship care (93%). Across all survey respondents, the most cited barriers to providing survivorship care are "limited or no funding for a program" (53%), "clinician time being prioritized in other clinical service" (45%), insufficient staff (38%) and lack of leadership support (36%).

Conclusions: Survivorship care clinical programs exist at most NCI-designated Cancer Centers, though nearly half limit their focus to patients who have completed curative intent treatment, a narrower definition than the NCI-supported concept that patients are survivors "from the time of diagnosis until the end of life." Survivorship services for patients living with advanced cancer and lung cancer-specific clinics are limited. Funding, staffing and lack of leadership support for survivorship care are the main limiting factors. Research to demonstrate the value of lung cancer-specific survivorship care is urgently needed.

Keywords: Survivorship Programs, Cancer Centers, Survey Study

P2.15 .25 Trilaciclib'S Myeloprotection in 1L Advanced Solid Tumors: Lung Cancer Data Analysis

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Introduction: Chemotherapy-induced myelosuppression (CIM) is a common toxicityin chemotherapy, which often necessitates dose reduction, treatment delays, or regimen changes. CIM-related complications—such as severe anemia, infections, or bleeding—may increase medical costs, and significantly worsen the prognosis. Trilaciclib is a highly potent, selective, and reversible CDK4/6 inhibitor designed to protects HSPCs before chemotherapy, thereby reducing chemotherapy-induced HSPC damage. Furthermore, its transient T-cell suppression may favorably alter the tumor immune microenvironment, ultimately improving patient survival outcomes.

Methods: This analysis was based on data from a prospective study , which enrolled 25 advanced lung cancer patients receiving first-line chemotherapy-based treatment. Patients received trilaciclib (240 mg/m^2) via a 30-minute IV infusion within 4 hours before daily chemotherapy. The incidence of CIM and antitumor efficacy were observed during chemotherapy.

Results: Enrollment began in October 2023, and to date, 25 patients receiving first-line chemotherapy-based treatment have been enrolled. 22 were male, and 3 were female, with a median age of 68 (57-84) years. Histopathological subtypes included SqCC (6 , 24.0%), LUAD(2, 8.0%), and SCLC(17 , 68.0%). Trilaciclib was used as primary prophylaxis in 20 patients (80.0%) and secondary in 5 (20.0%). Treatment cycles and patient distribution: 1 (7, 28.0%), 2 (4 , 16.0%), 3 (8 , 32.0%), 4 (5 , 20.0%), and 5 (1, 4.0%). Chemotherapy regimens followed clinical guidelines. CIM incidence is shown in the figure 1.A total of 20 patients underwent antitumor efficacy evaluation, with ORR of 50.0% and DCR of 85.0%. Detailed results are shown in the figure 2.

Conclusions: Conclusion: As of cutoff, no enrolled patients developed grade IV CIM. Primary prophylaxis demonstrated superior myeloprotective effects. Study data indicate that trilaciclib provides favorable platelet protection, offering a clinical strategy to better manage chemotherapy-induced thrombocytopenia (CIT). In lung cancer, Trilaciclib exhibits clear myeloprotective benefits, significantly enhancing the safety of first-line chemotherapy.

Figure1

CIM	ALL	PP	SP	CIN	ALL	PP	SP	CIT	ALL	PP	SP	CRA	ALL	PP	SP
I	8.7%	10.3%	12.8%	I	12.1%	12.8%	7.7%	I	7.5%	6.4%	15.4%	I	6.8%	5.3%	15.4%
II	4.4%	2.1%	2.6%	II	4.7%	5.3%	0.0%	II	1.9%	1.1%	7.7%	II	0.0%	0.0%	0.0%
III	0.6%	0.7%	0.0%	III	0.9%	1.1%	0.0%	III	0.9%	1.1%	0.0%	III	0.0%	0.0%	0.0%
IV	0.0%	0.0%	0.0%	IV	0.0%	0.0%	0.0%	IV	0.0%	0.0%	0.0%	IV	0.0%	0.0%	0.0%
ALL	13.7%	12.1%	15.4%	ALL	17.8%	19.2%	7.7%	ALL	10.3%	8.5%	23.1%	ALL	6.8%	5.3%	15.4%

*PP：primary prophylaxis；SP：secondary prophylaxis

Figure2

Objective response	Evaluable patients N=20, n(%)
CR	0(0%)
PR	10 (50.0%)
SD	7 (35%)
PD	3(15%)
ORR	50.0%
DCR	85.0%

Keywords: Myeloprotective, First-Line Chemotherapy and Combination Regimens, Trilaciclib

P2.15 .26 Frequency of Adverse Events Reported Digitally by Patients With Advanced NSCLC: Analysis From CLIMEDIN, a HeCOG Study

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Introduction: CLIMEDIN (NCT05372081) is a prospective, randomized clinical trial with 200 patients with advanced non-small cell lung cancer (NSCLC), funded by the Stavros Niarchos Foundation. It aims to evaluate the feasibility and effectiveness of online digital intervention regarding adverse events (AEs), quality of life (QoL), costs and the interrelation with clinical and molecular characteristics.

The purpose of this sub-analysis is to provide insights on the Real World Evidence resulting from the patient-reported AE data.

Methods: After their diagnosis, staging, and molecular analysis, all patients received the indicated treatment (mainly chemo-immunotherapy).

Patients reported digitally on their symptoms through the CareAcross online platform, at their convenience, by identifying which of the 22 pre-selected AEs they have been experiencing.

Through randomization, half of them subsequently receive personalized supportive information to assist their self-care; the other half only received generic information. The information did not constitute medical advice, nor was it intended to replace it.

This analysis focuses on the PROs and specifically the percentage of patients who reported each AE, at any point throughout their participation.

Results: Out of 200 patients, 188 reported their AEs, from 1 to 557 times throughout their participation (average of 37.3, median of 10 submissions per patient). Submissions contained an average of 3.1 AEs, excluding the 36.4% that indicated absence of any of the 22 preselected AEs.

AE frequencies ranged from 13% to 88%. The most frequently reported AEs were fatigue (88% of patients), cough (63%), anorexia (54%), nausea (51%), diarrhea (41%), constipation (41%), dyspnea (40%). Further analysis of patient subgroups formed by factors such as their age group, education level, urban or rural location, indicated only minor differences in the frequency of each reported AE.

The Table contains the percentage of patients reporting each AE once or more.

Adverse Event	% of patients reporting once or more (N=188)
Fatigue	88%
Cough	63%
Anorexia	54%
Nausea	51%
Diarrhea	41%
Constipation	41%
Dyspnea	40%
Weight Loss	37%
Bone Pain	34%
Dysgeusia	32%
Sleeping Problems	32%
Dry Skin	30%
Chest Pain	29%
Dysphagia	27%
Pruritus	23%
Stomatitis	21%
Fever	20%
Rash	20%
Hair Loss	19%
Vomiting	16%
Hemoptysis	13%
Peripheral Neuropathy	13%

Table: Frequency of AEs as digitally reported by patients

Conclusions: Patients engage with online platforms, even with a challenging diagnosis such as advanced NSCLC, illustrating the feasibility of online interventions.

The resulting Real World Data help improve the understanding of the experience of NSCLC patients. It also enables advanced analyses that have the potential to support decisions on patient-centered care, optimize resource allocation, and prevent the onset or aggravation of adverse events.

Finallym, the timely online reporting of AEs may facilitate improvement of patients' symptoms and quality of life by increasing the effectiveness of their oncology teams.

Keywords: NSCLC, Adverse Events, Patient Reported Outcomes

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .27 Symptom Screening Using the Patient-Generated Subjective Global Assessment Adds Value to Routine Clinical Review

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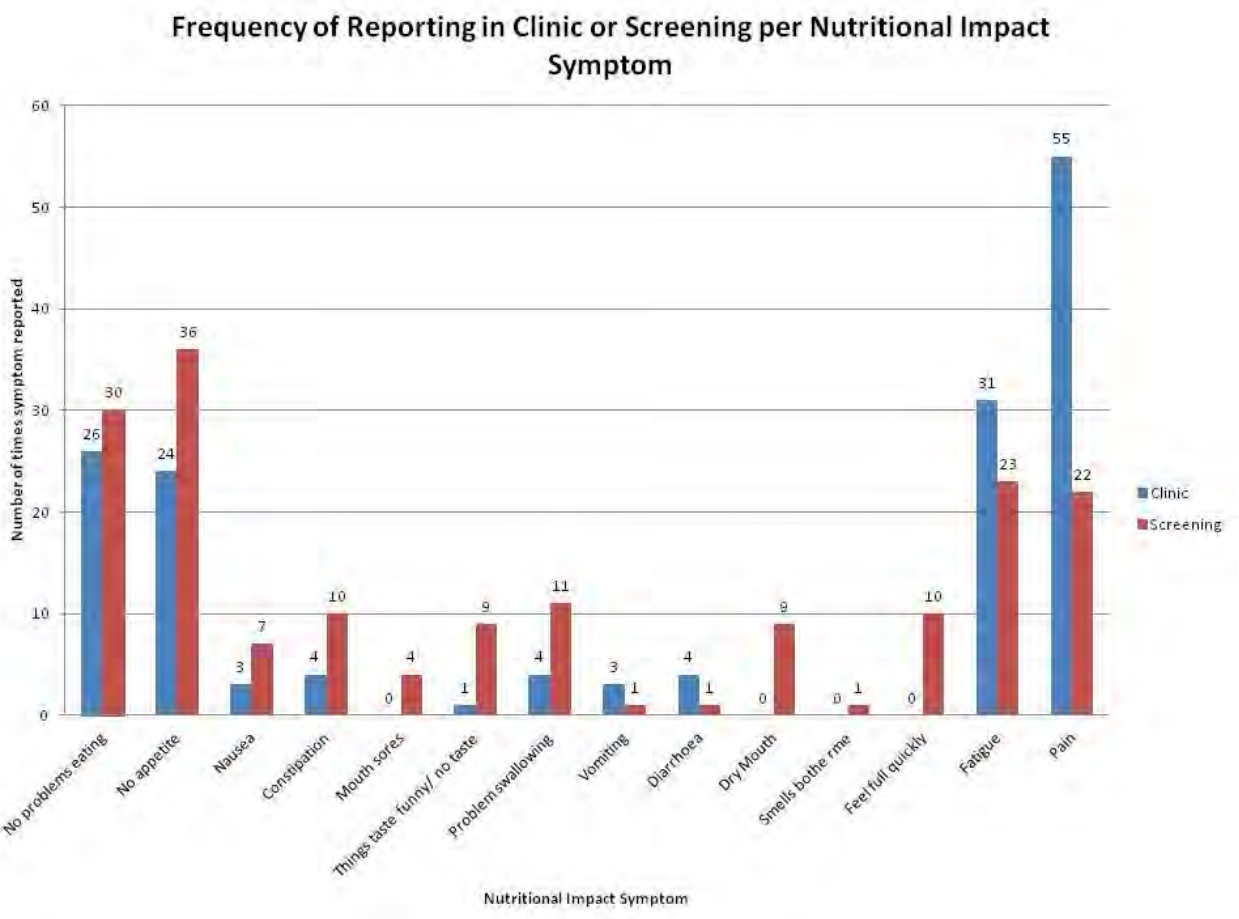
Introduction: NHS Lothian has developed a prehabilitation service for patients who have radiologically-diagnosed Stage III or IV lung cancer. This patient population tends to skew older, present with co-morbid conditions, and have a high symptom burden at diagnosis. These symptoms may affect or limit the treatment tolerated by, or offered to, these patients. Identifying and mitigating these symptoms may lead to a difference in treatment options available, patients' quality of life, and/or better outcomes.

Methods: A retrospective single-centre project was undertaken at St. John's Hospital, Livingston between June 2021 and February 2025. All patients saw a palliative care physician, physiotherapist and dietician within 2 weeks of a CT scan suspecting stage III or IV lung cancer. All patients were screened using the patient-generated subjective global assessment (PGSGA) for Nutritional Impact Symptoms (NIS). The PGSGAs were compared with initial respiratory clinic letters from TrakCare Electronic Patient Records to assess frequency and distribution of NIS reported in each setting.

Results: Data was available for 94 of 108 patients who attended prehabilitation. Median number of NIS per clinic review and PGSGA were 1 and 2, respectively. Screening identified additional symptoms in 44% of patients when compared to clinic review alone, with a median of 2 additional NIS detected in these patients. 9 NIS were identified more frequently in prehabilitation screening compared to in clinic, the commonest of these being reduced appetite and early satiety, swallowing problems, and constipation. The biggest discrepancies between screening and clinic findings were in early satiety (10 in screening, none in clinic) and reduced appetite (36 in screening, 24 in clinics). 4 NIS were exclusively identified by PGSGA screening: early satiety, dry mouth, mouth sores and adverse reaction to smell. 4 symptoms were more commonly recorded in clinic than via PGSGA. These were pain, fatigue, diarrhoea and vomiting, with pain being reported 150% more frequently in clinic compared to PGSGA screening.

Conclusions: PGSGA screening before prehabilitation is an effective way to identify additional, and often clinically under-recognised, NIS in patients with locally advanced or metastatic lung cancer. The next phase of this work will be to assess what treatments - and/or how many cycles of treatment - the relevant patients received, to understand whether that is related to their declared NIS burden at presentation.



Keywords: Prehabilitation, Screening, Nutrition

P2.15 .28 Lorlatinib-Associated Dyslipidemia: A Multicenter, Retrospective Analysis and Implications for Future Cardiovascular Disease

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Introduction: Cardiovascular disease (CVD) and cancer are the two leading causes of death worldwide. Among patients who had developed hyperlipidemia after Lorlatinib consumption, 55% did not have resolved hyperlipidemia even after taking lipid-lowering drugs in post-hoc analysis of CROWN study. This raises concerns that while Lorlatinib can bring long progression-free survival for cancer patients, these cancer survivors may now at risk of developing CVD. However, how to evaluate Lorlatinib-related hyperlipidemia's impact on CVD in this tumor-bearing population remains an unresolved question.

Methods: We reviewed 120 Lorlatinib-treated patients from ten tertiary medical centers. Since both inflammation and dyslipidemia play roles in atherosclerosis formation, we reviewed C-reactive protein (CRP), the biomarker of inflammation, and blood lipid levels before and after 3 months' Lorlatinib consumption. To check atherosclerosis early formation, we also reviewed the changes in maximum carotid intima-media thickness (CIMT) examined by B-ultrasound before and after 6 months' Lorlatinib consumption.

Results: In our real-world cohort, 89 patients who had Lorlatinib-related hyperlipidemia were retrospectively enrolled. After 3 months of lipid-lowering drug uptake, re-evaluation of blood lipid levels revealed that 56/89 (63%) patients had not reach normal levels. Among these patients, only 12 had CRP test before and after 3 months' Lorlatinib consumption, 83% (10/12) of which had their CRP decreased down within normal range. Among 4 patients who underwent carotid artery B-ultrasound examination before and after 6 months' Lorlatinib consumption, 2/4 patients had increased maximum CIMT (both from 1.5mm to 2.2mm) and 2/4 patients had decreased maximum CIMT (from 2.1mm to 1.9mm, 3.1mm to 1.9mm, respectively). This was intriguing as atherosclerotic plaque thickness did not parallel blood lipid levels.

Conclusions: Oncologists in the real world do not pay enough attention to lipid management in Lorlatinib-related hyperlipidemia patients, especially CRP inflammation biomarker and carotid artery B-ultrasound. Oncologists should form a multidisciplinary team with ultrasonographers and cardiologists to evaluate Lorlatinib-related hyperlipidemia's impact on CVD in these cancer survivors. As now, we are conducting a multi-center, prospective study addressing this important issue (Lipid-Long Study, NCT06876675).

Keywords: Lorlatinib, Dyslipidemia, Cardiovascular disease

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .29 Understanding the Psychosociological Burden of ALK+ NSCLC: Findings From the French Study «Living With ALK+ Cancer»

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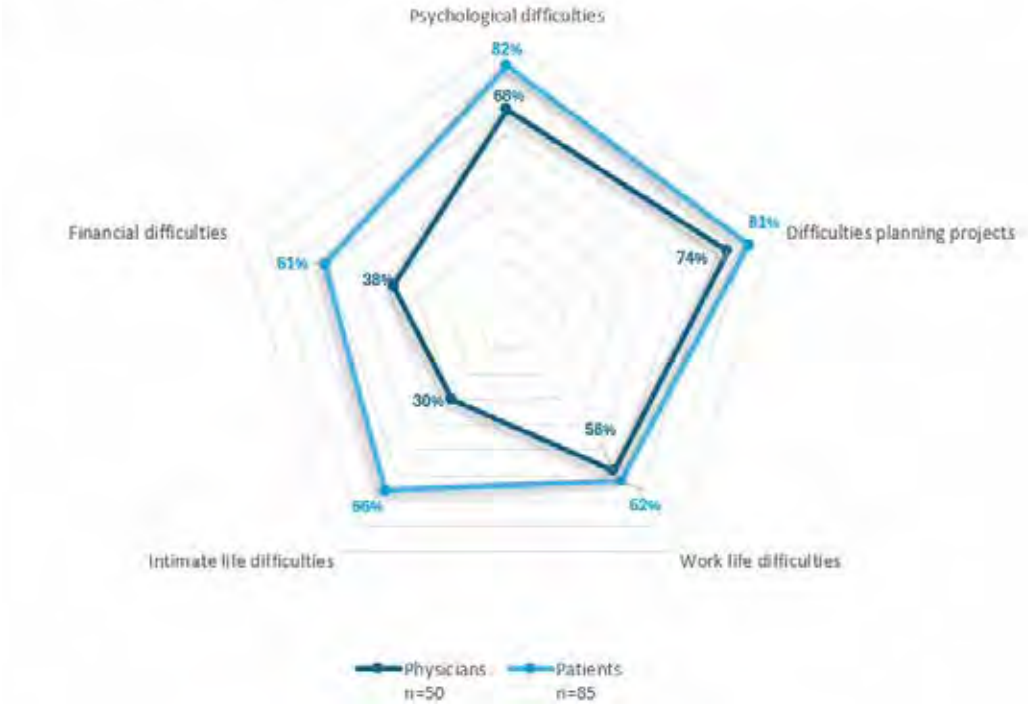
Introduction: ALK fusion positive (ALK+) adenocarcinoma accounts for about 5% of NSCLC. Their prognosis has been drastically improved by therapeutic sequences incorporating different generations of ALK inhibitors (ALKi), extending median overall survival from 12 months to several years. This prolonged survival on treatment may have sociological impacts in this usually young, active and nonsmoker population. This study aims to understand the impact of the disease and treatments on various aspects of ALK+ NSCLC patients' daily lives and perception of physicians.

Methods: « Living with ALK+ cancer » is a psychosociological survey conducted in two parts: a qualitative phase selecting areas of interest and the second phase quantifying their impact in 85 patients, 27 caregivers and 50 thoracic oncologists. Here, we present the results of the quantitative phase conducted between November 2024 and February 2025. To be enrolled in the study, patients in first line (1L) had to have started treatment at least a year prior to inclusion. Data collection was performed through self-administered online surveys, each one lasting approximately 35 minutes. Patients were recruited through patient associations or directly through their physicians. Thoracic oncologists and caregivers were not necessarily those of the patients.

Results: Seventy percent of patients had advanced disease, and 62% of them had brain metastases. 74% of participants were women. Median age was 57 years. Average current line duration at data collection was 2.4 years both for patients in 1L and 2L+. The figure presents a spider chart comparing the frequency of preidentified daily life difficulties based on patients' reports and physicians' perception. Psychological difficulties emerged as the most frequent daily challenges for patients, with common issues including feelings of insecurity (49%), anxiety (48%), anger (42%), and mood disorders (38%). Patients also faced professional challenges, including sick leave periods (26%) and reduced working hours (19%) due to the disease. Impact on driving ability was reported by 63% of patients, while only 10% stated that they had stopped driving, and only 26% indicated that this topic was addressed by their physician. Challenges in maintaining physical activity was also highlighted in 49% of patients and 42% reported a decrease or loss of libido, indicating an impact on intimate life.

Conclusions: Our study highlights the extensive challenges faced by patients with ALK+ NSCLC, emphasizing the need for comprehensive support systems that address both medical and non-medical aspects of patient care.

Figure: Spider Chart comparing the frequency of preidentified daily life difficulties: patients' reports (n=85) versus physicians' perception (n=50)



Keywords: ALK+ NSCLC, Psychosociological impact, Patient care

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .30 Impact of an Incidental Pulmonary Nodule Course Series on the Professional Development of Under-Resourced Multidisciplinary Teams

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Introduction: While early detection in the high-risk screening population yields a 6% detection rate, lung cancer detection in the 1.6 million incidental pulmonary nodules (IPN) identified annually in the U.S. through imaging studies holds as much, if not more, promise. To improve early lung cancer detection in IPNs, this project aimed to provide affordable, current, and quality professional IPN-specific education for key healthcare providers (HCPs) and personnel, including nursing and allied health professionals in under-resourced and healthcare professional shortage areas.

Methods: Informed by current evidence and key stakeholders, including GO2 for Lung Cancer Centers of Excellence, we identified topics and subject-matter experts for the development of an IPN comprehensive course series. The GO2 Global Knowledge Center (GKC) team designed interactive activities, which underwent a thorough review process. Continuing Medical and Nursing Education credits were made available. The course series was promoted through the GKC messaging platform and other professional networks. Data was collected from registrations, post-tests and course evaluations and analyzed to determine the learner population served and impact of the IPN series.

Results: This project and reporting occurred from May 1, 2024, through March 20, 2025. Of 491 enrollments, 230 (47%) enrolled in at least one course. Learners consisted of Navigators (25%), Nurses (24%), Allied Health Professionals (11%), Medical Doctors (8%), and Other (13%) with more than 50% in Pulmonology/Respirology (31%), Patient Navigation (17%), Medical Oncology (10%). Of the 83% of learners practicing in the U.S., 30% practice in community hospitals and 19% in ambulatory settings, which may represent practice locations with limited access to subspecialists with expertise in IPN management. Additionally, 68% of learners reported serving urban populations, while 8% serve urban areas with broad catchment and 7% serve rural populations. Table 1. summarizes learner course evaluation responses, including course satisfaction, practice implications, and credit achievement. According to a recent Google search, this IPN course series appears to be the only one of its kind available.

Conclusions: Incidental pulmonary nodule-specific provider education enhances current knowledge and practice skills. This course series demonstrated value to multidisciplinary professionals, who commonly practice in under-resourced, non-academic, and geographically isolated settings. These multidisciplinary professionals serve an important role in IPN management and early lung cancer detection. By providing free and accessible education, knowledge gaps may be minimized, and lung cancer outcomes may be improved. This project informs future course project opportunities to reach and educate under-resourced multidisciplinary teams about lung cancer.

Table 1. Impact of Course Series for Learners

		Satisfaction with learning activity	Motivation to participate in this activity		Credit request type			Based on what I learned today, I will improve my practice by incorporating the following:		
Course	# of learners who earned CE out of total GKC learners	# of learners who were satisfied/ very satisfied	# of learners who reported topic or therapeutic area	# of learners who reported CME/CE credits	# of learners who requested ACCME AMA PRA Category 1 Credits™	# of learners who requested ANCC Nurse Contact Hours	# of learners who requested a Certificate of Attendance	# of learners who reported "improved diagnosis/ patient assessment"	# of learners who reported "useful therapies and appropriate uses"	# of learners who reported "cutting-edge science in this therapeutic area"
Incidental Pulmonary Nodules 101	68/144 (47.2%)	69/71 (97.18%)	55/71 (77.46%)	41/71 (57.75%)	14/68 (20.59%)	46/68 (67.65%)	8/38 (11.76%)	46/71 (69.79%)	20/71 (28.17%)	5/71 (7.04%)
Safe and Responsible Detection, Reporting, Tracking, and Management of Pulmonary Nodules	54/89 (60.7%)	5656 (100%)	39/56 (69.64%)	33/56 (58.93%)	7/54 (12.96%)	39/54 (72.22 %)	8/54 (14.81 %)	36/56 (64.29%)	21/56 (37.50%)	12/56 (21.43%)
Artificial Intelligence in Pulmonary Nodule Management – A Practical Guide	23/78 (29.5%)	24/25 (96%)	20/25 (80%)	11/25 (44%)	6/23 (26.09%)	13/23 (56.52%)	4/23 (17.39%)	6/25 (24%)	7/25 (28%)	10/25 (40%)
Building an Incidental Pulmonary Nodule Program	37/67 (55.2%)	37/37 (100%)	30/37 (81.08%)	15/37 (40.54%)	6/37 (16.22%)	26/37 (70.27%)	5/37 (13.51%)	21/37 (56.76%)	10/37 (27.03%)	9/37 (24.32%)
Diagnostic Workup of Pulmonary Nodules	39/59 (66.1%)	40/41 (97.56%)	35/41 (85.37%)	25/41 (60.98%)	7/40 (17.5%)	26/40 (65%)	7/40 (17.5%)	24/41 (58.54%)	23/41 (56.10%)	13/41 (31.71%)
Determination of Malignancy Risk of Incidental Pulmonary Nodules	24/39 (61.5%)	25/25 (100%)	14/25 (56%)	14/25 (56%)	5/24 (20.83%)	15/24 (62.5%)	4/24 (16.67%)	14/25 (56%)	10/25 (40%)	8/25 (32%)
Surgical Management of Incidental Pulmonary Nodules	7/15 (46.7%)	7/7 (100%)	7/7 (100%)	4/7 (57.14%)	1/7 (14.29%)	4/7 (57.14%)	2/7 (28.57%)	4/7 (57.14%)	3/7 (42.86%)	0/7 (0%)

Keywords: Incidental Pulmonary Nodules, Online Continuing Education, Multidisciplinary Teams

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .31 Integrating Biomarker Testing in Early-Stage Lung Cancer With a Nurse-Led Multidisciplinary Approach Using the 4R Oncology Model

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Introduction: Nurses and Allied Health Professionals (AHPs) play a critical role in delivering timely and guideline-concordant multidisciplinary cancer care. For early-stage non-small cell lung cancer (NSCLC), biomarker testing is a recent guideline-based standard necessary to inform neoadjuvant and adjuvant therapy decisions. However, integrating timely biomarker testing in early-stage NSCLC care remains challenging and variable. The lack of expedient ordering causes delays in receiving testing results, therapy decisions and treatment initiation. The 4R Oncology model (4R=Right Info/Care/Patient/Time) has demonstrated effectiveness in facilitating timing and sequencing of care across specialties, including reducing time between biomarker testing and treatment decisions. We designed and evaluated a nurse and AHP-led approach using the 4R model to implement timely biomarker testing in early-stage NSCLC at a hospital in a large U.S. health system.

Methods: A prospective cohort study was conducted among patients with operable Stage I-III NSCLC who received the 4R model vs. those who received usual care (control). In the 4R group, we designed a systematic multidisciplinary process maximizing and expediting biomarker testing on biopsy or surgical samples. To ensure process consistency and expediency, testing was facilitated by a nurse-navigator and AHP team responsible for ordering, communication across specialties, and issue resolution. Patients referred to surgeons within the same hospital underwent either the 4R approach (one surgeon) or usual care (other surgeons) between January - December 2024. The rates and timing of biomarker testing were compared between the two groups.

Results: The patients in the 4R (N=42) and control group (N=139) were demographically similar (median age at surgery: 69 vs. 70 years; female: 64% vs. 62%; non-Hispanic White: 43% vs.52%; Elixhauser comorbidity index: 3.88 vs. 3.85; and Stage I: 79% vs. 77%). The rates of post-diagnostic biopsy and receipt of surgery as first treatment were similar (Table). The 4R-based (vs. usual care) approach improved the overall rates of biomarker testing (100% vs. 40%, p<0.001) as well as the rates of testing on diagnostic biopsy and surgical tissue. It also reduced the median time between surgery and receiving test results: 26 (control) vs. 6 days (4R).

Conclusions: Our 4R-based, nurse and AHP facilitated approach resulted in significant benefit, with increased biomarker testing and sooner return of results to guide decisions in a population with predominantly Stage I NSCLC. This intervention may inform other institutions' efforts to leverage nurse and AHP resources to improve biomarker testing in operable lung cancer patients.

Table: Timing and Rates of Biomarker Testing

Metric	4R n=42	Control n=139	p value
Patients who received biomarker testing*	100% (42/42)	40% (56/139)	**<0.001**
Diagnostic biopsy	69% (29/42)	67% (95/139)	1.00
Biopsy and biomarker testing on biopsy sample	79% (23/29)	26% (25/95)	**<0.001**
Neoadjuvant as first treatment	7% (3/42)	8% (11/139)	1.00
Surgery as first treatment	93% (39/42)	92% (128/139)	1.00
Surgery and biomarker testing on surgical sample	48% (19/39)	24% (31/128)	**0.005**
Time from surgery to biomarker test result (median)	6 Days	26 Days	**0.03**

*Biomarker testing conducted by Next Generation Sequencing of tumor tissue sample

4R=Right Info/Care/Patient/Time

Keywords: Multidisciplinary, Biomarker, 4R

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .32 Early Lung Cancer Detection and Multidisciplinary Care

W. Liao[1], J. Goss[1], T. Qureshi[1], S. Johnson[1], A. Harris[1], K. Dortch[1], A. Porter[1], Y. James[1], A. Patel[1], J. Roma[1], H. Marshall[1], C. Fehnel[1], A. Mehrotra[1], O. Ogbeide[1], P. Lammers[1], K. Tonkin[1], J. Machin[1], J. Zhao[1], T. Ng[1], M. Smeltzer[2], M.A. Ray[2], R. Osarogiagbon[1]
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Introduction: Lung cancer screening (LCS) and incidental pulmonary nodule programs (IPN) are associated with improved overall survival (OS); multidisciplinary care (MDC) enhances guideline concordance. We compared OS among patients diagnosed with lung cancer through LCS or IPN programs with, versus without, structured MDC within a regional community healthcare system.

Methods: Prospective observational study of patients enrolled into LCS and IPN programs in the 'Detecting Early Lung Cancer (DELUGE) in the Mississippi Delta' cohort cross-linked with institutional MDC database. We compared patients' demographic, clinical characteristics, and OS and constructed a Cox model to estimate hazard for death adjusting for age, sex, race, smoking history, insurance status and histologic type (aHR). We conducted a propensity-matched sensitivity analysis, matching for age, sex, race, insurance, rurality and clinical stage.

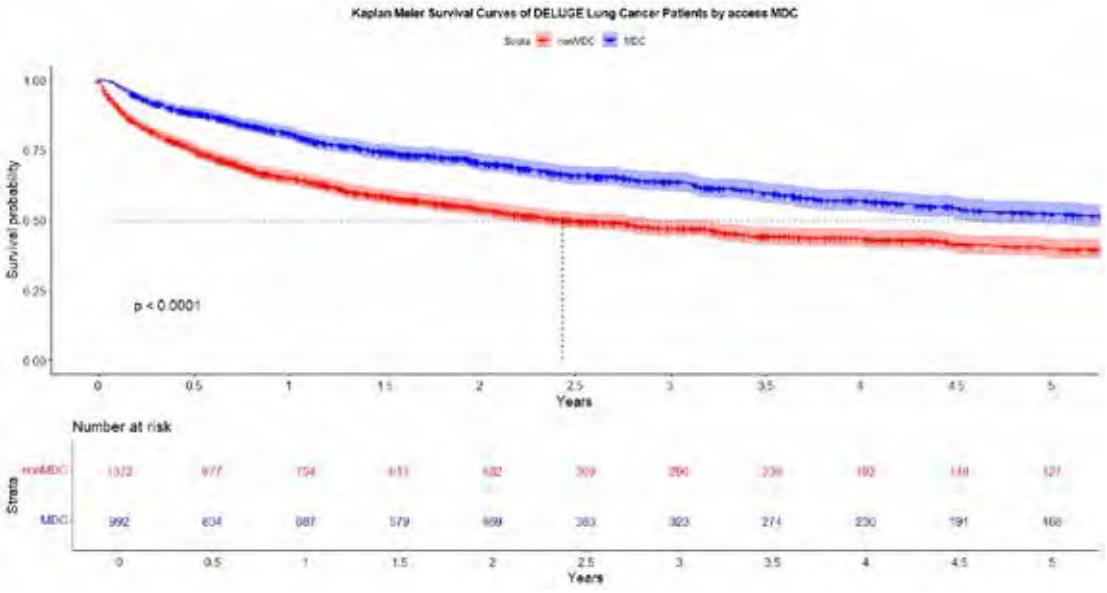
Results: From Jan 2015 to June 2024, 613 patients were diagnosed through LCS, 220 (36%) had MDC; 1913 through IPN, 818 (43%) had MDC; 2,526 in total through both early detection programs, 1038 (41%) had MDC (Table). There was a median of 1 (IQR 1-2) comorbidity across all subsets. The proportions with adenocarcinoma were 45% v 37% LCS, 56% v 43% IPN; small cell lung cancer: 11% v 16% LCS, 8% v 14% IPN (p=0.0005).

OS was significantly better with MDC (Figure). Aggregate 5-year OS rates were 65% (CI:56-76) v 54% (47-62) for LCS; 48% (44-53) v 35% (31-39) for IPN ; 51% (48-56) v 39% (36-43) for the combined programs. The aHR was significant for non-MDC in each early detection program; propensity-matching yielded similar results (Table).

Conclusions: Structured MDC was strongly associated with significantly better OS among patients diagnosed with lung cancer through LCS or IPN programs. For optimal results, multidisciplinary decision-making should be embedded within early lung cancer detection programs.

Variable	LCS: MDC?		LNP: MDC?		Both Programs: MDC?	
	Yes; n=220	No; n=393	Yes; n=818	No; n=1095	Yes; n=1038	No; n=1488
Median (IQR) age, years	68 (64-73)	68 (63-72)	69 (62-76)	71 (64-77)	69 (63-75)	70 (64-76)
Female, %	51	51	50	51	50	51
Black race, %	14	20	29	22	26	21
Medicaid/uninsured, %	3	4	7	7	6	6
Metropolitan residence	87	53	88	61	88	59
Actively smoking, %	72	72	47	52	52	58
Stage I/II v IV, %	73 v 10	58 v 21	58 v 19	40 v 34	61 v 17	45 v 31
Surgical resection, %	54	31	42	19	44	22
aHR for death	Ref	1.7 (1.2- 2.4) 0.002	Ref	1.6 (1.4, 1.8) <0.0001	Ref	1.6 (1.4, 1.8) <0.0001
Propensity matched	Ref	1.5 (1.0-2.3) 0.0304	Ref	1.3 (1.1-1.5) 0.0018	Ref	1.3 (1.2-1.6) 0.0002

Table. Characteristics and outcomes of patients with LCS or IPN-detected lung cancer with and without MDC.



Keywords: Early Detection, Multidisciplinary Care, Lung Cancer

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .33 A Comparative Study of the Significance of GPT-Enabled Counseling and Management of Pulmonary Nodules

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Introduction: Effective pulmonary nodule management is critical for early lung cancer detection, yet faces significant challenges including inconsistent guideline implementation, limited patient awareness, uneven resource distribution, poor follow-up adherence, and insufficient psychological support. AI-powered specialized GPT models (e.g., BAIMGPT, DeepSeek GPT) address these issues through advanced natural language processing capabilities, offering intelligent patient consultations, preliminary risk assessments, and personalized management recommendations. The purpose of this study is to compare the performance of specialized AI model BAIMGPT with general-purpose models in pulmonary nodule management, validate the advantages of digital human technology in enhancing doctor-patient communication efficiency and diagnostic accuracy, and provide evidence-based support for optimizing intelligent healthcare products.

Methods: This study comprises three phases: (1) Literature review analyzing GPT applications in pulmonary nodule management; (2) BAIMGPT model development by a multidisciplinary team, optimizing eight key metrics (convenience, user-friendliness, safety perception, question comprehension, accuracy, voice interaction, visual assistance, and demand); (3) Multicenter evaluation using dual assessments: user ratings and blinded expert reviews of response accuracy against clinical guidelines. The research aims to establish evidence for specialized AI in nodule management through systematic comparison of BAIMGPT's performance against benchmarks, with particular focus on both technical efficacy and user experience metrics.

Results: This study conducted a comparative analysis of consultation experiences from 109 pulmonary nodule patients, revealing that the specialized BAIMGPT model significantly outperformed the general-purpose large language model DeepSeek GPT across multiple key metrics. In terms of emotional interaction, BAIMGPT achieved 92.7% satisfaction for friendliness and 89.0% for perceived safety through its digital human technology, demonstrating significant advantages over DeepSeek GPT's 41.3% and 38.5% respectively ($p<0.001$). Regarding functional experience, BAIMGPT's voice interaction (90.8% satisfaction) and visual interface (87.2% satisfaction) received high praise, while DeepSeek GPT scored no points due to lacking these features. In core competencies, BAIMGPT surpassed the control group in both question comprehension (88.1% vs 82.6%) and answer accuracy (85.3% vs 80.7%). Notably, 84.4% of patients rated BAIMGPT as "urgently needed," far exceeding DeepSeek GPT's 52.3%. These findings demonstrate that by integrating specialized knowledge bases with digital human interaction technology, BAIMGPT has not only enhanced the technical accuracy of medical consultations but also made breakthroughs in doctor-patient communication experience, establishing a "precision medicine + humanistic care" paradigm for AI applications in specialized disease management. The study recommends expanding sample sizes and incorporating objective physiological indicators for multidimensional validation in future research.

Conclusions: This study demonstrates the significant advantages of the specialized AI model BAIMGPT in pulmonary nodule management. Data shows BAIMGPT outperforms the general-purpose model DeepSeek GPT in emotional interaction , functional implementation , and core metrics . Notably, 84.4% of patients expressed urgent demand for BAIMGPT, significantly higher than the control group's 52.3%. The research validates the innovative value of combining "specialized medical knowledge with digital human technology," establishing a new paradigm of "precision medicine with humanistic care." Future studies should expand sample sizes, incorporate objective indicators, and deepen clinical integration, providing important references for AI applications in healthcare.

Keywords: BAIMGPT, pulmonary nodules, DeepSeek

P2.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE
MONDAY, SEPTEMBER 8, 2025 - 10:30 - 12:00

P2.15 .34 Prompting and Medical Expertise Influence Large Language Model in Clinical Data Extraction: Findings From the APOLLO 11 Trial

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Introduction: Data retrieval in clinical research is often time-consuming and error-prone. Large Language Models (LLMs) have shown zero-shot capabilities in structuring unstructured clinical texts. These models could aid the data retrieval stage by exploiting the information reported in Electronic Health Records (EHRs). This study is conducted within the APOLLO 11 trial (NCT0550961), a multicentric Italian study which leverages a federated infrastructure for the analysis of advanced non-small cell lung cancer (NSCLC) data.

Methods: We evaluated four privacy-preserving LLMs on anonymized EHRs of 679 NSCLC patients from Fondazione IRCCS Istituto Nazionale dei Tumori di Milano. We assessed English/Italian prompts and zero/few shot techniques using the information extraction pipeline proposed by Wiest et al. We selected smoking, ECOG, histology, PD-L1, staging, T, N, M as multiclass variables and bone/brain/liver metastases as binary variables. Additionally, we examined if medical expertise could affect the extraction accuracy in a two-phase prompting study among experienced oncologists, resident oncologists and medical students. In the second phase, the medical user was asked to refine prompts, as "human-in-the-loop", according to the performance achieved in the first phase.

Results: Overall, few-shot prompting improved the average extraction performance compared to zero-shot. Additionally, few-shot, enriched with annotated examples from the original dataset, further increased the accuracy in variables like smoking and PD-L1 (Table 1). Histology and staging were originally unbalanced resulting in poor F1-score, while T, N, M remained the variables with the lowest performance (Table 1). LlaMa 8B achieved the highest average accuracy in few-shot with annotation (0.81), followed by Mistral 7B (0.69) and MedLlaMa and BioMistral (less than 0.5). An improvement of 10% in extraction accuracy was observed in phase two of the experiment for the medical students, especially in T and N staging. Experienced oncologists achieved comparable performance between the two phases for variables like staging and metastatic sites, demonstrating the impact of medical expertise on prompting.

Conclusions: LLMs demonstrated strong performance in extracting clinical data from EHRs, even with minimal prompt optimization. The findings also highlight the importance of leveraging domain-specific medical expertise to further enhance their effectiveness. This study confirms the feasibility of using LLMs to support clinicians and clinical study coordinators during the initial phase of data retrieval. However, subsequent steps such as quality check must remain distinct and human-supervised to ensure accuracy and resolve potential discrepancies. Notably, the study shows this approach reduces several months of manual data entry, while maintaining high performance.

Prompting	Smoking	ECOG	Histology	T	N	M	PD-L1	Staging	Liver metastases
Zero-shot	0.62/0.53	0.94/0.92	0.87/0.63	0.46/0.27	0.48/0.29	0.76/0.63	0.74/0.66	0.76/0.41	0.89/0.70
Few-shot	0.89/0.82	0.96/0.95	0.84/0.56	0.39/0.22	0.51/0.29	0.91/0.75	0.73/0.71	0.90/0.42	0.90/0.67
Few-shot + annotation	0.93/0.89	0.97/0.96	0.81/0.51	0.48/0.20	0.42/0.24	0.93/0.74	0.79/0.78	0.91/0.36	0.90/0.70

Keywords: Large Language Model, prompt engineering, data extraction

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.01 Asian-Americans With Tobacco Use History Are Less Often Eligible for Screening Than White Individuals With Lung Cancer

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Introduction: The US Preventive Services Task Force (USPSTF) guidelines for lung cancer screening (LCS), which rely on age, smoking pack-years, and quit-years, have been shown to disproportionately exclude minority groups, including Asian-Americans. Recent recommendations propose eliminating quit-years - from the American Cancer Society (ACS) - or replacing pack-years with smoking duration. The objective of this multi-center study was to evaluate the impact of alternative LCS criteria on differences in screening eligibility (i.e., sensitivity) between Asian-American and White patients with lung cancer.

Methods: Asian-American and White patients with a lung cancer diagnosis between 2008-2024 were identified at two multi-center healthcare systems in Philadelphia and New York City. At Jefferson Health (JH), lung cancer cases were identified from the electronic health record and confirmed via chart review, while at Weill Cornell Medicine (WCM), cases were identified using both hospital-based cancer registry data and chart review. To ensure statistical power for racial comparisons, a representative subcohort of White patients was sampled at JH, whereas all available cases were included at WCM. Smoking status and quantitative smoking history were manually reviewed at JH, while at WCM, a natural language processing tool extracted smoking data from progress notes. Following data extraction, patients with a never-smoking history were excluded. LCS eligibility (age range-pack-years-quit-years) was assessed using USPSTF2013 (55-80-30-15), USPSTF2021 (50-80-20-15), USPSTF2021 with a 20- or 30-year smoking duration replacing pack-years, and ACS 2023 criteria (50-80-20, no quit-year restriction).

Results: The final cohort included 242 Asian-Americans (39.7% Chinese-Americans, 12.4% Vietnamese-Americans, 10.3% Korean-Americans, and 37.6% other Asian-American subgroups) and 431 White patients at JH (2015-2024), as well as 954 Asian-Americans and 3,304 White patients at WCM at WCM (2008-2024). In the combined cohort, Asian-American patients included a higher proportion of males (80.4% vs. 45.1%), lower mean pack-years (33.8 vs. 39.2), and a shorter mean quit-time (7.4 vs. 15.4 years) than White patients. The gap in screening eligibility between Asian-American and White patients was reduced with USPSTF2021 (4.8% [p=0.002] vs. 5.2% in USPSTF2013 [p<0.001]) and further narrowed with USPSTF2021 with a 30-year duration (3.4%, p=0.03), though differences remained statistically significant. The ACS criteria increased overall eligibility but showed the largest disparity (15.0%, p<0.001).

Conclusions: Revised criteria such as USPSTF2021 and USPSTF2021 with 30-year smoking duration reduced differences in screening eligibilty, but significant gaps persist. Future investigation of lung cancer in underserved populations should consider comprehensive evaluation of risk factors that are not currently included in determining LCS eligibility.

Lung Cancer Screening Eligibility by Race Among Lung Cancer Cases (n= 4,931)

	Asian-Americans n= 1,196		Whites n= 3,735		*p*	Difference in screening sensitivity
LCS Eligibility, n(%)						
USPSTF 2013	278	23.30%	1064	28.46%	<0.001	5.16%
USPSTF 2021	348	29.17%	1269	33.95%	0.002	4.78%
USPSTF 2021-Dur20*	410	34.37%	1420	37.99%	0.026	3.62%
USPSTF 2021-Dur30*	361	30.26%	1260	33.71%	0.029	3.45%
ACS 2023	475	39.82%	2049	54.82%	<.001	15.00%
Reasons for LCS Ineligibility, n(%)						
USPSTF 2021-Ineligible	515	43.17%	1883	50.37%		
Age						
<50 years old	57	11.07%	69	3.66%		
>80 years old	171	33.20%	663	35.21%		
Smoking intensity						
<20 pack-years	276	53.59%	802	42.59%		
Quit time ≥15 years	181	35.15%	1231	65.37%		

*USPSTF 2021-Dur20 or -Dur30 applies ≥20 or ≥30 years smoking duration, respectively, to USPSTF 2021 criteria in place of ≥20 pack-years.

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.02 Association Between Age and Lung Cancer Risk: Evidence From Lung Lobar Radiomics

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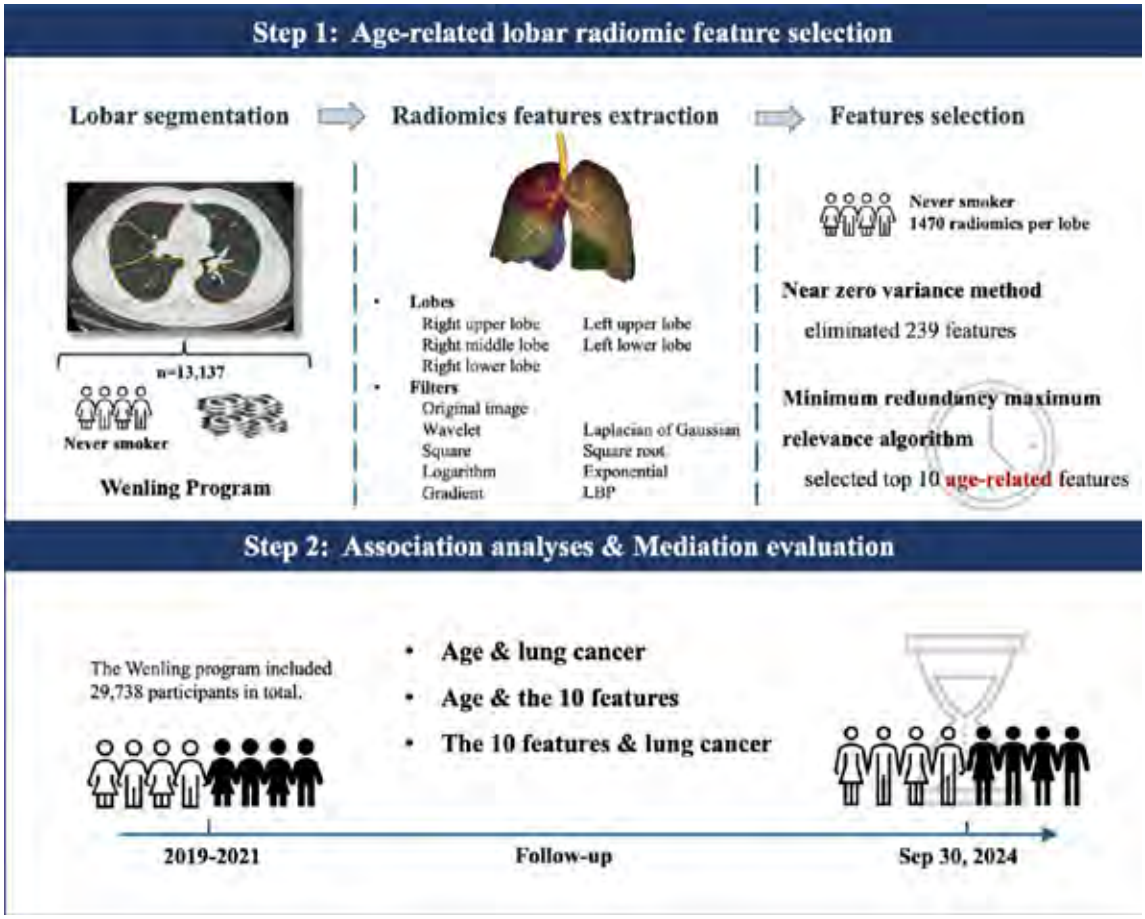
Introduction: Previous studies have highlighted the prominent role of age in lung cancer risk, with signs of lung aging visible in computerized tomography (CT) imaging. This study aims to characterize lung aging using quantitative radiomic features extracted from five delineated lung lobes and explore how age contributes to lung cancer development through these features.

Methods: We analyzed baseline CT scans from the Wenling lung cancer screening program, consisting of 29,810 participants. Deep learning-based segmentation was used to delineate lung lobes. A total of 1,470 features were extracted from each lobe. The minimum redundancy maximum relevance algorithm was applied to identify the top 10 age-related radiomic features among 13,137 individuals without a history of tobacco use. Multiple regression was used to adjust for confounders in the association of age, lobar radiomics, and lung cancer. Linear, Cox proportional hazards, and parametric accelerated failure time models were applied as appropriate. Mediation analyses were conducted to evaluate whether lobar radiomic features mediate the relationship between age and lung cancer risk.

Results: Age was significantly associated with an increased lung cancer risk, particularly among individuals with current tobacco use (hazard ratio = 1.07, P = 2.81×10^{-13}). Age-related radiomics exhibited distinct effects across lung lobes. Specifically, the first-order mean (mean attenuation value) filtered by wavelet in the right upper lobe increased with age (β = 0.019, P < 2×10^{-16}), whereas it decreased in the right lower lobe (β = -0.028, P < 2×10^{-16}). Three features were independently associated with lung cancer risk at a Bonferroni-adjusted P value. Mediation analyses revealed that density and shape features partially mediated the relationship between age and lung cancer risk, while a suppression effect was observed in the first-order mean of the right upper lobe.

Conclusions: This study reveals lobe-specific heterogeneity in lung aging patterns through radiomics and their associations with lung cancer risk. These findings may contribute to developing new approaches for early intervention in lung cancer related to aging.



Keywords: lung cancer, aging, radiomics

P3.01.03 Night Shift Work and Lung Cancer Risk: A Prospective Cohort Study With Mediator Analysis From the Uk Biobank

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Introduction: This study investigated the association between night shift work and lung cancer risk using data from the UK Biobank cohort of 278,650 participants, while exploring potential biological mediators and gene-environment interactions.

Methods: Cox proportional hazards models assessed relationships between current night shift status, lifetime duration, and frequency of night shifts with lung cancer incidence. Mediation analyses examined blood immune cell parameters and plasma proteins as potential mediating pathways. Polygenic risk scores evaluated genetic predisposition interactions.

Results: During a median follow-up of 10.4 years, 1,524 incident lung cancer cases were identified. A significant dose-response relationship was observed between increasing categories of current night shift work and lung cancer risk. Specifically, individuals engaged in some night shifts had a higher risk of lung cancer (HR 1.28, 95% CI: 1.06-1.55, P = 0.010, P for trend = 0.009). Subgroup analysis revealed that smoking status significantly modified this relationship, with smokers engaged in night shift work exhibiting a synergistic increase in lung cancer risk. Mediation analysis identified PRSS8, ALPP, and CEACAM5 as key mediators, collectively explaining over 25% of the total effect.

Conclusions: This study suggests that night shift work, particularly when combined with smoking, is associated with an increased risk of lung cancer. The identification of potential mediators such as PRSS8, ALPP, and CEACAM5 provides insights into the underlying biological mechanisms. Future research should validate these findings and explore targeted prevention strategies for high-risk populations.

Table 1 Current night shift work and lung cancer risk in the UK Biobank (N = 278,650)

	Category	Cases / person-years	Model 1	P-value	Model 2	P-value	Model 3	P-value
Current night shift work	Day workers	1175 / 2,401,935.00	1[Reference]		1[Reference]		1[Reference]	
	Shift but never/rarely night shifts	171 / 250,186.30	1.41 (1.20-1.65)	<0.001	1.50 (1.28-1.76)	<0.001	1.18 (1.00-1.38)	0.047
	Some night shifts	124 / 182,815.50	1.40 (1.16-1.68)	<0.001	1.75 (1.46-2.11)	<0.001	1.28 (1.06-1.55)	0.010
	Usual/permanent night shifts	54 / 73,329.52	1.52 (1.16-2.00)	0.003	1.84 (1.40-2.42)	<0.001	1.19 (0.90-1.57)	0.221
P value for trend				<0.001		<0.001		0.009

Model 1 was unadjusted model; Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, race, BMI, Townsend deprivation index, education, smoking status, alcohol frequency, sleep duration, family history of lung cancer, fruit intake, oily fish intake, and processed meat intake

Table 2 Association of lifetime employment assessment of night shifts worked and lung cancer risk (N = 74,345)

	Category	Cases / person-years	Model 1	P-value	Model 2	P-value	Model 3	P-value
Average lifetime night shift frequency	None	171 / 670,175.00	1[Reference]		1[Reference]		1[Reference]	
	≤3/month	14 / 26,962.28	2.03 (1.18-3.50)	0.011	2.11 (1.22-3.65)	0.007	1.88 (1.08-3.25)	0.025
	3-8/month	12 / 78,895.89	0.59 (0.33-1.07)	0.081	0.68 (0.38-1.23)	0.205	0.61 (0.34-1.10)	0.102
	>8/month	35 / 101,895.60	1.34 (0.93-1.93)	0.113	1.46 (1.01-2.11)	0.043	1.19 (0.82-1.73)	0.365
P value for trend				0.418		0.158		0.777
Lifetime duration of night shift work	None	173 / 67,4706.90	1[Reference]		1[Reference]		1[Reference]	
	<10 years	25 / 85,834.93	1.13 (0.74-1.72)	0.564	1.24 (0.81-1.88)	0.321	0.81 (1.88-0.32)	0.687
	≥10 years	34 / 117,386.90	1.13 (0.78-1.63)	0.523	1.28 (0.88-1.85)	0.196	0.88 (1.85-0.20)	0.729
P value for trend				0.452		0.141		0.667

Model 1 was unadjusted model, Model 2 was adjusted for age and sex; Model 3 was adjusted for age, sex, race, BMI, Townsend deprivation index, education, smoking status, alcohol frequency, sleep duration, family history of lung cancer, fruit intake, oily fish intake, and processed meat intake.

Keywords: Lung Cancer, Night shift work, Proteomic mediators

P3.01.04 Bootstrap-Based Mediation Mendelian Randomization Unveils Gut Microbiota-Driven Metabolic-Immune Networks in Lung Cancer

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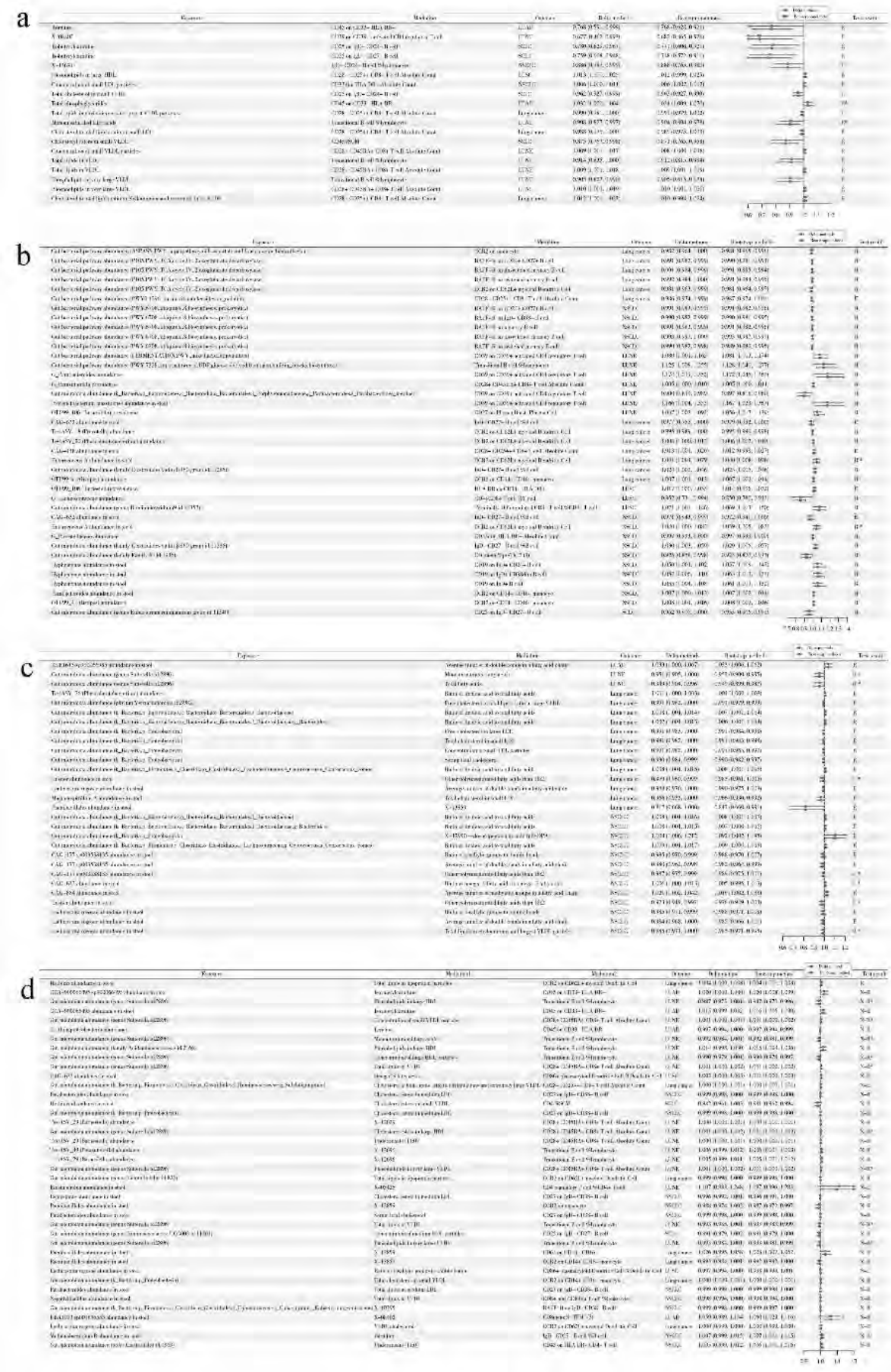
Introduction: Mendelian randomization (MR) with mediation analysis has gained widespread use in research, but reliable validation standards are still lacking. The gut microbiota-plasma metabolome-immune cell-lung cancer axis plays an important role in lung cancer development.

Methods: This unprecedented study included gut microbiota, metabolites, and immune cells genome-wide association studies from 4, 3, and 2 sources. 6 lung cancer-related datasets were collected from Finngen. The Bootstrap method was used to validate results obtained from traditional MR mediation analysis by Delta method, and we assessed the consistency and correlation between the results from both methods.

Results: The mediation effects calculated using the Bootstrap method showed consistency (Intraclass correlation coefficient: 1.000; Sum rank test P=0.978) and correlation (Spearman correlation: 0.999, P<0.001) with traditional MR. We identified that Herbinix abundance induces plasma total lipids in lipoprotein particles, increases CCR2 on CD62L+ myeloid dendritic cells, and reduces the incidence of lung cancer (OR: 1.004, 95% CI: 1.000~1.007). More than 80 mediation effects in the gut microbiota-plasma metabolome-immune cell-lung cancer axis were found. Furthermore, the results of the Delta method were validated using our constructed Bootstrap-mediated MR analysis and excluded some inconsistent results.

Conclusions: This study proposes a method based on the Bootstrap approach to validate the reliability of traditional MR mediation effects by Delta method. Using multiple mediation effects, we identified that Herbinix abundance induces plasma total lipids in lipoprotein particles, elevates CCR2 on CD62L+ myeloid dendritic cells, and raising the risk of lung cancer. Additionally, plenty of mediation effects in the gut microbiota-plasma metabolome-immune cell-lung cancer axis were found.

	Intraclass correlation	P of rank sum test	Spearman correlation	P	Pearson Correlation	P
All results	1.000	0.978	0.999	<0.001	0.999	<0.001
Pathology						
Lung cancer	1.000	0.955	0.994	<0.001	1.000	<0.001
NSCLC, LUAD and LUSC	0.999	0.952	0.998	<0.001	0.999	<0.001
LUNE and SCLC	1.000	0.942	1.000	<0.001	0.999	<0.001
Pleiotropy						
Without pleiotropy	1.000	0.971	0.999	<0.001	0.999	<0.001
With pleiotropy	0.999	0.890	0.999	<0.001	0.999	<0.001



Keywords: Lung cancer, Bootstrap method, Mediation analyse

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.05 Decoding the Sleep Enigma: A Proteomic Mediation Analysis Linking Healthy Sleep Patterns to Lung Cancer Risk

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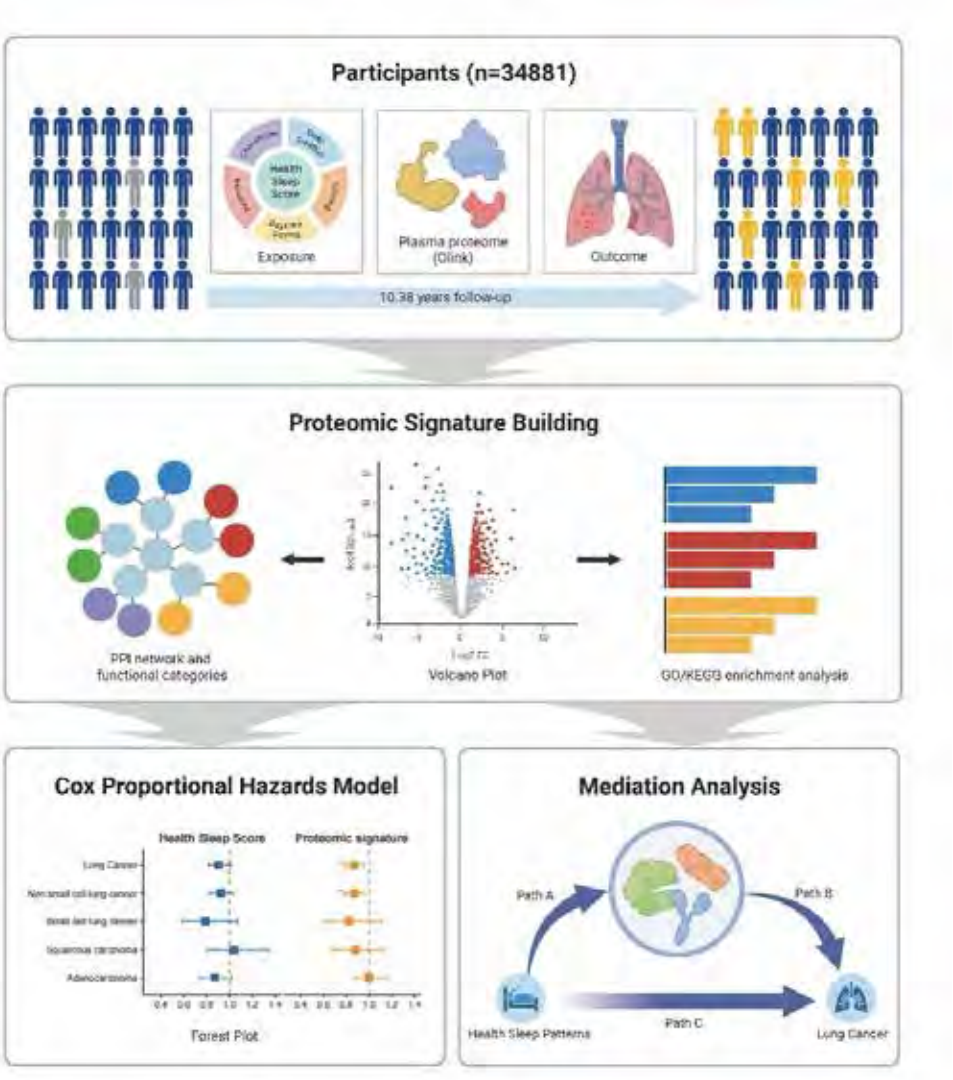
the First Affiliated Hospital of Guangzhou Medical University, Guangzhou/CN

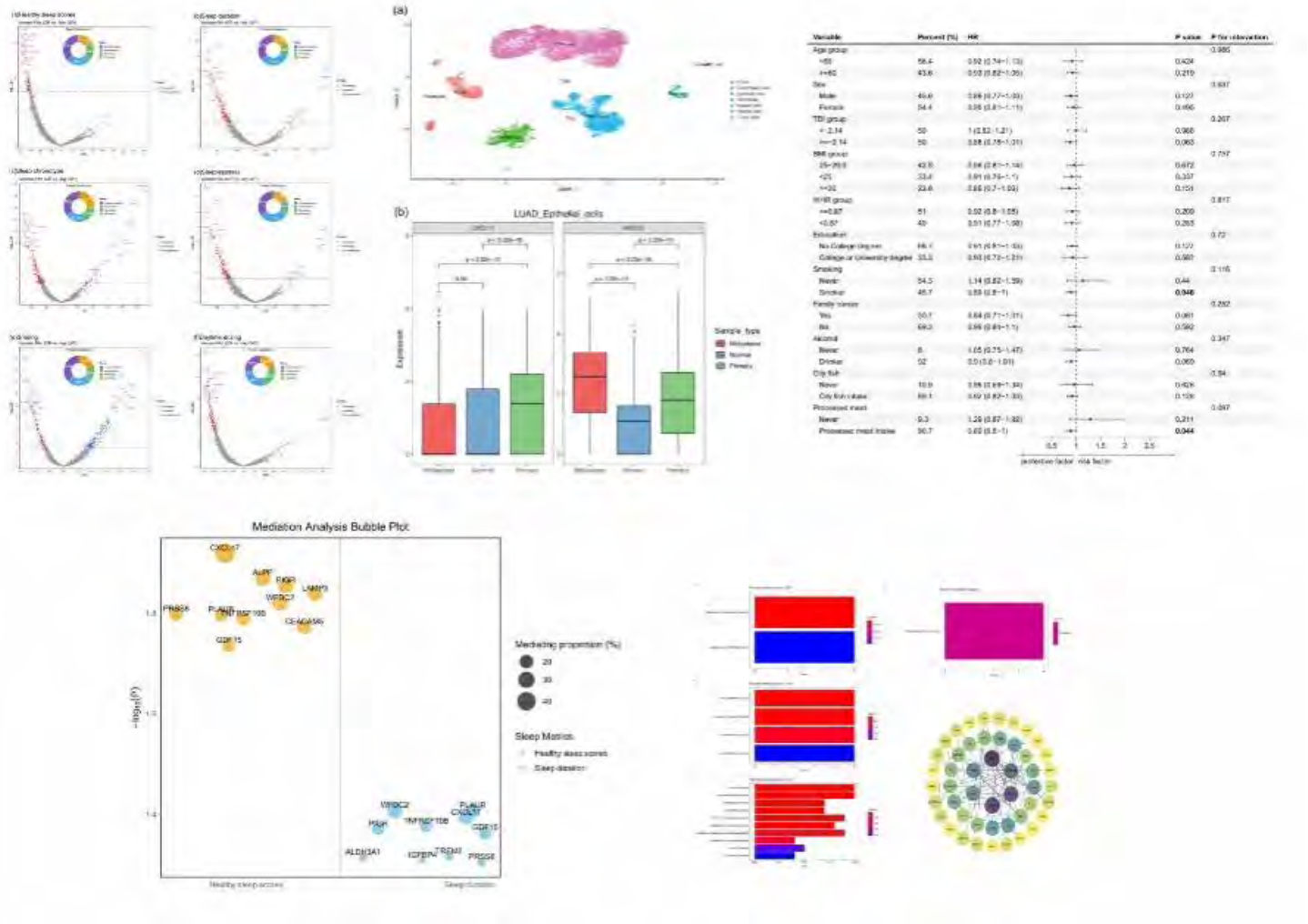
Introduction: The biological link between sleep patterns and lung cancer remains an enigma. This study aims to explore how healthy sleep patterns modulate lung cancer risk through proteomic mediation.

Methods: This study analyzed 34,881 UK Biobank participants with complete proteomic and sleep profiles. A composite sleep score (0-5) incorporating five sleep parameters—duration, chronotype, insomnia, snoring, and daytime sleepiness—was constructed. Proteomic profiling quantified 2,862 plasma proteins using the Olink Explore 3072 platform. Sleep-associated proteomic signatures were developed through logistic regression with LASSO regularization to select key biomarkers. Associations between sleep patterns, proteomic profiles, and lung cancer risk were assessed via Cox models and structural equation modeling (SEM). Subgroup and sensitivity analyses validated result robustness.

Results: Higher healthy sleep scores were significantly associated with reduced lung cancer risk, with hazard ratios (HR = 0.579, CI = 0.345-0.973, p = 0.039) for a score of 3 and (HR = 0.513, CI = 0.305-0.863; p = 0.012) for a score of 4. Similar trends were observed in NSCLC and lung adenocarcinoma. Proteomic signature analysis revealed that protein signatures associated with healthy sleep scores had a significant protective effect against lung cancer (HR = 0.866, CI = 0.784-0.957, p = 0.005) and NSCLC (HR = 0.871, CI = 0.783-0.968, p = 0.011). Enrichment analysis further identified associations between healthy sleep scores and various biological processes, molecular functions, and pathways. PPI network analysis identified ERBB2, CDH1, and MME as key hub proteins. Additionally, mediation analysis identified 125 proteins mediating the relationship between healthy sleep scores and lung cancer risk, with CXCL17 showing the highest mediation proportion (47.62%).

Conclusions: This study highlights the association between healthy sleep patterns and lung cancer risk, identifying key proteins such as CXCL17 and WFDC2 through proteomic analysis.





Keywords: Healthy Sleep Patterns, Proteomics, Lung Cancer

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.06 Lung Cancer in Incidentally Detected Pulmonary Nodules: Stratified Analysis by Smoking History and Nodule Morphology

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Real Hospital Português de Beneficência em Pernambuco, Recife/BR

Introduction: Incidentally detected pulmonary nodules are an increasingly relevant source of lung cancer diagnosis, especially in patients not eligible for screening. We aimed to evaluate clinical and radiological features of lung cancers diagnosed through incidental nodules, stratified by smoking history.

Methods: This retrospective study included 72 patients diagnosed with primary lung cancer through incidental nodules between January 2023 and December 2024. Patients were categorized as never smokers (n=32) or with a smoking history (former or current, n=40). Variables included sex, age group, race, nodule location, density, contour, size, and TNM stage. Associations were analyzed using chi-square or Fisher's exact tests (p<0.05).

Results: Non-smokers were predominantly female (78.1%) and younger (median age: 61-70 years), while those with a smoking history were mostly male (65%) and older (median age: 71-80) (p<0.001 and p=0.033). Nodule location and size did not differ significantly. Solid nodules predominated in both groups (65.6% in non-smokers vs. 75.0% in smokers; p=0.653). However, non-smokers had a higher proportion of subsolid nodules: partially solid (21.9% vs. 17.5%) and ground-glass (12.5% vs. 7.5%), suggesting a distinct pattern, though not statistically significant. Irregular margins were more frequent in smokers (50% vs. 18.8%, p=0.006). Most nodules in both groups measured ≥15 mm (94% vs. 85%, p=0.394), and proportions ≥30 mm were similar (40.6% vs. 37.2%). TNM stage was available in 69 patients. Stage I was more frequent in non-smokers (76.9%) than in smokers (58.1%), while Stage III-IV disease occurred in 39.5% of smokers and 19.2% of non-smokers (p=0.446).

Conclusions: Lung cancers diagnosed via incidental nodules in non-smokers occurred more often in younger women with regular, subsolid nodules. Smokers had more irregular nodules and a trend toward advanced disease. These findings support tailored strategies for incidental nodule management that consider patients beyond traditional smoking-based risk groups.

Table 1

Demographic variables	Total (Cancer) N= (72)	People who never smoked N=32	Smoking History (n=31)	Actually smoke (n=9)	p
Gender; n(%)					p<0,001
Male	33 (45,9)	7 (21,9)	21 (63,6)	8 (88,8)	
Female	39 (54,1)	25 (78,1)	12 (36,4)	1 (11,1)	
Age; median (interval)	70,5 (27-95)	67 (27 - 91)	74 (62 - 95)	70,5 (56-79)	
BMI; median (interval)		30,2 (22,31 - 31,7)	24 (16,8 - 35,2)	24,3 (14,5-28,9)	
Nodules variables					
Nodule size; n(%)					p=0,394
< 15mm	8 (11)	2 (6,3)	5 (15,2)	1 (11,1)	
15 to 29mm	37 (51,3)	17 (53,1)	14 (42,4)	6 (66,6)	
> 30mm	27 (37,5)	13 (40,6)	14 (42,4)	2 (22,2)	
Nodule location; n(%)					p=0,429
Right upper lobe	24 (33,3)	8 (25)	11 (33,3)	5 (55,5)	
Right lower lobe	16 (22,2)	8 (25)	6 (18,3)	1 (11,1)	
Middle lobe	6 (8,3)	2 (6,3)	3 (9,1)	1 (11,1)	
Left upper lobe	14 (19,4)	5 (15,6)	13 (30,3)	0	
Left lower lobe	5 (6,9)	7 (21,9)	3 (9,1)	2 (22,2)	
Density categories n(%)					p=0,653
Solid	51 (70,8)	20 (62,5)	27 (81,8)	6 (66,6)	
Ground-glass	7 (9,7)	4 (12,5)	1 (3)	1 (11,1)	
Partially solid	14 (19,4)	8 (25)	5 (15,2)	2 (22,2)	
Contours; n(%)					p=0,006
Regular	46 (63,9)	26 (81,3)	16 (48,5)	6 (66,6)	
Irregular	26 (36,1)	6 (18,8)	17 (51,5)	3 (33,3)	
TNM Staging; n(%)					p=0,446
Stage I	40 (55,5)	20 (76,9)	15 (53,6)	5 (62,5)	
Stage II	2 (2,7)	1 (3,8)	1 (3,6)	0 (0)	
Stage III	7 (9,7)	2 (7,7)	3 (10,7)	2 (25)	
Stage IV	13 (18,1)	3 (11,5)	9 (32,1)	1 (12,5)	

Keywords: Lung Cancer, Incidental Nodule, Early Detection

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.07 Socioeconomic Inequalities and Lung Cancer Outcomes: Evidence From an Integrated EHR Database and State Cancer Registry Data

T.Y. Lee[1], C.C. Su[1], E. Choi[2], V.Y. Ding[1], M. Satoyoshi[3], A. Bhat[3], T. Chen[4], I. Luo[1], Y. Liu[1], S. Henry[3], L.M. Backhus[1,5], T.J. Ellis-Caleo[1], S.L. Gomez[6], N.S. Lui[1,5], A. Leung[5], C. Langlotz[5], J.W. Neal[1,5], A.W. Kurian[1,5], H.A. Wakelee[1,5], S-Y. Liang[4], S.S. Han[1,5]
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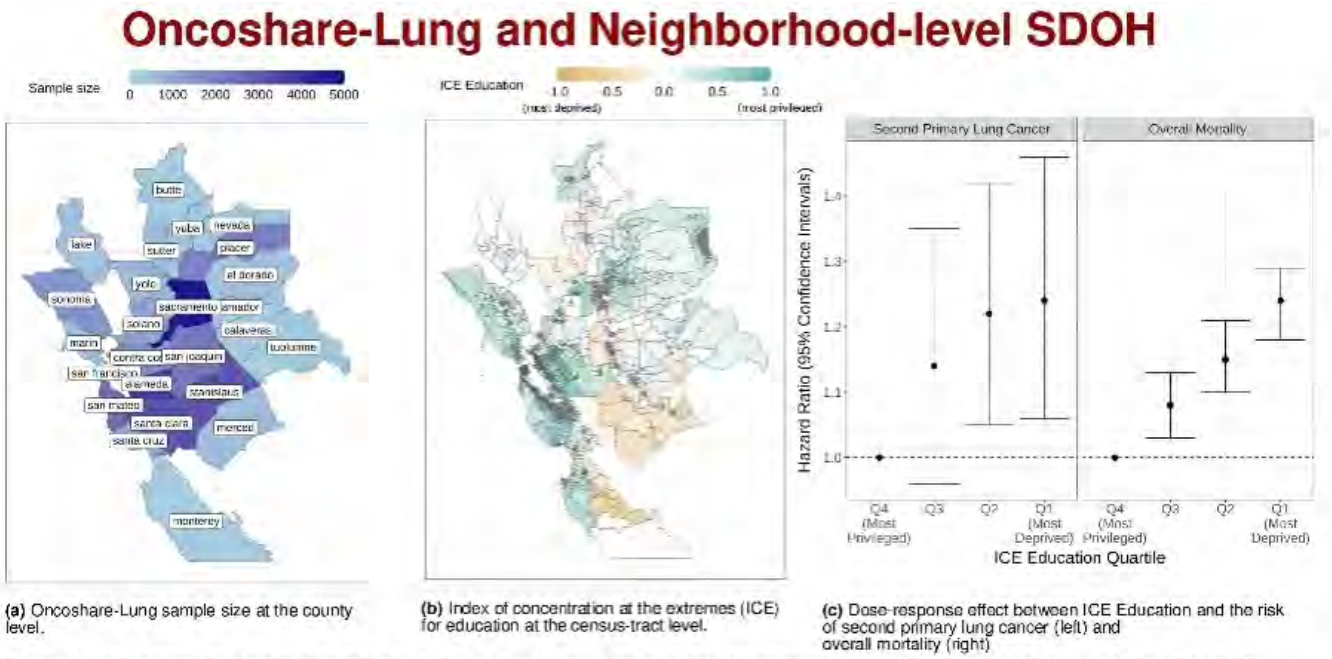
Introduction: With advances in therapy and early detection of lung cancer (LC), the number of LC survivors is rapidly increasing, underscoring the need to understand factors influencing their long-term outcomes. Neighborhood-level social drivers of health (SDOH) are crucial in cancer research, as they relate to access to healthcare and quality of care. However, previous studies on developing second primary LC (SPLC) and mortality among LC survivors have primarily focused on individual-level SDOH, often overlooking neighborhood influences. Many studies using electronic health records (EHRs) rely on data from single healthcare systems, which may have limited diversity of patient populations and uniformity clinical practice patterns. This study aimed to evaluate the associations between multiple SDOH and SPLC and overall mortality among LC survivors, leveraging an integrated database to address these gaps.

Methods: We utilized an integrated EHR database called Oncoshare-Lung, linking two independent healthcare systems—Stanford Health Care (academic) and Sutter Health (community)—and the California Cancer Registry, encompassing over 40,000 LC cases. We used patients' mailing addresses at initial primary LC (IPLC) diagnosis to calculate well-validated neighborhood-level SDOH indices at the census-tract level, including indices of concentration at the extremes (ICEs) that measure polarization between privileged and deprived populations. For SPLC and mortality analyses, we used cause-specific Cox regression and standard Cox regression, respectively, adjusting for demographic (e.g., smoking) and clinical factors (e.g., histology). Main exposures included the social vulnerability index and ICE indices for income, education, and race/ethnicity (Black/White) as quartiles.

Results: Among 43,965 patients diagnosed with IPLC and followed up for SPLC and mortality between 2000 and 2022 (Figure-1a), there were 1,314 SPLC cases and 31,750 deaths over 143,108 person-years (average follow-up: 3.3 years). The cohort included 51.2% (N=22,385) adenocarcinoma IPLC, 52.3% (N=22,854) female, 13.8% (N=6,030) Asian American/Pacific Islander, 6.6% (N=2,877) non-Hispanic Black/African American, and 7.3% (N=3,207) Hispanic. Our analysis revealed that the most deprived region in terms of ICE-Education (Figure-1b) was significantly associated with an increase in SPLC risk (hazard ratio [HR]:1.24, 95%CI: 1.06-1.46) and mortality (HR:1.24, 95%CI: 1.18-1.29) when compared with the most privileged region (Figure-1c).

Conclusions: This study underscores the importance of understanding socioeconomic disparities within communities and their impact on LC survivors' health outcomes. Survivors residing in segregated neighborhoods with greater concentration of low educational attainment face increased risks of SPLC and overall mortality, independent of sex, race/ethnicity and smoking status. Addressing these neighborhood-level SDOH disparities is essential for improving healthcare access and outcomes in this population.



(a) Oncoshare-Lung sample size at the county level.

(b) Index of concentration at the extremes (ICE) for education at the census-tract level.

(c) Dose-response effect between ICE Education and the risk of second primary lung cancer (left) and overall mortality (right)

Figure 1. Geographic distribution of (a) the lung cancer survivors in the Oncoshare-Lung database at the county level and (b) the area-level social drivers of health (SDOH) factor, index of concentration at the extremes (ICE) Education, at the census-tract level, and (c) the dose-response effect between ICE-Education as a quartile (with Q4 as the reference level) and the risk of second primary lung cancer (left) and overall mortality (right)

Keywords: Lung cancer survivor, Electronic health record, Social drivers of health

P3.01.09 Survival Determinants and Socio-Demographic Disparities in Early Onset Lung Cancer in Young Adults: Insights From AI Modeling

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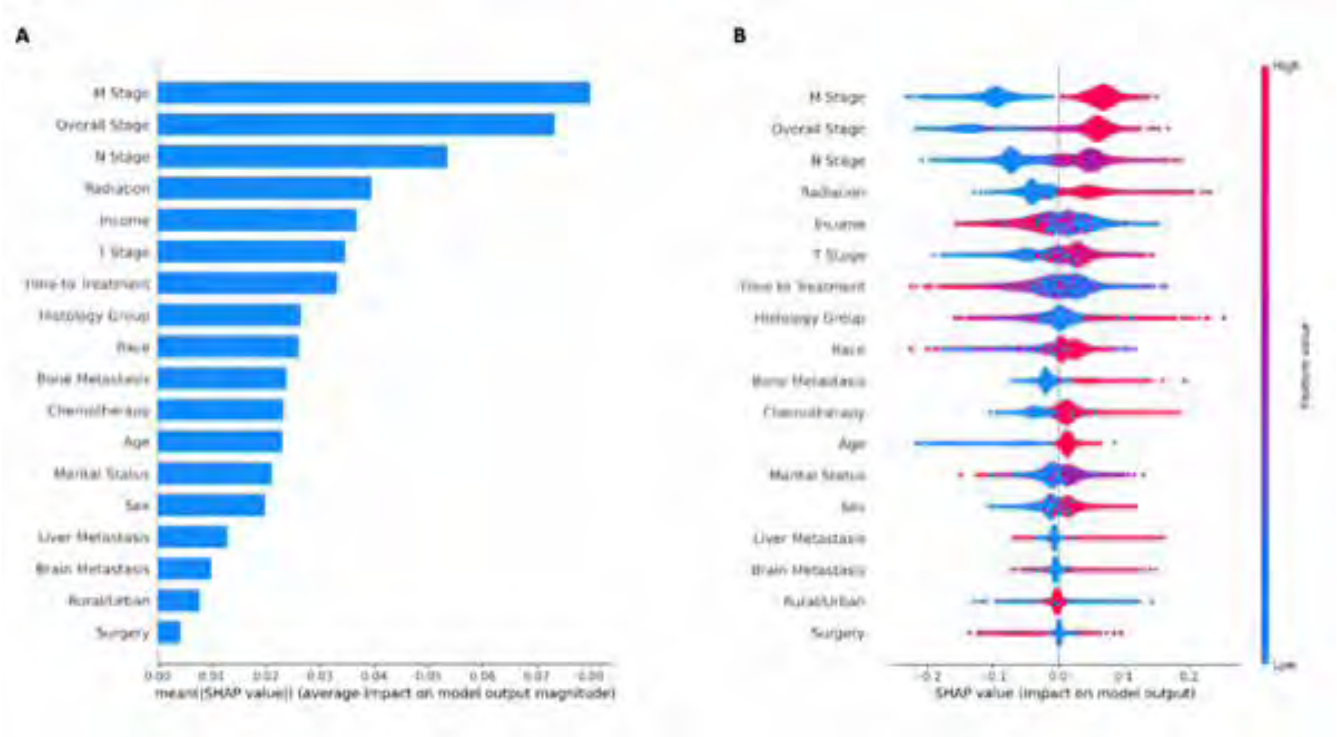
Introduction: The increasing trends in both incidence and mortality of lung cancer in women (LCW) are significantly more pronounced than those in men. Currently, the etiological mechanisms underlying a substantial proportion of LCW cases remain incompletely understood. Existing evidence suggests that female reproductive factors may be associated with lung cancer risk, but findings from relevant studies remain inconsistent, necessitating further validation.

Introduction: Early onset non-small cell lung cancer (NSCLC) accounts for 5% to 10% of cases and is becoming more prevalent, affecting more patients in the future. In this study, our goal was to employ machine learning to identify the key factors influencing the survival of these patients.

Methods: We analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database for young adults aged 18-50yrs diagnosed with NSCLC between 2010 and 2021. We used a combination of classical statistical methods and machine learning techniques to identify survival determinants and assess disparities. Kaplan-Meier survival curves visualized differences in OS and time-to-treatment, with the log-rank test applied for group comparisons. Additionally, we employed SHapley Additive exPlanations (SHAP) to evaluate the contribution of each feature in our machine learning predictive models. The random survival model and the C-index were checked.

Results: From 2010 to 2021, 18,595 NSCLC patients aged 18 to 50yrs were identified, with a median age of 44.6yrs(SD = 6.0). Most patients (83.9%) were aged 40-50yrs, and the largest racial group was non-Hispanic White (60%), followed by non-Hispanic Black (14.5%). Over half (53.4%) were diagnosed at stage IV. Mean OS was 31.6 months (SD = 36.4), with a median OS (mOS) of 16 months (IQR: 5-43 months). Patients aged 18-29yrs had the longest survival (mOS: 34m), while those aged 40-50 had shorter survival (mOS: 15m, p=0.0001). Females had better outcomes than males (mOS: 20 vs. 12m, p=0.005), and higher income levels correlated with improved survival (HR low 1.45 vs high 1.09, p=0.001). SHAP modeling identified key factors affecting OS. Five-year OS rates were higher for stage I and II patients who started treatment within 2w of diagnosis, with rates of 91.4% for stage I and 77.9% for stage II. For stage III, 5-year OS improved when treatment was initiated 4-6w after diagnosis (45%), while stage IV patients had better outcomes at 8 weeks or more (19.9%). Stage IV patients who started treatment within 2 weeks exhibited significantly worse outcomes, likely due to the severity of the disease, which required rapid treatment (5 yr OS 14.3% vs. 19.9%)

Conclusions: While Machine learning is consistent with traditional survival modeling, it is more comprehensive in detecting factors that contribute to early onset NSCLC patients survival. Stage, income, and time from dx-to-tx were key factors influencing the OS of young adult NSCLC in the SEER database.



SHAP modeling identified key factors affecting OS

Keywords: non small cell lung cancer, artificial intelligence, machine learning

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.10 Income, Tumour Stage, and Treatment in Patients With Non-Small Cell Lung Cancer: A Population-Based Study in the Netherlands

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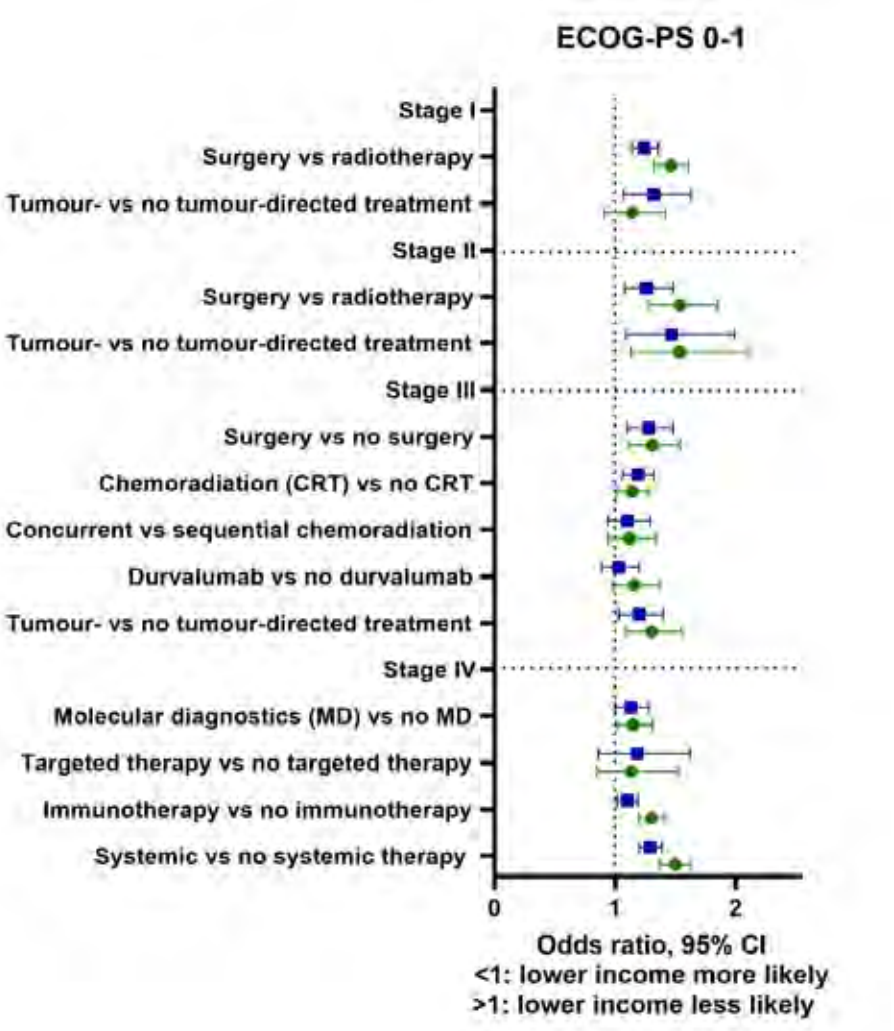
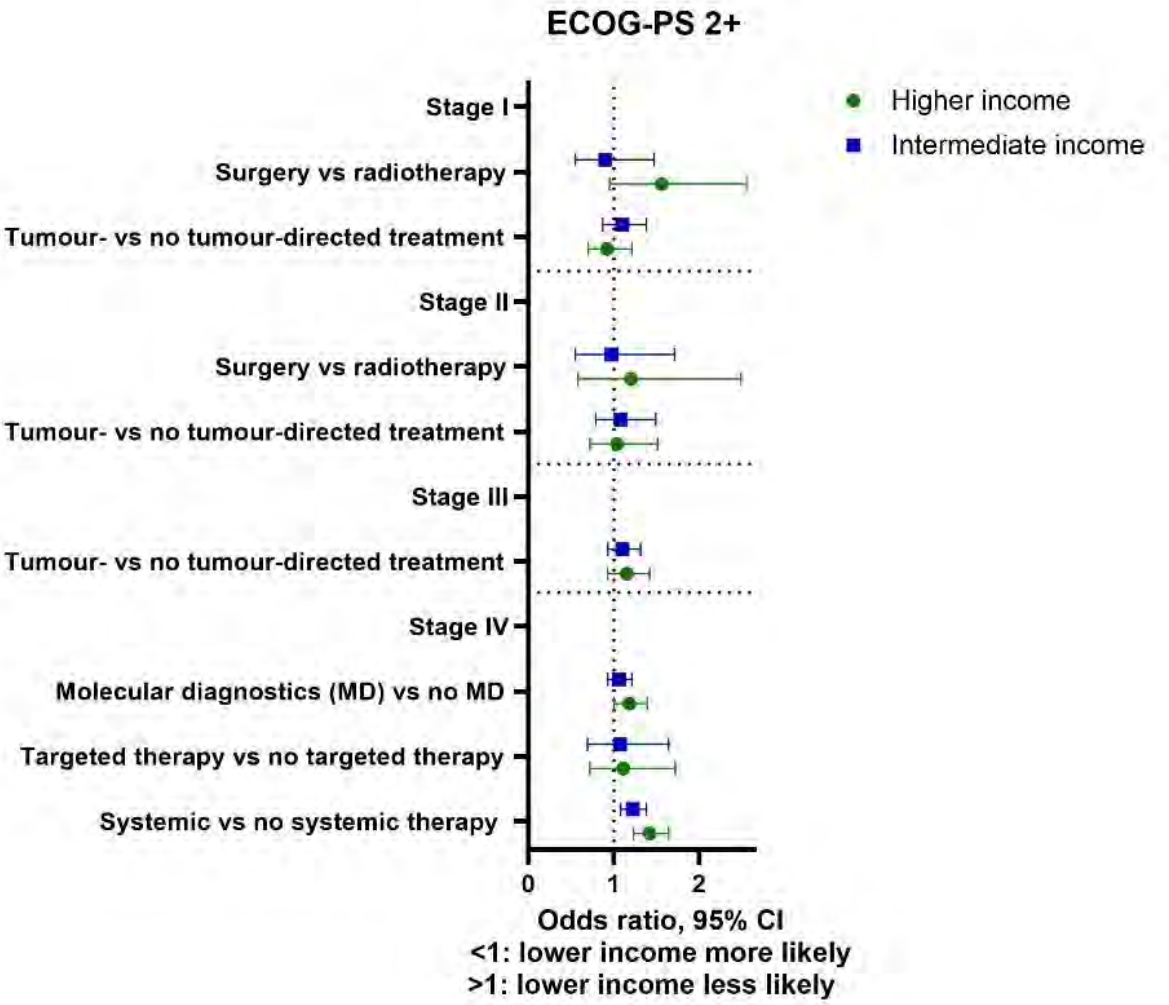
Introduction: The current study investigated the association between income, tumor stage at diagnosis, and treatment in non-small cell lung cancer (NSCLC) patients, stratified by Eastern Cooperative Oncology Group performance status score (ECOG-PS). Stratification by ECOG-PS was performed as it is part of the causal pathway between income and tumor stage, and income and treatment (i.e. a mediator).

Methods: Patients diagnosed with NSCLC between 2017-2022 were selected from the Netherlands Cancer Registry. Logistic regression was used to investigate the association between income and 1) tumour stage at diagnosis and 2) treatment. All analyses were stratified by ECOG-PS (PS0-1 vs PS2+). Median household income at postal code level (median 17 households per postal code) was used as proxy for income.

Results: A total of 71,025 patients were included. Patients with an intermediate or higher income were more likely to be diagnosed with stage III-IV tumours than those with a lower income. This was seen in patients with PS0-1 (odds ratio (OR)intermediate_vs_lower: 1.12, ORhigher_vs_lower: 1.12) and PS2+ (ORintermediate_vs_lower: 1.21, ORhigher_vs_lower: 1.28). In patients with PS0-1 and a stage II or III tumour, those with a higher or intermediate income more often received a tumour-directed treatment (stage II ORintermediate_vs_lower: 1.47, ORhigher_vs_lower: 1.54, stage III ORintermediate_vs_lower: 1.20, ORhigher_vs_lower: 1.30) (Figure). In patients with a stage IV tumour, those with a higher or intermediate income more often received systemic treatment, irrespective of performance status (PS0-1 ORintermediate_vs_lower: 1.29, ORhigher_vs_lower: 1.50), PS2+ ORintermediate_vs_lower: 1.22, ORhigher_vs_lower: 1.42).

Conclusions: Even in a country with an universal healthcare system like the Netherlands, large differences were seen between the treatments of NSCLC patients according to income. Our findings underline the importance of person-centred care, specifically focusing on the reasoning behind someone's treatment decision. Additionally, our results showed the importance of stratification by ECOG-PS.





Keywords: Income, Treatment, Stage

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.11 Lung Cancer in Young Patients Under 45 Years: Clinical Characteristics, Histology and Molecular Profile

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Introduction: Lung cancer in young patients under 45 years is relatively rare, but it has a number of clinical and biological features that distinguish it from a similar disease in the elderly. In recent years, thanks to the development of molecular oncology and targeted therapy, characteristic genetic drivers have been identified, which are more common in young patients. Despite this, the clinical behavior, histological subtypes and molecular profile of lung cancer in this age group remain poorly understood.

Methods: We conducted a retrospective single-center study at the Loginov Moscow Clinical Scientific Center between 2022 to 2024. The study included patients under the age of 45 with a confirmed diagnosis of non-small cell lung cancer. The following clinical parameters were analyzed for each patient: age, gender, smoking status and stage of the disease at the time of diagnosis. The histological classification of tumors was carried out in accordance with WHO recommendations. The molecular profile included the determination of driver mutations (EGFR, ALK, ROS1) using standard methods of molecular genetic testing.

Results: The study included 44 patients under the age of 45 with non-small cell lung cancer. The median age was 41 years (range 37-45 years). Women prevailed over men (24 versus 20). The most common histological type of tumor was adenocarcinoma - 36 (81.8%) cases. Squamous cell carcinoma and neuroendocrine tumors were detected in 4 (9.1%) patients in each group. 31 (70.5%) patients were smokers, and 3 (6.8%) patients were former smokers. Surgery was performed in 12 cases (27.3%). Distribution by stages of the disease: Stage IA - 5 (11.4%), IB - 4 (9.1%), IIA - 2 (4.5%), IIB - 5 (11.4%), IIIA - 1 (2.3%), IIIB - 4 (9.1%), IVA - 11 (25.0%), IVB - 4 (9.1%), IVC - 8 (18.1%). EGFR or ALK or ROS1 alterations were found in 16 patients (36.4 %) and PD-L1 expression in 11 patients (25.0%). Tabaco smokers had mostly no molecular alterations and negative PD-L1 expression

Conclusions: Lung cancer in young patients under 45 years is a rare but clinically and biologically unique form of the disease. Adenocarcinoma prevails in this age group and a significant proportion of patients have a history of smoking. The high detection rate of the disease in its late stages highlights the need to improve early diagnosis strategies. Additional studies of the molecular profile of tumors in young patients may contribute to the development of a more personalized approach to treatment.

Keywords: Young adults, Non-small cell lung cancer

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.12 Associations Between Respiratory Diseases and Lung Cancer Risk, With New Insights Into Acute Infections

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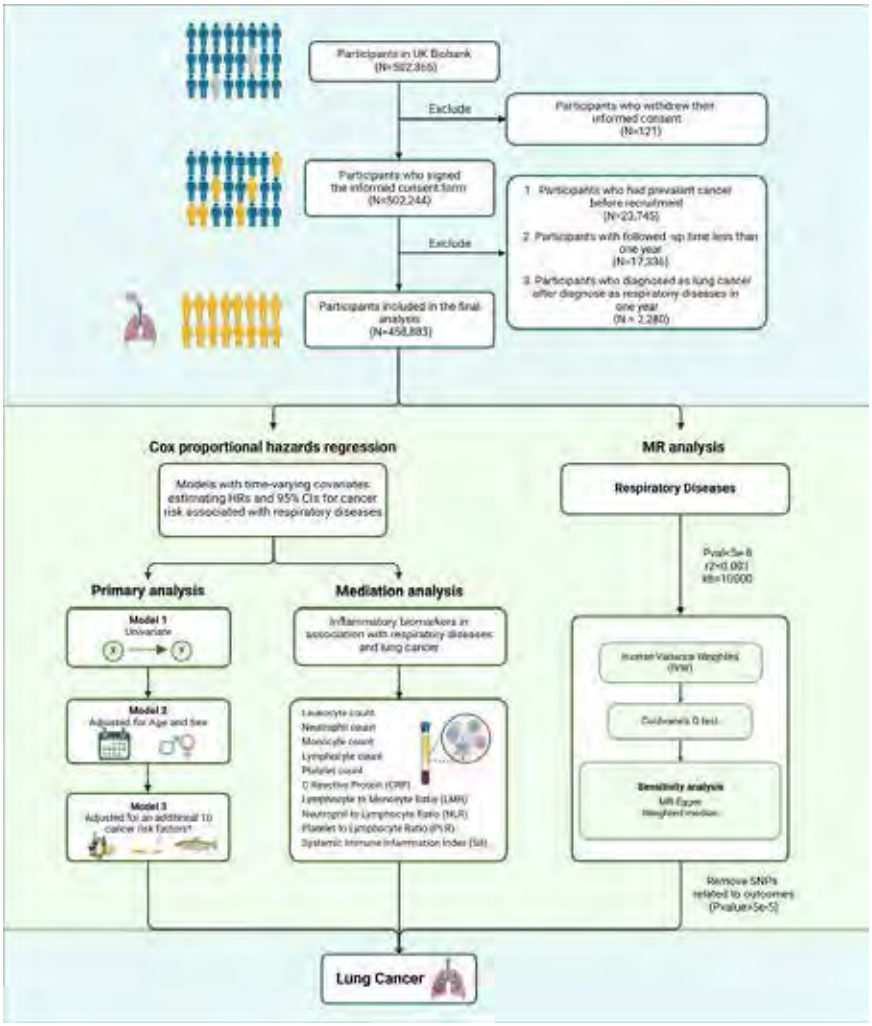
Introduction: Respiratory diseases are significant risk factors for lung cancer; however, association between acute respiratory infections and the incidence of lung cancer requires further explore.

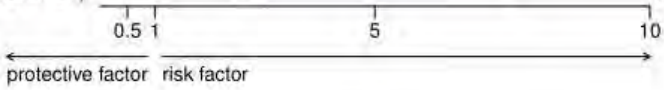
Methods: We conducted a large-scale prospective cohort study using data from the UK Biobank. This study involved participants aged 40 to 69 years who were recruited from 22 assessment centers across the UK between January 1, 2006, and December 31, 2010. Cox proportional hazards models were used to calculate the hazard ratios (HR) for newly diagnosed lung cancer based on the presence or absence of respiratory diseases. Additionally, mediation analysis was employed to identify potential biomarkers and mendelian randomization analysis was used to assess causal relationships between these diseases.

Results: During an average follow-up of 10.44 years (4,790,738 person-years), 2,189 participants developed lung cancer. Of these, 1,322 cases occurred among 107,007 individuals with respiratory diseases (incidence rate 27.6 per 10,000 person-years), whereas 867 cases were observed among 351,876 participants without respiratory diseases (incidence rate 7.9 per 10,000 person-years). Overall, respiratory diseases were associated with an elevated lung cancer risk (HR = 2.97, 95% CI: 2.75-3.21). Notably, acute respiratory infections including acute nasopharyngitis (HR = 3.41; 95% CI: 1.83-6.41) and influenza (HR = 3.90; 95% CI: 2.53-6.01), viral pneumonia (HR,9.86; 95% CI, 6.55-14.85), bacterial pneumonia (HR,6.28; 95% CI, 4.40-8.96)—showed significant associations with increased lung cancer incidence. In subtype analyses, squamous cell carcinoma demonstrated the strongest risk elevation (HR = 3.65; 95% CI: 3.06-4.36). Mediation analysis suggested that neutrophil counts contributed partially (proportion mediated up to 8%) between respiratory diseases and lung cancer. The Mendelian randomization results indicate a causal relationship between (COPD)(p=0.015,beta=0.09), tonsil and adenoids(p=0.01,beta=-11.8), interstitial lung diseases(p=0.02,beta=17) and lung cancer.

Conclusions: Acute respiratory infections increase the risk of lung cancer incidence. In future lung cancer screening programs, patients with these conditions should receive increased attention.



Variable	Percent (%)	HR	P value	P for interaction
Overall	100	2.93 (2.71–3.17)	**<0.001**	
Age group				0.168
<60	55.51	2.98 (2.57–3.45)	**<0.001**	
=60	44.49	2.91 (2.65–3.19)	**<0.001**	
Sex				0.051
Male	46.49	3.17 (2.84–3.53)	**<0.001**	
Female	53.51	2.7 (2.41–3.02)	**<0.001**	
Race1				0.205
White	94.1	2.94 (2.71–3.18)	**<0.001**	
Non–White	5.21	2.23 (1.28–3.88)	**0.004**	
Unknown	0.69	2.92 (1.4–6.12)	**0.004**	
TDI group				0.077
<–2.14	49.67	3.14 (2.75–3.58)	**<0.001**	
=–2.14	50.33	2.81 (2.55–3.09)	**<0.001**	
BMI group				0.735
<25	32.69	2.91 (2.54–3.35)	**<0.001**	
25–29.9	42.13	2.85 (2.53–3.22)	**<0.001**	
=30	25.18	2.98 (2.56–3.46)	**<0.001**	
WHR group				0.471
<0.87	47.29	2.91 (2.54–3.33)	**<0.001**	
=0.87	52.71	2.93 (2.67–3.23)	**<0.001**	
Education				0.903
No College degree	67.28	2.95 (2.71–3.21)	**<0.001**	
College or University degree	31.62	2.79 (2.26–3.45)	**<0.001**	
Unknown	1.1	2.26 (1.26–4.05)	**0.006**	
Smoking				0.257
Never	53.46	2.52 (1.96–3.24)	**<0.001**	
Smoker	45.96	2.96 (2.73–3.22)	**<0.001**	
Prefer not to answer	0.58	3.06 (1.64–5.68)	**<0.001**	
Family cancer				0.464
No	67.83	2.94 (2.66–3.24)	**<0.001**	
Yes	30.42	2.96 (2.58–3.38)	**<0.001**	
Unknown	1.75	2.19 (1.37–3.51)	**0.001**	
Alcohol				**0.046**
Never	8.21	2.65 (2.14–3.28)	**<0.001**	
Drinker	71.04	2.91 (2.64–3.21)	**<0.001**	
Almost everday	20.45	3.15 (2.67–3.71)	**<0.001**	
Unknown	0.29	2.17 (0.76–6.16)	0.146	
Oily fish				0.535
Never	11.05	2.53 (2.05–3.11)	**<0.001**	
Oily fish intake	87.9	3.01 (2.76–3.28)	**<0.001**	
Almost everday	0.24	0.07 (0–7.79)	0.265	
Unknown	0.81	2.7 (1.47–4.96)	**0.001**	
Processed meat				0.788
Never	9.12	2.74 (2.02–3.73)	**<0.001**	
Processed meat intake	89.6	2.95 (2.71–3.2)	**<0.001**	
Almost everday	0.84	3.09 (1.66–5.72)	**<0.001**	
Unknown	0.44	2.61 (0.94–7.27)	0.067	



Keywords: lung cancer, acute respiratory infections, UK Biobank

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.13 Lung Cancer Characteristics and Survival Among Smokers, Former Smokers, and Never Smokers Within an Australian Lung Cancer Registry

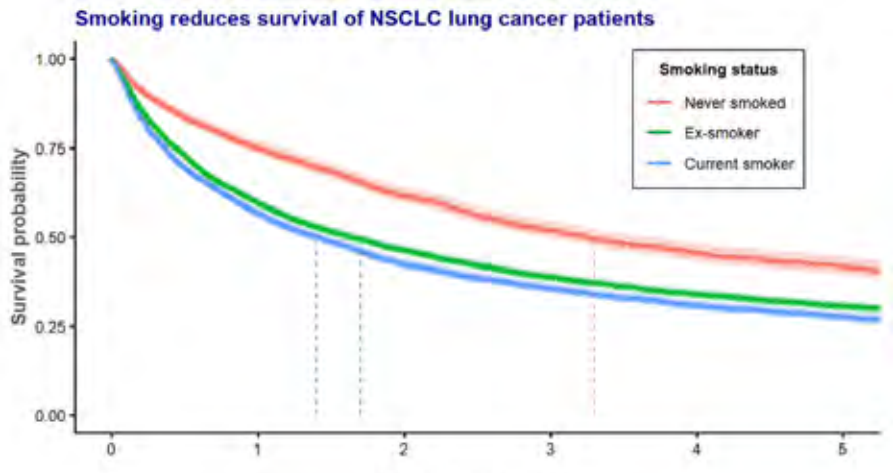
J. Zeng[1], S. Tissera[1], J. Zalcberg[1], L. Briggs[2], T. Wood[2], J. Lesage[2], M. Lloyd[1], C. Underhill[3], S. Parakh[4], W. Faisal[5], R. Blum[6], M. Caldecott[7], G. Richardson[8], P. Parente[9], I. Olesen[10], J. Torres[11], E. Samuel[12], C. Lyne[13], K. See[14], J. Bartlett[15], D. Langton[16], T. John[17], L. Irving[18], G. Wright[19], M. Conron[19], G. Adabi[12], M. Moore[12], N. Zeps[1], M. Alexander[17], Z. McQuilten[1], R. Stirling[12], S. Harden[17]
[1]Monash University, Melbourne/AU ,[2]Consumer advocate, Melbourne/AU ,[3]University of NSW, Albury/AU ,[4]Austin Hospital, Melbourne/AU ,[5]Grampians Health, Ballarat/AU ,[6]Bendigo Health, Bendigo/AU ,[7]Epworth Health, Melbourne/AU ,[8]Cabrini Health, Melbourne/AU ,[9]Eastern Health, Melbourne/AU ,[10]Barwon Health, Geelong/AU ,[11]Goulbourn Valley Health, Shepparton/AU ,[12]Alfred Health, Melbourne/AU ,[13]Monash Health, Melbourne/AU ,[14]Northern Health, Melbourne/AU ,[15]Western Health, Melbourne/AU ,[16]Peninsula Health, Melbourne/AU ,[17]Victorian Comprehensive Cancer Centre, Melbourne/AU ,[18]Melbourne Health, Melbourne/AU ,[19]St Vincent's Hospital, Melbourne/AU

Introduction: Cigarette smoking is a major risk factor for lung cancer. Lung cancer in never smokers differs from lung cancer in smokers, with higher female prevalence, earlier onset, and greater proportion of adenocarcinoma, and increased chance of an associated genetic predisposition. This study aimed to explore differences in patient, disease and management factors between smokers, former smokers, and never smokers diagnosed with primary lung cancer, using an Australian registry-based dataset to describe real world lung cancer survival outcomes.

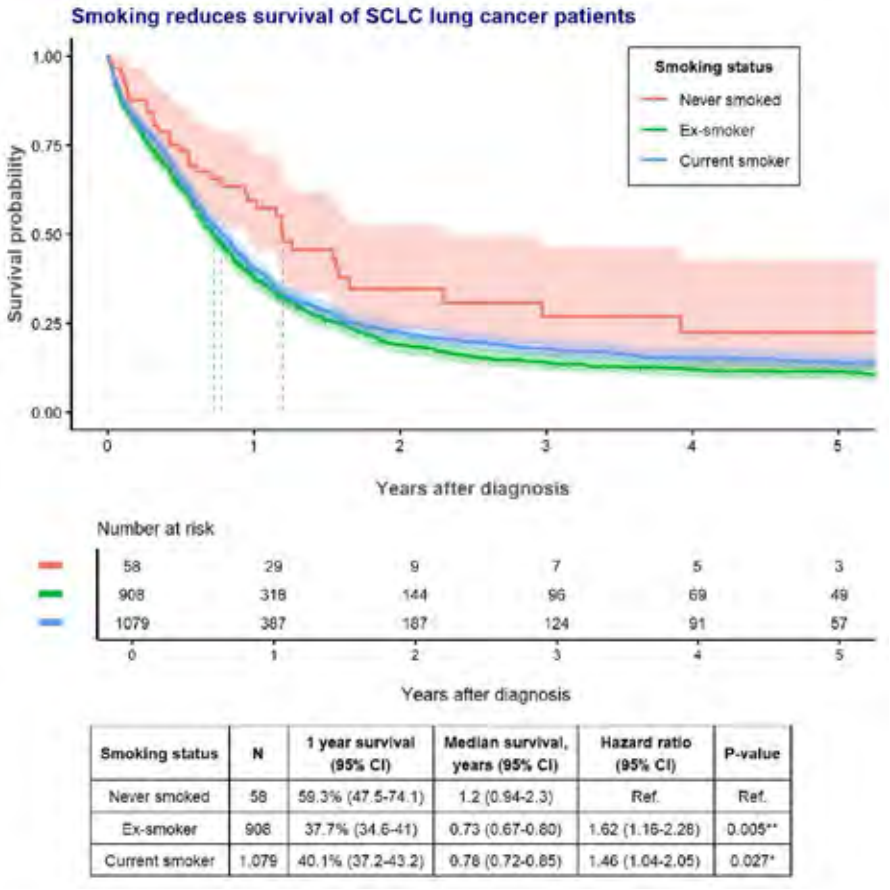
Methods: This retrospective cohort evaluated consecutively diagnoses registered into the Victorian Lung Cancer Registry in Australia from July 2011 to September 2024. Demographics, clinical outcomes and overall survival analyses were stratified smoking status defined as never, ex and current smokers.

Results: This study included 2,451 never smokers (12.8%), 9,954 ex-smokers (51.8%) and 6,799 current smokers (35.4%). Current smokers were younger at diagnosis (68 years IQR 60-75), never smokers 70 (IQR 61-79) and ex-smokers 73 (IQR 67-80). Never smokers were more likely female (70% vs 44% overall), less likely of Indigenous status (0.1% vs 1.0% overall) and more likely from a higher socioeconomic background (61% vs 47%). Never smokers had a ECOG performance score of 0 (47% vs 33% overall), and with no comorbidities (62% vs 44% overall). Median survival for NSCLC never smokers (n=15,292) was 3.3 years (95% CI 2.9-3.7), ex-smokers 1.7 years (HR 1.48 (1.39-1.58), p<0.001) and current smokers 1.4 years (HR 1.63 (1.52-1.75), p<0.001), Figure 1. Median survival for SCLC (n=2,045) never smokers was 1.2 years (95% CI 0.94-2.3), ex-smokers 0.73 years (HR 1.62 (1.16-2.28), p=0.005), and current smokers 0.78 years (HR 1.46 (1.04-2.05), p=0.027) Figure 2.

Conclusions: Smoking status affected the real world lung cancer survival outcomes in our Australian cancer registry. This highlights the importance of clearly defining and collecting smoking history in addition to smoking cessation strategies.



Smoking status	N	1 year survival (95% CI)	Median survival, years (95% CI)	Hazard ratio (95% CI)	P-value
Never smoked	2,133	75.0% (73.2-76.9)	3.3 (2.9-3.7)	Ref.	Ref.
Ex-smoker	8,075	59.7% (58.6-60.8)	1.7 (1.6-1.8)	1.48 (1.39-1.58)	<0.001***
Current smoker	5,084	56.8% (55.4-58.2)	1.4 (1.3-1.5)	1.63 (1.52-1.75)	<0.001***



Smoking status	N	1 year survival (95% CI)	Median survival, years (95% CI)	Hazard ratio (95% CI)	P-value
Never smoked	58	59.3% (47.5-74.1)	1.2 (0.94-2.3)	Ref.	Ref.
Ex-smoker	908	37.7% (34.6-41)	0.73 (0.67-0.80)	1.62 (1.16-2.26)	0.005**
Current smoker	1,079	40.1% (37.2-43.2)	0.78 (0.72-0.85)	1.46 (1.04-2.05)	0.027*

Keywords: Smoking status, Lung cancer registry

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.14 The Rising Toll: Global Burden and Future Projections of Tracheal, Bronchus, and Lung Cancer in Women, 1990-2050

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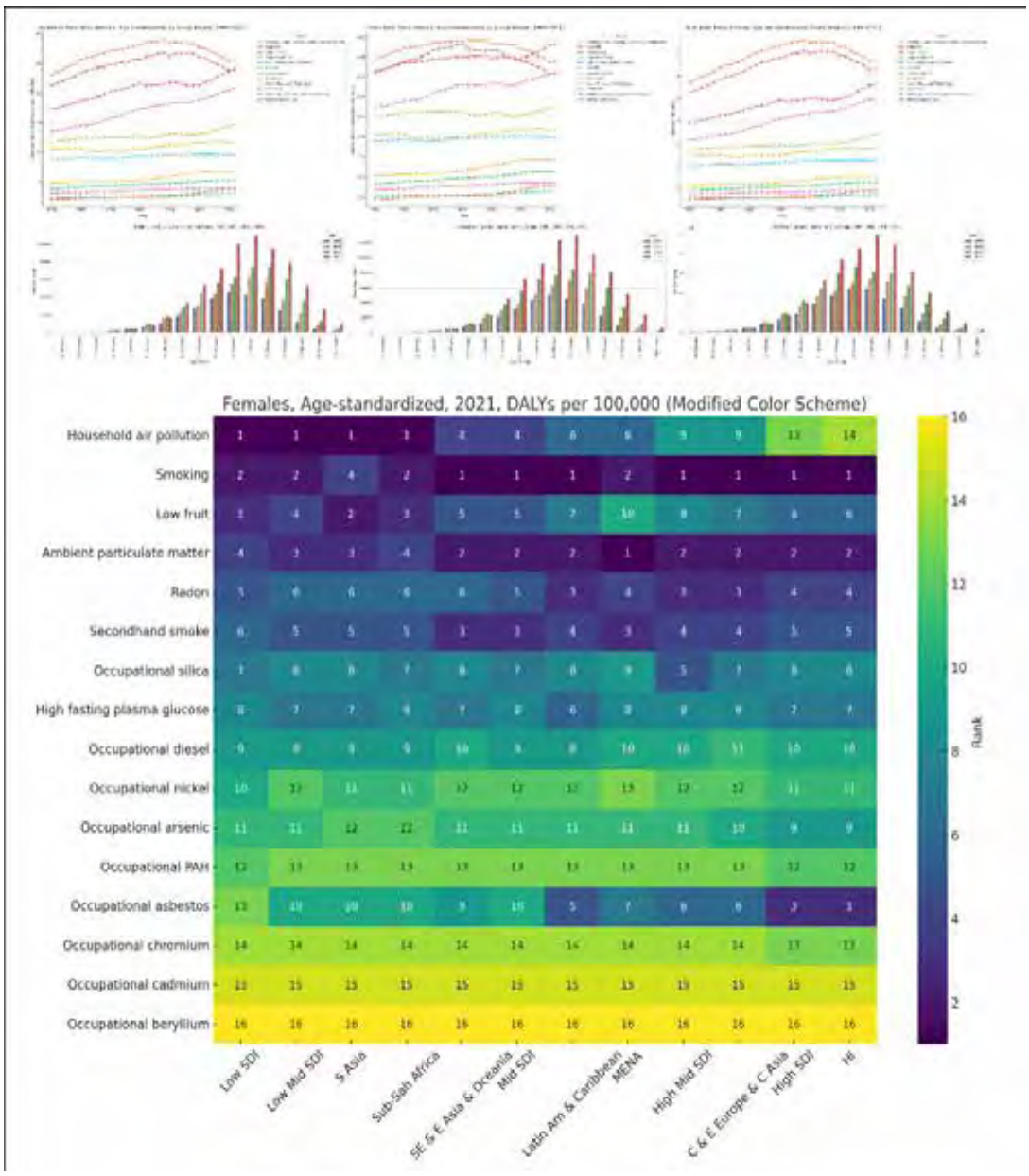
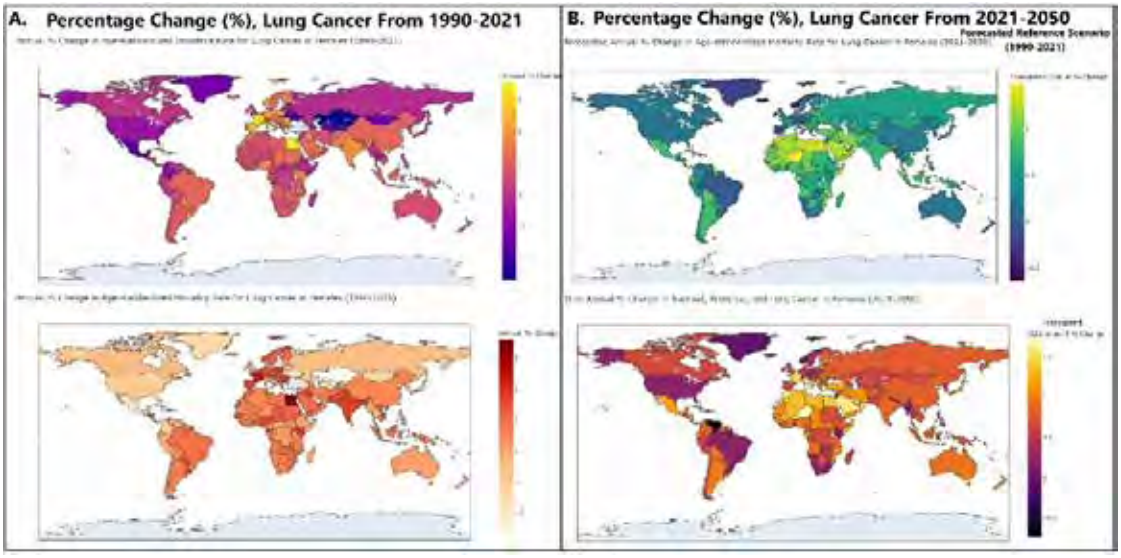
Introduction: Tracheal, bronchus, and lung (TBL) cancer is the leading cause of cancer-related death and the second leading cause of disability in women worldwide, with a growing burden over time. Despite evolving burden, TBL-cancer remains insufficiently studied across many regions.

Methods: Using the Global Burden of Disease analytical framework, we quantified the incidence, prevalence, mortality, disability-adjusted life years(DALYs), and years lived with disability(YLDs) attributable to TBL cancer and its attributable risk factors by age, year, and location across 204 countries and territories in women from 1990-2021. We projected TBL cancer deaths through 2050 using age-period-cohort modeling.

Results: Between 1990-2021, the global prevalence of TBL cancer in women rose from 381,144 (95% UI:356,712-403,802) to 1.1 million(1-1.2 million), deaths increased from 281,306 (259,309-301,716) to 674,006(595,385-747,508), and DALYs doubled from 7.1 million (6.6-7.7 million) to 15-million(13.5-16.6 million). By socio-demographic-index(SDI), the highest annual percentage change(APC) in age-standardized incidence rate(ASIR) was observed in high-middle-SDI countries at 1.36%. Regionally, South Asia recorded the greatest rise in both ASIR(1.71%) and age-standardized-mortality-rate(ASMR) (1.66%) from 1990-2021. In 2021, 39.24% of TBL cancer deaths in women were attributable to behavioral RF, 27.97% to environmental RF, and 2.45% to metabolic RF. In 2021, the highest incidence rate was seen in women aged 55+ years at 87.4 per 100,000, compared to 4.86 in those aged 20-54 and 0.03 in those under 20. By 2050, total deaths from TBL-cancer in women are projected to reach 1.4 million(1.1-1.8 million), with an ASMR of 14.45(11.3-18.3) per 100,000.

Conclusions: TBL-cancer accounted for 15.72% of all cancer causalities in women in 2021. Our findings highlight the urgent need for coordinated action by public health officials, policymakers, and clinicians to address the rising and underrecognized burden of TBL cancer in women, with projections indicating a continued increase in deaths through 2050.





Keywords: Global burden, Lung cancer, Epidemiological trend

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.15 Quantifying the Burden of Lung Cancer Attributable to Behavioral Risk Factors in OECD Countries Over Three Decades

U. Gohel[1], V. Jetani[2], A. Dodhia[3], A. Gopi[4], H. Zinzala[5], D. SAKARIYA[6], R. Shah[7], J. Verma[8], G. Luthra[9], A. Aleem[10], H.A. . Sami[11], H.D. Desai[12]
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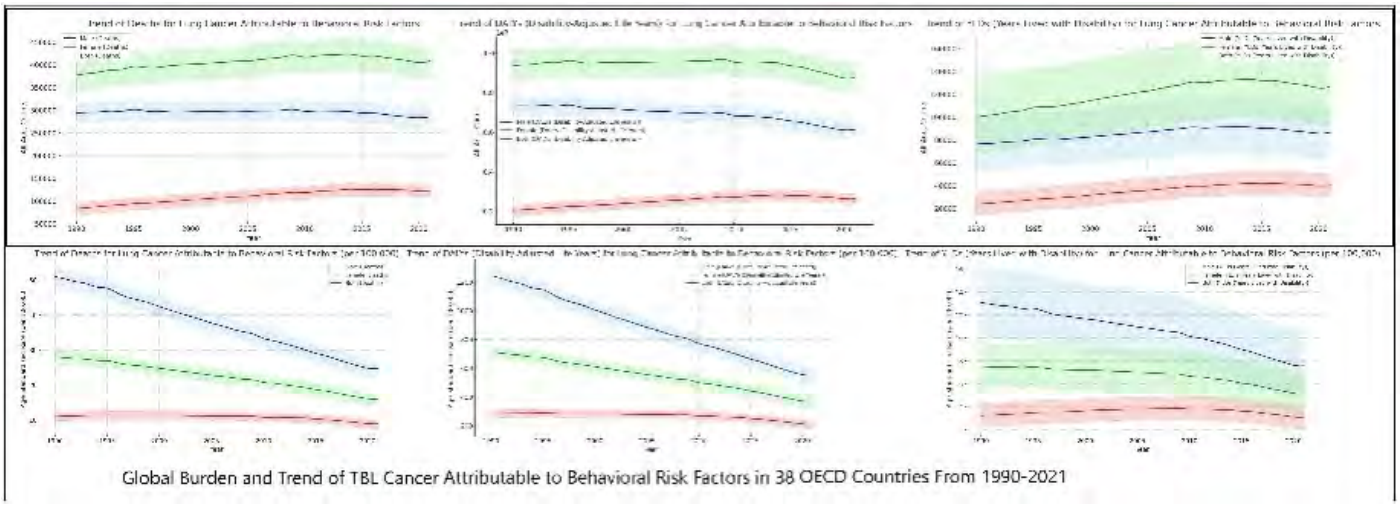
Introduction: Tracheal, bronchus, and lung (TBL) cancer, significantly influenced by behavioral risk factors (BRF) such as smoking and dietary habits, represent a major health challenge in Organization for Economic Co-operation and Development (OECD) countries, where health policies and prevention strategies significantly influence cancer outcomes.

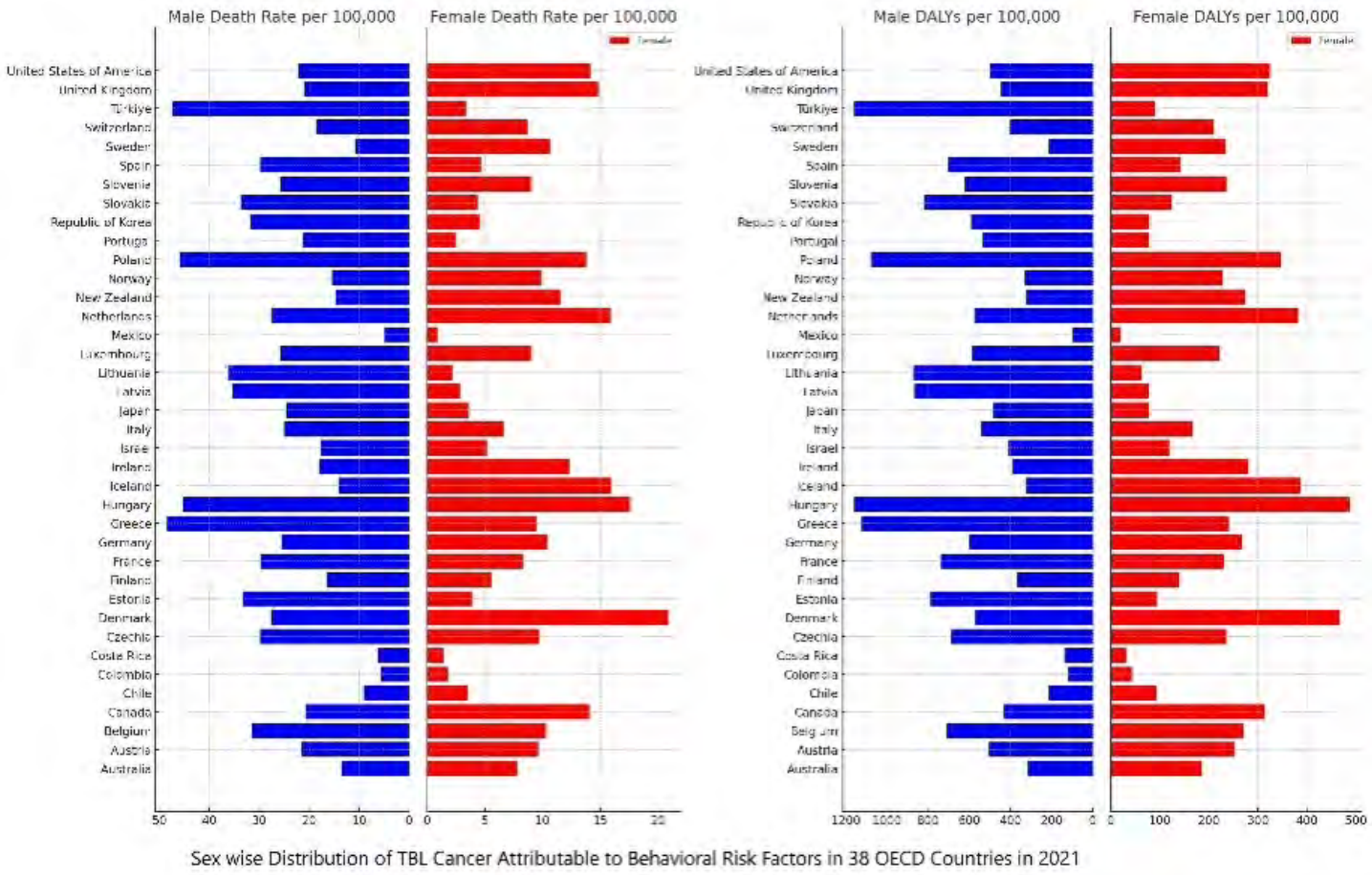
Methods: We estimated deaths, disability-adjusted-life-years(DALYs), years-lived with-disability(YLDs) due to TBL cancer attributable to BRF by age, sex, year and location across the 38 OECD countries from 1990-2021 using standardized global burden of disease framework.

Results: From 1990-2021, the total number of deaths due to TBL cancer attributable to BRF increased from 376,488(95% UI: 350,760-401,242) to 409,502(362,713-449,885), DALYs decreased from 9.3 million (8.7-9.9) to 8.7 million (7.9-9.5), and YLDs increased from 100,009 (72,064-128,799) to 126,973 (93,115-161,693). Nationally, Hungary recorded the highest age-standardized mortality rate (ASMR) of 29.21 per 100,000 in 2021, followed by Greece at 27.41, Poland at 27.32, and Turkey at 23.77, while the US observed an ASMR of 17.6 per 100,000. In terms of age groups, the 70-74 year-olds observed the highest death count at 77,299 (69,703-84,049) and DALYs were highest in the 65-69 age group at 1.6 million (1.4-1.7) in 2021. Regarding gender, females exhibited a higher increase in burden compared to males, with total percentage changes in deaths, DALYs, and YLDs for males versus females at -2% vs 49%, -16% vs 31%, and 14% vs 70%, respectively

Conclusions: In 2021, 60.63% of all TBL cancer-related deaths in OECD countries were attributable to behavioral risk factors (BRFs), with tobacco consumption accounting for the majority at 59.61%, followed by dietary risks at 2.47%. The substantial TBL cancer burden in OECD countries driven by behavioral risks, particularly tobacco use, demands urgent, coordinated action from both public health policymakers and clinicians to prioritize prevention and early intervention.



Global Burden and Trend of TBL Cancer Attributable to Behavioral Risk Factors in 38 OECD Countries From 1990-2021



Sex wise Distribution of TBL Cancer Attributable to Behavioral Risk Factors in 38 OECD Countries in 2021

Keywords: Global burden, lung Cancer, Behavioral Risk Factors

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.16 Global Burden of Lung Cancer Attributed to High Fasting Plasma Glucose: A Benchmarking Analysis of G20 Countries (1990-2021)

V.S. Jetani[1], U. Gohel[2], D. Upadhyay[3], K.M. Patel[4], A.S. Sethi[5], P. Savaliya[6], A. Gopi[7], A. Aleem[8], H.A. Sami[9], G. Luthra[10], H.D. Desai[11]
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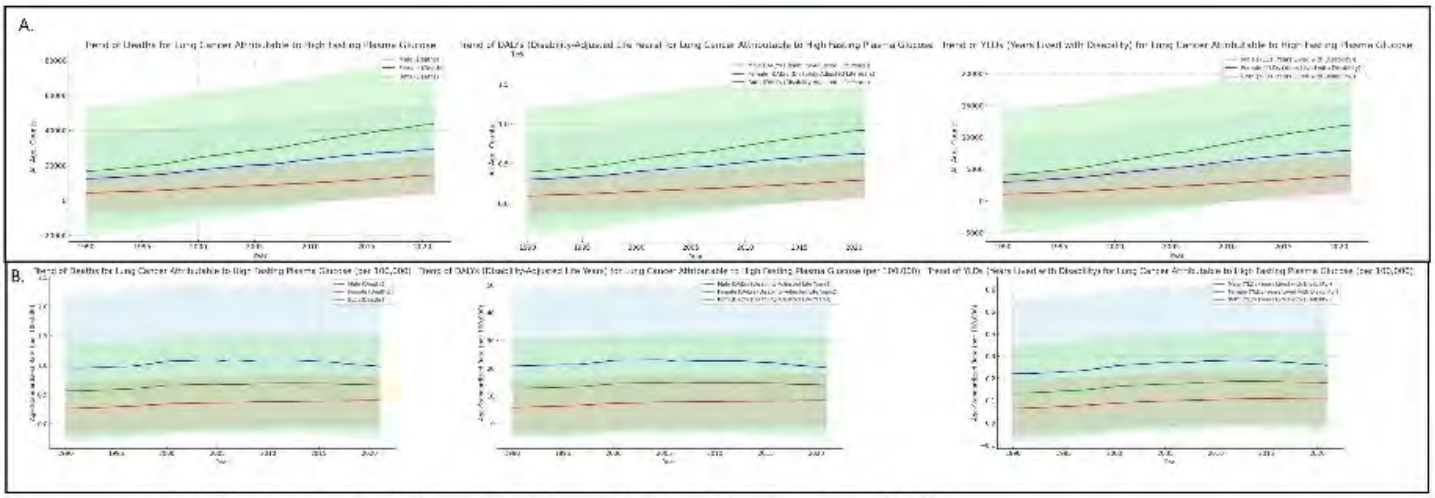
Introduction: Tracheal, bronchus and lung(TBL)-cancer is a leading cause of cancer-related deaths globally, with tobacco as the primary risk factor; however, high fasting plasma glucose (HFPG), linked to diabetes and prediabetes, is increasingly recognized as a contributing factor. G20 countries, facing rising HFPG levels due to urbanization and lifestyle changes, bear a substantial burden of both diabetes and lung cancer, highlighting the need to address metabolic health in cancer prevention efforts.

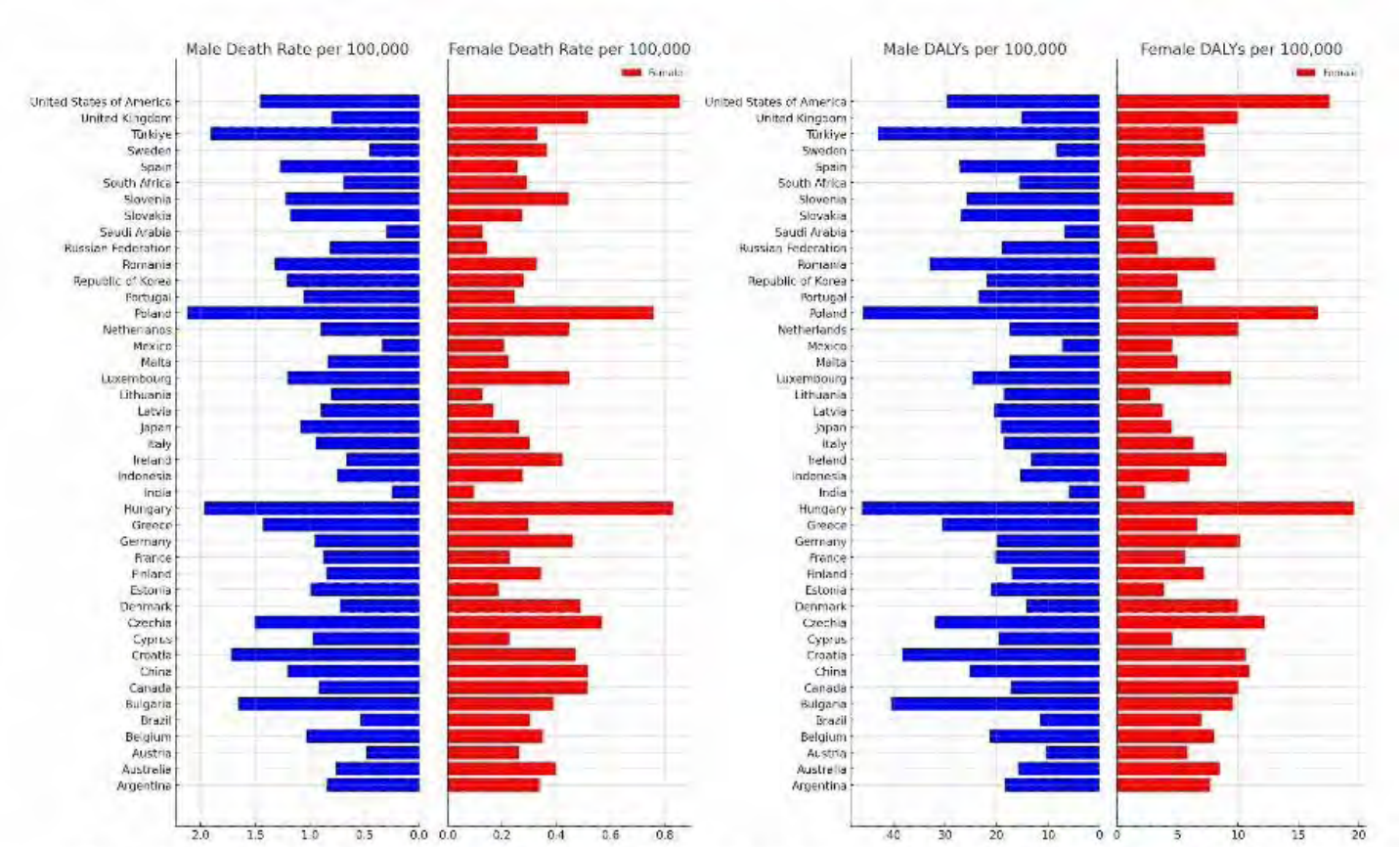
Methods: From 1990 to 2021, TBL cancer deaths, disability adjusted life years(DALYs), and years lived with disability(YLDs) attributable to HFPG were estimated across G20 countries, with temporal trends evaluated using total percentage of change (TPC) by age, sex, year and location using standardized global burden of disease study-2021.

Results: From 1990 to 2021, the total percentage change(TPC) in the absolute burden of tracheal, bronchus, and lung (TBL) cancer showed substantial increases: deaths rose by 162% (95% UI: 130%-193%), DALYs by 132%(103%-163%), and YLDs by 194% (160%-231%). Nationally, the highest increase in deaths was observed in Indonesia(456%), followed by India (350%) and Saudi Arabia (336%), while the United Kingdom reported the lowest increase at 43%. By age group, individuals aged 70-74 years experienced the highest number of deaths (8,466; range: -1,647 to 19,201), whereas the greatest number of DALYs occurred in those aged 65-69 years (178,661; range: -35,683 to 404,782) in 2021. When stratified by sex, females experienced a higher overall increase in burden compared to males, with TPC in deaths at 238% vs. 136%, DALYs at 203% vs. 109%, and YLDs at 279% vs. 164%, respectively.

Conclusions: TBL-cancer attributable to HFPG accounted for 2.51% of all TBL cancer related deaths in 2021. The rising burden calls for coordinated efforts in public health policy, clinical care, and preventive strategies to address the intersecting challenges of metabolic dysfunction and cancer risk.



Global Burden and Trend of TBL Cancer Attributable to high FPG in G20 countries From 1990-2021



Sex wise distribution of TBL cancer Attributable tohigh-FPG in G20 Countries, 2021

Keywords: Global burden, lung Cancer, Behavioral Risk Factors

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.17 Age-Sex Disparities in Global Burden and Trend of Lung Cancer and Its Attributable Risk Factors in the United Kingdom From 1990-2021

P.S. Gupta[1], J. Verma[2], G. Singh[3], D. Upadhyay[4], K. Patel[5], H. Zinzala[6], H.A. Sami[7], G. Luthra[8], A. Aleem[9], H.D. Desai[10]
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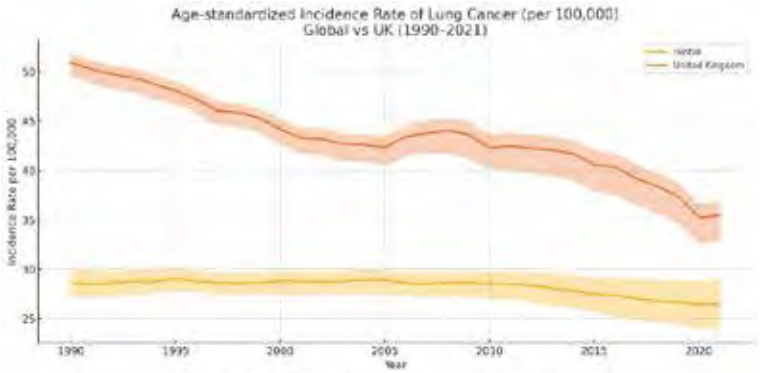
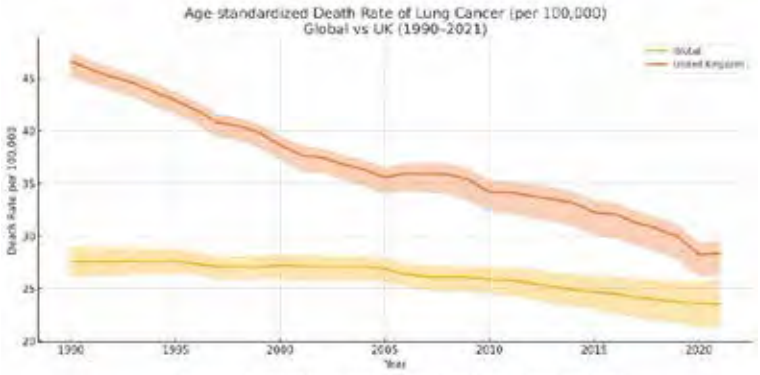
Introduction: Tracheal, bronchus, and lung(TBL) cancer is the leading cause of cancer-related deaths in the United Kingdom, contributing to over 21% of all cancer mortality. It disproportionately affects older adults and socioeconomically deprived populations, with an increasing burden observed among women. This study aims to explore the current trends, disparities, and factors contributing to the lung cancer burden in the UK to inform targeted interventions and public health strategies.

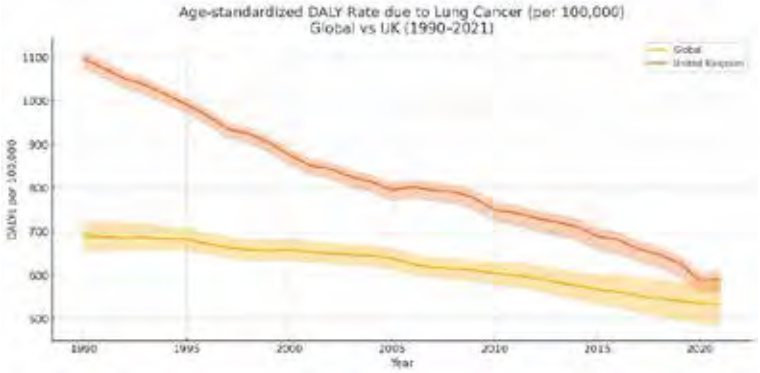
Methods: Using Standardized global burden of disease-study, we estimated fatal and non-fatal health outcomes due to TBL-cancer and its attributable risk factors stratified by age,sex, year and location across the UK from 1990-2021.

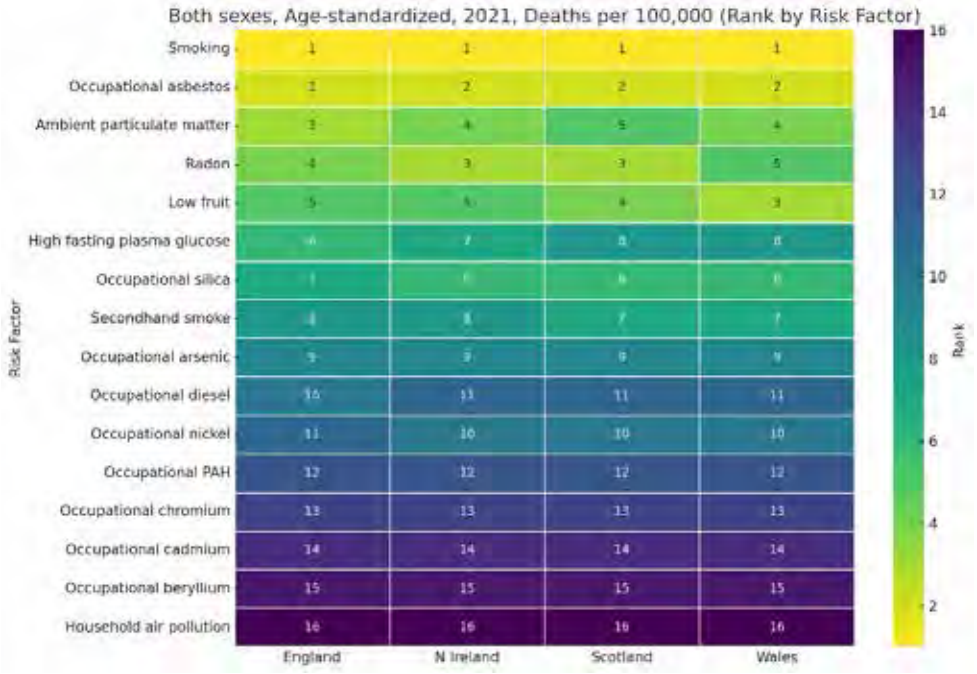
Results: From 1990-2021, the total percentage change(TPC) in TBL cancer prevalence increased by 37% (95% UI: 30%-42%), DALYs decreased by 22%(19%-25%), and deaths declined by 9% (6%-15%). Compared to other high-income countries, the UK showed lower TPC in incidence (3% vs. 45%) and a greater decline in deaths(9% decrease vs. 31% increase). Regionally, Northern Ireland(NI) had the highest rise in incidence(63%), followed by Scotland (22%) and Wales(9%), while England saw a 1% decrease. For deaths, Northern Ireland increased by 37%, Scotland by 4%, with decreases in England and Wales. In 2021, DALYs peaked in the 70-74 age group(141,480; 134,071-146,571), and deaths were highest in those aged 75-79(7,220; 6,650-7,533). Females showed a greater burden than males: TPC in incidence(+49% vs. -20%), deaths(+31% vs. -29%), and DALYs(+12% vs. -38%). TBL cancer attributable to smoking accounted for 59.23% death of call TBL-cancer related deaths in 2021.

Conclusions: Our findings highlight the urgent need for policymakers to prioritize targeted prevention and management strategies, particularly for high-risk groups such as older adults, socioeconomically deprived populations, and women. Strengthening smoking cessation programs,improving early detection, and addressing regional disparities will be critical to reducing the burden of TBL-cancer in the UK.









Keywords: Global burden, lung Cancer, Behavioral Risk Factors

P3.01.18 The Journey to a Lung Cancer Diagnosis: Reports From the LEAD Study

L. Kiel[1], M. Horiguchi[1], R. Kaufman[1], L. Tong[2], A. Morabito[1], K. Meza[3], O. Abioye[4], O. Fakorede[1], C. Mantz[1], R. Lederman[1], J. Marks[1], L. Alder[5], F. Wilder[6], C. Pozo-Kaderman[1], E. Warner[7], C-F.J. Yang[7], L. Sequist[7], N. Florez[1]
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Introduction: Women are less likely to have lung cancer (LC) screening discussions with their healthcare providers (HCP) and may experience longer time to LC diagnosis compared to men. This multi-institution cohort study evaluated how sex, age, and cancer stage at diagnosis influenced the time interval from LC symptom(s) presentation to diagnostic events.

Methods: Patients ≥18 years old, diagnosed with LC stages I-IV within the prior 6 months, were enrolled at Dana-Farber Cancer Institute and Massachusetts General Hospital from 1/2024-5/2024. Patients completed a questionnaire exploring LC risk factors and perceptions of diagnostic timeliness. Objective diagnostic timepoints were abstracted from the electronic medical records (EMR). Wilcoxon tests compared results by age (younger: <50 vs older: ≥50), sex (male vs female), and LC stage (I-IIIB vs IV).

Results: Among 112 patients, most (63%) reported former or current tobacco use. Most tobacco non-users were female (76%). Based on EMR data, 14 patients were diagnosed from incidental findings and 17 from LC screening; 73 of 112 patients had information regarding initial date of symptom(s) presentation to an HCP. Median time-to-events are presented as days relative to this date of symptom(s) presentation to an HCP (Table 1). Time to biopsy and first visit with an oncology HCP were significantly faster for younger patients compared to older patients (3 vs 60 days; p=0.009, 12 vs 58 days; p=0.007; respectively). Similarly, time to treatment initiation was faster for younger patients (38 vs 98 days, p=0.005). No significant sex differences were observed from time of symptom(s) presentation to LC diagnosis and treatment initiation. Time from symptom(s) presentation to plasma biomarker testing (62 vs 155 days; p=0.035) and from tissue biopsy to treatment initiation (26 vs 36 days; p=0.040) were accelerated for patients with stage IV disease. Though not statistically significant, 12% of women, compared to 0% of men, reported that their HCP initially attributed their symptom(s) to anxiety instead of LC (p=0.538). Thirty-four of 105 patients (33%) believed that they experienced diagnostic delays despite seeking medical care, including a higher proportion of younger patients, though this was not statistically different than the older cohort (50% vs 30%; p=0.220).

Conclusions: Younger patients and patients with stage IV LC experienced faster time from symptom(s) presentation to diagnostic events in two large academic centers. While non-statistically significant, anxiety was a common LC symptom misattributed to women. Planned participant interviews will expand on this quantitative data and factors negatively impacting time to LC diagnosis.

Table 1. Days from First Presentation of Symptom(s) to an HCP to Diagnostic Event, Displayed as Median (Q1, Q3)

Event	Female (n= 49)	Male (n=24)	p-value	Older (≥50; n=62)	Younger (<50; n=11)	p-value	Stage I-IIIB LC (n=23)	Stage IV LC (n=50)	p-value	Total (n=73)
X-ray/CT scan	13 (0, 62)	15 (6, 39)	0.614	15 (1, 57)	1 (0, 21)	0.119	13 (0, 31)	13 (2, 62)	0.421	13 (0, 50)
First oncology HCP visit	43 (19, 99)	50 (23,109)	0.587	58 (27,106)	12 (8, 33)	0.007	54 (25, 127)	46 (17, 97)	0.445	46 (19, 99)
Biopsy	44 (14, 90)	54 (14, 145)	0.720	60 (17,101)	3 (2, 42)	0.009	65 (30, 95)	38 (10, 90)	0.170	44 (14, 91)
Treatment initiation	74 (41, 125)	93 (46, 180)	0.725	98 (57, 142)	38 (24, 65)	0.005	98 (74, 157)	72 (38, 124)	0.099	84 (41, 131)
Plasma biomarker test	106 (34, 157)	88 (34,182.0)	0.916	113 (52, 187)	23 (13, 83)	0.020	155 (104, 211)	62 (28, 148)	0.035	104 (34, 172)
Tissue biomarker test	97 (52, 190)	149 (58, 195)	0.467	124 (64, 200)	51 (11, 87)	0.013	101 (45, 272)	100 (54, 193)	0.760	101 (52, 193)
Time from biopsy to treatment initiation	27 (14, 43)	30 (20, 42)	0.856	30 (19, 48)	24 (12, 34)	0.141	36 (24, 62)	26 (14, 37)	0.040	29 (16, 43)

***Note: Missing values were excluded from the analysis and are not reported in this Table.**

Keywords: diagnostic delays, sex differences, young patients

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.19 Gender Differences in Lung Cancer Diagnosis, Treatment Patterns and Outcomes: A Systematic Literature Review

N.F. Abdel Karim[1], C. Aggarwal[2], A. Kobayashi[3], C. Pompili[4,5], D. Molena[6], E. Shum[7], G. Friedrich[8], H. Wakelee[9], J.R. Brahmer[10], L. Woldmann[8], M. Boron[11], N. Florez[12], P. Garrido[13], R. Shenolikar[11], S. Peters[14], J. Naidoo[15,16], M.L. Hsu[17,18], E. Felip[19]
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Introduction: Globally, lung cancer incidence and mortality are rising in women while declining in men. Understanding how these disparities may be affected by diagnosis and treatment decisions is crucial to improving outcomes for all patients and promoting equitable care for both men and women.

Methods: A systematic literature review was conducted using a PICOS framework to identify English-language publications reporting information on gender differences throughout the patient journey. The review examined differences in time to lung cancer diagnosis, access to biomarker testing, time from diagnosis to treatment initiation, treatment patterns, and outcomes. Embase, MEDLINE, MEDLINE In-Process, and Cochrane databases were searched for articles published between January 2004 and February 2024, as well as relevant conference proceedings and expert literature. Data from articles that provided adjusted estimates of gender comparison using regression analysis were reported.

Results: A total of 11,088 unique publications were identified, of which 9,710 were excluded based on initial screening; 1,366 were reviewed in full, of which, 126 were excluded due to lack of reporting on gender differences in diagnosis, testing, treatment, patient preferences, and outcomes. Eight of 11 studies showed that men were more likely to present with late-stage disease at diagnosis, while two studies showed that women were more likely to present with early-stage disease at diagnosis versus men (OR in these 2 studies: 1.85 and 1.30). Four of six studies reported that men started treatment earlier than women following diagnosis; for example, one study reported an average of 72 days for men and 87 days for women ($p<0.01$). Men were more likely to receive timely treatment for Stage I/II non-small-cell lung cancer (NSCLC). Alternatively, women were more likely to receive timely treatment for Stage III NSCLC. One analysis showed that older women were more likely to receive care not concordant with guidelines ($p=0.008$ vs younger women), and women with early-stage NSCLC (stage I and IIIa/b) were less likely to receive guideline concordant care. Only two reports indicated that men with NSCLC were less likely to receive biomarker testing (e.g. for select biomarkers including ROS1 and EGFR mutations and ALK rearrangement) compared with women. Treatment patterns were reported in 33 studies; overall, women were more likely to undergo treatment such as surgery or receive tyrosine kinase inhibitors (TKIs), while men were more likely to receive radiotherapy or chemotherapy. Of the six studies assessing patient preferences, women were more inclined to opt for surgery while men with NSCLC were more likely to choose radiotherapy, chemoradiotherapy, or end-of-life care. In general, women reported better responses (HR in individual therapeutic trials ranged from 0.53-0.88), longer progression-free survival (HR: 0.33-1.32) and improved overall survival (HR: 0.31-0.885) compared with men.

Conclusions: These data suggest gender differences in diagnosis receipt and treatment initiation, as well as treatment decisions and outcomes for patients with lung cancer. The synthesized evidence, although limited, should elevate the need to further solidify the evidence base and understand underlying reasons behind these differences. These efforts can advance this discussion to promote equitable care to everyone.

Keywords: Gender, Treatment, Outcomes

P3.01.20 Lung Cancer Risk Factors in 35,530 People From the UKLS Trial Who Have Never Smoked

L. Shire, J.K. Field, M.P.A. Davies
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Introduction: Lung cancer in people who have never smoked (LCiNS) is widely considered to be a distinct disease from cancer caused by smoking, with different aetiology and demographics. Whilst significantly less common than lung cancer in people who have smoked, it still accounts for 15% of lung cancers in the UK and is responsible for approximately 6000 deaths per year. Risk factors for LCiNS are poorly understood but have been widely studied in East Asian populations where rates are highest.

Methods: Questionnaire data completed by 75,948 participants in the UKLS trial was analysed: including 35,470 who never smoked (NS) with 58 lung cancers (0.16%) within the five-year follow-up from Public Health England (compared to 541 lung cancers in 40,418 people who smoked,1.34%). The Risk data for the LLPv2 risk model was available: age, sex, smoking duration, previous respiratory diseases, family history of lung cancer, previous history of cancer and exposure to asbestos. Statistical analysis included odds ratios (OR) and binary logistic regression for lung cancer within 5 years.

Results: All risk factors except for sex were significant in the whole cohort and in people who smoked (see Table). However, for LCiNS only older age and low socioeconomic status, measured by the most deprived quintile of Index of Multiple Deprivation, were significantly associated with increased risk. It is of note that the odds ratios were higher for LCiNS for both age (OR 4.30 vs 2.25) and deprivation (OR 2.87 vs 1.99). In contrast, lung disease was associated with lower LCiNS 5-year risk (OR 0.41 vs 2.01). In binary logistic regression with conditional backward selection, age (OR 4.35), deprivation (OR 2.72) and any lung disease (OR 0.37) were independently significant.

The limitation of this study is the low number of lung cancers in people who have never smoked, thus requiring a much larger study population for conclusive results. In addition, data on additional risk factors, second-hand smoke, air pollution, and occupational exposures, should be collected in a larger study.

Conclusions: This study demonstrated that LCiNS risk is driven by older age and socioeconomic deprivation. Surprisingly, in contrast to East Asian populations, a family history of lung cancer was not significant in this UK population, and neither was a personal history of cancer. Also, lung disease had a limited protective effect for LCiNS, indicating an interplay between smoking and risk associated particularly with COPD and emphysema (and to a lesser extent asbestos).

Table: Factors associated with 5 year lung cancer risk in UKLS Questionnaire		Odds Ratio (95% Confidence Interval)		
		All	Smokers	Never Smokers
Sex	M vs F	1.23 (1.05 - 1.45)	1.04 (0.88 - 1.24)	0.72 (0.42 - 1.24)
Age	65+ vs <65	2.54 (2.15 - 2.99) ***	2.25 (1.89 - 2.68) ***	4.30 (2.42 - 7.65) ***
Deprivation (IMD quintile)	Q1 vs Q2-5	2.51 (2.12 - 2.96) ***	1.99 (1.66 - 2.37) ***	2.87 (1.64 - 5.01) ***
Asbestos exposure	Yes vs No	1.58 (1.30 - 1.93) ***	1.39 (1.14 - 1.7) **	0.43 (0.14 - 1.39)
COPD	Yes vs No	4.61 (3.73 - 5.69) ***	3.14 (2.53 - 3.90) ***	1.16 (0.16 - 8.40)
Emphysema	Yes vs No	5.93 (4.48 - 7.86) ***	4.44 (3.34 - 5.89) ***	NA
Pneumonia	Yes vs No	1.44 (1.13 - 1.83) **	1.42 (1.11 - 1.82) **	0.40 (0.10 - 1.64)
Bronchitis	Yes vs No	1.30 (1.05 - 1.60) *	1.18 (0.95 - 1.46)	0.54 (0.19 - 1.48)
TB	Yes vs No	0.7 (0.35 - 1.42)	0.75 (0.37 - 1.51)	NA
Any lung condition	Yes vs No	2.23 (1.89 - 2.62) ***	2.01 (1.69 - 2.38) ***	0.41 (0.16 - 1.02) *
Personal history of cancer	Yes vs No	1.59 (1.28 - 1.96) ***	1.48 (1.18 - 1.85) ***	1.85 (0.96 - 3.58)
Family history of lung cancer	Yes vs No	1.62 (1.34 - 1.96) ***	1.59 (1.31 - 1.93) ***	0.89 (0.42 - 1.87)

Statistical significance Chi-Square (* P<0.05, ** P<0.01, *** P<0.001)

Keywords: Never smoked, Risk factors, UKLS

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.21 Lifting the Smoke Screen: A Real-World Comparative Study of Lung Cancer in Never-Smokers Versus Ever-Smokers

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Introduction: Despite smoking being inextricably associated with lung cancer, recent decades have witnessed a marked rise in the occurrence of lung cancer in non-smokers. The understanding of the disease biology and the clinical profile of lung cancer in non-smokers is still evolving. Here, we present our comparative retrospective real-world data on the clinico-epidemiological profile of lung cancer in smokers compared to non-smokers, from a tertiary care cancer centre in South India.

Methods: Data on all lung cancer patients treated at Cancer Institute (WIA) from 2017 to 2021 were extracted from medical records. Patients without histopathological confirmation of a carcinoma were excluded. The clinico-epidemiological details, driver mutation status, and survival status were captured. Differences between ever-smokers and never-smokers for continuous variables was assessed using the Chi-square test and categorical variables by the t-test. Overall survival (OS) was calculated using the Kaplan-Meier method and difference between groups was analysed by log-rank test.

Results: The study included 802 patients. Never-smokers comprised 53% (n=425) and Ever-smokers made up 47% (n=377). Majority of females were never-smokers [(n=261; 87.3%) vs (n=38; 12.7%)], whereas males were predominantly ever-smokers [(n=339; 67.4%) vs (n=164; 32.6%)]. The median age was less for never-smokers (55.6years), compared to ever-smokers (60.5years), with p-value of <0.001. The commonest forms of smoking were Cigarettes (n= 166/377; 44%), Beedis (n=147/377; 39%) and both in 18 (4.8%) patients, with a median of 30 pack-years. Passive smoking was seen in 36 patients (9.5%). Squamous cell carcinoma (19.1% vs 7.5%) and small carcinoma (14.3% vs 2.3%), had a higher occurrence in Ever-smokers, whereas Never-smokers were more likely to have adenocarcinoma (83.8% vs 57.9%). Never-smokers had a significantly higher distribution of metastatic lung cancer at diagnosis, compared to ever smokers (n= 356; 83.8% vs n= 255; 67.6% with p-value <0.001). Amongst non-small cell lung cancer patients (n=739), Never-smokers (n=416), driver alteration analysis was positive in 215 (51.7%), negative in 103 (24.7%), and not available in 98 (23.6%); whereas in ever-smokers (n=323), driver alteration was positive in 78 (24.1%), negative in 125 (38.7%) and not available in 174 (37.2%). Driver alterations were more frequently detected in never-smokers, while data was more often not available in ever smokers (p <0.001). The median follow-up was 41.9 months. The median OS in never-smokers (11.9 months; 95% CI 10.3-13.5 months) was significantly longer, compared to ever-smokers (7.3 months; 95% CI 5.9 - 8.6 months), p <0.001. Median OS was better in never-smokers across all stages. In patients harbouring a driver alteration, median OS was not significantly different between never and ever smokers (16.5 vs 15.3 months; p=0.057).

Conclusions: Lung cancer is never-smokers contributes to a significant proportion of the disease burden, tend present in later stages, are more likely to harbour a driver-alteration and have longer survival. Even among ever-smokers, more than a third harbour a driver alteration, reinforcing the need for universal testing for maximizing eligibility to effective targeted therapy. Survival of driver alteration positive lung cancer patients was similar between never- and ever-smokers.

Keywords: Never-smokers vs Ever-smokers, Real-world, South-Asia

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.22 Deep Learning-Based CT Analysis Enhances Lung Cancer Risk Prediction in Never Smoking Women

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Introduction: Lung cancer incidence is increasing among never smoking women but there are few risk assessment tools designed for this population. "Sybil," a validated, publicly available deep learning model applied to low-dose chest CT, is reported to predict lung cancer risk in patients who have smoked. There are limited data regarding its real-world performance, particularly in the high-risk population of never smoking women. We sought to compare lung cancer risk assessment using exposure data, an existing clinical risk calculator, and Sybil in a population of never smoking women.

Methods: We conducted a retrospective analysis of a prospectively maintained single institution thoracic surgery database. Patients included adult never-smoking women treated for lung adenocarcinoma between 2022 and 2024. Data regarding prevalence of factors associate with high lung cancer risk (asbestos, family history, prior cancer, marijuana use, secondhand smoke exposure) were collected. Lung cancer risk was calculated using the PLCOALL2014 model. Among patients with available CT chest imaging from 1 to 3 years prior to lung cancer diagnosis, Sybil was used to calculate lung cancer risk. Analyses were performed using Stata 18 (StataCorp, College Station, TX). Two-tailed p-values <0.05 were considered statistically significant.

Results: The study cohort included 216 never smoking women: median age 67 years, 59% White, 22% Asian; stage I (161/216, 75%), stage II (23/216, 11%), stage III (25/216, 12%), stage IV (7/216, 3%). Common risk factors included prior cancer diagnosis (81/216, 38%), secondhand smoke exposure (64/216, 30%), chronic pulmonary disease (47/216, 22%), and family history of lung cancer (44/216, 20%). Asbestos exposure (9/216, 4%) and marijuana use (8/216, 4%) were uncommon in this cohort. A total of 38 patients had CT imaging 1-3 years prior to diagnosis. Patients with prior imaging were more likely to be cancer survivors (63% vs. 32%, p<0.001) and to be diagnosed with stage I or in situ disease (89% vs. 71%, p=0.02). Median one-, three-, and six-year risks of developing lung cancer from the Sybil model were 3.9% (IQR 0.4-79%), 9.1% (2.8-35%), and 16.5% (7.4-75%), respectively. Using a risk threshold of 1.3%, Sybil predicted high one-year risk in 66%, three-year risk in 95%, and six-year risk in 100%. By contrast, the PLCOALL2014 model predicted six-year lung cancer risk of 0.16% (IQR 0.08-0.34%) in the full cohort and 0.2% (IQR 0.1-0.4%) among patients with a prior CT scan.

Conclusions: Sybil, a novel publicly available deep learning tool developed for analysis of screening CT imaging in smokers, predicts significantly higher lung cancer risk in a cohort of never smokers compared to existing clinical calculators. Future work will incorporate clinical, genomic, and deep learning data to better characterize the population of high-risk never smokers and develop personalized, scalable, population-based lung cancer screening protocols.

Keywords: early cancer detection, lung cancer, never smoker

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.23 The Impact of PM2.5 Exposure on the Genome of Patients With Lung Adenocarcinoma Who Have Never Smoked

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Introduction: Up to 25% of patients with lung cancer have never smoked. Due to the high mortality of lung cancer, this means that this subset of patients alone constitutes the fifth most deadly cancer worldwide, highlighting the need for understanding the underlying causes of lung cancer in these patients. While pollution exposure, specifically particulate matter smaller than 2.5 µm in diameter (PM2.5), is a leading risk factor for lung cancer in patients who have never smoked, its impact on the lung cancer genome in patients with defined levels of pollution exposure is unknown.

Methods: A total of 119 patients with lung adenocarcinoma who have never smoked and received lung resection at Vancouver General Hospital or Surrey Memorial Hospital in British Columbia, Canada between 2019 and 2024 were included in this study. These patients were categorized as having high (≥10 ug/m3/year) or low (<10 ug/m3/year) cumulative PM2.5 exposures by their residential history in the 20 years before their diagnoses. This classification was done using a model that combined Aerosol Optical Depth (AOD) retrievals with a chemical transport model using geographically weighted regression. DNA from these patients' FFPE tumor tissue and matched normal tissue underwent whole exome sequencing (WES) at a depth of 100x. Upon somatic variant calling for these samples with Mutect2, mutational signature profiling, analysis of driver mutations, copy number alteration analysis, and functional analysis will be conducted. This will reveal the features in the lung adenocarcinoma genome associated with high levels of PM2.5 exposure in patients who have never smoked.

Results: Preliminary analysis of a subset of 55 patients revealed that 51 patients had low cumulative PM2.5 exposure (mean: 6.61 µg/m3/year, SD: 1.86), while 4 patients had high exposure (mean: 29.7 µg/m3/year, SD: 16.05) over a 20-year period. The average tumor mutational burden was 10.23 mutations per megabase (SD: 5.84), and 20 patients harbored EGFR mutations (L858R or exon 19 deletion) while 4 had KRAS G12D mutation. An additional 64 patients' samples have been procured and are undergoing sequencing. Mutational signature and copy number alteration analysis for this group of patients is ongoing. Further updated results and integrated genomics analysis on the entire cohort will be presented at the Conference.

Conclusions: Overall, this study has the potential to identify unique molecular features in lung adenocarcinoma that are associated with high PM2.5 exposure, offering novel insights for therapeutic development and early detection, particularly in people who have never smoked.

Keywords: genomics, lung adenocarcinoma, pollution

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.24 Economic Burden of Radon Attributable Non-Small Cell Lung Cancer: A Cost Analysis

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Introduction: Lung cancer accounts for 23% of cancer deaths in Canada and is the leading cause of cancer deaths. Besides smoking, radon inhalation is the most prevalent cause of non-tobacco related non-small lung cancer (NSCLC). Long term radon exposure results in a 16% increase in lifetime risk of lung cancer per 100 Bq/m3. Estimates are 2402 - 3377 lung cancer cases are attributable to radon in Canada in 2025. We estimated the economic burden of radon attributable lung cancer from the Canadian healthcare system perspective.

Methods: We evaluated the cost of radon attributable NSCLC based on radon attributable risk (PAR) estimates. Based on estimates in literature, 62% of NSCLC in nonsmokers are diagnosed at stage IV. The remaining 38% of stages I-III cancers were broken down according to current early-stage distributions reported in the literature. Direct healthcare costs were estimated including consult and follow up physician visits, bronchoscopy, next-generation sequencing, laboratory and imaging costs, surgery, radiation and systemic therapy costs. Costs were obtained from the provincial medical benefit schedule, national health technology assessment reports, local experts and the literature and were then weighted by prevalence of treatment type as represented in the reviewed chart data. In stage IV NSCLC, treatment costs were applied for the median duration of response for the first line regimens followed by the second line regimens in the actionable (estimated 30%) and non-actionable NSCLC (estimated 70%) settings. All costs are in CAD$ adjusted for inflation to January 2025.

Results: Radon attributable NSCLC in 2025 is estimated to cost the healthcare system an overall $511,401,937 from diagnosis to completion of treatment at the median PAR estimate of 2890 NSCLC diagnoses [range $425,047,562 (for 2402 diagnoses) to $597,579,357 (for 3377 diagnoses)]. Total cost for treatment of all Stage I, II and III NSCLC diagnoses were $8,774,925, $3,803,535 and $47,740,347 respectively, at the median PAR estimate. Stage IV NSCLC comprised 86% of total costs with NSCLC containing actionable mutations taking up a disproportionate 31% of total costs while only representing 19% of estimated cancer diagnoses. At the median PAR estimate, radon attributable NSCLC costs approximately $1,401,101 per day, or $973 per minute in Canada.

Conclusions: Our results demonstrate the costs of radon attributable NSCLC in the era of precision medicine. Radon attributable NSCLC results in substantial costs to the health care system. Future work will determine the impact of radon reduction strategies in decreasing the economic burden of NSCLC.

StageI-III/Case	StageI	StageII	StageIII
Surgery	19,701.14	21,203.41	68,582.02
Radiation	10,603.28	17,125.55	
Systemic		40,493.51	183,521.41
Weighted Cost/Case	15,365.92	24,738.78	127,096.62
StageIV/Case/Year	Actionable	PD-L1<50%	PD-L1>50%
First Line	140,594.34	238,844.21	170,958.88
Second Line	106,524.79	35,261.67	105,064.79
Hospitalization	9959.97		
Palliative Care	5772.61		

Keywords: Radon, Health Economics, Lung Cancer

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.25 Residential Radon and Molecular Alterations in Non-Small Cell Lung Cancer

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Introduction: Residential radon exposure is a significant risk factor for lung cancer, being the second cause after tobacco consumption, and the first in never smokers. According to the World Health Organization (WHO), radon is responsible for approximately 3% to 14% of all lung cancer cases. Despite this, the molecular mechanisms underlying radon-induced carcinogenesis remain poorly understood. In this study, we investigate the relationship between residential radon exposure and a set of molecular alterations in non-small cell lung cancer (NSCLC) patients.

Methods: A total of 207 patients with confirmed NSCLC were included in the study. Radon exposure was measured at an Accredited Laboratory using alpha-track radon detectors (CR-39; Radosys Ltd, Budapest, Hungary) which are the most reliable technique and recommended by the Nuclear Safety Council. Pre-treatment tumor biopsies were analyzed using next-generation sequencing (NGS).

Results: Sixty percent of patients were male. The average age at diagnosis was 65 years. Regarding the histological subtype, the majority were adenocarcinomas (71%). At the time of diagnosis, 65% of patients presented with metastatic disease, 23% were at a locally advanced stage (stage IIIA-C), and 12% were diagnosed at an early stage (stage IA-IIB). Regarding smoking status, 9% of patients were never-smokers, 54% were former smokers, and 37% were current smokers. Median residential radon concentration in our cohort was 78 Bq/m3 (IQ25-75%: 45-137); min 4 Bq/m3, max 1,035 Bq/m3. A molecular alteration was identified in 141 patients (68%). Specifically, 6% of tumors harbored an ALK translocation, and 10% had EGFR common mutations. Other targetable alterations included KRAS G12C mutations (10%), BRAF V600E (2%), MET amplification (1%), MET exon 14 skipping mutations (2%), and HER2 alterations—including amplification or exon 20 insertions—in 2% of cases. Additionally, ROS1 fusions and RET fusions were each identified in 0.6% of tumor Overall, patients whose tumors harbored targetable molecular alterations—excluding BRAF V600E and KRAS G12C mutations—were significantly more exposed to higher levels of residential radon compared to those without such alterations (139 Bq/m3 vs. 68 Bq/m3; $p < 0.001$). Specifically, patients whose tumors carried druggable gene fusions were exposed to significantly higher radon levels (144 vs. 88 Bq; $P < 0.001$). More specifically, ALK-positive NSCLC patients had markedly higher radon exposure compared to ALK-negative cases (142 Bq/m3 vs. 74 Bq/m3; p=0.006). In contrast, tumors harboring a BRAF mutation (including non V600E) were associated with significantly lower radon exposure (39 Bq/m3 vs. 78 Bq/m3; p=0.034).

Conclusions: Druggable gene fusions in non-small cell lung cancer are significantly associated with higher levels of residential radon exposure. These findings suggest a potential link between residential radon exposure and the development of specific molecular alterations, particularly ALK rearrangements. Further research is warranted to explore the biological mechanisms underlying this association and to assess the implications for lung cancer prevention and targeted therapy strategies.

Keywords: RADON, Spanish Lung Cancer Group, molecular alterations

P3.01.26 Respiratory Hazard Index Is Associated With Lung Cancer Development in Underrepresented Lung Cancer Screening Individuals

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Introduction: Lung cancer (LC) is the leading cause of cancer -related mortality in the United States. Lung cancer screening (LCS) in high-risk individuals with LDCT significantly reduces LC mortality. Generally, approximately 1% of individuals undergoing LCS develop LC. At UI Health, an academic health system serving the west and south sides of Chicago, patients in our majority, minority-based LCS program have a higher rate of LC development. Therefore, we aim to understand clinical and population-based social determinants of health (SDOH) metrics that may be associated with higher rates of LC development.

Methods: We used logistic regression to assess the effect of demographic and SDOH metrics on cancer diagnosis as well as high and low Lung-RADS scores. Lasso regularization was applied for variable selection due to its ability to shrink some coefficients to zero, thereby improving model interpretability. The optimal regularization parameter (lambda) was determined via 10-fold cross-validation.

Results: We conducted a retrospective analysis of clinical data and linked geospatial level SDOH metrics for 2645 patients enrolled in our hybrid LCS program at UI Health from 2015-2024. Of these individuals, 96.4% did not develop LC (NLC), while 3.6% developed LC (DLC). Individuals in the NLC group had a higher percentage of low Lung-RADS scores (<2) whereas those in the DLC group had a higher percentage of high Lung RADS (3+). Among 30 population-level SDOH metrics, we found that the Respiratory Hazard Index (RHI), the ratio of air toxic exposure (~187 chemicals) concentrations to health-based reference concentrations, was higher at all geospatial levels (zipcode, community, census) in LCS individuals with baseline high Lung-RADS scores compared to individuals with low scores (Zipcode: 0.384 vs. 0.379 (p=0.09), Community: 0.390 vs 0.385 (p=0.034), Census: 0.383 vs. 0.376 (p=0.057)). Therefore, we looked at the effect of RHI (as well as other factors) on lung cancer development and found that there was a trend towards higher RHI scores and lung cancer development at the census tract level (Table 1).

Conclusions: This is the largest study to characterize the demographic and population-level SDOH in a hybrid LCS Program primarily serving underrepresented individuals. LCS individuals with higher Lung-RADS scores, which are associated with higher rates of LC detection, as well as higher Respiratory Hazard Index (RHI) scores, are more likely to develop LC. The current study suggests that exposures to air toxics may significantly impact the development of LC, especially amongst underrepresented LCS populations which warrants further investigation.

Using the median and 75th cutoff for RHI
(In this case, median and 75th quantile are the same for this variable)

Logistic Regression Results with Lasso Regularization

	Cancer: Yes (outcome)		
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.02	0.01 – 0.03	**<0.001**
Lund Rads: 1 or 2	*Reference*		
Lund Rads: 3 or above	10.44	6.55 – 17.19	**<0.001**
Alone: No	*Reference*		
Alone: Yes	1.86	1.16 – 2.94	**0.009**
Non-Hispanic White	*Reference*		
Non-Hispanic Black	0.70	0.41 – 1.22	0.190
Hispanic	0.26	0.08 – 0.66	**0.009**
Others	0.36	0.13 – 0.89	**0.037**
Census RHI: Low	*Reference*		
Census RHI: High	1.69	0.95 – 2.90	0.063
Observations	2284		

Keywords: Lung Cancer Screening, Geospatial Social Determinants of Health, Respiratory exposure

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.27 Environmental Carcinogenesis in Lung Cancer: Sodium Arsenite-Induced PML Dysregulation and LINE-1 Activation

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Introduction: Lung cancer is the leading cause of cancer-related mortality, with rates of lung cancer increasing in non-smokers. Thus, other environmental carcinogens pose a significant risk for the development of lung cancer. Sodium arsenite (NaAsO2) is a known environmental carcinogen implicated in lung cancer development. NaAsO2 exposure has been associated with the activation of LINE-1 (L1) retrotransposons. L1 activation commonly occurs in cancer cells and is linked to genomic instability, and activation of innate inflammatory pathways, both being hallmarks of cancer. The promyelocytic leukemia protein (PML), a tumour suppressor, is under-expressed in lung cancer and has been recently implicated in the suppression of L1. This study examines the role of PML in arsenic induced L1 activity and their potential contributions to lung cancer pathogenesis.

Methods: Human bronchial epithelial (HBEC3-KT) and small airway epithelial (HSAEC1-KT) cell lines were treated with low doses (0.08-10μM) of NaAsO2. Immunofluorescence microscopy (IF), Western blot, qPCR, and ELISA-based assays were used to assess PML localization and L1 activation. A L1 retrotransposition reporter assay was used to assess L1 integration. A cGAMP ELISA assay was used to assess the inflammatory cGAS response to double stranded DNA in the cytoplasm.

Results: Immunofluorescence microscopy revealed that NaAsO2 exposure led to cytoplasmic accumulation of PML and a reduction in nuclear PML bodies (PML NBs). Given that PML plays a role in suppressing L1 retrotransposons, and that arsenic exposure has been shown to increase L1 activity, we used RT-qPCR to assess L1 expression and found increased endogenous L1 activation following NaAsO2 treatment. Additionally, a L1 reporter assay confirmed upregulated L1 integration in NaAsO2 treated cells, which was suppressed by PML overexpression. Using IF we observed co-localization of endogenous PML and L1 ORF1P in both NaAsO2 and control cells within the nucleus. We also observed an increased abundance in ORF1P puncta in NaAsO2 treated cells compared to untreated cells. The nuclear co-localization of PML and ORF1P suggests that there may be a nuclear function of PML in L1 suppression. We also assessed downstream inflammatory consequences of arsenic-induced L1 activation using a cGAMP ELISA assay and found that PML overexpression was able to eliminate cGAS activation. These results suggest that degradation of PML by NaAsO2 is detrimental for L1 suppression and may pose a significant step in the development and progression of lung cancer due to the ability of L1 to create genomic instability and activate inflammatory pathways.

Conclusions: These findings suggest that NaAsO2 exposure activates L1 and disrupts PML NBs, both of which are implicated in genomic instability and tumor suppression. Chronic NaAsO2 exposure may promote lung cancer development by degrading PML, thereby impairing its ability to repress L1 activity. This arsenic-induced and unsuppressed L1 activity could enhance genomic instability and activate inflammatory pathways, such as the cGAS-STING pathway, contributing to tumor progression. Understanding the mechanisms for arsenic induced L1 activity is essential for identifying environmental risk factors, understanding lung cancer development, and developing early screening strategies to improve patient outcomes.

Keywords: Arsenic, Line-1, PML

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.28 Household Air Pollution and Mitochondrial DNA Fragmentation

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Introduction: Lung cancer is the leading cause of cancer-related death globally and the seventh among never smokers. Though cigarette smoke is the principal lung cancer carcinogen, air pollution is also a significant risk factor. With declining smoking rates and rising air pollution, understanding air pollution's role in lung cancer is essential. Fine particles with diameters of 2.5 micrometers and smaller (PM2.5) have been linked to lung cancer. Though the mechanism remains unclear, prior studies noted that exposure to PM2.5 is associated with mitochondrial DNA copy number, a measure of mitochondrial quantity. Mitochondrial loss occurs with aging and is associated with several age-related diseases. To explore these relationships, we examined the association between PM2.5 and intermediary biomarkers suspected to reflect lung cancer risk, including total mitochondrial DNA copy number (mtDNA), mtDNA fraction with breaks (mtDNAfb) and mtDNA fraction without breaks (mtDNAfwb), in Peru and Guatemala, countries with a high prevalence of household air pollution. This is the first study to assess the association between PM2.5 and mtDNA fragmentation.

Methods: From 2018 - 2020, participants in Peru and Guatemala were enrolled in a randomized control trial (Household Air Pollution Intervention Network, HAPIN) to evaluate the effect of transitioning from burning biomass to cooking with liquefied petroleum gas (LPG), a cleaner alternative to traditional biomass fuels, on health outcomes and intermediary biomarkers. Participants were randomized into an intervention arm, which received an LPG stove, or a control arm, which continued using biomass fuel. Biological samples and personal 24-hour PM2.5 concentrations were collected at baseline and 18 months post-intervention. Generalized estimating equations explored the association between PM2.5 and three endpoints (total mtDNA, mtDNAfb, and mtDNAfwb). Models were adjusted for batch, age and randomization arm, and sensitivity analyses further adjusted for body mass index (BMI; kg/m2) and education.

Results: 219 never-smoking older women (age >50 years) from Peru (n=84) and Guatemala (n=135) were included in our analyses. Though no association was observed between PM2.5 and total mtDNA (B= -0.0002, 95% confidence interval (CI): -0.069, -0.069), a 1 standard deviation (SD) increase in PM2.5 exposure was associated with a 3.89% (B= -0.04, 95% CI: -0.06, -0.01) decrease in mtDNAfb and a 2.1% (B= 0.02 ,95% CI: 0.002, 0.04) increase in mtDNAfwb. In Guatemala, 1 SD increase in PM2.5 exposure was associated with a 5.29% (B = -0.05, 95% CI: -0.09, -0.01) decrease in mtDNAfb and a 3.0% (B= 0.03 ,95% CI: 0.007, 0.05) increase in mtDNAfwb. Similar findings were appreciated when adjusting for BMI and education. Noteworthy findings were neither observed in analyses restricted to Peruvian participants nor in analyses assessing the effect of the intervention.

Conclusions: We observed that increased exposure to PM2.5 is associated with a decrease in mtDNAfb and an increase in mtDNAfwb. Notably, a population-based cohort study in Asia identified an association with lower mtDNAfb values and increased risk of lung cancer in female never-smokers. Future investigation is needed to validate our findings.

Keywords: Lung cancer in never-smokers, Air pollution, Biomarkers

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.29 Identifying Long Term Air Pollution Exposure for Lung Cancer Risk in Canada

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Introduction: Lung cancer in persons who have never smoked is on the rise globally, and accounts for up to 33% of lung cancers diagnosed in Canada. A strategy to identify light and never tobacco users who are at high risk and who may benefit from lung cancer screening (LCS) is urgently needed. In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution and particulate matter less than 2.5 µm in diameter (PM2.5) as a carcinogen to humans and a cause of lung cancer. There are challenges to estimating lifetime air pollution exposure, as satellite-based air pollution data is only available from 1995 onward. This limits our ability to accurately estimate the risk of lung cancer associated with air pollution, which may be particularly relevant for individuals who do not qualify for LCS due to smoking exposure and/or history. Our study aims to compare the predictive accuracy of using cumulative air pollution exposure to predict lung cancer risk when air pollution is estimated from residential histories which are taken at different periods and for different time durations.

Methods: A case-control study design was employed with all participants enrolled sequentially through early detection studies at BC Cancer, Vancouver. The cumulative outdoor PM2.5 exposure was estimated using a high-spatial resolution global exposure model based on postal codes for all residences occupied going back 20 years. The associations between lung cancer and current, 3-, 5-, 10-, and 20-year annual mean PM2.5 exposures were evaluated using odds ratios (OR) with 95% confidence intervals (CI). Predictive performances were evaluated using the receiver operator characteristic area under the curve (AUC).

Results: In this study, 59 of 616 (9.6%) participants were diagnosed with lung cancer, 32 (52.8%) were female. Lung cancer was detected in 11.1% of women and 7.9% of men. Mean age was 66.7 (SD 7.0, range 42-80). Current, former, and never tobacco users comprised 11%, 54%, and 34% of the sample respectively.

Twenty-year annual mean exposure was statistically significantly higher than that based on the current address (7.02 vs 6.25; $p<0.001$). Foreign-born Canadians had significantly higher cumulative air pollution exposure than Canadian-born when evaluating 3, 5, 10, and 20-year annual mean exposures ($p=0.02$) but no significant difference was seen when only the current address was used ($p=0.08$). Five percent of Canadian-born individuals had lung cancer vs 17% of foreign-born Canadians ($p<0.001$). The odds ratio for lung cancer ~ air pollution (PM2.5) adjusted for age and sex for the first (earliest) collected one year of exposure was 1.055, 95% confidence interval (CI) 0.997-1.116, $p=0.063$; AUC=0.579), and for the most recent one year of exposure was 0.978 (0.883-1.158; $p=0.797$; AUC=0.551).

Conclusions: Incorporating accurate estimates of air pollution exposure into risk assessments and risk prediction models for ever- and never-smoking individuals is of great public health and clinical importance. Our study suggests that measurement of air pollution exposure over an extended period is more predictive than just using current residence.

Keywords: Air Pollution, Never smokers, Exposure

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.30 The Relationship of Particular Matter 2.5 and Mortality Rate of Patients With Lung Cancer and Lag Time Effect in Northern Thailand

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Introduction: Open burnings, agricultural, and forest fires contribute significantly to particulate matter (PM) pollution in Chiang Mai, Thailand particularly during the dry season. In this study, we investigated the association between increased monthly particulate matter (PM) with an aerodynamic diameter ≤ 2.5 µg/m 3 (PM2.5) levels and mortality among patients with lung cancer receiving treatment at a tertiary care center in Chiang Mai.

Methods: A retrospective observational cohort study was conducted on patients with non-small cell lung cancer at all stages, receiving treatment at Chiang Mai University Hospital (Maharaj Nakorn Chiang Mai Hospital) from January 2012 to December 2016. Using a generalized linear model with Poisson distribution, we analyzed the association between PM levels and daily non-accidental mortality, adjusting for other pollutants (SO2, NO2, CO, and O3), as well as temperature, humidity, and wind speed.

Results: The annual average PM2.5 concentration in Chiang Mai was 32.7 µg/m3 . After adjusting for confounding variables, including other pollutants and meteorological factors, we found that every 10 µg/m3 increase in both PM2.5 and PM10 was significantly associated with an increased likelihood of mortality among patients with lung cancer (lag 0 month adjusted incidence rate ratio (IRR) for PM2.5: 1.175; 95% CI: 1.093 - 1.263; lag 3 months IRR for PM2.5: 1.079; 95% CI: 1.005 - 1.158; lag 0 month IRR for PM10: 1.125; 95% CI: 1.067 - 1.185; lag 3 months IRR for PM10: 1.063; 95% CI: 1.010 - 1.119). Mortality rates were higher in Mae Hong Son province, among patients with large cell histology and stage IIIA lung cancer. Additionally, higher PM2.5 levels were associated with lower humidity and higher atmospheric pressure.

Conclusions: PM10 and PM2.5 are associated with monthly mortality among patients with lung cancer, with a lag time of three months. Policymakers should implement measures to reduce PM exposure in high-risk areas, and healthcare providers should closely monitor patients, extending follow-up beyond a few days to three months.

Keywords: PM 2.5, Lung cancer mortality, Northern Thailand

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.31 Physical Characterization of PM2.5 - Effects on Cellular Uptake, Dispersion, and Lung Cell Interactions

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Introduction: Environmental pollutants resulting from urban expansion, climate change, and forest fires produce airborne particles that are associated with increased rates of cardiorespiratory diseases. Particulate matter smaller than 2.5 microns (PM2.5) can penetrate deep into the lungs, where it may damage the alveolar epithelium (AE). These particles possess a chemical profile that is unique to their source—e.g., urban pollution, forest fires, or industrial emissions. The chemicals associated with PM2.5 are likely delivered to the AE, eliciting an inflammatory response. However, the physical properties of these particles—such as size, morphology, and aggregation—can independently induce cellular damage. Understanding the physical characteristics of PM2.5 prior to in vitro exposure experiments is essential for determining how factors such as solvent, concentration, and processing methods influence its properties and subsequent cellular interactions. Given the established link between PM2.5 and lung cancer, investigating these physical interactions is fundamental for understanding its broader implications for lung health.

Methods: To characterize the physical properties of commercially sourced urban PM2.5 (NIST 2786), scanning electron microscopy (SEM) was used to examine particle shape and surface features. Dynamic light scattering (DLS) was employed to assess particle size distribution and aggregation as a function of concentration (µg/mL) following sonication and dilution in different solvents. Human bronchial epithelial cells (HBECs; ATCC CRL-4051) were exposed to 10 µg/mL of PM2.5 for 24 hours in 2D culture. SEM was used to observe particle-cell interactions, while transmission electron microscopy (TEM) was employed to examine intracellular localization of the particles.

Results: SEM imaging revealed that PM2.5 exhibits irregular shapes, porous surfaces, and a size range extending from 2.5 µm to the nanoscale. This porosity increases the surface area, potentially providing additional binding sites for toxic chemicals. DLS analysis demonstrated that both solvent type and particle concentration influence aggregation behaviour. Solvents such as ethanol and water promoted increased aggregation, whereas PBS and DMSO facilitated better dispersion. Higher particle concentrations reduced the effectiveness of sonication, suggesting that lower concentrations yield more consistent and physiologically representative particle distributions. SEM images of HBECs exposed to PM2.5 showed cell surface protrusions extending toward the particles, indicating an active uptake mechanism. TEM confirmed internalization of PM2.5, with particles localized within membrane-bound vesicles. These findings suggest that PM2.5 is internalized by HBECs, potentially enabling the intracellular delivery of associated toxic compounds.

Conclusions: This study highlights the complex interactions between PM2.5 and lung epithelial cells, demonstrating that physical properties such as irregular morphology and porosity may enhance their capacity to adsorb and deliver harmful chemicals. Characterizing particle aggregation and dispersion is critical for accurately modelling physiological exposure conditions. These findings provide evidence that PM2.5 is internalized by HBECs, supporting the hypothesis that such particles serve as vectors for cellular uptake of toxic compounds. Understanding these interactions is essential for elucidating the role of environmental pollutants like PM2.5 in lung carcinogenesis.

AI tools were utilized.

Keywords: PM2.5 characterization, Alveolar epithelium interactions, Cellular toxicity

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.32 Association of Long-Term Exposure to Fine Particulate Matter, Ozone, and Greenness With Lung Cancer Risk

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Introduction: Considering the increasing incidence of lung cancer in never smokers, research is needed on the risk of lung cancer due to exposure to air pollution. We investigate the association between lung cancer incidence and long-term exposure to air pollution including particulate matter less than 2.5 µm or less in diameter (PM2.5), ozone (O3) and normalized difference vegetation index (NDVI), widely used metric for quantifying the health and density for vegetation representing greenness.

Methods: This is a population-based case-control study using covering 7,155 lung cancer patients and 28,620 controls selected from National Sample Cohort-National Health Insurance Service in Korea from 2002 to 2019, matched by propensity score at 1:4 ratios with age, sex, and enrollment year. Individual-level long-term exposure to PM2.5, O3 and NDVI was assessed based on region of residence. Kaplan-Meier analysis and the log-rank test were used to examine the statistical significance of differences in lung cancer incidence according to the distribution of air pollution and green space. The Cox proportional hazards model estimates the effects of air pollution and green space on lung cancer risk by adjusting for available confounding factors such as age, gender, smoking status, household income, residential area, body mass index, and Charlson Comorbidity index. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were calculated for lung cancer risk.

Results: The lung cancer group showed lower body mass index, higher rural residence, higher pack-years of smoking, and higher Charlson comorbidity index. The Kaplan-Meier analysis of lung cancer incidence rates according to air pollution and green space levels showed that the cumulative incidence of lung cancer was higher when O3 was high and NDVI was low ($p < 0.001$, $p < 0.001$, respectively). The level of exposure to air pollution was analyzed by dividing it into tertiles. PM2.5 showed an increase in the lung cancer risk in the 3rd tertile (aHR =1.064; 95% CI =1.006-1.127); O3 showed an increase in the lung cancer risk regardless of tertile (aHR=1.421; 95% CI= 1.342-1.503), NDVI showed a significant protective effect in the 3rd tertile (aHR=0.709; 95% CI = 0.658-0.764). Subgroup analysis according to sex and smoking status showed that PM2.5 had a risk effect especially in never-smoker males, O3 had a significant lung cancer risk in males and never-smoker females, and NDVI showed a protective effect against lung cancer regardless of sex and smoking status.

Conclusions: This study provides evidence that PM2.5, O3, and greenness influence lung cancer development.

Keywords: lung cancer, PM2.5, ozone

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.33 Global Trends in Tracheal, Bronchus, Lung Cancer Burden From Household Air Pollution

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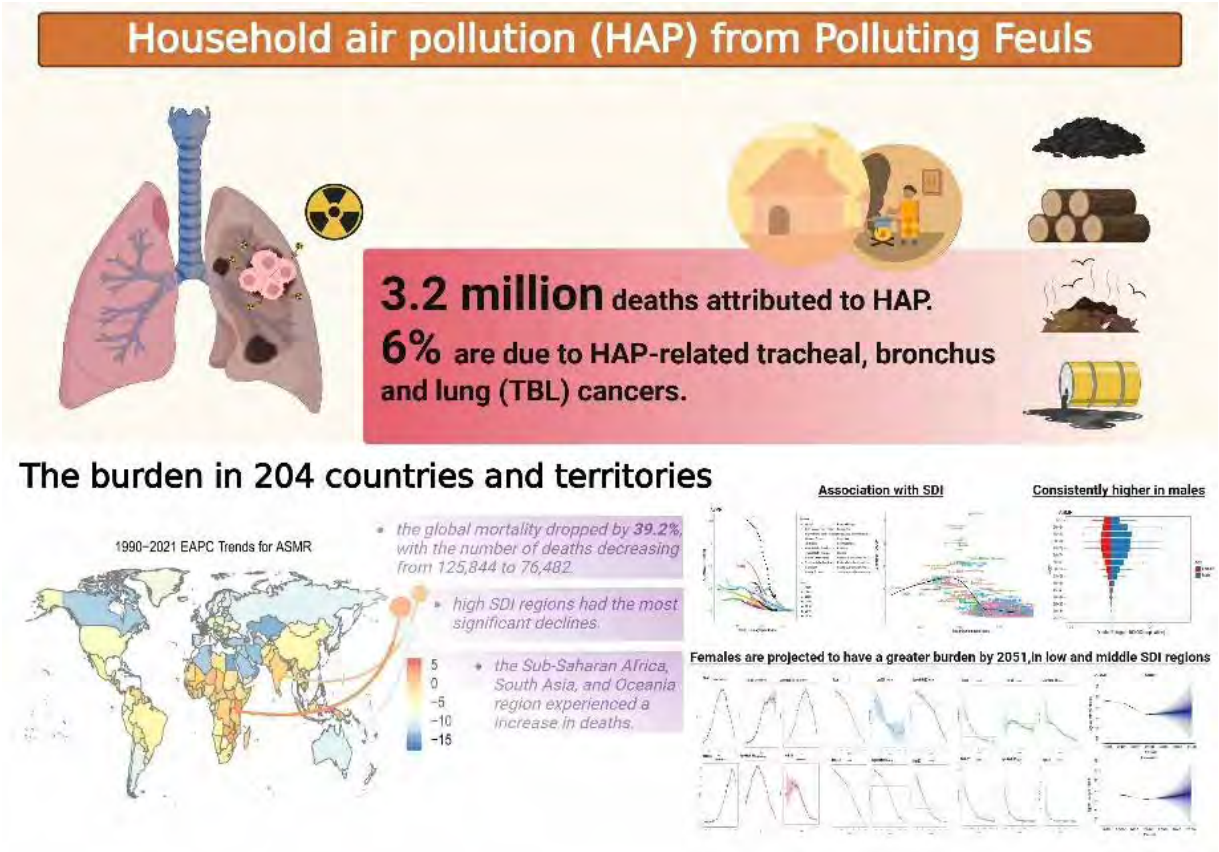
Introduction: Tracheal, bronchial, and lung (TBL) cancers, largely attributable to household air pollution (HAP), remain a critical public health challenge, particularly in low- and middle-income countries. Using data from the Global Burden of Disease 2021 (GBD), this study evaluates global trends in HAP-related TBL cancer burden from 1990 to 2021 and projects future trends to 2051.

Methods: The study extracted data on deaths and disability-adjusted life years (DALYs) from the GBD 2021 and assessed the burden of TBL cancer attributable to HAP by sex, age, region, and socio-demographic index (SDI). The age-period-cohort (APC) model was used to examine the independent effects of age, period, and cohort on the burden of TBL cancer attributable to HAP. The Bayesian age-period-cohort (BAPC) model was applied to predict future trends in the burden of TBL cancer attributable to HAP over the next 30 years.

Results: From 1990 to 2021, the global burden of TBL cancer due to HAP for deaths and DALYs cases decreased by 39.2% and 44.1%, respectively, with the steepest declines in high SDI regions. Conversely, mortality and DALYs rates rose in Oceania and sub-Saharan Africa. The global age-standardized mortality rate (ASMR) peaked in the 85-89 age group, and the age-standardized disability rate (ASDR) peaked in the 70-74 age group. Males experienced a higher burden than females, with significant differences observed across SDI regions. Projections suggest that mortality and DALYs rates will rise over the next 30 years, with a higher burden forecast for females.

Conclusions: Despite significant reductions in the global burden of TBL cancer from HAP, the disease remains a major issue in low SDI regions, particularly in China. Projections for the next 30 years indicate increasing mortality and DALYs rates, with a disproportionate impact on women. These findings highlight the urgent need for targeted policies to reduce HAP exposure, especially in low SDI regions.



Keywords: Household air pollution, tracheal, bronchial, and lung cancer, Global Burden of Disease 2021

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.34 Associating Pollution-Related Anthracotic Pigments Within Normal Lung Tissue With Lung Cancer Characteristics

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Introduction: Worldwide, particulate matter (PM) pollution with an aerodynamic diameter of less than 2.5 µm (PM2.5) is the second most common cause of lung cancer after tobacco smoking. Thus, there is an urgent need to understand the adverse effects of air pollution on lung cancer development. While pollution-associated anthracotic pigment (black carbon deposits) can be seen in hematoxylin and eosin (H&E) slides of background lung tissue from tumor resections and heavy anthracosis has been associated with clonal expansions of cells harbouring oncogenic mutations, microscopic anthracotic pigment is not commonly used for pollution exposure estimates because there is currently no standard quantitative measure of anthracosis.

Methods: We developed an automated pixel classifier method using QuPath to quantify anthracotic pigment. Our method involves two pixel classifiers in which one is optimized to detect dark-coloured regions, and the other is optimized to detect H & E negative regions. Applying these classifiers in succession allows the anthracotic regions to be isolated and quantified as a proportion of the total tissue area.

Results: In 64 H&E whole slide images of normal lung tissue from never-smoker lung cancer patients, we observed a significant correlation between the quantity of anthracosis (Figure 1) and 3-year PM2.5 exposure estimated based on patient addresses in three years prior to diagnosis ($R = 0.28$, $p < 0.05$). Notably, 20-year PM2.5exposure, EGFR mutation status, and histologic growth were not significantly associated with the degree of anthracosis.

Conclusions: Our data indicate that our automated quantification of anthracotic pigment on H&E slides may be representative of geographically estimated recent PM2.5 exposures. Importantly, our method can be used in large scale studies to relate anthracotic pigment to clinical and molecular correlates in lung cancer patients, to further our understanding of how air pollution promotes lung cancer development. Expansion of our study to an additional 95 cases and correlations with genomic, transcriptomic, and methylation profiling data are in progress.

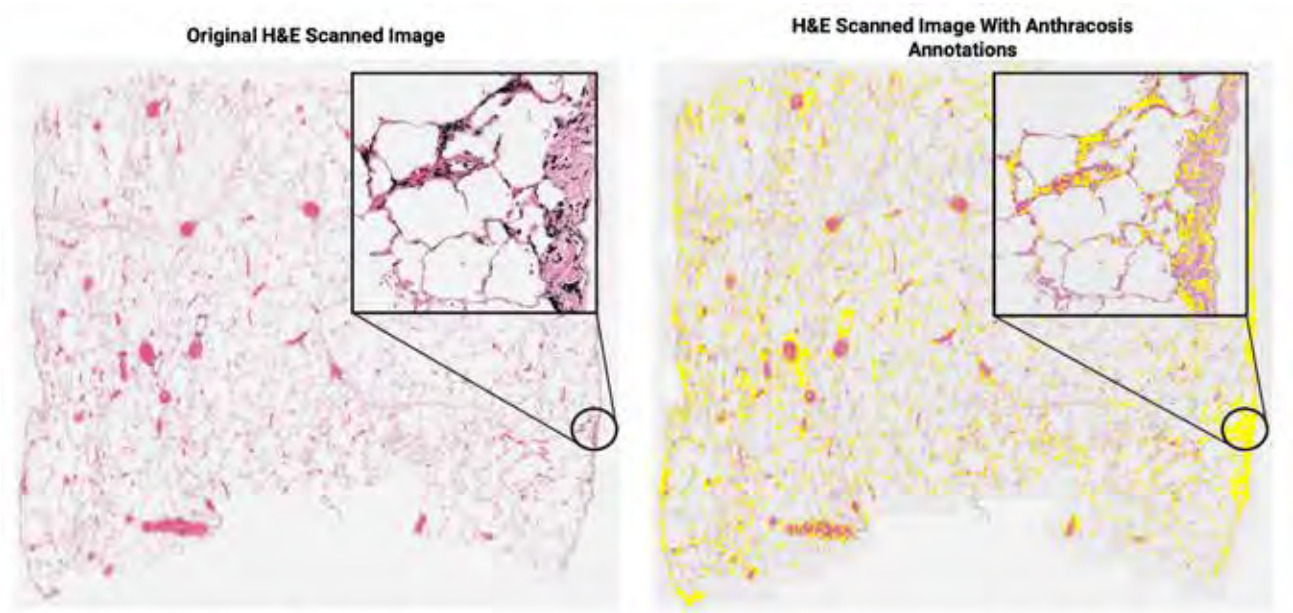

Figure 1: Before and after application of the anthracosis quantification method. The yellow overlay indicates anthracotic pigment as identified by our method. Relative to total tissue area, anthracotic pigment comprised 0.31% of this tissue.

Keywords: Anthracosis, Air pollution, Normal lung tissue

P3.01.35 Air Pollution and Lung Cancer Risk by Smoking Status: Findings From the Uk Biobank

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Introduction: Lung cancer (LC) is one of the most diagnosed cancers and remains the leading cause of cancer-related deaths worldwide. While smoking is the primary risk factor, 15-20% of LC cases globally—and up to 50% in certain Asian countries—occur in people who have never smoked (PNS). Air pollution has been identified as a major risk factor in this population. However, many previous studies have focused on regions with severe pollution or relied on outdated environmental data that may not reflect current exposure levels. This study aims to address these gaps by examining the relationship between air pollution and LC in both people who smoked (PS) and PNS using data from the UK Biobank, a recent, large-scale population-based prospective cohort study from the UK, where pollution levels are comparatively lower.

Methods: The UK Biobank includes sociodemographic, behavioral, environmental, family history, self-reported medical history, linked hospital records, and cancer registry data from over 480,000 participants without a history of lung cancer or any cancer diagnosis within five years prior to enrollment. Residential concentrations of particulate matter—specifically fine particles (PM ≤2.5 µm/m3)—and nitrogen dioxide (NO2) at baseline were estimated using land-use regression models. The association between these air pollutants and incident lung cancer was assessed using Cox proportional hazards models. Covariates were selected based on the disjunctive cause criterion and included age, sex, education, income, second-hand smoke exposure, glycated hemoglobin (HbA1c), family history of lung cancer, personal history of cancer, history of chronic obstructive pulmonary disease, history of tuberculosis, presence of long-term illness, body fat percentage, and physical activity.

Results: The mean annual concentrations of PM2.5 were 10.1 µg/m^3 and 9.9 µg/m^3 in PS and PNS, respectively (Figure 1). During the 6-year follow-up period, 1,583 and 239 incident LC cases among PS and PNS were identified, corresponding to absolute risks of 0.72% and 0.09%, respectively. Among PS, associations were observed between LC risk and both natural log-transformed PM2.5 (HR = 4.49; 95% CI: 1.70-11.8) and log-NO_2 (HR = 1.52; 95% CI: 1.08-2.16). In contrast, no associations were found in PNS for log- PM2.5 (HR = 1.26; 95% CI: 0.19-8.20) or log-NO_2 (HR = 1.07; 95% CI: 0.57-2.00).

Conclusions: In a region with comparatively low pollution, our findings suggest that air pollution is associated with an increased risk of lung cancer among people who smoked, but not among people who have never smoked.

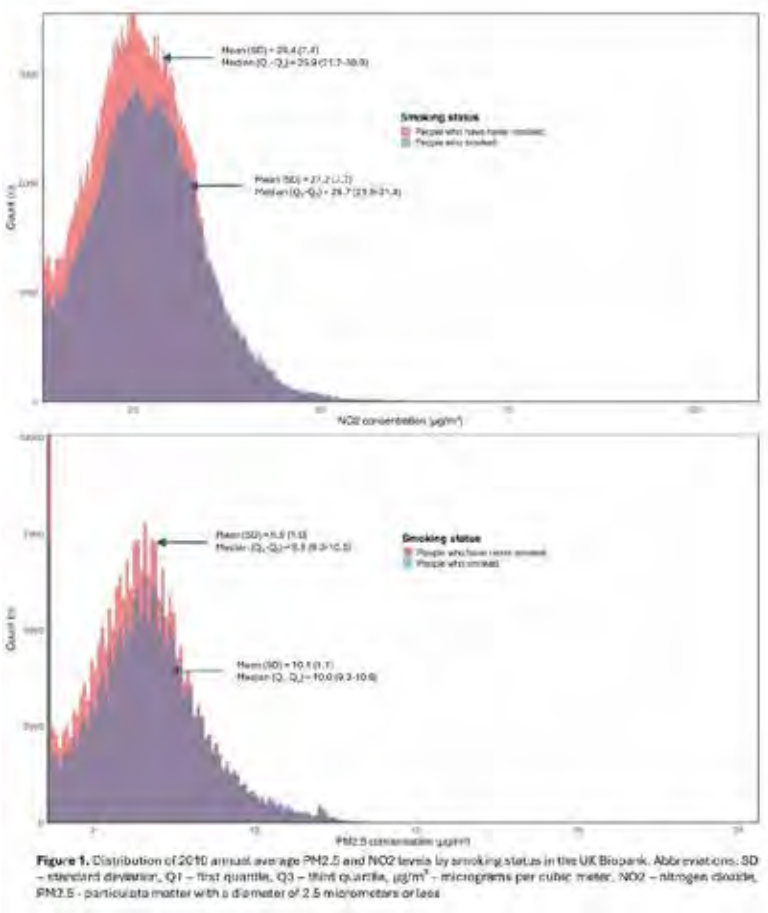

Figure 1. Distribution of 2010 annual average PM2.5 and NO2 levels by smoking status in the UK Biobank. Abbreviations: SD – standard deviation, Q1 – first quartile, Q3 – third quartile, µg/m^3 - micrograms per cubic meter, NO2 – nitrogen dioxide, PM2.5 - particulate matter with a diameter of 2.5 micrometers or less

Keywords: lung cancer, air pollution, smoking status

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.36 Feasibility of Implementing a Virtual Nursing-Led Smoking Cessation Clinic for Patients With Cancer

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Introduction: Continuing to smoke after a diagnosis of cancer can worsen both cancer and treatment-related outcomes. Despite the importance of smoking cessation in cancer care, patients often find it challenging to quit smoking. Moreover, many patients interested in quitting may not be provided with adequate support or opportunities to be connected to smoking cessation resources. Given the advances in virtual care, we piloted a virtual nursing-led smoking cessation clinic to follow up with cancer survivors who were identified using tobacco at their initial clinic visit but were never offered or initially declined referral to cessation support.

Methods: A virtual nursing-led clinic was piloted from November 2023 to May 2024 at the Princess Margaret Cancer Centre (Toronto, Canada). The clinic was operated by a trained oncology nurse for one half day per week. The nurse received training in motivational interviewing, providing support towards cessation, and assessing and referring patients. Using the electronic health record system, EPIC, monthly reports were generated of new patients diagnosed with cancer who reported smoking within 6 months of their initial visit but were either not offered referrals to smoking cessation support or initially declined a referral. Patients were called weekly up to four times through the clinic until successfully contacted. Descriptive statistics were used to characterize the feasibility outcomes.

Results: From November 2023 to May 2024, a total of 191 patients were eligible for contact by our virtual clinic. Among the eligible patients, the median age was 64 years old (range: 26 to 94 years) and 63% were male. The most common disease sites were head and neck (16%), gastrointestinal (15%), hematological (15%), and lung (10%). A total of 339 calls were conducted and an average of 1.4 calls (range: 1 to 4) were needed to successfully reach a patient. A total of 22 clinics were conducted, where an average of 22 calls were made per clinic. Most patients (73%) reached after one call, while 13% required two calls, and 15% required three or more calls. Among the patients reached (n = 196), the average duration per call was 3.6 minutes (range: 1 to 15 minutes). Among patients contacted, 14% accepted a referral for smoking cessation support, while among those who declined, 36% had already quit prior to receiving a phone call. For patients accepting a referral, call durations were slightly longer (5.5 minutes vs. 2.7 minutes, $p < 0.001$). Common patient reported barriers to accepting a referral included a lack of readiness to quit, stress and exposure to second-hand smoke.

Conclusions: A virtual nurse-led smoking cessation clinic is feasible to help provide referrals to supporting smoking cessation among patients with cancer who initially declined support or have never been offered support. Many patients declining referral to support had already quit smoking, while other barriers include stress, exposure to second-hand smoke, and readiness to quit. Strategies to minimize and reduce these barriers should be further explored.

Keywords: Smoking Cessation, Virtual Care, Nursing

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.37 Time-Dependent Analysis Reveals the Dual Role of Smoking in Non-Small Cell Lung Cancer Immunotherapy

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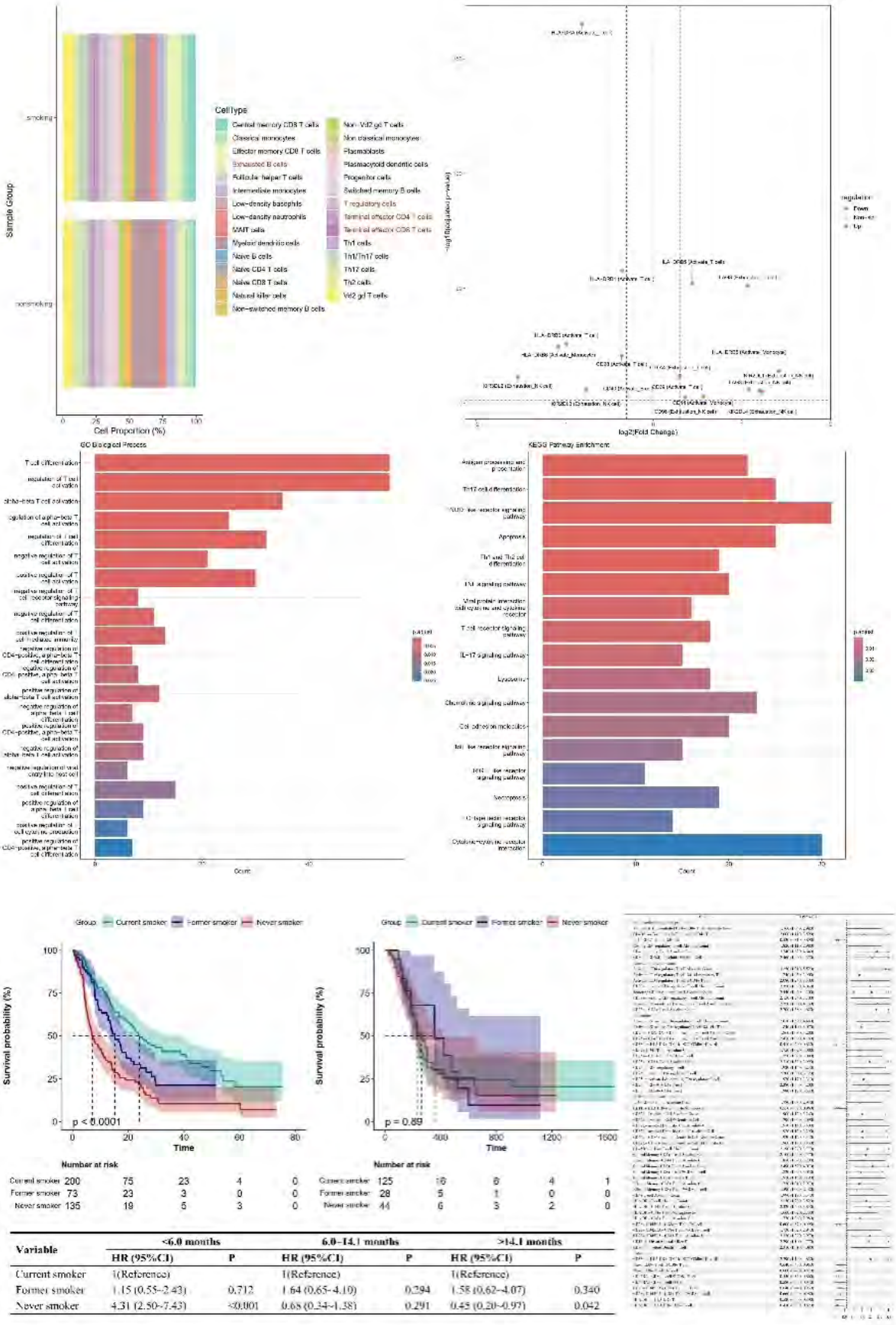
Introduction: Smoking history is a risk factor for lung cancer, but its role in immunotherapy remains unclear. This study investigates the impact of smoking on lung cancer immunotherapy and its effects on immune cells. This study was previously presented at ACLC 2024. The current update incorporates clinical data from SCLC patients, along with Mendelian randomization (MR) and single-cell analyses to validate findings.

Methods: This study enrolled patients from Guangdong Provincial People's Hospital, who were stratified by pathological type into SCLC and NSCLC groups. Kaplan-Meier analysis were used to access the impact of smoking history on immunotherapy efficacy. Time-dependent cox regression using a time-stratified method was used when the Schoenfeld residuals test failed. MR and single-cell analyses were employed to investigate the impact of smoking on immune cells.

Results: Kaplan-Meier analysis suggested smoking might be a protective prognostic factor in NSCLC, but this effect was not observed in SCLC. Further analysis of NSCLC employed time-stratified Cox regression due to violation of proportional hazards assumption. In patients with PFS less than 6.0 months, never smokers had shorter PFS (HR: 4.31; 95%CI: 2.50~7.43). In patients with PFS beyond 14.1 months, never smokers showed longer PFS (HR: 0.45; 95%CI: 0.20~0.97). Both MR and single-cell analyses revealed that smoking history simultaneously increased both activated and exhausted/tolerant immune cell populations. Similarly, both pro-tumor and anti-tumor immune cell populations were significantly increased.

Conclusions: This study demonstrates that smoking history exerts dual effects on NSCLC immunotherapy. Single-cell and MR analyses suggest this temporal dynamic may stem from concurrent increases in activated, exhausted, and tolerant immune cell populations. Specifically, the initial therapeutic advantage likely results from predominant immune activation, while progressive treatment resistance correlates with accelerated immune exhaustion and tolerance development in smokers. Smoking cessation may represent a viable strategy to improve long-term immunotherapy outcomes in NSCLC.



Variable	<6.0 months		6.0–14.1 months		>14.1 months	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Current smoker	1(Reference)		1(Reference)		1(Reference)	
Former smoker	1.15 (0.55~2.43)	0.712	1.64 (0.65~4.10)	0.294	1.58 (0.62~4.07)	0.340
Never smoker	4.31 (2.50~7.43)	<0.001	0.68 (0.34~1.38)	0.291	0.45 (0.20~0.97)	0.042

Keywords: NSCLC, Smoking, Immunotherapy

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.38 Effect of Smoking Cessation Duration on Lung Cancer Incidence: A Nationwide Retrospective Cohort Study in Korea

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Introduction: It is well-known that smoking cessation can mitigate lung cancer risk in smokers compared with those who continue smoking. Nevertheless, the extent to which smoking cessation duration mitigates lung cancer risk remains unclear. In this study, we aimed to analyze the association between smoking cessation duration and the reduction in lung cancer incidence using large-scale health insurance data from South Korea.

Methods: In this retrospective cohort study, we utilized the cohort from the Korea National Health Insurance Corporation. Approximately 50% of the adults aged ≥50 years who underwent health examinations in 2009-2013 were randomly sampled. The index date was defined as the last health examination date between 2009 and 2013. The midpoint of the interval between the date of the examination where they reported quitting and the date of the preceding examination was used to estimate the quit date. The participants were classified into three groups: never-smokers, former smokers, and current smokers, and the incidence rates of lung cancer were compared among these groups.

Results: We analyzed 165,512 individuals selected through propensity score matching (82,756 never-smokers, 41,378 former smokers, and 41,378 current smokers). (Figure 1) Lung cancer risk significantly decreased after two years of smoking cessation (2-3 years after cessation: hazard ratio 0.760, p<0.001) but remained higher than that of never-smokers for up to 10 years. (Figure 2) Subgroup analyses revealed similar tendencies among males, whereas no consistent patterns were observed among females. Light smokers (<20 pack-years) reached lung cancer risk levels comparable to never-smokers after seven years of cessation, whereas heavy smokers (≥20 pack-years) required nine years to reach such levels.

Conclusions: This nationwide cohort study highlights the significant impact of smoking cessation duration on lung cancer risk, emphasizing the substantial benefits of even short-term cessation regardless of prior smoking history.

Figure 1. Flowchart of the study participant inclusion process

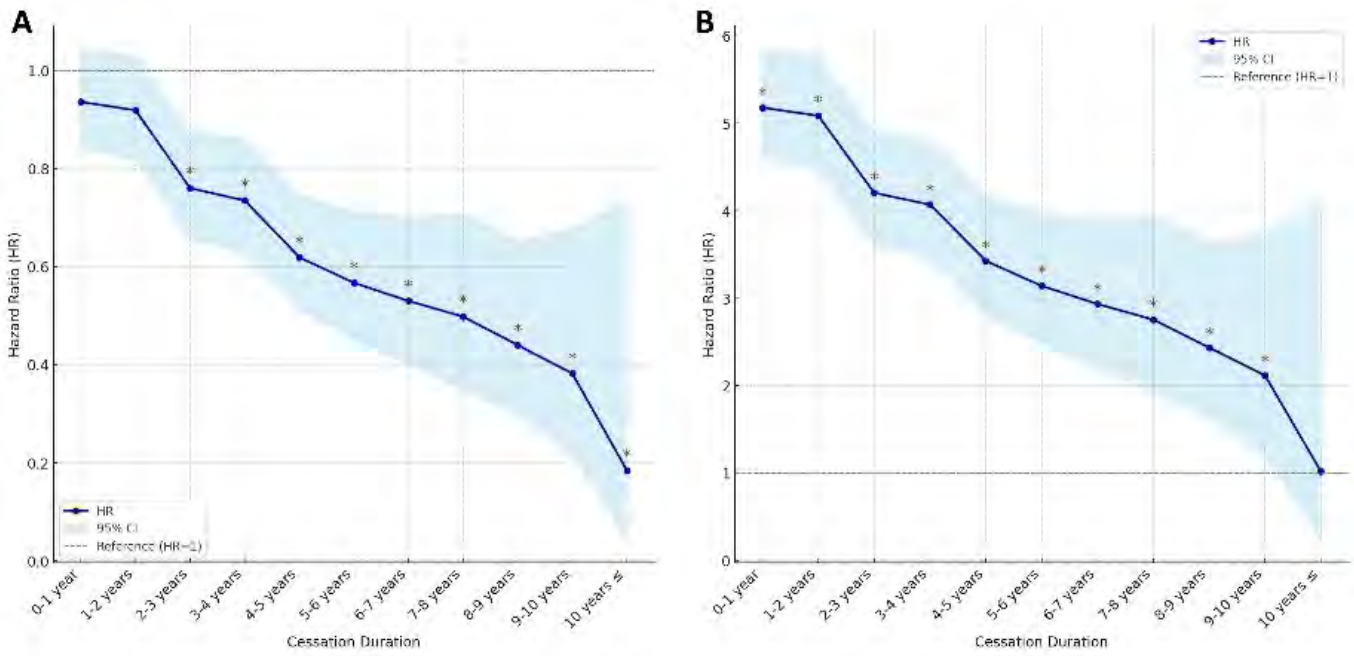

Figure 2. Hazard ratio of lung cancer incidence according to smoking cessation duration. (A) Former smoker versus current smoker (reference). (B) Former smoker against never-smoker (reference). *p < 0.05

Keywords: Lung cancer incidence, Smoking cessation, Health insurance data

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.39 From Nodule-Free to Nodule-Positive: Blood Biomarkers Bridge Smoking and Lung Cancer Risk

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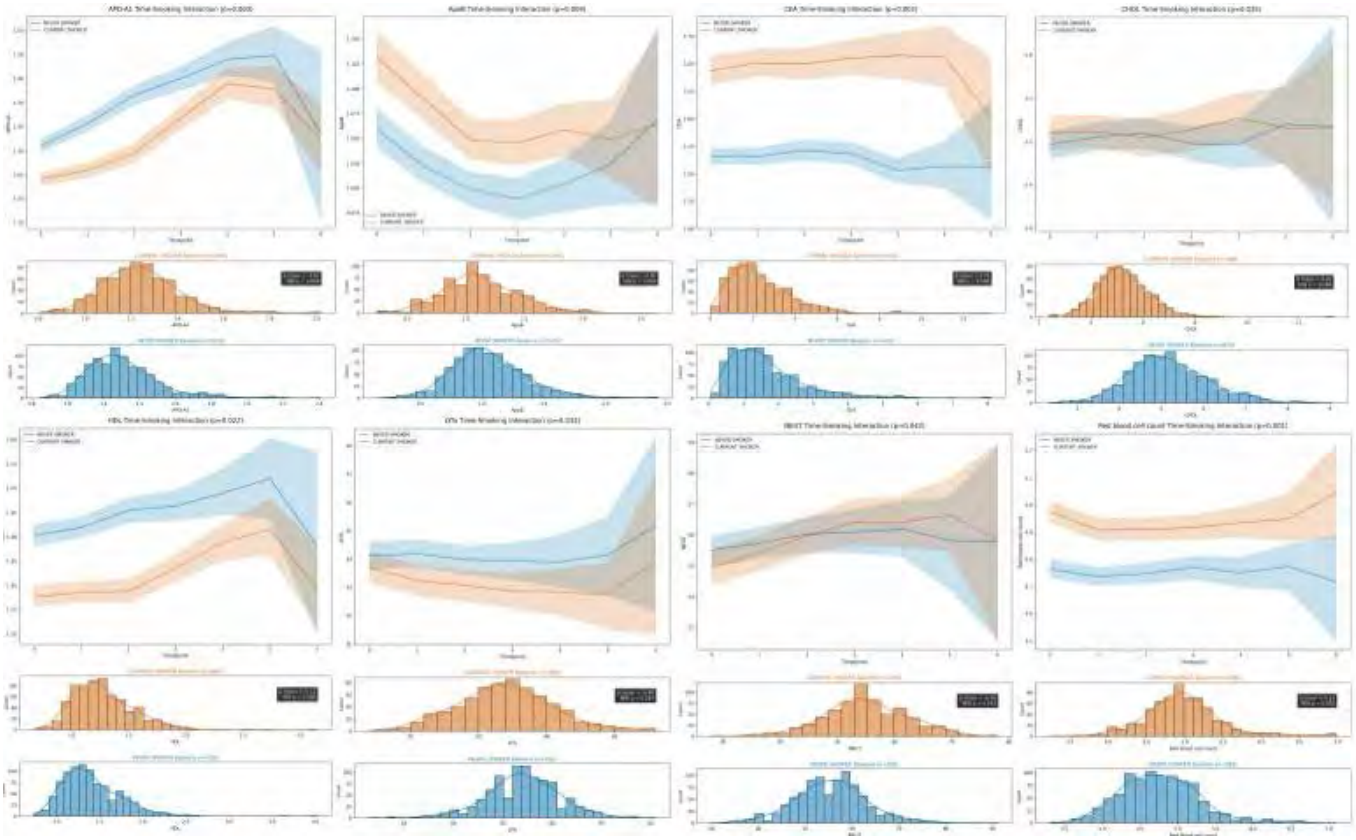
Introduction: While smoking is a recognized risk factor for lung cancer, the biological pathways linking smoking to early-stage pulmonary nodule progression remain unclear. This study explored the mediating role of blood biomarkers in smoking-associated lung cancer development among individuals with pulmonary nodules.

Methods: We retrospectively analyzed a cohort of 1,586 individuals who underwent routine low-dose CT and blood tests from 2017 to 2024. All participants had no detectable lung nodules in 2017 but developed nodules ≥6 mm by 2024. Dynamic measurements of 40 blood biomarkers were extracted from multiple follow-up timepoints. We first applied linear mixed-effect models to assess whether smoking status modified the temporal trajectories of blood markers. Subsequently, both univariate and joint mediation analyses were conducted to evaluate whether these biomarkers mediated the effect of smoking on lung cancer diagnosis, using multiple imputation and bootstrap procedures. Four extraction strategies for mediators (initial value, latest value, peak value, mean value) were compared. A structural equation model (SEM) and PCA-based clustering were used to visualize and stratify mechanism subtypes.

Results: Linear mixed-effects models showed that smokers exhibited significantly steeper increases in biomarkers compared to non-smokers, including CEA (0.035 ng/mL/year vs. 0.012 ng/mL/year, p = 0.001) and RBC (0.14×10^9/L/year vs. a slight decline, p = 0.002). LY% declined faster in smokers (p = 0.022), indicating impaired immunity. Similar trends were observed for NEUT, CHOL, TG, and ApoB, suggesting smoking-related immunometabolism alterations. However, per-patient slope mediation analyses showed no significant indirect effects. Cross-sectional mediation modeling identified significant average causal mediation effects (ACME) for RBC (ACME = 0.0055, p = 0.024), MCV, MONO%, AST, NA1-IgA, and UBG (p < 0.05 for all), with mediation proportions ranging from 10.6% to 50.1%. SEM revealed parallel indirect pathways, indicating a multifactorial mechanism. Unsupervised clustering based on biomarker principal components identified three subtypes with distinct lung cancer risks: Cluster 1 (9.8%), Cluster 2 (2.1%, p < 0.01). Cluster 1 had a higher risk (OR = 1.87, 95% CI: 0.90-3.59), while Cluster 2 had a lower risk (OR = 0.79, 95% CI: 0.43-1.38), reflecting divergent immunometabolism profiles among smokers.

Conclusions: Smoking accelerates immunometabolism alterations during pulmonary nodule evolution, with select blood biomarkers (e.g., CEA, MCV, MONO%) mediating its oncogenic impact. Integrative modeling identified a high-risk biological subtype with a nearly fivefold increase in lung cancer risk, supporting biomarker-driven stratification in smokers with indeterminate nodules.



Keywords: Smoking, Pulmonary nodules, Blood biomarkers

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.40 10 Years Post Implementation of a Smoking Cessation (SC) Program in Regional Cancer Centres in Ontario, Canada:Successes and Ongoing Challenges

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Introduction: In 2012, Cancer Care Ontario began screening for the smoking status of new ambulatory cancer patients in Ontario's 14 regional cancer centers (RCCs). Individuals who had smoked in the past 6 months were to be advised of the health benefits of (SC) and current tobacco users were offered referral to SC services (SCS). RCCs were required to appoint a Regional SC champion and in 2015, to begin submitting data on the proportion of new ambulatory cancer patients screened for tobacco use, advised on the benefits of quitting, and referred to comprehensive SC support services. In 2018, RCCs were encouraged to implement an opt-out approach when utilizing the 3As (Ask, Advise, Act) brief SC intervention model. The provincial program supported RCCs with data management, a clinical leader who provided educational sessions at RCCs on the value of SC; e-learning modules for providers and patients; posters/pamphlets on the benefits of quitting for patients and other ongoing resources. Although the volume of new ambulatory patients per center varies widely (130 to 1,000 per month), each center receives the same amount of central funding support for SCS.

Methods: The individual RCC SC program performance metrics are reviewed quarterly with the regional champions and during an annual in-depth discussion of successes and challenges with provincial and regional leadership. Trends since the beginning of data capture in 2015 and results from the Q2 2024/25 review are presented against targets and access to SCS.

Results: Since 2015, the performance metrics for screening, advising and referring current tobacco users to SC services have shown steady improvement, except during Covid 19. However, the performance by RCC has shown considerable variability across the 14 centers. In Q2 of 2024/25, the provincial rate (PR) for screening for tobacco use was 63.5%, range 40.4-96.0%; six centers exceeded the provincial target of 75%. Greater variability existed in advising (PR 68.1%, range 0-91%) and referring patients to cessation services (PR 69.7%, range 13.8.-98.3%). Five RCCs have dedicated on-site quit coaches, 10 RCCs have internal referral options (e.g., STOP program, hospital pharmacists, on-site group sessions) and all centers can refer to a quit line (Health811). Three centers use survey questions at electronic kiosks to ask about tobacco use, quit attempts and cessation aids alongside regular symptom management screening tools. Inconsistencies in the SCS offerings across RCCs and limited adoption of the tobacco use survey hamper the program's ability to evaluate the effectiveness of the SCS interventions in helping cancer patients quit. Challenges to uniform implementation include size of cancer center, population demographics, extent of funding and human resources for internal SCS supports, variable SC offerings, different EMRs and/or recent implementation of new IT systems (EPIC, Cerner, Mosaiq, Aria), and variable access to free NRT. The introduction of virtual visits during the Covid 19 pandemic contributed to a reduction in all metrics.

Conclusions: Best performance was seen in RCCs with committed leadership, HCP role descriptions that included responsibility to discuss SC with patients, funding appropriate for patient volumes, access to free NRT and on-site counselling.

Keywords: smoking cessation, performance metrics, regional programs

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.41 Impact of Smoking Status on Survival and Radiation Toxicity in Lung Cancer Patients Receiving RT

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Introduction: Although smoking is widely recognized as a leading cause of lung cancer, its direct impact on radiotherapy outcomes—particularly regarding survival and treatment-related toxicity—remains insufficiently understood. This study aims to clarify the relationship between smoking status, radiation-induced pulmonary toxicity, and survival outcomes in lung cancer patients undergoing radiotherapy, with the goal of informing more personalized and effective treatment strategies.

Methods: A retrospective review was conducted on 207 lung cancer patients treated with radiotherapy from 2020 to 2024. Patients were categorized based on smoking status: active smokers (11%), ex-smokers (50%), and non-smokers (39%). Radiotherapy was delivered with either curative or palliative intent. Key dosimetric variables included lung volumes receiving at least 5% (V5%) and 20% (V20%) of the prescribed dose, along with mean lung dose (MLD). Primary endpoints were overall survival (OS) and incidence of Grade ≥2 radiation pneumonitis. OS was analyzed using Kaplan-Meier estimates and Cox proportional hazards models; toxicity data were assessed using chi-square tests.

Results: Active smokers had significantly worse OS compared to non-smokers (median OS: 12 vs. 20 months, p=0.004). Ex-smokers showed intermediate survival outcomes, suggesting ongoing effects of past tobacco exposure, with 2-year OS ranging from 68.1% to 78.9%. Grade ≥2 radiation pneumonitis was more prevalent among active smokers (22%) than non-smokers (12%, p=0.03), and they also experienced higher rates of pulmonary fibrosis. Dosimetric analysis revealed significantly elevated V20% values in smokers, indicating greater exposure of lung tissue to harmful radiation levels. No significant differences were observed in MLD or V5% between groups. These findings highlight the dual negative impact of active smoking on both survival and radiotherapy-induced toxicity.

Conclusions: Active smoking is associated with significantly reduced survival and increased pulmonary toxicity in lung cancer patients receiving radiotherapy. Higher V20% values among smokers may partially explain the increased incidence of radiation-induced lung injury. These results underscore the importance of integrating smoking cessation programs into oncologic care and the potential value of personalized, adaptive radiotherapy planning for patients who smoke. Future research should explore the underlying biological mechanisms—such as tumor hypoxia and inflammation—that may mediate these effects, aiming to further refine treatment approaches for this high-risk population.

Keywords: Smoking Status, Radiotherapy, Radiation-Induced Toxicity

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.42 Transitions in Cigarette and E-Cigarette Use in the PATH Study: A Multistate Transition Model Analysis of Us Adults by Race and Ethnicity

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[1]BC Cancer Research Institute, Vancouver/BC/CA ,[2]University of British Columbia, Vancouver/BC/CA ,[3]University of Michigan, Ann Arbor/MI/USA

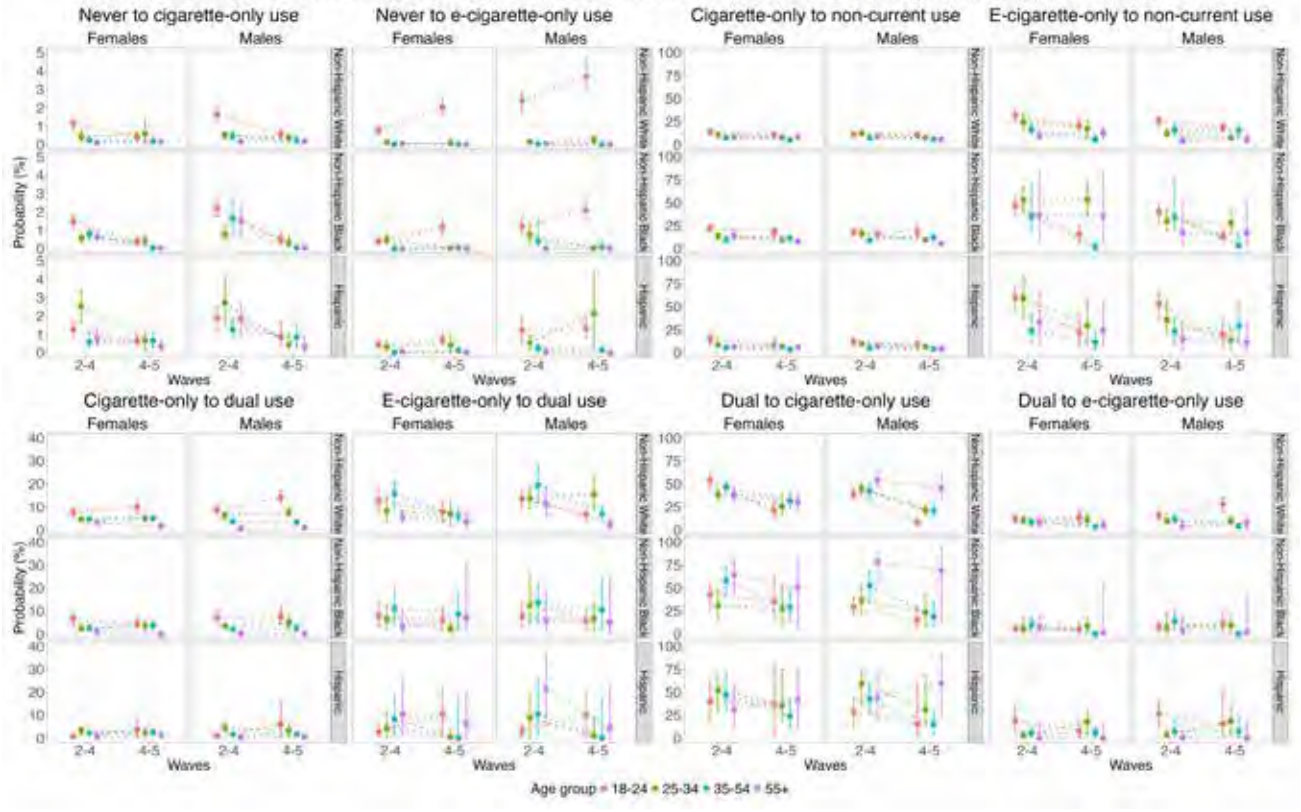
Introduction: While e-cigarette use has increased in US adults, cigarette smoking has reached historical lows, particularly in younger adults. However, use patterns and trends vary considerably by race and ethnicity.

Methods: We used a Markov multi-state transition model to estimate probabilities of exclusive and dual cigarette and e-cigarette use initiation, cessation, and switching between these products using data from the Population Assessment of Tobacco and Health Study (PATH). We calculated transition probabilities (%) for two, two-year PATH wave-periods (Wave 2-4 [2015-17] and Wave 4-5 [2017-19]) by sex (Males/Females), age (18-24, 25-34, 35-54, 55+ years), and race/ethnicity (Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic).

Results: Cigarette initiation probabilities decreased between the two periods across all racial/ethnic and age groups, with the largest declines observed among NHB and NHW individuals and smaller declines among Hispanic adults. E-cigarette initiation had the opposite pattern, with the greatest increases in NHW adults ages 18-24, with initiation rising from 2.4% to 3.7% for males and from 0.8% to 2.0% for females. Cigarette cessation probabilities decreased for all groups, with the most significant decline in NHB males aged 55+ (from 15.5% to 5.3%). E-cigarette cessation decreased in most groups, with the largest declines in the NHB individuals aged 18-24 or 35-54. The probability of transitioning from cigarette-only to dual-use remained approximately constant in most groups, but there was a statistically significant increase in NHW males, rising from 8.6% to 14.0%. The transition from e-cigarette-only to dual-use significantly declined for NHW males aged 18-24 or 55+. Transitions from dual to cigarette-only use statistically significantly decreased among NHW females aged 18-24 or 35-54 and males in all age groups except 55+. However, transitions from dual to e-cigarette-only use increased in most groups, although these changes were not statistically significant.

Conclusions: Transitions in cigarette and e-cigarette use across race/ethnicity and age groups are changing, revealing declines in cigarette-only initiation, with the most significant decreases among NHB and NHW individuals. E-cigarette initiation is on the rise, particularly among young NHW adults. These patterns indicate a shift toward e-cigarette use among younger NHW adults, while adult cigarette use continues to decrease across all demographics.

Figure 1. One-year transition probabilities of exclusive and dual cigarette and e-cigarette use initiation, cessation, and switching for adults in the Population Assessment of Tobacco and Health Study (PATH). Each panel shows the probabilities and their confidence intervals from 2015-2017 (waves 2-4) and 2017-2019 (waves 4-5) by age, sex, and race/ethnicity.



Keywords: e-cigarettes, cigarettes, transition probabilities

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.44 Comparison of Age-Adjusted Charlson Comorbidity Index and Modified Frailty Index as a Postoperative Prognostic Indicator for Lung Cancer

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National Cancer Center Hospital, Tokyo/JP

Introduction: With the increase in the number of elderly patients with lung cancer, comorbidities at the time of surgery are becoming more important when considering surgical indications. We investigated the usefulness of the Age-adjusted Charlson Comorbidity Index (ACCI: an index based on 19 factors including heart disease, diabetes, liver function, history of cancer, and age) and the Modified Frailty Index (mFI-11: an index based on 11 factors including hypertension, diabetes, and a history of angina pectoris) in predicting prognosis.

Methods: We included 422 patients aged 75 years or older who underwent resection of primary lung cancer at our hospital between 2007 and 2012 in this study. We calculated the ACCI and mFI-11 for each patient and retrospectively examined their relationship with postoperative prognosis.

Results: The median age of the patients was 78 years (range: 75-87). The ACCI scores were 4/5/6/≥7 in 210 (49.8%)/130 (30.8%)/48 (11.4%)/33 (7.8%) patients, respectively. The mFI-11 scores were 0/1/2/≥3 in 171 (40.5%)/170 (40.3%)/68 (16.1%)/13 (3.1%) patients, respectively. The estimated 5-year survival rates for mFI-11 of 0/1/2/≥3 were 82.3%/83.1%/84.3%/65.3%, respectively, with no difference among the scores (p=0.56). For ACCI, the estimated 5-year survival rates for 4/5/6/≧7 were 86.6%/79.5%/73.6%/77.6%, respectively, with a significant difference among the scores (p=0.04). Univariate analysis showed that patients with vascular invasion (p<0.01), non-adenocarcinoma (p=0.03), a history of smoking (p<0.01), lobectomy or more (p=0.04), male (p=0.04), stage 2 or more (p<0.01), and ACCI 5 or more (p=0.01) had a poor prognosis. In multivariate analysis, vascular invasion (p<0.01), pathological stage 2 or more (p<0.01), and ACCI 5 or more (p=0.01) were shown to be independent poor prognostic factors.

Conclusions: Although both the ACCI and mFI-11 are used as indicators of postoperative comorbidities and surgical tolerance, the non mFI-11 but ACCI is useful as a prognostic factor for lung cancer patients aged 75 years or older after surgery.

Keywords: Comorbidity Index, Frailty Index

P3.01.45 Restrictive Lung Function and Smoking Increase Lung Cancer Risk in Tuberculosis Survivors: A Cohort Study

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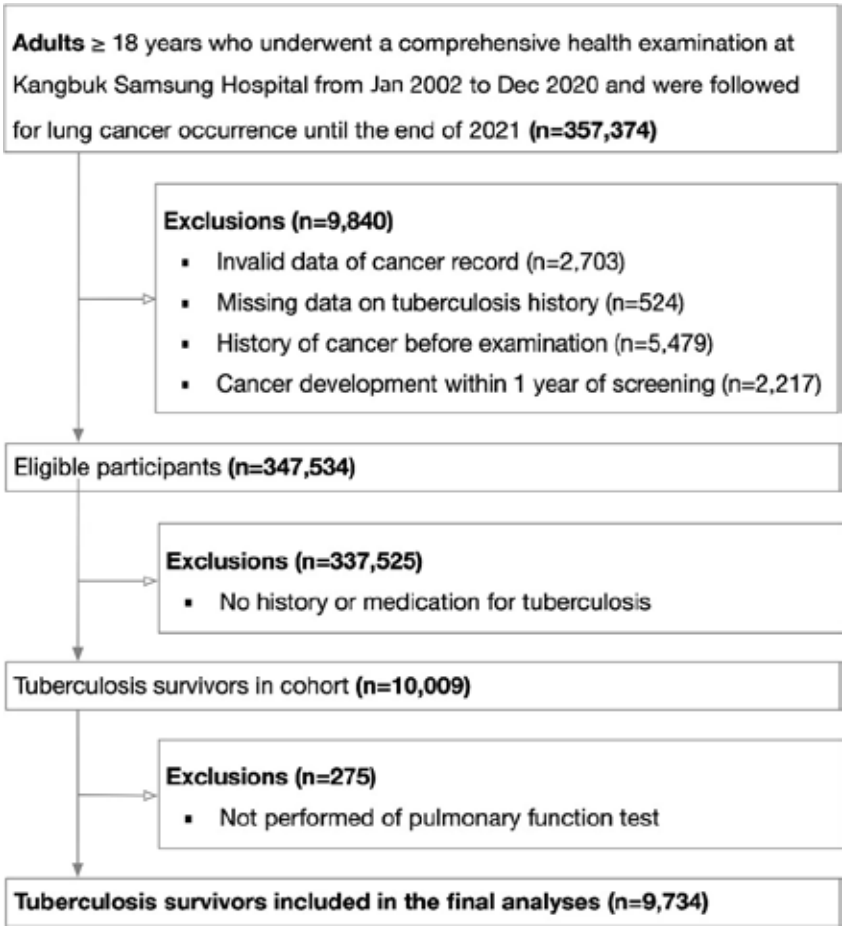
Introduction: Tuberculosis (TB) survivors are at an elevated risk for lung cancer due to chronic inflammation and following pulmonary damage. Although prior studies have consistently shown a link between previous TB infection and increased lung cancer risk, specific pulmonary functional abnormalities predictive of lung cancer development remain unclear. This study aimed to investigate the pulmonary function patterns and additional clinical risk factors significantly associated with lung cancer occurrence in a cohort of TB survivors

Methods: Using data from the Kangbuk Samsung Cohort Study (2011-2021), we analyzed 9,734 TB survivors (median follow-up: 12.3 years). Lung function was assessed via prebronchodilator spirometry and categorized as normal (FEV1/FVC ≥0.7, FVC ≥80% predicted), restrictive (FEV1/FVC ≥0.7, FVC <80%), or obstructive (FEV1/FVC <0.7). Lung cancer diagnoses were confirmed by linkage with the Korea National Cancer Incidence Database, excluding cancers diagnosed within one year of baseline assessment to avoid reverse causation. Multivariable Cox proportional hazards models evaluated associations between lung function, smoking, alcohol consumption, comorbidities, and lung cancer risk, adjusting for age, sex, and covariates.

Results: Participants were predominantly male (65.4%), with an average age of 41.2 years. Over a median follow-up of 12.3 years, lung cancer developed in 22 participants. Univariate analysis identified restrictive (HR 2.58, 95% CI 1.00-6.65; p=0.050) and obstructive pulmonary patterns (HR 6.48, 95% CI 2.05-20.43; p<0.001), older age (HR 2.35 per 5-year increase; p<0.001), heavy smoking (≥20 pack-years; HR 6.62; p<0.001), diabetes (HR 6.40; p=0.003), and alcohol consumption (≥20 g/day; HR 3.05; p=0.019) as significant risk factors for lung cancer. In multivariable models, restrictive lung function (HR 2.94, 95% CI 1.00-8.65; p=0.050), age (HR 2.35; p<0.001), and heavy smoking (HR 3.00; p=0.050) persisted as independent risk factors. Obstructive lung function lost significance after adjusting for covariates, indicating confounding by smoking.

Conclusions: This study highlights restrictive lung function, likely indicative of post-TB fibrotic changes, heavy smoking, and older age as significant predictors of lung cancer development in TB survivors. The findings underscore the utility of spirometry in identifying high-risk individuals and emphasize the need for surveillance strategies to enhance early detection and prevention of lung cancer in this vulnerable population. Our results suggest that post-TB fibrotic changes may contribute to oncogenesis, supporting the importance of monitoring lung function in TB survivors.



Keywords: Tuberculosis, Lung cancer risk, Restrictive lung function

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.46 Characterization of Patients With Lung Cancer Not Meeting Lung Cancer Screening Criteria: Identifying a High-Risk Group Beyond Tobacco Smoking

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Introduction: Lung cancer screening (LCS) based on smoking criteria reduces mortality through early detection. However, many non-small cell lung cancer (NSCLC) cases arise in individuals excluded from LCS programs. We aimed to characterize the clinical and tumor profiles, as well as familial and individual susceptibility in patients with NSCLC who didn't meet LCS criteria to identify a high-risk population beyond tobacco smoking.

Methods: Prospective study of 350 patients with all-stages NSCLC treated at Hospital Clinic (Spain) between 10/2020-01/2025. After signature of the informed-consent form, patients had a personal interview to collect personal/family history of cancer (three-generation pedigree) (PHC, FHC), demographic data, and exposure to environmental carcinogens. Clinical and tumor data was collected from medical records. Patients were classified as LCS-eligible or ineligible at the time of NSCLC diagnosis according to Nelson criteria (50-74 years old (yo) current or former smokers [who had quit ≤10 years ago] who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years). The patient/tumor/family profile was analyzed in each LCS-ineligible group and compared with LCS-eligible patients.

Results: Out of 350 patients enrolled, 217 (62%) didn't meet LCS criteria, due to age (34%), NSCLC diagnosis >10 years after tobacco cessation (25%), never-smoking status (21%), or low tobacco exposure (19%). Among LCS-ineligible group, median age was 43 in <50 yo (30-49) and 79 in >74 yo (75-90) groups, 47% were female (53% of female in those aged ≤ 50 yo), 28% non-smokers, 70% with FHC of 1st-degree relative and 31% with PHC. 59% of cases were diagnosed at stage IV, with adenocarcinoma as predominant histology (78% vs. 64%, p<0.001). A high prevalence of driver alterations was observed in the LCS-ineligible group (80% vs. 52%, p<0.001), including 30% KRASm (n=64), 24% EGFRm (n=51) and 8% ALKf (n=17). Different prevalence was observed in LCS-eligible group, with 31% KRASm (n=39), 4% EGFRm (n=5) and <1% ALKf (n=1) in LCS-eligible patients. Regarding FHC, the prevalence of 1st-degree affected relatives was similar in both groups (69% in the LCS-ineligible group vs. 74% in the LCS-eligible group). However, the LCS-ineligible group due to non-smoking status showed the highest rate of FHC (82%), particularly colorectal (20%), breast (18%), and lung (12%) cancers with a median of two 1st-degree relatives affected. Surprisingly, we don't find a higher rate of FHC among young compared to LCS-eligible patients (59 vs 74%). Distinct PHC spectra was observed between groups: non-smoking-related tumors such as breast (20%), prostate (19%), and colorectal (13%) cancers were more frequent in LCS-ineligible patients vs. urinary bladder (32%) and head and neck cancers (10%) in LCS-eligible patients.

Conclusions: LCS current criteria exclude a significant proportion of individuals that will develop NSCLC. FHC may help to identify a high risk-population in LCS-ineligible group, particularly in non-smokers which may benefit of LCS. However, a deeper characterization of this population is needed to develop more inclusive criteria for LCS.

Keywords: lung cancer screening, family history of cancer, epidemiology

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.47 Presentation and Validation of Three Engage Variants of the PLCOm2012 Lung Cancer Risk Prediction Model

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Introduction: Lung cancer is a major public health problem. Computed tomography lung cancer screening (LCS) significantly reduces lung cancer mortality. The most effective and efficient ways to implement LCS are unknown. The ENGAGE framework adapts screening intervals based on a dynamic, individualized assessment of tradeoffs between expected benefits and potential harms related to screening. ENGAGE has been shown to be superior to fixed interval and other adaptive screening-interval approaches. The ENGAGE approach estimates lung cancer risk, incorporates life expectancy, and uses simulation to estimate the optimum time to the next screening. The PLCOm2012 lung cancer risk prediction model was adapted for application in ENGAGE by categorizing some of the continuous predictors. We present ENGAGE versions of PLCOm2012 and their validation.

Methods: Cox proportional hazards regression was used to derive models. The outcome was incident lung cancer diagnosed within six years. Predictors included age, race and ethnicity, education, BMI, COPD, personal history of cancer, family history of lung cancer, and smoking status, smoking intensity, smoking duration, and quit-years in former smoking individuals. BMI and smoking intensity were converted from continuous into 4-level categorical variables (Table 1). Three models were produced with varied race/ethnicity categorization (Table 1). Predictive performances of these models were evaluated in PLCO intervention arm and NLST validation data. Comparisons were made between ENGAGE models and a Cox version of the original PLCOm2012 model. Predictive performance and calibration was evaluated using Harrell's c-statistic or receiver operating characteristic area under the curve (AUC), Brier statistic, Expected/Observed ratio, and Spiegelhalter's statistic p-value.

Results: Table 1 presents the models, and Table 2 compares their predictive performances. All models demonstrated good and comparable discrimination, calibration and validation.

Conclusions: Models with categorized continuous variables and variable race/ethnicity predictors demonstrated good predictive performance making them useful in simulation modeling and for different sociodemographic settings.

Table 1. Hazard ratios and 95% confidence intervals for predictors in three ENGAGE versions of the PLCOm2012 and the original PLCOm2012 (Cox model) version

Predictors	6-Race Model N=36,558	3- Race Model N=36,558	No-Race Model N=36,558	Cox PLCOm2012 N=36,498
Age, centered on 62	1.0835 (1.0601-1.1075)	1.0833 (1.0598-1.1072)	1.0832 (1.0597-1.1071)	1.0825 (1.0591-1.1065)
Education in 6 levels, centered on 4	.9257 (.8789-.9749)	.9275 (.8808-.9767)	.9242 1 (.8776-.9732)	.9234 (.8767-.9726)
Race/ethnicity Black *	1.4950 (1.1017-.0286)	1.5326 (1.1301-2.0784)	NA	1.5267 (1.1248-2.0720)
Race/ethnicity – Hispanic *	.4811 (.1991-1.1624)	Part of the referent group	NA	.4876 (.2018-1.1779)
Race/ethnicity – Asian *	.6230 (.3326-1.1668)	Part of the referent group	NA	.6213 (.3318-1.1635)
Race/ethnicity – American Indian/Alaskan Native *	2.4779 (.9244-6.6419)	2.5306 (.9442-6.7824)	NA	2.5744 (.9603-6.9014)
Race/ethnicity – Pacific Islander *	Grouped with Whites	Part of the referent group	NA	1.31e-14 (0 to .)
BMI in 4 levels, Level 1 † <18.5 kg/m^2	.6940 (.3083-1.5624)	.7059 (.3136-1.5890)	.6993 (.3107-1.5743)	NA
BMI in 4 levels, Level 3 † 25 to <30 kg/m^2	.8674 (.7266-1.0355)	.8708 (.7295-1.0395)	.8782 (.7358-1.0483)	NA
BMI in 4 levels, Level 4 † >30 kg/m^2	.72412 (.5765-.9095)	.7301 (.5815-.9168)	.7454 (.5938-.9357)	NA
BMI continuous	NA	NA	NA	.9727 (.9553-.9904)
Chronic obstructive pulmonary disease	1.4740 (1.2091-1.7969)	1.4812 (1.2151-1.8056)	1.4809 (1.2148-1.8053)	1.4712 (1.2072-1.7931)
Personal history of cancer (No=0, Yes=1)	1.5531 (1.1592-2.0808)	1.5693 (1.1714-2.1023)	1.5678 (1.1703-2.1002)	1.5411 (1.1503-2.0645)
Family history of lung cancer (No=0, Yes=1)	1.7796 (1.4657-2.1609)	1.7839 (1.4692-2.1660)	1.7779 (1.4643-2.1587)	1.7645 (1.4523-2.144)
Smoking Status (0, former; 1 current)	1.3012 (1.0567-1.6025)	1.3053 (1.0599-1.6076)	1.3109 (1.0645-1.6145)	1.2829 (1.0418-1.5797)
Smoking intensity, 2nd of 4 levels (15 to <25 cig/day)	2.3498 (1.7363-3.1801)	2.3833 (1.7615-3.2246)	2.2940 (1.6976-3.0999)	NA
Smoking intensity, 3rd of 4 levels (25 to <45 cig/day) ‡	3.3331 (2.4611-4.5141)	3.4123 (2.5210-4.6188)	3.1960 (2.3704-4.3091)	NA
Smoking intensity, 4th of 4 levels (≥45 cig/day) ‡	4.8166 (3.3615-6.9015)	4.9345 (3.4451-7.0677)	4.6377 (3.2474-6.62324)	NA
Smoking Intensity Transformed¶	NA	NA	NA	.1638 (.1110-.2417)
Smoking duration in years, centered on 28	1.0316 (1.0135-1.0500)	1.0317 (1.0136-1.0501)	1.0318 (1.0137-1.0502)	1.0322 (1.0140-1.0507)
Quit years in former smoking, centered on 16	.9690 (.9495-.9889)	.9691 (.9496-9890)	.9685 (.9490-.9884)	.9698 (.9502-.9897)

Abbreviations: BMI, body mass index; cig/day, cigarettes per day.
* Race/ethnicity – White is the referent group for the 6-race model and Race/ethnicity – Other is the referent group for the 3-race model
† BMI level 2 (18.5 to <25 kg/m^2) is the referent group.
‡ Categorical smoking intensity level 1 is the referent group (>0 to <15 cig/day).
¶ Smoking intensity has a non-linear association with lung cancer. Transformation of smoking intensity = (((Average number_cigarettes_smoked_per_day/10)^-1)-0.40215).
Note: Education is an ordinal 6-level variable, centered at level 4, for all models.

Table 2. Predictive performance of ENGAGE 6-race, 3-race and no-race Cox model versions of the PLCOm2012 and a Cox regression version of the original PLCOm2012

Predictors	ENGAGE 6-Race	ENGAGE 3- Race	ENGAGE No-Race	Cox PLCOm2012
PLCO controls (Development data)				
Expected / Observed	1.052	1.052	1.052	1.052
Spiegelhalter's statistic p-value	0.874	0.873	0.867	0.877
ROC AUC / c-statistic	0.803	0.802	0.801	0.804
Brier statistic*	0.0165	0.0165	0.0165	0.0165
PLCO intervention (Validation data)				
Expected / Observed	1.011	0.989	0.989	0.994
Spiegelhalter's statistic p-value	0.266	0.264	0.247	0.292
ROC AUC / c-statistic	0.796	0.796	0.795	0.791
Brier statistic*	0.0174	0.0174	0.0174	0.0173
NLST (Validation data)				
Expected / Observed	1.014	1.011	1.017	1.003
Spiegelhalter's statistic p-value	0.387	0.356	0.465	0.211
ROC AUC / c-statistic	0.698	0.698	0.697	0.699
Brier statistic*	0.0339	0.0339	0.0339	0.0339

Abbreviations: NLST, National Lung Screening Trial; PLCO, Prostate Lung Colorectal and Ovarian Cancer Screening Trial; ROC AUC, receiver operator characteristic area under the curve
* The Brier statistic is a measure of general prediction and ranges from 0 for perfect prediction to .25 for random classification. Lower values indicate better prediction.

Keywords: Lung cancer risk prediction models, PLCOm2012, Differences in risk by race/ethnicity

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.48 Familial Lung Cancer and Hereditary Patterns in NSCLC - Implications for Risk Redefinition

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Introduction: While tobacco remains the primary cause of lung cancer, up to 25% of cases occur in never-smokers, suggesting additional risk factors. A positive family history (FHx) increases risk by 2 to 3 folds, pointing to a heritable component that may interact with environmental exposures. Lung cancer incidence is rising in younger women and now surpasses that of men under 65; notably, lung cancer in never-smokers is more common in females. These patterns underscore the need to better define high-risk populations, where genetic susceptibility and environmental factors may contribute. This study evaluates the burden and patterns of cancer FHx in lung cancer to inform future risk stratification.

Methods: We retrospectively analyzed a curated cohort of 2,037 lung cancer patients with clinical, demographic, and social history at the University of Chicago (2014-2024). Patterns associated with family history and genetic profiles were evaluated.

Results: Among the 2,037 lung cancer patients, 92.2% (n=1,879) had non-small cell lung cancer (NSCLC) and 7.7% (n=158) had small cell lung cancer (SCLC). Mean age at diagnosis was similar (65.4 for NSCLC vs. 66.1 for SCLC). Adenocarcinoma was the most common NSCLC subtype (84.0%), with 41.0% diagnosed at Stage IV. Among SCLC patients, 72.2% had extensive-stage disease. Most NSCLC patients were female (55.8%) and White (56.5%), followed by African American (33.0%) and Asian (3.6%). Overall, 18.6% of the cohort were never smokers. Among NSCLC patients with available family history data (n = 1,839), individuals were categorized into three groups: those reporting a lung cancer FHx (LCa FHx, 27.0%), a non-lung cancer FHx (non-LCa FHx, 46.4%), or no FHx of cancer (NegCa FHx, 26.6%). Females were significantly overrepresented in both the LCa FHx (60.9%) and non-LCa FHx (57.1%) groups, with no sex difference observed in the NegCa FHx group. FHx patterns also differed by race, with White (76.2%) and Black (67.7%) patients more likely to report any FHx of cancer than Asian. In early-stage NSCLC (Stage I-III), White and Black females were significantly more likely than their male counterparts to report a family history of lung cancer, with 1.37-fold and 2.0-fold higher, respectively ($p = 0.0179$ and 0.0197). This sex difference was insignificant in Stage IV, though a similar trend remained. Among former smokers, ATRX mutations were significantly more common in females ($\log_2 OR = -1.97$, FDR = 0.027), suggesting a sex-specific molecular pattern in NSCLC patients with a smoking history. Exploratory analysis using nominal p-values ($p < 0.05$) revealed sex-specific trends in FHx-associated mutations, including RET, AXL, ATR, EPHA5, and APC in males, and GRIN2A, ALK, EPHA3, ERBB2, CSF3R, RAD51, and STAT3 in females.

Conclusions: Cancer family history is common in lung cancer patients, particularly among women, and may reflect patterns of familial lung cancer. These findings support redefining high-risk populations using family history, sex, and ancestry. Underrepresented groups, such as those of Asian ancestry, highlight the need for multi-center studies. Prospective studies with detailed history and genetic testing are essential to uncover familial lung cancer, define genetic mechanisms, and guide personalized risk models, screening, and treatment strategies.

Keywords: Familial Lung Cancer, Genetics, High Risk

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.49 A Pro-Mitotic Gene Expression Module in Small Airways Links COPD Severity to Non-Small Cell Lung Cancer

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Introduction: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally, while lung cancer is the leading cause of cancer-related mortality worldwide. Cigarette smoking is the primary risk factor for both diseases; however, COPD confers a six-fold increased risk of lung cancer, independent of smoking history. The severity of COPD, indicated by decreasing forced expiratory volume in one second (FEV1%), is the strongest clinical predictor of lung cancer risk. We hypothesized that molecular signatures from small-airway tissues associated with reduced FEV1% could provide insights into the cancerization process in COPD-affected lungs.

Methods: We performed weighted gene co-expression network analysis on small airway epithelial (SAE) transcriptional profiles from 267 patients to investigate transcriptional changes associated with COPD severity and lung cancer risk. Functional enrichment analyses were conducted to characterize the biological processes associated with COPD severity. To determine whether SAE modules were transcriptionally active in lung tumors, we conducted a module preservation analysis using adenocarcinoma (LUAD; n = 433) and squamous cell carcinoma (LUSC; n = 474) tumor samples from TCGA dataset. Tumors were further analyzed for DNA, mRNA, and protein-level alterations (including mutation, copy number variation, and gene expression changes) in module genes associated with COPD severity. An independent cohort of sputum and bronchial biopsies (n = 3,270) was used to validate these findings. Finally, we performed functional experiments in airway epithelial (HBEC) and LUAD (H1299) cell lines to explore the functional role of genes in the COPD module.

Results: We identified a gene module containing 31 genes correlated with FEV1% and COPD status. This module was enriched for pathways regulating cell cycle progression, mitotic checkpoints, and DNA damage repair and was preserved in lung tumors (MedianRank = 1 LUAD and 2 LUSC). Multi-omic analysis of LUAD and LUSC tumors revealed that genes within this module underwent frequent somatic alterations, including TP53, which was frequently mutated, subjected to copy number variations, and transcriptionally dysregulated. LUAD tumors with alterations in module genes showed increased genomic instability compared to those without, including a significantly higher tumor mutational burden, enrichment for cell cycle activation, and downregulation of DNA repair pathways. Cytological and morphological abnormalities were validated in sputum and bronchial biopsies with increased lung cancer risk, correlating with reduced FEV1%. Among the 31 genes in this module, PLK4 was upregulated in reduced FEV1%. Since PLK4 deregulation is known to cause centriole overduplication, leading to centrosome amplification (CA) and genomic instability, we investigated its effects on these phenotypes in HBEC and LUAD cells. Overexpression of PLK4 significantly increased CA in both cell types, reinforcing its role in genomic instability related to lung cancer.

Conclusions: Our findings provide evidence that lung cancer arises in the context of COPD from the transformation and oncogenic selection of small airway epithelial cells in which a pro-mitotic transcriptional program is activated. These data suggest that repetitive tissue injury and repair in COPD, exacerbated by smoking-induced damage, promote a transcriptional landscape conducive to tumorigenesis. These findings have implications for biomarker discovery and early detection in high-risk individuals.

Keywords: Non-Small Cell Lung Cancer, Chronic Obstructive Pulmonary Disease, Genomic Instability

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.50 Association Between Chronic Lung Diseases and Lung Cancer: A Bidirectional Two-Sample Mendelian Randomization Study

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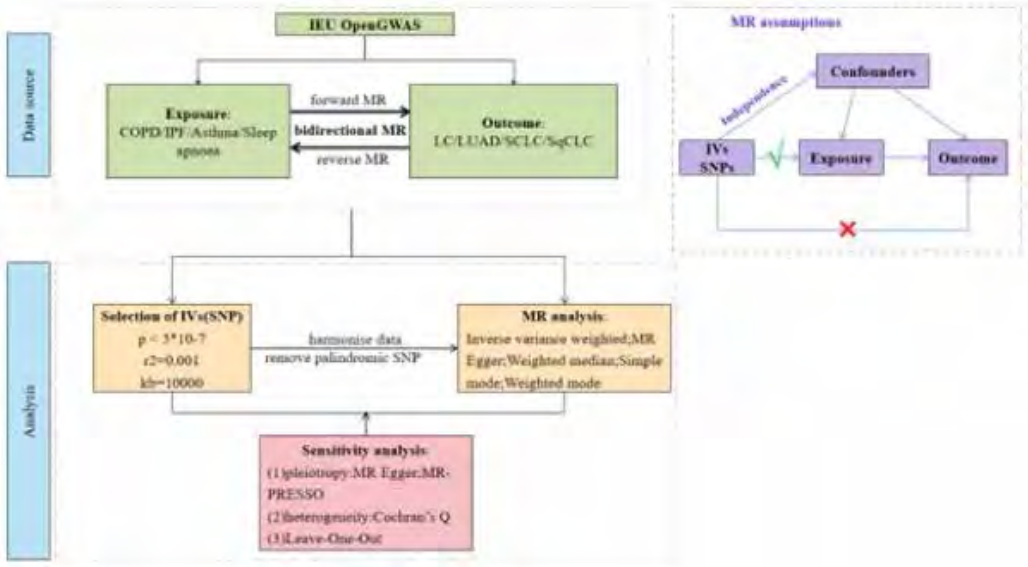
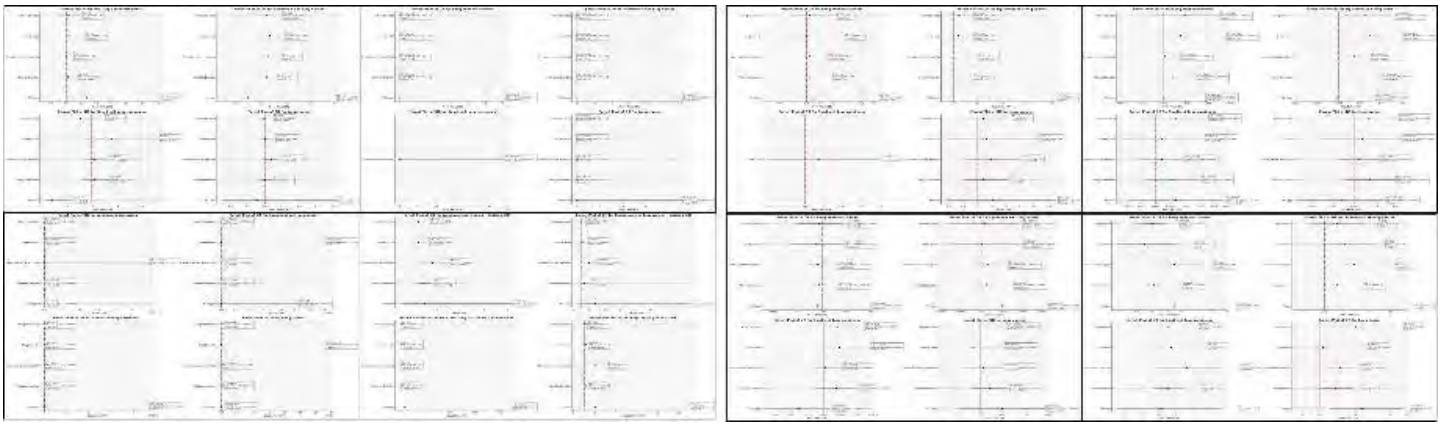
Introduction: Chronic lung diseases, including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), asthma, and sleep apnea, share common risk factors with lung cancer, but their causal relationships remain unclear. This study employed bidirectional Mendelian randomization (MR) to investigate potential causal links between these conditions and major lung cancer subtypes.

Methods: We analyzed summary-level genetic data from large GWAS cohorts, including 20,898 chronic lung disease cases and 51,603 lung cancer cases. Single nucleotide polymorphisms (SNPs) associated with exposures ($p < 5\times10^{-7}$) were selected as instrumental variables. Inverse-variance weighted (IVW), MR-Egger, and weighted median methods were applied, with sensitivity analyses to assess pleiotropy and robustness.

Results: In forward MR analyses, COPD was causally associated with increased risk of lung adenocarcinoma (β=1.15, 95% CI: 1.01-1.32, P=0.0398) and squamous cell carcinoma (β=1.27, 1.05-1.58, P=0.0138). Reverse MR confirmed bidirectional relationships, showing all lung cancer subtypes increased COPD risk (all P<0.005). Asthma demonstrated unidirectional causality with squamous cell carcinoma (forward MR: β=1.24, 1.05-1.46, P=0.0125), but no reverse association (P=0.117). Similarly, sleep apnea showed forward effects on squamous cell carcinoma (β=1.00, 1.00-1.00, P=0.0456), though reverse analysis was unfeasible due to insufficient SNPs. No significant associations were detected for IPF in either direction (all P>0.05).

Conclusions: Chronic inflammation and shared etiological pathways may underlie the COPD-lung cancer relationship, while asthma and sleep apnea may promote squamous cell carcinoma via distinct mechanisms. These findings highlight the need for targeted screening in high-risk populations and further exploration of molecular interactions.





Keywords: chronic lung diseases, lung cancer, Mendelian randomization study

P3.01.51 Evidence Synthesis of Non-Screen-Eligible Cohorts and Implications for Lung Cancer Advocacy

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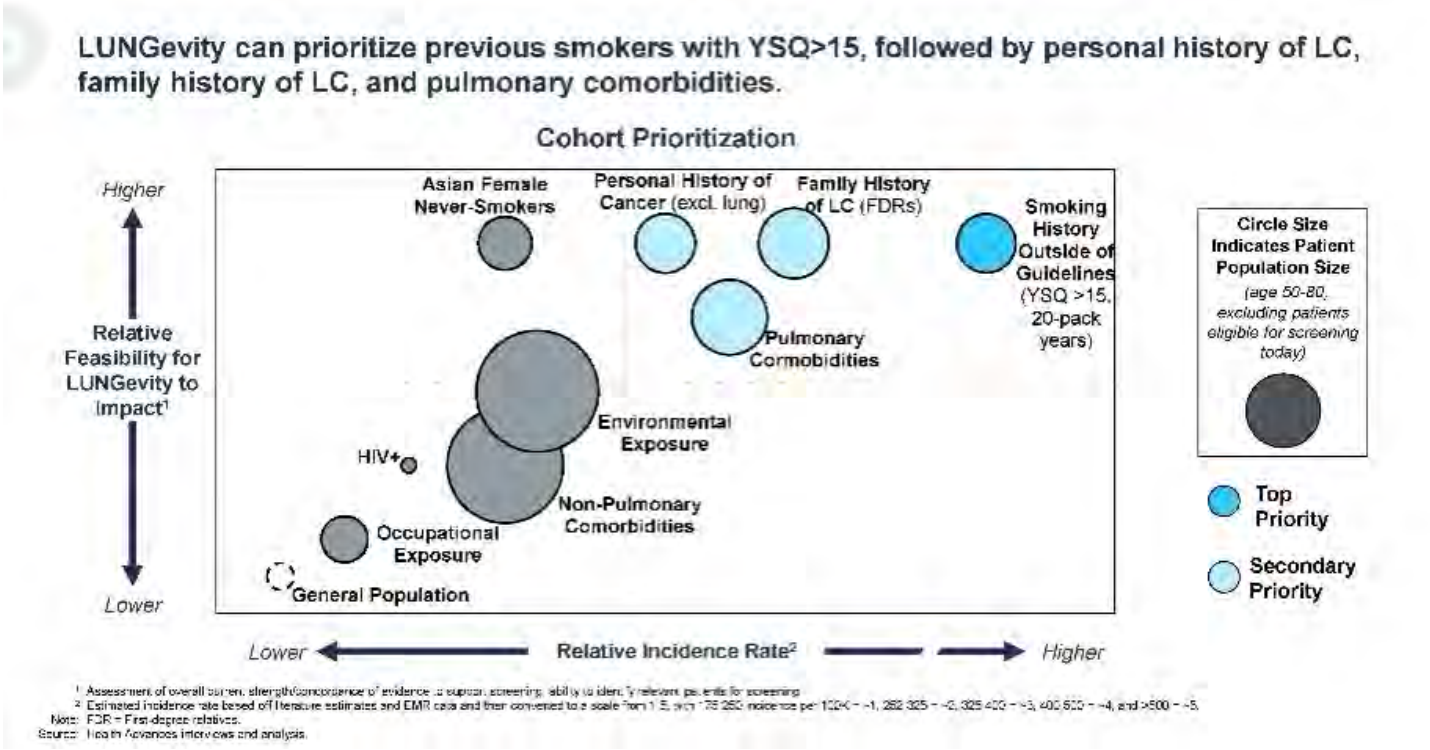
Introduction: Of the more than 234,000 people who will be diagnosed with lung cancer in 2025, roughly ~50% are ineligible for screening according to current USPSTF criteria. This limitation leaves many patients vulnerable to late-stage or delayed diagnosis and high mortality.

Methods: LUNGevity partnered with Health Advances to conduct an analysis of data from 9 separate cohorts outside of 2021 USPSTF guidelines. The quantitative and qualitative study was conducted with no a-priori hypothesis to see where the evidence leads. It included a review of 80 unique publications; real-world EMR and claims data, government databases, and in-depth interviews with 3 KOLs/subject matter experts.

Results: First, several barriers were identified that prevent screening of non-USPSTF cohorts today, including a high bar of evidence to change the guidelines, disease perception, and current technology shortfalls with LDCT. Historically only randomized controlled clinical trials supplemented with large cohort studies have driven expansion of screening eligibility. Secondly, it demonstrated elevated risk levels above the general population for each cohort. We conducted a structured prioritization of how LUNGevity and the advocacy community may reach targeted populations. Several of these cohorts have strong evidence bases as well as defined and accessible populations. Cohorts include: 1) Smoking history outside guidelines; 2) Personal history of cancer; 3) Family history of lung cancer; 4) Pulmonary comorbidities and 5) Asian Female (no smoking history). See Diagram.

Conclusions: Opportunities exist for the advocacy community to drive inclusion of the criteria for people with smoking history of >15 years since quit, adding nearly 5 million more eligible people. Additionally, there are potential ways to reach and impact other high priority cohorts. Finally, our analysis explores the possible role of risk-based models and emerging technologies including blood tests in shifting the balance of benefits/risk in favor of screening moderate-risk cohorts.



Keywords: Screen-ineligible, Guidelines, Risk

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.52 Unseen Risks: Rethinking Lung Cancer Screening for Hispanic Communities

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Introduction: Lung cancer screening (LCS) using low-dose computed tomography (LDCT) has been shown to significantly improve early detection and survival rates, as evidenced by landmark trials supporting LDCT's role in reducing lung cancer mortality. However, existing guidelines, particularly those from the U.S. Preventive Services Task Force (USPSTF), may miss many high-risk individuals. Emerging evidence suggests that expanding eligibility criteria, such as incorporating the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) risk model, could better capture individuals at risk by considering a wider range of factors. The GUIAR trial (Promoting Lung Cancer Screening Awareness and Implementation in Hispanics/Latinx Head and Neck Cancer Survivors, NCT06124508) aims to address disparities in LCS among Hispanic/Latinx populations, investigating barriers to screening and comparing eligibility between USPSTF and PLCO criteria.

Methods: In the GUIAR trial, we assessed LCS eligibility in Hispanic/Latinx survivors of head and neck cancer (HNC) through survey-based tools. We identified patients who met USPSTF criteria and separately categorized those who qualified under PLCO criteria but not USPSTF. PLCO eligibility was evaluated in two ways: assuming White race and assuming Hispanic race, creating distinct groups for comparison. Variables including gender, smoking status, COPD, cancer history, family history, age, cigarettes per day, smoking years, pack-years, and BMI were compared across groups using chi-square tests for categorical data and Mann-Whitney U tests for continuous data.

Results: Since August 2024, 199 patients have been screened, with 18 enrolled based on USPSTF criteria. Of those not enrolled, 16 patients met PLCO Hispanic criteria, and 21 met PLCO White criteria with a risk score above 1.5%. Compared to USPSTF criteria, patients eligible under PLCO were significantly older (PLCO Hispanic: 81 ± 11.6 vs. 65 ± 7.3 years, $p < 0.01$; PLCO White: 78.8 ± 12 vs. 65.1 ± 7.2, $p < 0.001$), had a lower BMI (PLCO Hispanic: 23.8 ± 3.7 vs. 26.6 ± 3.1, $p = 0.076$; PLCO White: 23.5 ± 3.7 vs. 26.6 ± 3.1, $p = 0.026$), and smoked fewer cigarettes per day (PLCO Hispanic: 21 ± 7.7 vs. 27.5 ± 7.5, $p = 0.026$; PLCO White: 21.4 ± 9.0 vs. 27.5 ± 7.5, $p = 0.026$). No significant differences were observed in gender, COPD, cancer history, family history, or pack-years.

Conclusions: Our findings underscore the limitations of USPSTF criteria in identifying high-risk Hispanic HNC survivors for LCS. By using PLCO criteria, eligibility expanded significantly, with variations based on racial classification. More patients qualified under PLCO when race was classified as White, revealing the complexity of screening Hispanic populations. These patients were older, had lower BMI, and smoked fewer cigarettes per day, suggesting that USPSTF criteria may miss at-risk individuals with different risk profiles. Incorporating broader models like PLCO could improve early detection and help reduce disparities in lung cancer mortality.

Keywords: screening, survivorship, tobacco use

P3.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.01.53 Germline EGFR Mutations Are Enriched in the Southeast United States and Associated With High Penetrance of Non-Small Cell Lung Cancer

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Introduction: Routine use of next generation sequencing in non-small cell lung cancer (NSCLC) has enabled identification of multiple targetable oncogenic variants and germline variants that may predispose patients to cancer. Recent publications suggest that 1% of patients with NSCLC harbor germline EGFR mutations and that 55% of these individuals were affected by NSCLC. We sought to better understand the prevalence of germline EGFR mutations.

Methods: We performed a retrospective analysis of patients with clinical germline mutations catalogued within the Duke Molecular Registry of Tumors and patients who enrolled in the Duke CATHGEN study, which enrolled patients who presented to the cardiac catheterization laboratory for any reason for germline genetic testing. Of patients who underwent testing, patients with EGFR mutations were identified. We queried the dataset from the All of Us Research Program to identify individuals with germline EGFR mutations and their geographic location. This program is an ongoing federally funded study that seeks to sequence one million or more individuals and prospectively monitor their health data. We also queried the gnomAD database which is an international genome aggregation database composed of exome and genome sequences from ~800,000 individuals.

Results: A total of 68 individuals with germline EGFR mutations were identified in the data from the All of Us Research program in a total of 414825 (1 in 6000). We found 85 total individuals with germline EGFR mutations were identified in the gnomAD dataset in a total of 807050 (1 in 9400). The most common mutations in both datasets were T790M, E330K, R776H, V843I, D761N, P596L, and T725M. Four of the most common EGFR variants, T790M, R776H, D761N, and T725M, have been associated with hereditary lung cancer representing 60% of identified mutations across both datasets. Germline EGFR T790M mutations were regionally enriched in the southeast United States in this cohort. We identified 3 individuals with germline EGFR mutations in the Duke CATHGEN study cohort of 10,000 patients tested, all of which were T790M mutations. Of these individuals, one has been diagnosed with lung cancer and another has a diagnosis of lung nodules. This represents a tenfold increase in the EGFR T790M germline mutation frequency in the Duke catchment area compared with the data from All of Us or gnomAD datasets. We have also identified 23 patients in seen in our clinics over the last 8 years with putative EGFR germline mutations, 20 with NSCLC, 3 with other malignancies.

Conclusions: Multiple variants of germline EGFR mutations are found across the United States and internationally. The most common of these germline variants are associated with a hereditary risk for lung cancer. Prevalence of germline EGFR T790M mutations is enriched in the southeast United States. Given the increased hereditary risk, this warrants studies investigating the role of familial testing and screening in these individuals.

Keywords: EGFR, Germline Mutations, Cancer Predisposition

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.01 Rb Inactivation as a Hallmark of Squamous Transformation in EGFR-Mutant Lung Cancers

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Introduction: Histologic transformation to squamous carcinoma (LUSC) is a resistance mechanism in EGFR-mutant lung adenocarcinoma (LUAD), occurring in 5-8% of patients receiving osimertinib and associated with poorer outcomes. While our prior work implicated the AKT pathway as a promoter of LUSC transformation, a comprehensive genomic characterization of this process remains lacking.

Methods: We performed genomic characterization (MSK-IMPACT) on EGFR-mutant specimens undergoing LUSC transformation, including pre- and post-transformation tumors from TKI-treated patients. Time-to-treatment discontinuation (TTD) was analyzed in patients with EGFR-mutant lung cancer on frontline osmertinib (n=177). Xenograft models of squamous transformation (HCC827 cell lines overexpressing Myc and myrAKT +/- Rb inactivation) were treated with osimertinib, and cellular phenotype was assessed using immunohistochemistry (IHC) and single-cell RNA sequencing.

Results: Among patients with EGFR-mutant lung cancer undergoing LUSC transformation (n=20), 50% and 60% had alterations in the AKT or Rb pathway, respectively. In contrast, patients with never-transforming EGFR-mutant LUAD (n=1515) trended towards fewer alterations in the AKT (18%) or Rb (32%) pathways. Patients with EGFR-mutant LUAD harboring Rb and/or AKT (Rb/AKT) pathway mutations (n=70) experienced shorter TTD on frontline osimertinib (median 18 vs 23 months, p=0.03; Figure 1) compared to a Rb/AKT wild-type cohort (n=107); TP53 co-mutations were similar between groups. In xenograft models treated with osimertinib, Rb inactivation via CRISPR deletion of Rb1 or upstream regulators (CDKN2A/B) promoted a squamous-like phenotype, demonstrated by increased P40 and CK5/6 protein expression and single-cell transcriptomic profiling (Figure 2). Rb inactivation also resulted in more rapid in vivo tumor growth during osimertinib treatment compared to controls.

Conclusions: Rb and AKT pathway alterations occur often in EGFR-mutant lung cancers with LUSC transformation and are associated with shorter osimertinib benefit. Rb inactivation promoted a squamous-like phenotype and osimertinib resistance in preclinical models. Detecting these mutations may help identify patients at high risk of treatment resistance and transformation.

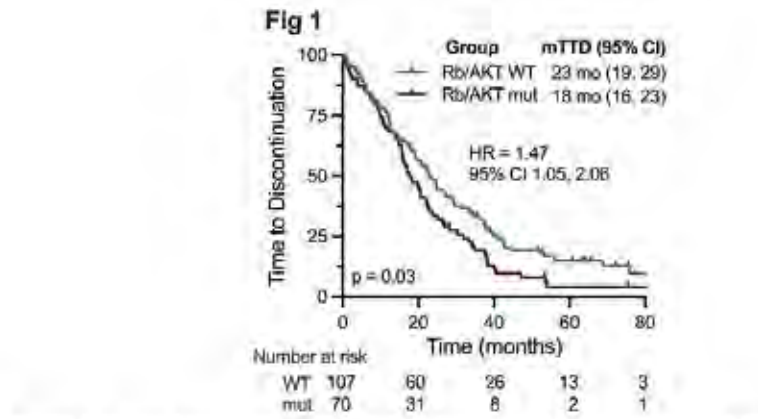

Figure 1. Kaplan-Meier curve of median time-to-treatment discontinuation (mTTD) for patients with *EGFR*-mutant lung cancer on frontline osimertinib with (mut) and without (WT) Rb/AKT pathway mutations.

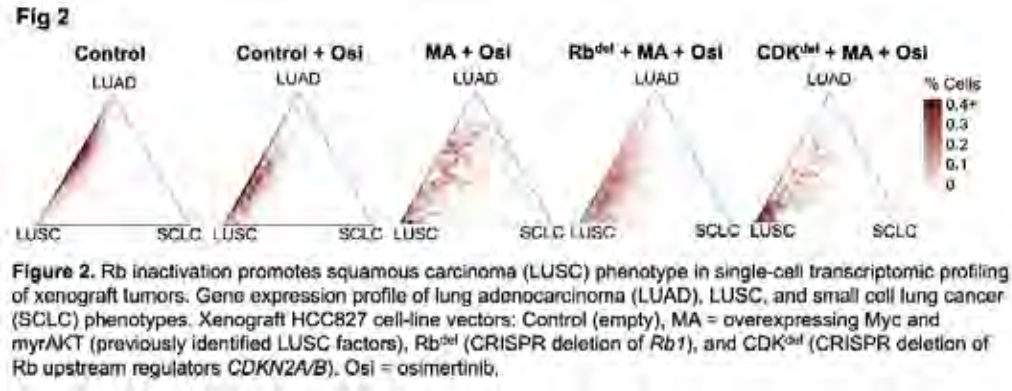

Figure 2. Rb inactivation promotes squamous carcinoma (LUSC) phenotype in single-cell transcriptomic profiling of xenograft tumors. Gene expression profile of lung adenocarcinoma (LUAD), LUSC, and small cell lung cancer (SCLC) phenotypes. Xenograft HCC827 cell-line vectors: Control (empty), MA = overexpressing Myc and myrAKT (previously identified LUSC factors), Rb^{del} (CRISPR deletion of *Rb1*), and CDK^{del} (CRISPR deletion of Rb upstream regulators *CDKN2A/B*). Osi = osimertinib.

Keywords: Squamous transformation, EGFR-mutant lung cancer, Xenograft

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.02 WEE1 as the Target for Circumvention of ARID1A Mutation-Driven Osimertinib Resistance in EGFR-Mutated Lung Cancer

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Introduction: Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is widely used as a first-line treatment for EGFR-mutant non-small cell lung cancer (NSCLC). Despite its efficacy, resistance—particularly in cases involving central nervous system (CNS) metastases—remains a major clinical challenge, with the underlying mechanisms largely unknown. This study aimed to investigate the mechanisms driving osimertinib resistance and identify novel therapeutic strategies.

Methods: Using a mouse model of leptomeningeal carcinomatosis (LMC), we induced osimertinib resistance and performed next-generation sequencing to characterize resistance-associated mutations. Additionally, we analyzed clinical samples to correlate ARID1A status with progression-free survival in patients receiving osimertinib.

Results: Among these, mutations in the AT-rich interacting domain-containing protein 1A (ARID1A) gene were the most prevalent in resistant cells. Functional assays revealed that ARID1A knockout in parental cells and wild-type ARID1A gene expression in resistant cells played a critical role in conferring osimertinib resistance. A CRISPR-Cas9 knockout screen identified WEE1 kinase inhibition as potent enhancers of apoptosis in ARID1A-mutant osimertinib-resistant cells. Mechanistically, ARID1A-mutant cells exhibited reduced expression of genes involved in cell cycle regulation and DNA repair, rendering them particularly sensitive to WEE1 inhibition. In vivo, the combined inhibition of EGFR and WEE1 significantly suppressed tumor growth in the LMC mouse model. Clinically, patients with ARID1A mutations had markedly shorter median progression-free survival on osimertinib (6.25 vs. 18.0 months, p=0.0036) than those with wild-type ARID1A.

Conclusions: These findings suggest that ARID1A mutations are critical biomarkers for osimertinib resistance and highlight WEE1 inhibition as a promising therapeutic approach for ARID1A-mutant osimertinib-resistant NSCLC.

Keywords: Target drug resistance, EGFR mutation, Cell cycle

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.03 Mechanisms of Osimertinib Tolerance in Mutant EGFR Lung Cancer PDX Models

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Introduction: Understanding the cell state transitions of EGFRmut-driven drug-tolerant or persister states leading to acquired genetic resistance alterations remain obscure. Investigations on tumor biopsies from advancing disease are a challenge due to limited timepoints, specimens and low tumor cellularity. We here evaluated the drug tolerant states of two patient-derived xenograft (PDX) lung adenocarcinoma models with osimertinib (osi) sensitive EGFRL858R and EGFRex19del mutations to study the mechanisms of drug tolerance.

Methods: PHLC4672 was established from a liver metastatic lung adenocarcinoma with EGFRL858R of a patient previously treated with osi followed by standard of care conventional chemo- and radiation therapies. PHLC137 was derived from a primary resected lung adenocarcinoma with EGFRex19del mutation (Stewart et al., J Clin Oncol 2015;33:2472-80). Viable cryo-banked donor tumor fragments were grown in the subcutaneous flank of NOD SCID mice. Osimertinib was orally administered daily at 25 mg/kg until the mean lowest tumor volume was reached and continued 2 weeks on osi to endpoint. Bulk and single-nuclear RNA (snRNA) sequencing methods were used to identify differential expressed genes (DEGs) between osi- and vehicle-treated tumors based on fold changes in each model. Gene set enrichment analysis was performed on DEGs based on Hallmark 2020, Molecular Signatures Database, to identify enriched pathways.

Results: PHLC4672 showed an osi-induced G1 tumor growth arrest without size reduction, typical of a stable disease response. This contrasted to PHLC137 that formed drug-tolerant-persister (DTP) tumor following marked initial tumor size reduction. Single cell and bulk RNA analyses showed that the drug tolerant cell state in tumors of PHLC4672 compared to vehicle-treated tumors was associated with primarily a down regulation of proliferation associated genes including G2M checkpoint, E2F targets, mitotic spindle and glycolysis. In addition to down regulation of proliferation associated pathways, PHLC137 DTP tumor showed an upregulation in genes enriched in pathways associated with NFκB, epithelial mesenchymal transition and stress pathways including P53 and apoptosis.

Conclusions: Drug tolerance in osimertinib-induced DTP and non-DTP tumors showed variable common growth arrest and distinctive changes in pathway alterations. These results provide additional insights to vulnerabilities and molecular cell adaptation associated with tumors to osimertinib-induced responses.

Keywords: drug tolerant persister, osimertinib, patient derived xenograft

P3.03.04 Aggressive Lymph Node Dissection Is Linked to Poor Survival and Impaired Anti-Tumor Immunity in Non-Small Cell Lung Cancer

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Introduction: Perioperative systematic nodal dissection has been recommended for its survival benefit by improving staging accuracy and optimizing adjuvant treatment in patients with non-small cell lung cancer (NSCLC). However, the optimal extent of dissection and the ideal number of lymph nodes to be removed remain subjects of debate.

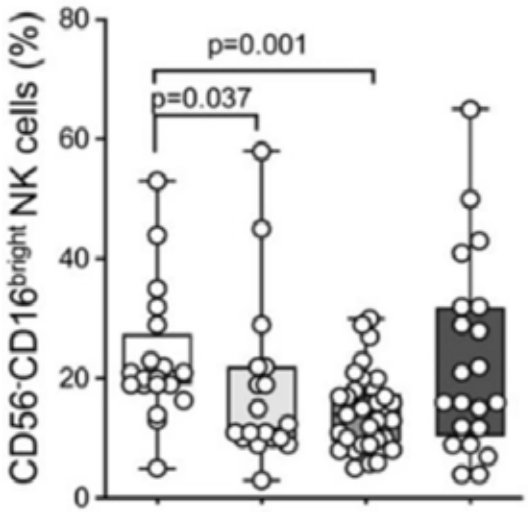
Methods: A total of 378 patients diagnosed with NSCLC who underwent surgical mediastinal staging prior to pulmonary resection at our institution between January 2010 and December 2023 were included. Propensity score (PS) matching was performed for variables including age, gender, smoking history, histopathological diagnosis, and pathological T and N status, resulting in a 1:1 ratio between groups with a low (<45) and high (≥45) number of dissected lymph nodes. Blood samples were collected before surgery and 4 weeks after. Lymphocytes were isolated from removed mediastinal lymph nodes (MLNs), and cytotoxic T lymphocyte (CTL) and natural killer (NK) cell phenotypes, functions, and anti-tumor activity against a lung cancer cell line were assessed.

Results: Demographic and clinical characteristics before and after PS matching are shown in Table 1. In the PS-matched cohort, patients in the low lymph node dissection group had a significantly longer median survival compared to those in the high dissection group (138 months vs. 68 months (odds ratio, 0.613, 95% confidence interval, 0.441 - 0.852; p = 0.003). CTLs isolated from MLNs exhibited significantly lower cytotoxicity compared to blood CTLs following lung cancer cell stimulation in patients who underwent aggressive lymph node dissection (p = 0.001). Similarly, NK cell anti-tumor activity was significantly reduced in this group compared to controls (p = 0.037) (Figure 1).

Table 1.

	Before PSM analysis			*After PSM analysis*		
	Dissected lymph nodes<45	**Dissected lymph nodes=>45**	**p-value**	**Dissected lymph nodes<45**	**Dissected lymph nodes=>45**	**p-value**
Age (mean ± SD)	62.7 ± 9.4	62.1 ± 9.2	0.549	62.8 ± 9.2	62.1 ± 9.0	0.512
Gender (n, %)			0.817			0.749
Male	159 (85.0%)	164 (85.9%)		129 (85.4%)	127 (84.1%)	
Female	28 (15.0%)	27 (14.1%)		22 (14.6%)	24 (15.9%)	
Smoking history (pack.years) (mean ± SD)	45.7 ± 29.6	45.5 ± 31.2	0.937	45.5 ± 29.7	44.7 ± 31.5	0.842
Histopathological diagnosis (n, %)			0.017			0.906
Adenocarcinoma	85 (45.5%)	64 (33.5%)		59 (39.1%)	58 (49.6%)	
Non-adenocarcinoma	102 (54.5%)	127 (66.5%)		92 (60.9%)	93 (61.6%)	
pT status (n, %)			0.422			0.963
pT1	33 (17.6%)	30 (15.7%)		26 (17.2%)	26 (17.2%)	
pT2	91 (48.7%)	82 (42.9%)		73 (48.3%)	69 (45.7%)	
pT3	37 (19.8%)	42 (22.0%)		29 (19.2%)	32 (21.2%)	
pT4	26 (13.9%)	37 (19.4%)		23 (15.2%)	24 (15.9%)	
pN status (n, %)			0.393			0.746
pN0	115 (61.5%)	106 (55.5%)		88 (58.3%)	87 (57.6%)	
pN1	58 (31.0%)	72 (37.7%)		51 (33.8%)	55 (36.4%)	
pN2	14 (7.5%)	13 (6.8%)		12 (7.9%)	9 (6.0%)	

PSM; propensity score matching. SD; standard deviation.



Conclusions: Mediastinal lymph node dissection of more than 44 lymph nodes during combined mediastinal staging and resectional surgery is associated with worse overall survival in NSCLC patients. Aggressive lymph node dissection may impair anti-tumor immune responses.

Keywords: non-small cell lung cancer, lymph node dissection, immunity

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.05 Proteomic Analysis of Pleural Mesothelioma

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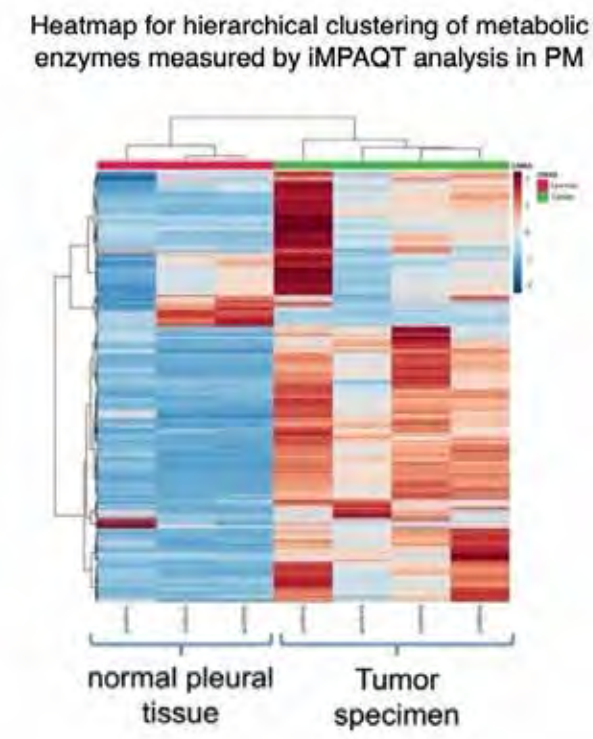
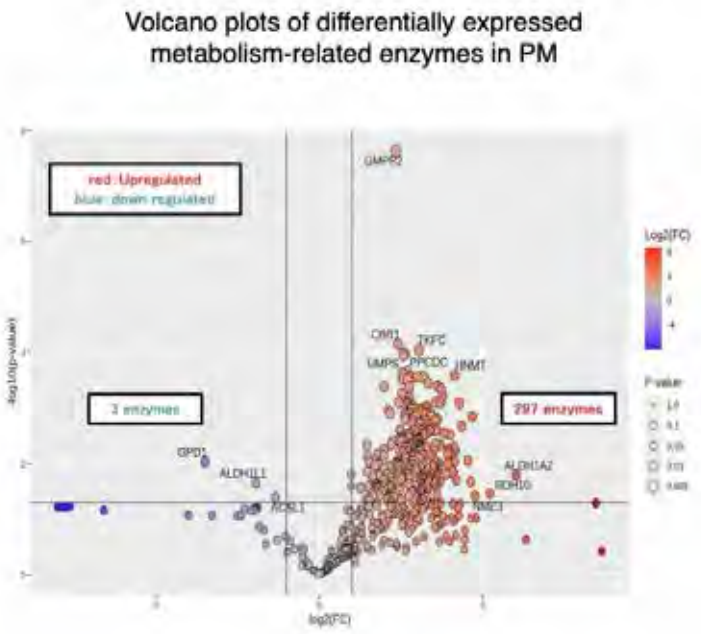
Introduction: Pleural mesothelioma (PM) represents one of the most aggressive and lethal human malignancies, arising within a highly specialized tumor microenvironment (TME). In recent years, cancer-associated metabolic reprogramming within the TME has emerged as a pivotal area of interest, particularly for enhancing the efficacy of immunotherapeutic approaches against various malignancies. However, the specific metabolic pathways that can be targeted in PM remain unclear. In this study, we conducted an in-depth proteomic analysis to elucidate the predominant metabolic pathways and key enzymes associated with PM.

Methods: Tumor specimen and corresponding normal pleural tissue samples were obtained from patients undergoing surgical resection for PM at our institution. The samples were processed into lysates and subjected to a large-scale targeted proteomics platform, known as in vitro proteome-assisted MRM for protein absolute quantification (iMPAQT). This platform allows for the absolute quantification of approximately 1100 metabolic enzymes.Principal-component analysis of protein expression level for the metabolic enzymes and gene set enrichment analysis were performed to compare expression level of enzymes between tumor and normal tissue.

Results: Our analysis identified 297 metabolic enzymes that were significantly upregulated in tumor samples compared to normal pleural tissue, while three enzymes were found to be decreased. Among various human metabolic pathways, the enzymes associated with the cofactor biosynthesis pathway demonstrated the most pronounced increase in tumors compared to normal pleural tissue. Notably, metabolic enzymes involved in folate metabolism, heme synthesis, and pyrimidine nucleotide metabolism were significantly upregulated in PM tumor samples.

Conclusions: This study has identified key metabolic pathways and enzymes within the TME of PM. These findings may serve as a foundation for developing novel therapeutic strategies for PM.





v**Keywords:** mesothelioma, proteomics

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.06 Integrated Bulk and Single-Cell Transcriptomics Reveals Immune Ecotype Heterogeneity in EGFR-Mutated Lung Adenocarcinoma

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Introduction: Over 50% of lung adenocarcinoma (LUAD) cases in non-smoking Asian populations exhibit EGFR mutations. However, these EGFR-mutated (EGFR-mut) patients often demonstrate limited responsiveness to immune checkpoint inhibitors (ICIs). Furthermore, there is scant clinical evidence supporting the efficacy of neoadjuvant targeted therapies in early-stage EGFR-mut LUAD, and most advanced-stage patients eventually develop resistance to targeted therapies. Therefore, it is essential to explore the characteristics of the tumor immune microenvironment in EGFR-mut tumors and to identify potential interventions that could improve the effectiveness of ICIs.

Methods: We prospectively collected 22 LUAD samples (August 2021-November 2023) for single-cell RNA sequencing (scRNA-seq) and retrospectively collected 141 LUAD samples (December 2023-June 2024) for bulk RNA sequencing (RNA-seq) at Shanghai Chest Hospital (SCH) from surgical resection patients without neoadjuvant therapy. Public RNA-seq data from 1515 LUAD cases were integrated to form two cohorts: a discovery cohort (SCH bulk data [n=141] + 876 public samples) and a validation cohort (22 SCH scRNA-seq samples + 639 public samples). Using EcoTyper, a machine-learning framework, we identified conserved LUAD cell states and ecotypes and analyzed their abundance differences between EGFR-mut and EGFR-wild-type (EGFR-wt) tumors. These cell states were further validated in the scRNA-seq dataset to enable single-cell functional characterization.

Results: Bulk RNA-seq included 141 patients (59 stage I, 60 stage IIA-IIIA, 22 stage IIIB-IV), and scRNA-seq encompassed 22 samples (3 AIS, 5 MIA, 6 stage I, 5 stage IIA-IIIA, 3 stage IIIB-IV). EGFR mutation subtypes (n[19del] = 47; n[L858R] = 48; n[wt] = 46) were balanced in SCH bulk data. Seven conserved LUAD ecotypes (E1-E7) were identified in discovery cohort and well recovered in validation cohort. EGFR-mut tumors exhibited elevated E5 (p=0.00014) and E6 (p=0.034) abundance but reduced E7 levels (p=0.024). Early-stage EGFR-mut cases showed diminished E2 abundance (p=0.015), an ecotype structurally resembling tertiary lymphoid structure (TLS) with B cells-S02, CD4T-S01, CD8T-S02, plasma cells-S02, and NK-S01. E2-enriched samples correlated strongly with TLS-associated gene signatures (p<0.0001). In a public neoadjuvant cohort (GSE207422, n=24), elevated baseline E2 abundance was associated with a higher likelihood of achieving major pathological response.

Conclusions: EGFR-mut tumors exhibits a distinct immune ecotypic profile characterized by enriched E5/E6 and diminished E7. The low abundance of E2, a TLS-like ecotype, in early-stage EGFR-mut patients suggests a relatively “immune-cold” microenvironment that may underlie poor ICI responsiveness. Specific mechanisms warrant further investigation to potentially provide more personalized treatment strategies for different immune subtypes.

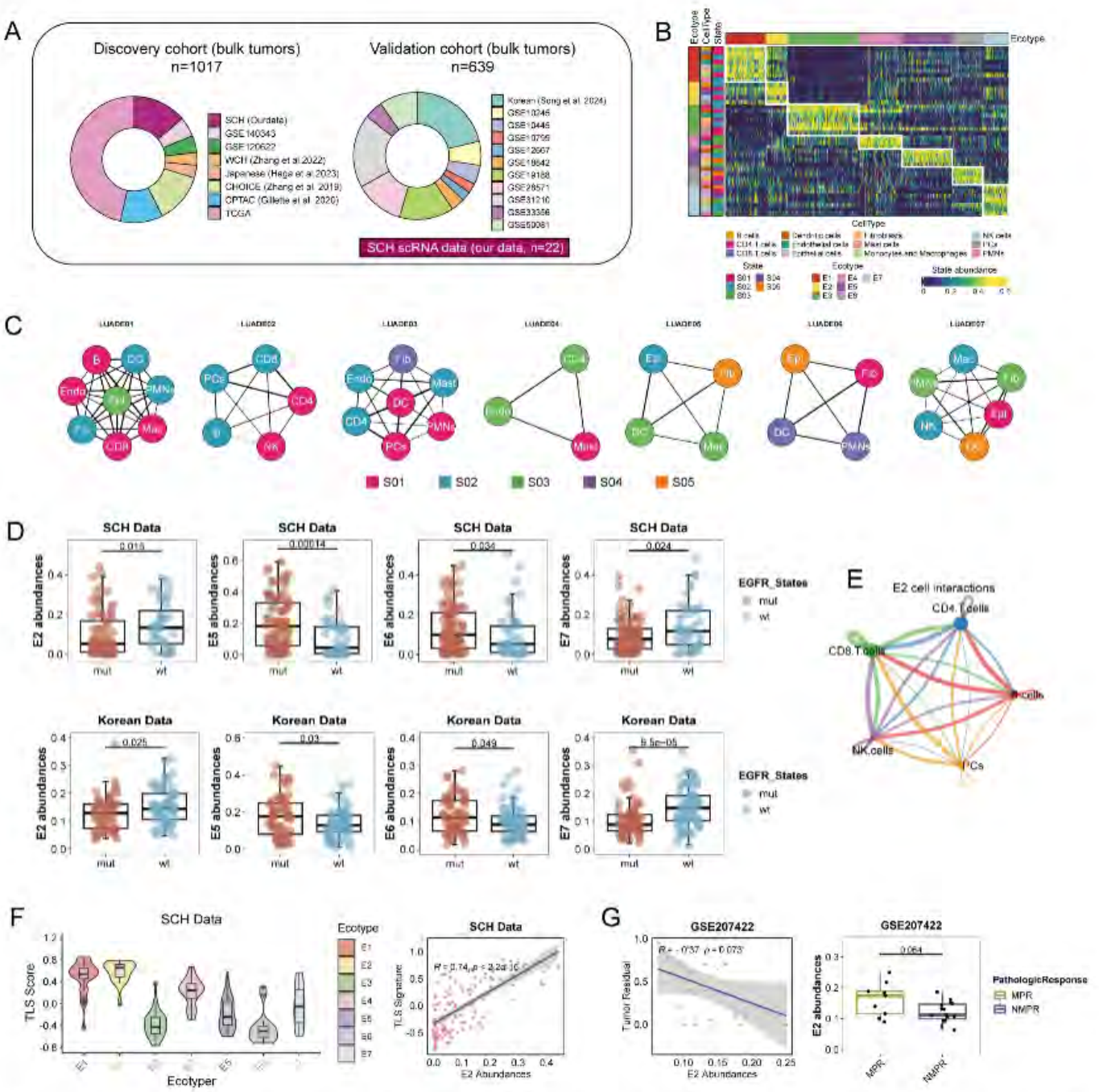

Figure Overview. (A) Discovery and validation cohorts employed for cell state and ecotype identification via EcoTyper. (B) Cell state abundance profiles in the discovery cohort, with cell states organized into seven ecotypes (E1–E7). (C) Ecotypes composition depicted as network diagrams. (D) Variations in E2, E5, E6 and E7 abundance between EGFR-mut and EGFR-wt patients. (E) The cell-cell interactions within E2 from CellChat. (F) Positive correlation between E2 abundance and TLS gene signature (GSVA score). (G) Association between E2 abundance and major pathological response (MPR) following neoadjuvant therapy.

Keywords: Lung adenocarcinoma, EGFR, Tumor microenvironment

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.07 Characterization of Live Cell Repository for Tumor Derived Pleural Mesothelioma Cells and Cancer Associated Fibroblasts

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Introduction: The use of primary cells cultivated from fresh patient material for research can overcome the limitations of long-term cell line cultures. Cancer-associated fibroblasts (CAFs) are a significant component of the tumor microenvironment, exhibiting heterogeneity and functional diversity. Here, we aimed at characterizing low-passage primary cultures of pleural mesothelioma (PM) enriched with PM and/or CAF cells to investigate cell-cell communication.

Methods: We generated primary cultures from 236 tissue specimens and characterized the doubling time of these cell cultures using MTT assays. Cell origin was evaluated by immunohistochemistry (IHC) with the epithelial marker pan-Cytokeratin (pan-CK), followed by mesothelial markers (podoplanin and WT1) in FFPE cell blocks. If corresponding tumor tissue was available, it was also assessed for the expression of tumor suppressor proteins often lost in PM, including BAP1 and p16. Cultures enriched for pan-CK negative cells were likely enriched with CAFs. We selected four cultures (CAF1-CAF4) showing complete pan-CK negativity for assessment of their functional heterogeneity. These cultures exhibited fibroblastic morphology and positivity for mesenchymal (Vimentin; VIM) and/or myofibroblast (α-SMA) markers. The intensity of these markers was scored as weak (1), moderate (2), and strong (3). Histo (H)-score (intensity multiplied by % positive cells, range 0-300) was calculated. VIM H-score was >250 in all cultures, while α-SMA was heterogeneous, ranging from negative H-score (<5), low (5-100), to high (>100). For co-culture experiments, we used two PM cells verified by extensive copy number variation, identical to the original tumor and non-PM cells generated from pleural effusion of patients without mesothelioma. Cell proliferation after co-culture was assessed using the mitotic marker Phospho-histone 3 (PH3) by immunofluorescent staining (IF), evaluated in tumor or mesothelial cells (pan-CK+) and fibroblast (pan-CK-) fractions. Additionally, we confirmed the findings using the proliferation marker Ki-67, assessed by flow cytometry.

Results: We identified 49 cell cultures with high expression of pan-CK (H-score >150). Among these, 31 cultures showed positivity for mesothelial cell markers or concordant BAP1 and p16 immunoreactivity with tumor tissues. We also identified 98 PM cultures expected to be enriched with fibroblasts (pan-CK H-score <150, median 29.8). The 4 cultures selected for co-culture experiments exhibited distinct doubling time (CAF1 (VIM+, SMAlow): 96.46 h; CAF2 (VIM+/SMA-: 111.4 h; CAF3 (VIM+/SMAhigh): 336.7 h; CAF4 (VIM+/SMA-): 137.3 h). In co-culture experiments assessing PH3, we observed a tendency for the CAF1 culture to inhibit the growth of both PM and non-PM cells, while other cultures did not. Due to the low number of PH3-positive cells, which led to high variability between experiments, we employed Ki-67 staining to further test the effect of CAF1 in tumor growth inhibition. Preliminary analysis of Ki-67 staining indeed indicated a tendency for reduced growth of PM and non-PM cells in the presence of CAF1 cells. Additionally, CAF2-4 proliferated less when co-cultured with tumor cells, while CAF1 did not.

Conclusions: Our study provides an initial characterization of a large repository of mesothelioma-derived cell cultures, composed of cells with heterogeneous characteristics and functions. These cell cultures can be utilized to investigate cell-cell communication and other tumor dynamics.

Keywords: mesothelioma, primary cells, cancer associated fibroblasts

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.08 Patient-Derived Tumour Organoids Recapitulate Keratinizing Lung Squamous Cell Carcinomas

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Introduction: Current treatment options for patients with lung cancer often have limited efficacy and significant toxicity, highlighting the need for more targeted and personalized approaches. However, many pre-clinical models fail to accurately represent intratumour heterogeneity and recapitulate the tumour microenvironment. This is partly responsible for the poor translation of clinical findings to approved therapies. Understanding the unique histological features that define lung cancer subtypes is essential to improving treatment options. Squamous cell carcinomas (SCCs) are the second most common subtype of lung cancer and are commonly pathologically diagnosed by the presence of keratinisation features, including keratin pearls, intracellular-bridges, abundant inflammation, and necrosis. Patient-derived organoids (PDOs) are 3D, self-organising tissue structures, derived from stem cells, which maintain tumour heterogeneity. Our objectives are to create a standardized protocol to develop lung cancer PDOs, to investigate the ability of PDOs to replicate the histological features of the keratinizing SCC subtype of lung cancer, and to use these models for drug testing studies.

Methods: Lung tumour tissue was obtained following surgical resection from consenting patients with lung cancer. PDOs were established from lung tumour tissue and maintained in CultrexTM extracellular matrix solution and specialised growth media. PDOs were imaged regularly to monitor expansion and morphology. PDOs were fixed in paraformaldehyde and immunofluorescent staining was performed to investigate the structural features of the organoid cultures, and to confirm expression of tumour markers and keratinocyte markers. PDO imaging data was compared with histopathological findings for the original tumour tissue using FFPE tissue blocks generated by the histopathology department of St. James's Hospital, Dublin.

Results: We created a standardized protocol to establish lung cancer PDO cultures from patients with lung adenocarcinomas and SCCs. We demonstrated that PDOs display patient-variable growth timelines but that the growth potential is not associated with the disease stage of the tumour. Importantly, PDOs were confirmed to express -tumour subtype-specific markers. Additionally, we established PDOs from patients presenting with invasive, keratinizing lung SCC. Keratin pearl structures spontaneously developed in these PDOs, matching the keratinizing pattern demonstrated by hematoxylin and eosin staining of the original tumours. These PDOs also demonstrated invasive features in culture, with cells migrating beyond the edges of the Cultrex™ gel and establishing 2D adherent layers outside the matrix. PDOs were confirmed to express lung SCC-specific markers, which were also expressed in the parent tissue. Additionally, PDOs were confirmed to express keratinocyte markers, further demonstrating recapitulation of histological features of the tumour. Future work involves treating these PDOs with standard-of-care therapies and comparing drug responses to the treatment outcomes of patients from whom the PDOs were developed.

Conclusions: PDOs have the capability to replicate key histological features of the original tumour, providing a more accurate reflection of tumour phenotypes, including keratin structures, which may impede drug delivery and better mimic hard-to-treat tumours. This highlights organoids as a valuable tool in pre-clinical drug testing. By better capturing tumour heterogeneity, organoid models have the potential to guide the development of novel targeted therapies and improve outcomes for patients with lung cancer.

Keywords: Patient-Derived Organoids, Squamous Cell Carcinoma, Keratinization

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.09 Synonymous Mutations in PDGFRA Exons 12 and 18 Correlate With Reduced Survival and Serum Iron Levels in Non-Small Cell Lung Cancer

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Introduction: PDGFRA (Platelet-Derived Growth Factor Receptor Alpha), a member of the receptor tyrosine kinase (RTK) family, serves as the receptor for platelet-derived growth factors (PDGF). It plays critical roles in tumor angiogenesis, tumor microenvironment maintenance, and normal vascular development. Aberrant PDGFRA signaling is implicated in gastrointestinal stromal tumors, hepatocellular carcinoma (HCC), glioblastoma (GBM) and so on. Recent studies highlight that synonymous mutations can modulate gene expression and protein function, contributing to disease pathogenesis.

Methods: We analyzed PDGFRA mutations in 302 patients with non-small cell lung cancer (NSCLC). Genetic testing results of patients were obtained using second or third generation sequencing data. The Chi-square test was employed to analyze the correlation between PDGFRA mutations and clinicopathological characteristics as well as treatment efficacy. Logistic regression analysis was used to assess the association between PDGFRA mutations and serum iron levels. Patient survival was analyzed using the Kaplan-Meier method, and comparisons were made using the Log-rank test. The COX regression model was applied for both univariate and multivariate risk analyses. Statistical analyses were performed using SPSS 27.0, and a P value < 0.05 was considered statistically significant.

Results: PDGFRA mutations were detected in 34.77% (105/302) of tumors, with a high prevalence of synonymous mutations in exon 12 (23.51%, 71/302). Co-occurring synonymous mutations in exons 12 and 18 were observed in 9.27% (28/302) of cases, while other mutations accounted for 1.99% (6/302). Compared to wild-type patients (median survival: 27.4 months), those with exon 12 mutations alone had reduced survival (24.2 months; P = 0.035), and patients with dual exon 12/18 mutations exhibited even worse outcomes (19.7 months; P < 0.0001). Notably, exon 18 mutations further diminished survival in exon 12-mutated cases (P = 0.036).PDGFRA mutations were associated with smoking (P = 0.069) and primary resistance to first-line chemoimmunotherapy (PD vs. DCR; P = 0.037). Intriguingly, dual exon 12/18 mutations correlated with decreased baseline serum iron levels (P < 0.0001), and multivariate analysis identified low serum iron as an independent risk factor for poor prognosis (HR = 4.216; P = 0.001).

Conclusions: In advanced NSCLC, co-occurring synonymous mutations in PDGFRA exons 12 and 18 may impair treatment response and survival via serum iron depletion. The underlying molecular mechanisms warrant further investigation.

Keywords: PDGFRA, Lung cancer, Chemoimmunotherapy resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.10 Establishment of Patient-Derived Organoids From EBUS-TBNA Cytological Samples in Lung Cancer Patients

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Introduction: One of the major challenges in the generation of lung cancer (LC) tumor organoids (LCOs) is their predominant derivation from surgical samples, and therefore, from patients in early stages of the disease. Obtaining samples from non-surgical patients is usually limited and often insufficient for organoid establishment and has, to date, focused on primary tumor sampling. In this study, we aimed to evaluate the effectiveness of growing LCOs using tumor cells that have undergone lymphatic metastasis, obtained through mediastinal endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and assess whether these organoids preserve the histopathological characteristics of the patients and can serve as a complementary diagnostic tool.

Methods: Cytological samples were obtained by EBUS-TBNA from 13 patients: 10 with non-small cell lung cancer (NSCLC) (7 adenocarcinomas, 2 squamous cell carcinomas, and 1 pleomorphic carcinoma) and 3 with small cell lung cancer (SCLC). The majority were metastatic patients (60%). The presence of tumor cells in all samples was confirmed by ROSE. Samples were enzymatically processed and cultured in Matrigel with an enriched medium optimized for LCO growth.

Results: Overall, the initial success rate of establishing LCOs from EBUS-TBNA samples was 61%. All SCLC samples were successfully established, while only 50% of NSCLC samples succeeded. Morphological analysis revealed differences compared to LCOs previously derived from primary tumor tissue in early stages. The new LCOs displayed larger growth and a “rosette”-like structure. Moreover, they retained the immunophenotypic characteristics of the primary tumors, with P40 expression in squamous subtypes and TTF1 in adenocarcinomas. The average culture time required to utilize LCO samples for immunohistochemistry was 20 days.

Conclusions: LCOs derived from EBUS-TBNA samples reproduce the histopathological features of the patient’s tumor, making them an innovative strategy to optimize sample utilization and study metastatic populations. Since EBUS-TBNA often needs to be repeated at different times due to insufficient sample volume for all currently required markers, we consider that LCOs emerge as a new potential source of material for these analyses, also paving the way for future personalized treatment studies.

Keywords: Cancer organoids, Lung cancer, EBUS-TBNA

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.11 Anlotinib Exerts a Protective Effect on Radiation Lung Injury Through the Regulation of the Immune Microenvironment Mediated by M2c Macrophages

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Introduction: Radiation-induced lung injury (RILI) is a prevalent complication associated with thoracic tumor radiotherapy. The aim of this study is to elucidate the role and mechanism of anlotinib in the progression of RILI.

Methods: The radiation pneumonia mouse model, idiopathic pulmonary fibrosis mouse model, and fibrotic cell model were successfully established. Pathological staining, qPCR, Western blot, ELISA, transcriptome sequencing, and cell co-culture experiments were employed to evaluate the protective effects of anlotinib on lung injury and elucidate its underlying biological mechanisms.

Results: 1.Anlotinib exhibits a protective effect against acute, subacute, and chronic radiation-induced lung injury.Compared with mice in the irradiation group, anlotinib treatment was found to ameliorate local hair loss, decrease acute inflammatory exudation and alveolar septum thickening, and suppress local collagen deposition as well as interstitial transformation of lung tissue.2.Anlotinib has the potential to delay the progression of bleomycin-induced idiopathic pulmonary fibrosis.Compared to the bleomycin injection group, anlotinib treatment mitigated weight loss in mice, decreased inflammatory cell infiltration and localized alveolar septum thickening, and inhibited collagen deposition as well as the interstitial transformation process within lung tissues.3.At the cellular level, anlotinib can inhibit the TGFβ-induced epithelial-mesenchymal transition process.At the cellular level, anlotinib inhibited the production and activity of TGF-β. Compared with the TGF-β1 induction group, anlotinib treatment significantly decreased the expression levels of mesenchymal markers.4.The progression of pulmonary fibrosis are intricately linked to alterations in the lung immune microenvironment mediated by macrophages.Transcriptome sequencing results indicated that the progression of pulmonary fibrosis were associated with significant enrichment of signaling pathways related to the immune microenvironment. Immunohistochemistry findings suggested that the antifibrotic effects of anlotinib were closely linked to changes in the lung tissue immune microenvironment mediated by M2-type macrophages.5.The protective effect of anlotinib on lung injury is intricately associated with M2c macrophages. The supernatant from the radiation-damaged cell culture medium (representing a radiation-damaged microenvironment) exhibited a tendency to promote the transformation of macrophages into the M2c subtype. Anlotinib demonstrated significant drug sensitivity towards M2c macrophages, effectively inhibiting the expression of M2c macrophage-associated active factors.

Conclusions: Anlotinib exhibits protective effects in both the lung injury mouse model and the fibrotic cell model. These protective effects are attributed to anlotinib's inhibition of TGFβ-induced epithelial-mesenchymal transition, its modulation of pulmonary immune microenvironment, and its suppression of M2c macrophages. In conclusion, anlotinib may serve as a promising candidate for the prevention and treatment of RILI.

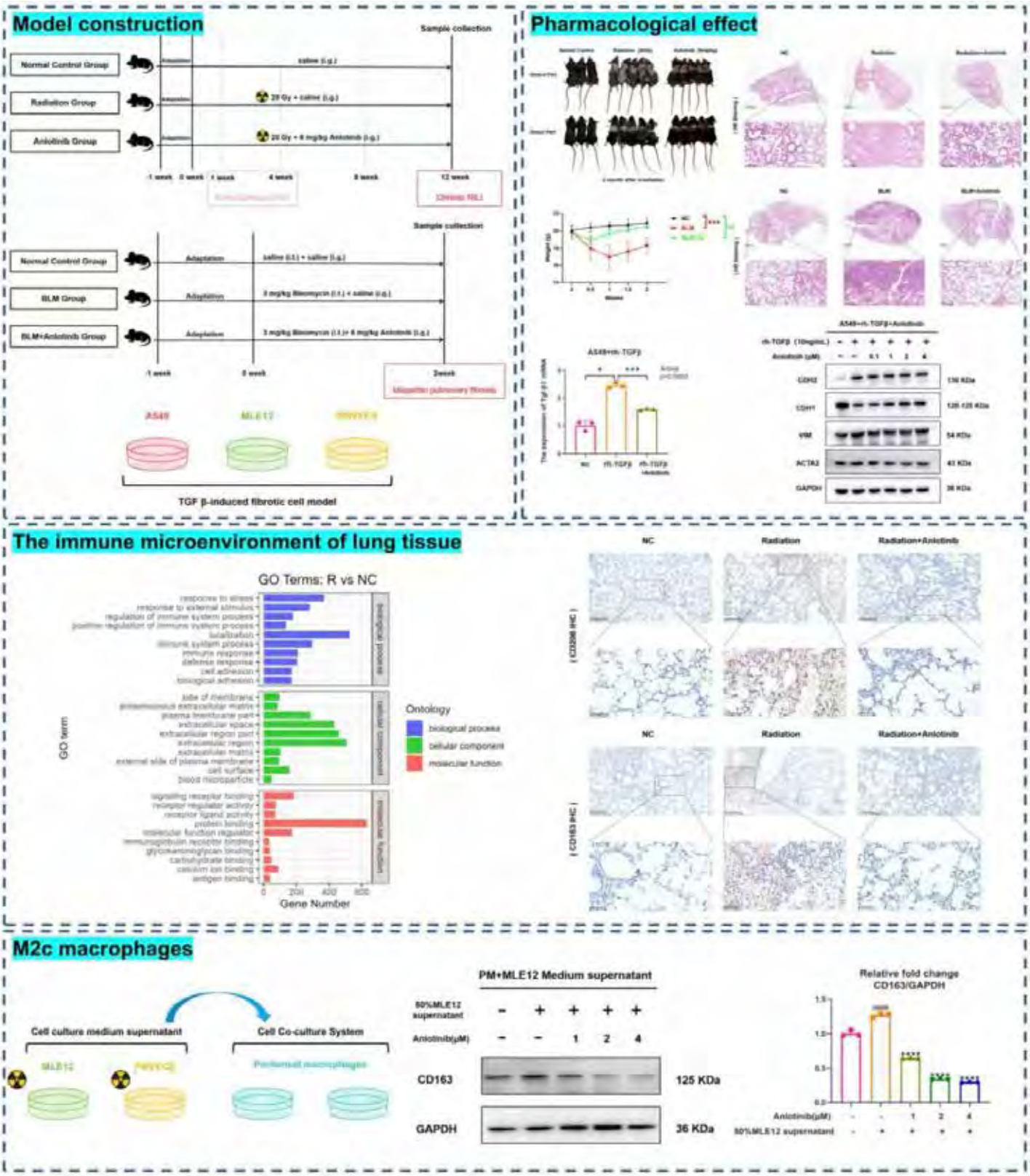

Illustration: The working flow chart of this study.

Keywords: Radiation-induced lung injury (RILI), Anlotinib, M2-type macrophages

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.12 YAP-Driven Modulation of HER3-Mediated Adaptive Resistance to RET Inhibitors in RET-Altered Cancer

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Introduction: Molecular targeted therapies have revolutionized cancer treatment, including RET-TKIs for RET fusion-positive tumors. Selpercatinib and pralsetinib have demonstrated high efficacy in lung and thyroid cancers; however, acquired resistance remains a major challenge. Resistance mechanisms involve on-target RET mutations (e.g., G810C/S/R) and off-target alterations, such as MAPK pathway reactivation and MET/FGFR1 amplification. Overcoming resistance is hindered by tumor evolution and heterogeneity. This study investigates adaptive resistance mechanisms during early RET-TKI treatment and explores novel therapeutic strategies to prevent resistance development, aiming to enhance treatment efficacy and improve clinical outcomes for patients with RET-aberrant cancers.

Methods: Four RET-aberrant cancer cell lines were tested for sensitivity to selpercatinib and pralsetinib. Resistance mechanisms were explored using RNA sequencing, phospho-RTK arrays, ChIP, and luciferase assays. Clinical specimens from RET fusion-positive lung cancer patients were analyzed for YAP expression and its correlation with treatment outcomes.

Results: Our study revealed that RET-aberrant cancer cells with low sensitivity to RET-TKIs exhibited ERK reactivation after prolonged treatment, suggesting adaptive resistance. Phospho-RTK profiling identified HER3 activation as a key mechanism underlying this resistance. HER3 knockdown suppressed ERK reactivation and enhanced sensitivity to RET-TKIs. Further analysis demonstrated that YAP activation, triggered by RET-TKI treatment, directly induced HER3 transcription. YAP knockdown inhibited HER3 expression, reducing resistance to RET-TKIs. High YAP expression correlated with poor RET-TKI response, and pharmacologic YAP or HER3 inhibition sensitized RET-aberrant cells to RET-TKIs. In vivo, co-administration of selpercatinib and afatinib significantly suppressed tumor growth compared to selpercatinib alone. A retrospective analysis of RET-fusion positive NSCLC patients showed that high pre-treatment cytoplasmic YAP expression was associated with shorter progression-free survival and overall survival following selpercatinib treatment. These findings suggest that YAP-HER3 axis activation drives adaptive resistance, and its inhibition may enhance RET-TKI efficacy in RET-aberrant cancers.

Conclusions: Our study highlights the critical role of the YAP-HER3 axis in mediating resistance to RET-TKIs in RET-aberrant cancer cells. We demonstrated that the activation of YAP and HER3 contributes to adaptive resistance, which remains a major hurdle in the effectiveness of molecular targeted therapy. Importantly, our findings suggest that co-targeting YAP and HER3 alongside RET-TKIs could provide a promising strategy to overcome this resistance and enhance therapeutic efficacy. Moreover, we identified a subset of patients with RET-aberrant cancers who exhibit low sensitivity to RET-TKIs, suggesting that these patients could benefit from a tailored treatment approach specifically targeting the YAP/HER3 axis. This novel therapeutic strategy has the potential to advance personalized medicine by refining patient selection and optimizing treatment regimens, ultimately leading to improved clinical outcomes for patients with RET-aberrant cancers. Further studies are warranted to validate these findings and explore the clinical applicability of YAP and HER3 inhibition in combination with RET-TKIs.

Keywords: RET, Drug resistance, YAP

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.13 HLA II Genetics Shapes Lung Cancer Immunosurveillance

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Introduction: The risk of developing cancer is one's lifetime is about 50% after the sixth decade of life and it is associated with internal factors such as inherited mutations in DNA repair genes, replication errors, and environmental factors. Lung cancer is the most common cancer worldwide and the leading cause of cancer-related deaths worldwide. Recent advances in immunotherapy demonstrate the need to understand the complex choreography of immune genetics and cancer risk, as well as how antigen presentation, particularly MHC molecules, shapes cancer immunosurveillance. MHC molecules are encoded by the polygenic HLA locus, which is the most polymorphic region of the human genome, therefore the possibility of presentation of diverse tumor antigens to the immune system. We hypothesize that germline heterozygosity at the HLA locus allows for binding of a greater repertoire of antigens that can be presented to the immune system, thereby decreasing lung cancer risk.

Methods: We used clinical and genetic information from over 390,000 individuals in the UK Biobank to study how HLA zygosity affects lung cancer risks among smokers. To study the mechanism behind this, we used a carcinogen murine model that allows us to assess tumor multiplicity across MHC homozygous and MHC heterozygous genotype groups. To explore how immune surveillance defers between genotypes, we used flow cytometry to explore early immunosurveillance across multiple mice genotypes and using cell lines we developed from the carcinogen model, we explored how tumor cell MHC II shapes tumor surveillance.

Results: We show that germline heterozygosity at the HLA class II loci confers decreased risk of cancer among smokers. Furthermore, we showed using murine models that maximal heterozygosity at the HLA locus (H2 in mice) leads to decrease tumor incidence, which we further show is due to increase in T lymphocytes in the tissue microenvironment at early tumor development. We further show using murine models that loss of HLA class II on the cancer cells as well as epithelial cells ameliorate this protective effect against cancer risks.

Conclusions: Our findings demonstrate that HLA class II heterozygosity enhances tumor immunosurveillance and reduces lung cancer risk, highlighting the critical role of immune genetics in cancer susceptibility. These results provide a foundation for developing immunopreventive strategies targeting MHC II neoantigens.

Keywords: Lung Cancer, immunosurveillance, Immunoprevention

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.14 PCSK9-Mediated Immune Escape as a Mechanism of Acquired Resistance to PD-1/PD-L1 Blockade

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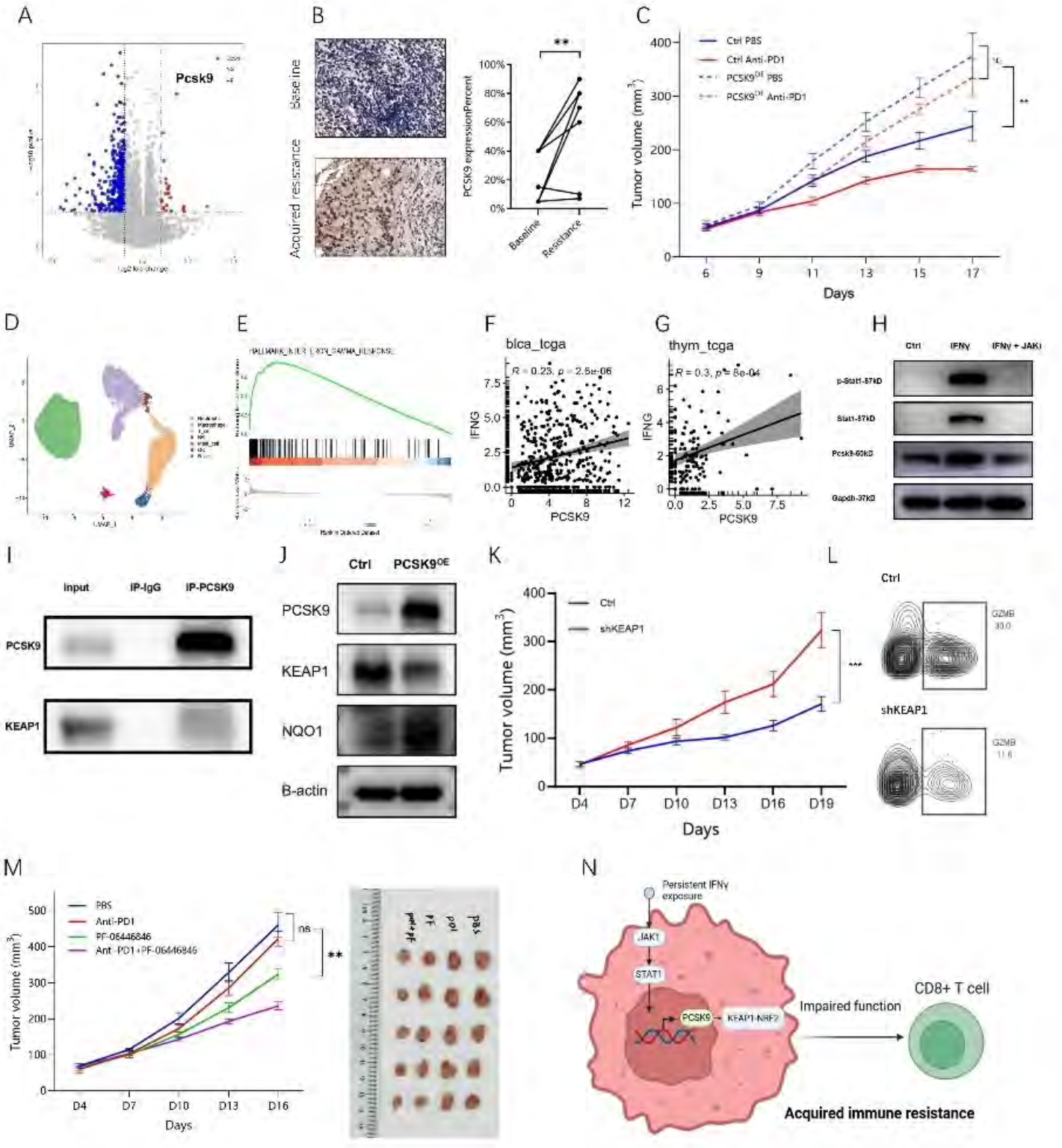
Introduction: Despite the significant clinical success of immune checkpoint blockade (ICB) in patients with non-small cell lung cancer (NSCLC), most patients developed acquired resistance during the treatment. Understanding the mechanisms of acquired immune resistance is essential for identifying novel therapeutic targets to overcome resistance.

Methods: We utilized patient-level data and a murine model to identify molecules associated with ICB resistance. An immune-resistant murine model was developed through chronically persistent ICB exposure, and single-cell RNA sequencing was conducted. The underlying mechanisms were evaluated using in vitro experiments, including western blot analysis, quantitative polymerase chain reaction, flow cytometry, immunofluorescence staining, and immunoprecipitation. In vivo experiments were conducted to investigate the efficacy of anti-PD1 therapy alone or in combination with various therapeutic strategies in immunocompetent mouse models.

Results: Through RNA sequencing and in vitro validation, we identified elevated PCSK9 expression in NSCLC patients with acquired resistance to ICB therapy compared to baseline tumors. PCSK9 overexpression impaired CD8+ T cell function, reducing the immune response to anti-PD1 therapy in vivo. Mechanistically, persistent IFN-γ stimulation induced PCSK9 upregulation via the JAK1-STAT1 pathway, which subsequently activated the KEAP1-NRF2 pathway, promoting immune evasion through dampening the function of CD8+ T cells. Inhibition of PCSK9 or JAK1-STAT1 pathway restored sensitivity to anti-PD1 treatment in immune-resistant models. Notably, the combination of PCSK9 inhibitor with anti-PD1 therapy demonstrated enhanced antitumor activity compared to monotherapy in immunocompetent mouse models.

Conclusions: Our preclinical study identified PCSK9 upregulation as a mechanism of acquired resistance to PD1/PD-L1 blockade in NSCLC. These findings support the therapeutic potential of combining PCSK9 inhibition with anti-PD1 therapy to overcome immune resistance. A phase II clinical trial investigating the efficacy of tolecimab (an anti-PCSK9 antibody) in combination with sintilimab (an anti-PD1 antibody) in NSCLC who have failed first-line Immunotherapy is currently ongoing (ChiCTR2500099426).



Keywords: NSCLC, immunotherapy, resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.15 Investigating Mechanisms of Resistance in EGFR-Mutated Non-Small Cell Lung Cancer Through High Resolution Transcriptomics

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Introduction: Non-Small Cell Lung Cancer (NSCLC) is the most common form of lung cancer. Most patients with NSCLC harbor epidermal growth factor receptor (EGFR) mutations like T790M/L858R (EGFRTL), L858R (EGFRLR), and exon 19 deletion (EGFRD19). While Osimertinib (Osi) is the standard treatment for patients with EGFR mutations, resistance to the drug inevitably develops, leading to therapeutic failure. The role of the tumor microenvironment (TME) in driving resistance remains underexplored, limiting the development of more effective therapies. Therefore, we employ in vitro models and genetically engineered mouse models (GEMMs) to investigate potential bypass mechanisms of Osi resistance using RNA sequencing (RNAseq), single-cell RNA sequencing (scRNAseq) and high-resolution transcriptomics.

Methods: In vitro studies: Osi-sensitive (OsiS) NSCLC cell lines (H1975 for EGFRTL; PC9 for EGFRD19; and H3255 for EGFRLR) were used to generate Osi-resistant (OsiR) cells, and RNAseq adopted to investigate resistance mechanisms. Differences in morphology, proliferation, migration and aggressiveness between OsiS and OsiR cells were assessed by microscopy, wound healing, cell cycle, and proliferation assays. Mitochondrial activity and morphology were analyzed using confocal microscopy and bioanalytical assays, including gas mass spectrometry and liquid chromatography.

In vivo studies: GEMMs harboring EGFR mutations (EGFRTL, EGFRLR , EGFRD19) were used to study resistance mechanisms in vivo (see Figure 1), with scRNAseq and spatial transcriptomics employed to explore gene expression changes and cellular interactions within the TME, focusing on the crosstalk between tumor and immune cells.

Results: In vitro studies revealed that H1975 OsiR cells exhibit increased migration, altered cell cycle dynamics, and nuclear structure abnormalities compared to OsiS cells, underscoring their more aggressive phenotype. Preliminary RNAseq analysis identified resistance-associated pathways, including mitochondrial dysfunction in Osi resistance. Metabolic profiling further uncovered mitochondrial and bioenergetic alterations in OsiR cells.

scRNAseq data from EGFR-mutant GEMMs revealed significant differences in tumor-immune infiltrates interaction compared to healthy controls. OsiR GEMMs are currently being interrogated by scRNAseq to elucidate resistance-driving pathways and TME crosstalk mechanisms.

Conclusions: By integrating high-resolution transcriptomics, in vivo models, and in vitro assays, this study provides novel insights into the molecular and cellular mechanisms of Osi resistance in EGFR-mutant NSCLC. These findings may pave the way to develop personalized therapies to address resistance, a major clinical challenge for patients with EGFR-mutant NSCLC.

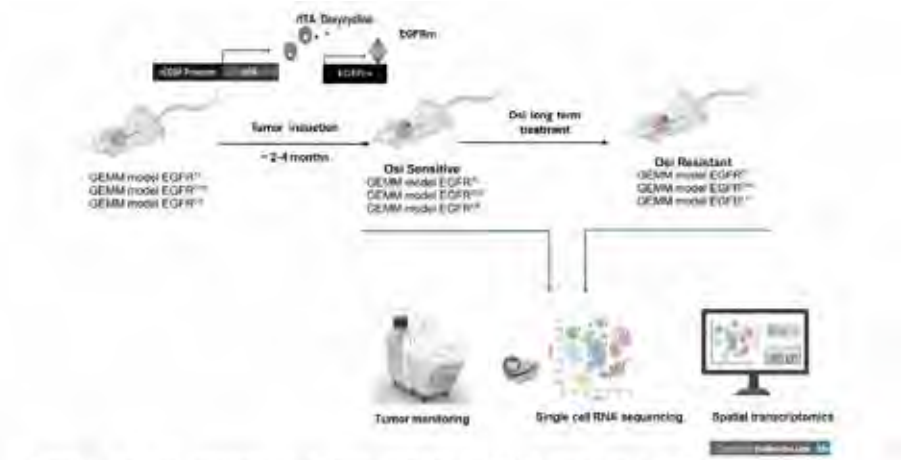

Figure 1: Graphical representation of tumor induction in GEMM models with EGFR mutations, tumor monitoring via MRI or MicroCT, generation of OsiR murine colonies, and high-resolution transcriptomic analysis comparing Osi-sensitive and Osi-resistant mice.

Keywords: Non-Small Cell Lung Cancer, Mouse models, Drug resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.16 CXCR2+ Neutrophils Influence Immunotherapy Efficacy in NSCLC Patients With KL Subtype

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Introduction: KRAS mutation is a common driver mutation in non-small cell lung cancer (NSCLC), and patients carrying this mutation may benefit from immunotherapy. However, patients with LKB1 deletion (KL subtype) rarely respond to immunotherapy, and the mechanism has not been clarified.

Methods: We retrospectively collected patients with KRAS mutation-positive advanced or postoperative recurrence NSCLC diagnosed in Shanghai Pulmonary Hospital from March 2024 to March 2025, and all patients received first-line chemotherapy combined with PD-1 monoclonal antibody therapy. We focused on analyzing the response of KRAS mutation combined with other mutations to immunotherapy. At the same time, the homologous KRASG12DLKB1−/−(KL) and KRASG12DTP53−/−(KP) lung cancer mouse models were respectively given different interventions and single cell sequencing was used to investigate the possible reasons for the non-response of KL subtype tumors to immunotherapy.

Results: A total of 137 patients were included in our analysis cohort, ranging in age from 48 to 88 years, with a median age of 69 years, including 114 males and 23 females. Of these, 33 patients had NGS results, 16 patients with TP53 mutations (KP subtype), 6 patients with LKB1 deletion (KL subtype), and the remaining 11 patients with other mutations or no mutations (other). Only 1 in 6 patients with the KL subtype achieved partial disease response (PR), compared to more than half of patients with the KP subtype (9/16). At present, PFS data is not mature. The single-cell sequencing results of animal models showed that there was a large number of neutrophils infiltrating in KL lung cancer, and CXCR2+ neutrophils were the main subgroup. When CXCR2 inhibitors combined with PD-1 monoclonal antibody were used to treat KL mouse tumors, it was found that the tumors of mice were significantly regression.

Conclusions: KL subtype patients are not sensitive to chemotherapy combined with immunotherapy. The infiltration of CXCR2+ neutrophil may be the key reason affecting the efficacy of chemoimmunotherapy in KRAS positive lung cancer. CXCR2 inhibitors may enhance the anti-tumor efficacy of PD-1 monoclonal antibody.

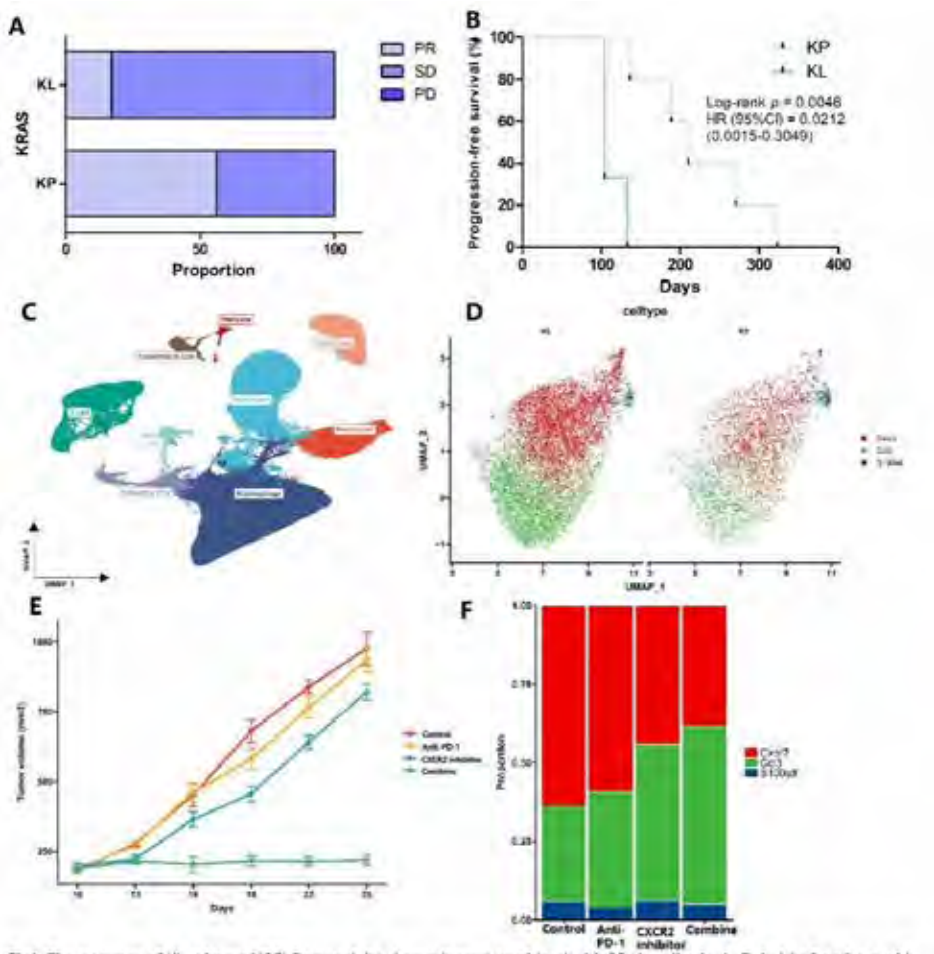

Fig1. The response of KL subtype NSCLC treated by chemotherapy combined with PD-1 antibody. A. Only 1 in 6 patients with the KL subtype achieved partial disease response (PR), compared to more than half of patients with the KP subtype (9/16). B. The PFS was longer in KP subtype patients compared with KL subtype. C-F. CXCR2+ neutrophils were the main subgroup in KL subtype. The KL mouse tumors were significantly regression when CXCR2 inhibitors combined with PD-1 monoclonal antibody were used to treat them.

Keywords: KRAS mutation, KL subtype, CXCR2+ neutrophils

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.17 Intermittent Caloric Restriction Synergies With KRAS(OFF) Inhibitors in Preclinical Models of KRASG12C Lung Adenocarcinoma

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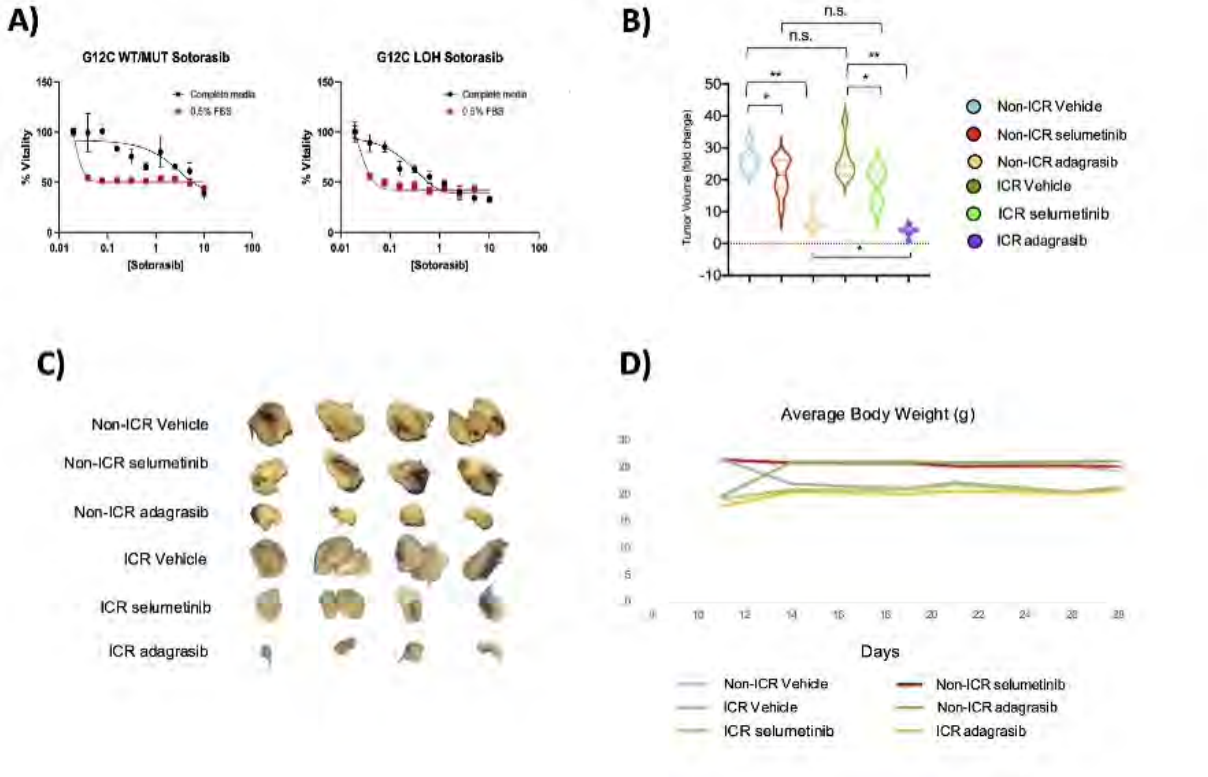
Introduction: The role of fasting-mimicking diets, including intermittent caloric restriction (ICR), in oncology remains controversial due to limited prospective evidence and an unclear mechanistic explainability, particularly in oncogene-driven non-small cell lung cancer (NSCLC). Given the rationale that promoting the GDP-bound state of KRAS may increase the availability of binding sites for KRAS(OFF) inhibitors, we investigated whether ICR could enhance their efficacy in preclinical models.

Methods: For in vitro studies, we utilized NRAS-/-; HRAS-/-; KRASlox/lox KRASG12C MEFs, both with and without loss of heterozygosity (LOH). Cells were cultured in either complete medium (CM) or nutrient-restricted (NR) medium containing 0.5% fetal bovine serum (FBS). Cells were treated with sotorasib with increasing concentrations to determine half-maximal inhibitory concentrations (IC50). For in vivo experiments, syngeneic murine lung adenocarcinoma (LUAD) cell lines were injected subcutaneously in C57BL/6 mice. Tumor volumes were measured every 48 hours using calipers, and final measurements were assessed post-mortem following surgical excision. ICR was implemented as 24 hours of complete fasting followed by 24 hours of ad libitum refeeding, repeated throughout the treatment course. We established six distinct treatment arms with 2 mice each combining ICR with either vehicle control, selumetinib (MEK-inhibitor), or adagrasib.

Results: In vitro experiments conducted on KRASG12C cell lines, with or without KRAS LOH, demonstrated lower IC50 values for sotorasib in cells cultured under NR conditions compared to those in CM (Figure 1A). In the in vivo experiment, all experimental groups underwent ICR for 27 days, while control groups were maintained on an ad libitum diet for the same duration. Tumor growth was most markedly reduced in the groups receiving adagrasib, consistent with its known efficacy (Figure 1B-C). Notably, mice treated with the combination of adagrasib and ICR exhibited a significantly lower median tumor volume increase compared to all other treatment groups ($p < 0.05$, Figure 1B). In contrast, vehicle- and selumetinib-treated groups displayed comparable tumor growth, with no significant differences observed between ICR and non-ICR conditions (Figure 1B-C). Regarding safety, longitudinal monitoring of body weight revealed no significant changes throughout the treatment period across all groups, indicating that ICR was well tolerated (Figure 1D).

Conclusions: These preliminary findings suggest that ICR specifically enhance the activity of KRAS(OFF) inhibitors in KRASG12C LUAD models. No safety concerns were observed during the in vivo experiments, supporting the potential feasibility of this combinatorial approach.

Figure 1. IC_{50} of the in vitro experiments (A), tumor volume changes (B), resected tumor specimens (C), and mice's body weight variations of in vivo experiments (D).



Keywords: KRAS, Intermittent Caloric Restriction, Targeted therapy

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.18 Single-Cell Transcriptomic Analyses of Lung Immune Cells Reveal That Mitf-Driven Plcb1HighMacrophages Induce Radiation-Induced Lung Injury

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Introduction: Radiation-induced lung injury is a significant clinical challenge, particularly due to the development of radiation pneumonitis. This study aimed to construct a mouse model of radiation-induced lung injury, identify macrophage subpopulations associated with radiation-induced pneumonia using single-cell transcriptome sequencing, and elucidate the molecular mechanisms underlying macrophage pro-inflammatory signaling.

Methods: A mouse model of radiation-induced lung injury was established by administering a thoracic irradiation dose of 15 Gy. The occurrence of radiation pneumonitis was confirmed using small-animal Micro-CT, HE staining, and Masson staining. Single-cell RNA sequencing was performed on 78,991 cells from nine samples, divided into three groups: non-irradiated, 7 days post-irradiation, and 30 days post-irradiation. Macrophages were analyzed using t-distributed stochastic neighbor embedding (tSNE) dimensionality reduction, and differential gene expression and Gene Ontology (GOBP) enrichment analyses were conducted. Transcriptional regulatory analysis was performed using SCENIC to identify key transcription factors.

Results: Analysis revealed a gradual increase in neutrophils and macrophages in the lungs post-irradiation. tSNE analysis identified eight macrophage subclusters, with cluster 0 being the most abundant and highly expressing genes such as Kcnip4, Ext1, Plcb1, Agap1, and Lrmda. Plcb1, associated with pro-inflammatory signaling and calcium regulation, was significantly upregulated in cluster 0. Monocle2 pseudotime trajectory analysis showed that clusters 0, 1, and 2 exhibited strong stemness characteristics. GOBP enrichment analysis indicated cluster 0 was enriched in pathways related to inflammatory responses, immune responses, and neutrophil recruitment. Cluster 0 cells secreted higher levels of chemokines (Ccl3, Ccl6, Cxcl2, Cxcl3), identifying them as pro-inflammatory macrophages (Plcb1high Macrophages). SCENIC analysis revealed Mitf as a key transcription factor in Plcb1high Macrophages, with high Regulon specificity and co-expression correlation with Plcb1 target genes. Mitf was implicated in promoting macrophage polarization and chemokine secretion, exacerbating inflammatory processes.

Conclusions: Mitf-mediated Plcb1high macrophages play a pro-inflammatory role in radiation-induced lung injury. These findings suggest that targeting Mitf could inhibit macrophage polarization and mitigate radiation-induced lung damage, offering a potential therapeutic strategy.

Keywords: Single-cell RNA sequencing, Macrophages, Radiation pneumonitis

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.19 SFRP2highCAFs Trigger CD8+T Cell Apoptosis to Sustain Abscopal Resistance to Radioimmunotherapy in Lkb1-Mutant Lung Tumors

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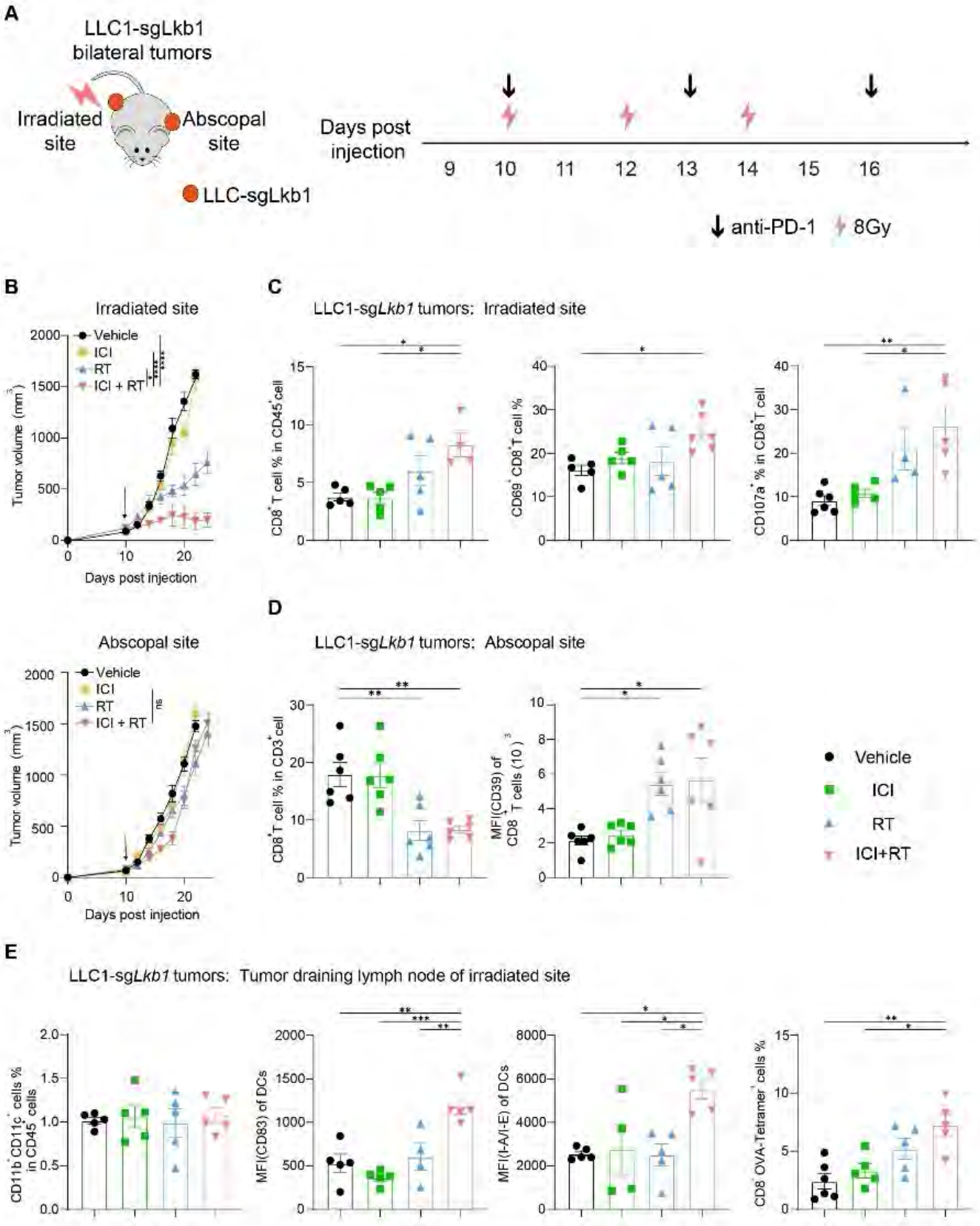
Introduction: Patients with LKB1-mutant tumors frequently exhibit primary resistance to immunotherapy, thereby limiting the efficacy of current treatment modalities. In this context, the integration of radiotherapy with immunotherapy, and its ability to induce an abscopal effect, offers a promising strategy to overcome this challenge. Nevertheless, the occurrence of abscopal responses following radioimmunotherapy remains lower than anticipated, and the underlying mechanisms restraining this effect are yet to be fully elucidated.

Methods: Murine bilateral lung tumor models (Lkb1-KO) were treated with radioimmunotherapy. Multi-compartment immune profiling was applied to assess differences in immune activation between the irradiated and distant tumors. In CAF-specific Sfrp2 knockout models, single-cell RNA sequencing was employed to elucidate the role of SFRP2-high CAFs, with subsequent validation performed via in vitro co-culture assays.

Results: In the bilateral Lkb1-KO lung tumor model, radioimmunotherapy, compared to monotherapy, markedly suppressed tumor growth in the irradiated field but not in the abscopal site. Multi-compartment immune profiling analyses demonstrated that radioimmunotherapy induced immune activation in irradiated tumors and elicited robust CD8+ T cell priming in tumor-draining lymph nodes. However, the LLC1-sgLkb1 model demonstrated suppressed CD8+ T cell infiltration in abscopal unirradiated tumors post-radioimmunotherapy. Further single-cell transcriptomic analyses revealed that Lkb1 deficiency orchestrates a dominant accumulation of SFRP2high cancer-associated fibroblasts (CAFs) within abscopal niches. These CAFs were found to upregulate transcriptional programs associated with T cell apoptosis while concurrently suppressing survival signals. In vitro co-culture assays further demonstrated that SFRP2high CAFs induce pronounced apoptosis in CD8+ T cells, thereby contributing to the diminished immune infiltration and the failure to control distant tumor growth.

Conclusions: This study uncovers SFRP2high CAFs as central executors of abscopal resistance in LKB1-mutant tumors, inducing CD8+ T cell apoptosis to undermine effective antitumor immunity. targeting SFRP2high CAFs may prevent CD8+ T cell apoptosis and reactivate the abscopal effect in LKB1-mutant lung cancer.


A
LLC1-sgLkb1
bilateral tumors
Irradiated site
Abscopal site
LLC-sgLkb1
Days post injection
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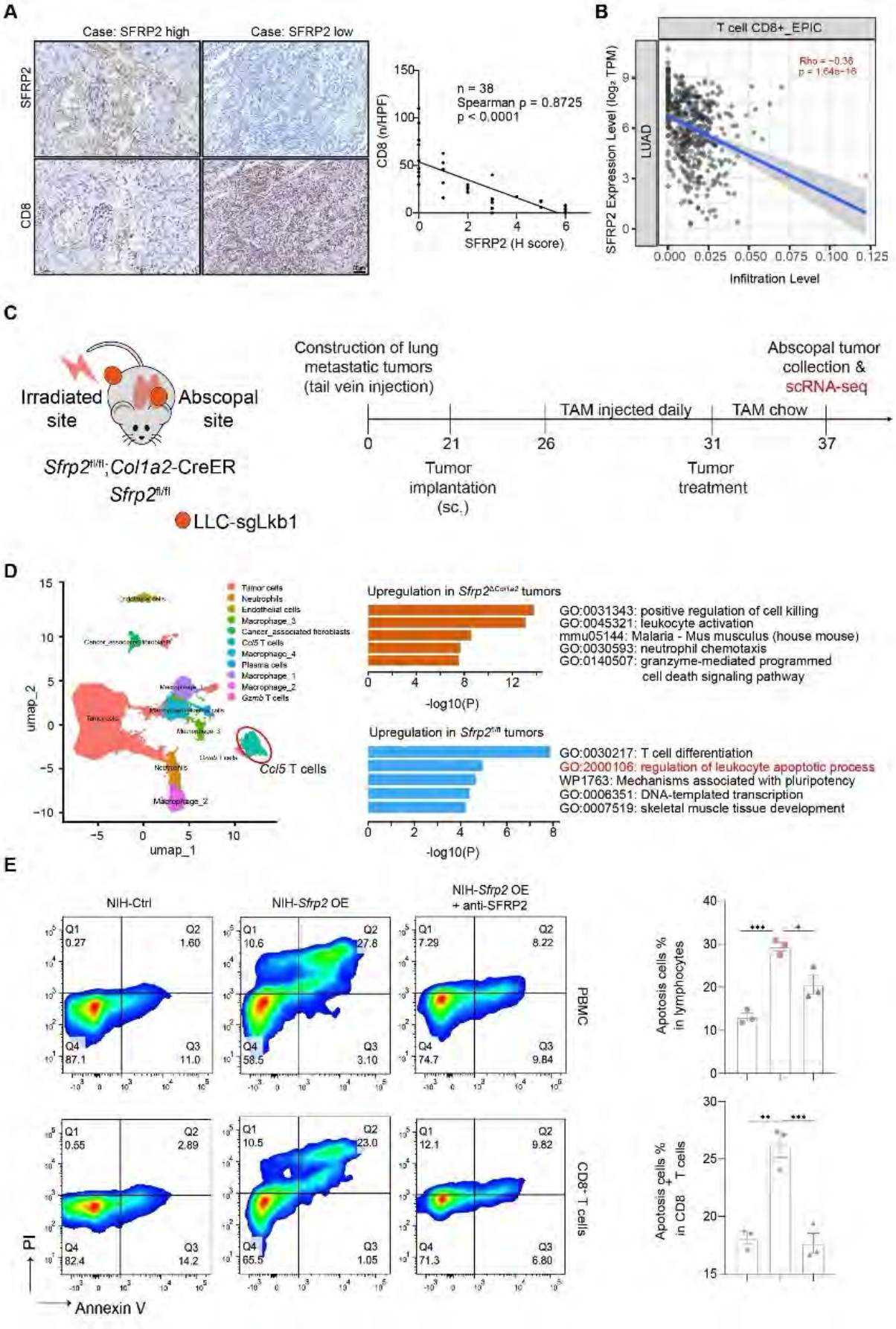
anti-PD-1
8Gy
B
Irradiated site
Vehicle
ICI
RT
ICI + RT
Tumor volume (mm3)
Days post injection
C
LLC1-sgLkb1 tumors: Irradiated site
CD8+ T cell % in CD45+ cell
CD69+ CD8+ T cell %
CD107a+ % in CD8+ T cell
D
Abscopal site
LLC1-sgLkb1 tumors: Abscopal site
CD8+ T cell % in CD3+ cell
MFI(CD39) of CD8+ T cells (10 3)
Vehicle
ICI
RT
ICI+RT
E
LLC1-sgLkb1 tumors: Tumor draining lymph node of irradiated site
CD11b+CD11c+ cells % in CD45+ cells
MFI(CD83) of DCs
MFI(I-A/I-E) of DCs
CD8+ OVA-Tetramer+ cells %



Keywords: Lkb1-Mutant Lung, Radioimmunotherapy, Abscopal Effect

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.21 Aptamer-Drug Conjugates for Leptomeningeal Carcinomatosis and Cancer-Associated Cachexia in Lung Cancer

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Introduction: Cancer-associated cachexia (CAC) occurs in up to 80% of the patients with advanced cancer, and leptomeningeal carcinomatosis (LM) developed in 3-10% of the patients with advanced-stage lung cancer. Treatment options for the LM are limited, and there is currently no U.S. FDA-approved pharmaceutical agent for the CAC. Aptamers are small oligonucleotides considered as chemical antibodies. Here we report the APC2, a novel aptamer-cisplatin conjugate, for the LM and CAC in lung cancer.

Methods: The lung cancer LM orthotopic mouse model served as the platform for aptamer identification (in vivo SELEX) and the model for the CAC. The aptamer was conjugated with cisplatin to form APC2. This study compared the efficacy of APC2 plus pemetrexed vs cisplatin plus pemetrexed for body weight maintenance and tumor suppression in mice bearing LM and CAC. The drugs were administered intravenously, the mouse body weight was measured daily, and the tumor burden was monitored via the In Vivo Imaging System.

Results: The APC2 showed a ~3% blood-brain barrier penetration rate. Signals for AP2, the backbone aptamer for the APC2, were detected in the brain regions related to the CAC. Efficacy studies showed that APC2 plus pemetrexed worked better than cisplatin plus pemetrexed for both body weight maintenance and tumor control. The circulating IL-6 levels were lower in the APC2 plus pemetrexed treatment group.

Conclusions: The APC2 is a novel aptamer-cisplatin conjugate that possessed a 3% blood-brain barrier penetration rate. The APC2 plus pemetrexed represents a new approach for lung cancer LM and CAC. Although further studies on mechanism elucidation are necessary, our data suggests its future translational potential.

Keywords: Aptamer-drug conjugate, Leptomeningeal carcinomatosis, Cancer-Associated Cachexia

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.22 Tumor Treating Fields (TTFields) Downregulate DNA Repair and Show Efficacy in Small Cell Lung Carcinoma Preclinical Models

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[1]Novocure Ltd, Haifa/IL ,[2]Novocure Inc, Fort Lauderdale/FL/USA ,[3]Novocure GmbH, Baar/CH

Introduction: Small cell lung cancer (SCLC) is a highly aggressive malignancy, representing 10-15% of all lung cancer cases. Current standard-treatment includes combination chemotherapy with a platinum-based agent plus etoposide, administered alongside immunotherapy and concurrent thoracic radiotherapy. The study described herein aimed to examine the efficacy of TTFields for treatment of SCLC and examine the effect of TTFields together with the standard chemotherapy agents.

Methods: Human SCLC cell lines H196 and DMS-53 were treated with TTFields (H196: 1.62 V/cm RMS, 150 kHz, 120 h; DMS-53: 1 V/cm RMS, 150 kHz, 72 h), alone or with the cisplatin and etoposide (H196: 0.15 µM cisplatin, 0.3 µM etoposide; DMS-53: 0.25 µM cisplatin, 0.5 µM etoposide). Efficacy was measured by analyzing cell count, colony formation, and apoptosis induction. The overall effect was calculated by multiplying cell count with colony formation. Expression of proteins from the Fanconi-Anemia-BRCA pathway for DNA repair was examined using western blot analysis. DNA damage was tested with fluorescence microscopy detection of H2AX. TTFields efficacy was further evaluated in vivo, in mice orthotopically inoculated with murine KP3 SCLC cells. 7 days after inoculation, TTFields or sham-heat were continuous applied for 9 days. Tumor volume was examined by magnetic resonance imaging (MRI) at treatment end. Tumor weight was also measured.

Results: TTFields reduced cell count, induced apoptosis, and provided an increased overall effect relative to control in both cell lines. While cisplatin plus etoposide also demonstrated efficacy by these measures, the effects were augmented when TTFields were applied concomitantly with these chemotherapies. TTFields downregulated the expression of proteins from the Fanconi-Anemia-BRCA pathway: BRCA2, FANCJ, FANCD2, and FANCA in both cell lines. TTFields alone, as well as cisplatin plus etoposide, had limited effect on DNA damage, while co-application of these treatments significantly elevated DNA damage relative to control and to the two treatment options alone (i.e. TTFields and cisplatin plus etoposide). Furthermore, TTFields significantly reduced tumor growth relative to control in the mouse model.

Conclusions: Our results demonstrate efficacy of TTFields for the treatment of SCLC in preclinical models, and a potential advantage for TTFields concomitant with standard-of-care chemotherapies. The enhanced efficacy of cisplatin and etoposide with TTFields may be attributed to the induction of DNA damage and downregulation of key DNA repair pathways by TTFields. Future studies will include immunotherapies together with TTFields and combination chemotherapy.

Keywords: Tumor Treating Fields, SCLC, cisplatin and etoposide

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.23 Circular Rna Vaccine Synergizes With Anti-PD-1 to Augment Therapeutic Efficacy in Lung Cancer

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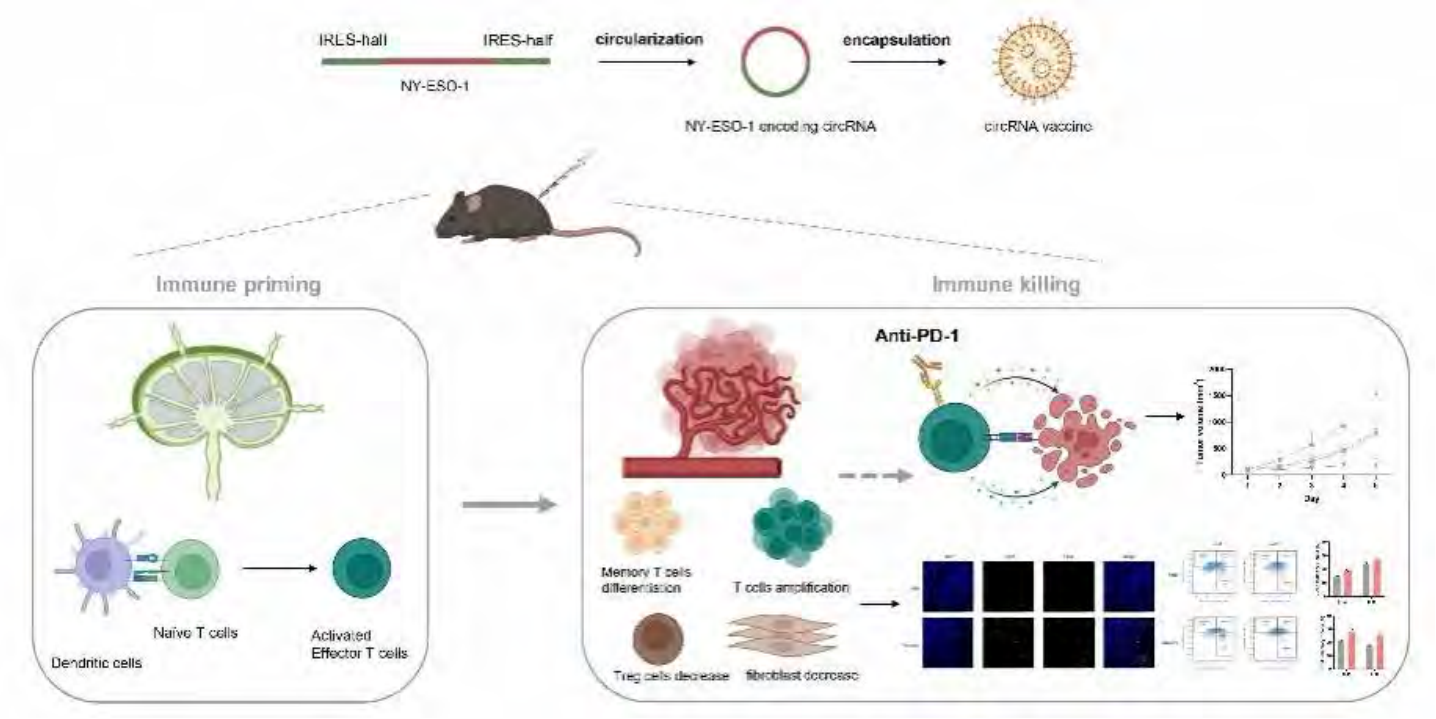
Peking University People's Hospital, Beijing/CN

Introduction: The successful deployment of RNA vaccines in infectious disease has accelerated the exploration of RNA-based platforms for cancer immunotherapy. Circular RNA (circRNA), characterized by its covalently closed structure, has emerged as a promising candidate for cancer vaccine development due to superior stability, prolonged half-life, and scalable manufacturing compared to linear mRNA. Here, we report a novel circRNA vaccine for its prophylactic efficacy and synergistic therapeutic potential with anti-PD-1 for lung cancer treatment.

Methods: The circRNA vaccine encoding NY-ESO-1 (a highly immunogenic cancer-testis antigen) was synthesized using our proprietary circular RNA platform and encapsulated in lipid nanoparticles. A mouse lung cancer model was established by subcutaneous implantation of LLC cells overexpressing NY-ESO-1. Tumor-infiltrating immune profiles were analyzed via immunofluorescence and single-cell transcriptome sequencing.

Results: The circRNA vaccine showed superior therapeutic efficacy compared to its mRNA counterpart, with a significantly increased proportion of apoptotic cells and decreased proliferating cells in tumor tissues after vaccination. Immunofluorescence staining revealed enhanced CD8+ T cells infiltration and reduced Treg cells population in the tumor microenvironment (TME). Additionally, the preliminary results of single-cell transcriptome sequencing showed that vaccination-induced alterations in the immune cell landscape. Increased infiltration of T cells and dendritic cells in tumor indicating enhanced antigen presentation and T cell activation, and decreased fibroblasts and endothelial cells potentially associated with inhibited tumor invasion and metastasis. In prophylactic models, intramuscular vaccination of circRNA vaccine significantly inhibited tumor growth and prolonged survival. Mechanistically, increased mature dendritic cells and memory-phenotype T cells in tumor tissues with corresponding decreases in the spleen, suggesting migratory infiltration. Given the low clinical responsiveness of lung cancer to immunotherapy, we investigated the synergistic effect of circRNA vaccine with anti-PD-1. Combination therapy significantly improved therapeutic outcomes, achieving over 90% tumor inhibition rata with complete response in 1/5 mice.

Conclusions: Our novel circRNA vaccine exhibits superior prophylactic and therapeutic effects against lung cancer, particularly through synergistic enhancement of immune checkpoint inhibitors. The vaccine mediates TME remodeling by promoting inflammatory transformation. This study proposes a promising strategy for lung cancer patients.



Keywords: RNA vaccine, immunotherapy, tumor microenvironment

P3.03.24 Oxydock: Optimizing Lung Cancer-Targeted Therapy Through Oxygen-Responsive Molecular Docking

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Introduction: Tumor hypoxia in lung cancer tumor microenvironment (TME) is highly prevalent. Through various adaptations, cancer cells not only thrive in hypoxia but are also resistant to treatment including novel targeted therapies. Computational docking has revolutionized drug discovery for lung cancer, but hypoxic TME poses significant challenges for making reliable predictions by altering protein structures. Current programs, such as AutoDock Vina, do not account for hypoxia-induced protein structural changes, leading to discrepancies between its predictions and in-vivo outcomes. In this study, we aimed to engineer an in-silico docking platform for accurate prediction in hypoxic lung cancer TME.

Methods: We created 'OxyDock', a novel docking platform that integrates hypoxia-driven post-translational modifications (PTMs), including phosphorylation, acetylation, and methylation into its algorithm enabling binding prediction in both normoxic and hypoxic conditions. The platform was created from scratch by modifying the 3D structures of proteins and ligands obtained from PDB files and PubChem. Eleven receptor-ligand pairs were selected for validating and training of OxyDock based on published experimental IC_{50} data in normoxia and hypoxia. XGBoost machine learning model was used to further refine the docking simulator based on experimental data. IC_{50} values were converted into binding affinities (ΔG) using the Cheng-Prusoff equation. Relationship between OxyDock's predicted ΔG values and experimental data was assessed using Pearson's correlation. We conducted linear regression for each drug-protein pair to model relationship between predicted and experimental ΔG values (fig 1). Root Mean Squared Error (RMSE) for both OxyDock and AutoDock Vina predictions was calculated and Bland-Altman plots used to visualize the agreement between experimental and predicted ΔG values. We also performed feature importance analysis to determine key factors influencing binding affinity predictions by XGBoost model.

Results: OxyDock outperformed Autodock Vina, achieving a RMSE of 1.16 kcal/mol compared to 2.85 kcal/mol for AutoDock Vina, with stronger correlation to experimental binding (r = 0.95 vs. r = 0.85). OxyDock's predictions were also accurate in 'outlier' situations such as Erlotinib-EGFR interaction, wherein the binding is stronger in hypoxia. Oxydock accurately predicted a higher binding affinity (ΔG = -8.7 kcal/mol) in hypoxia compared to normoxia (ΔG = -8.01 kcal/mol), mimicking experimental findings. This was possible because of XGBoost integration whose most important features were mainly ligand properties such as molecular weight and partition coefficient.

Conclusions: Our data supports the superiority of OxyDock over AutoDock in predicting drug binding under physiologically relevant conditions, making it a promising tool for designing targeted therapies for lung cancer.

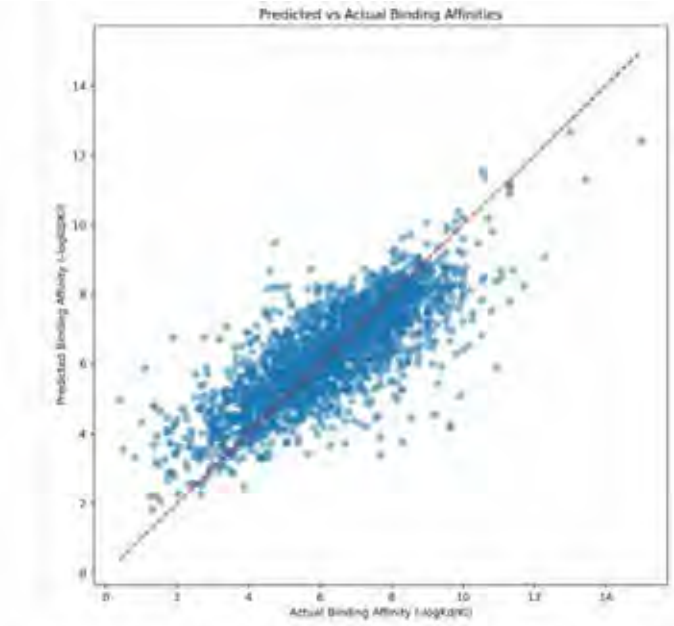

Figure 1: *Predicted vs. actual binding affinities for OxyDock simulations. Each point on the scatter plot represents a different protein-drug pair with X-axis representing the binding affinities predicted by OxyDock and the Y-axis showing the actual experimental binding affinities. The red line represents the line of perfect correlation. If a point is close to this red line, it means that OxyDock's prediction is very close to the actual experimental result.*

Keywords: Hypoxic tumor microenvironment, Molecular docking, Post-translational modifications

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.25 A Combination Therapy Strategy That Targets Both KRAS-G12C and GSK3 for Non-Small Cell Lung Cancer

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[1]Fujian Medical University Union Hospital, Fuzhou/CN ,[2]Xiamen University, Xiamen/CN

Introduction: Lung cancer is the leading cause of cancer mortality, and nearly 80% of cases are non-small cell lung cancer (NSCLC). KRAS mutants, including G12C, are critical cancer drivers that used to be difficult to drug Despite progresses in allosteric KRAS-G12C inhibitors, e.g. sotorasib and adagrasib,, their drug response is still suboptimal. Here, we employ a high-throughput drug screening pipeline to identify compounds that potentially sensitize NSCLC to KRAS-G12C inhibitors, and further investigated the molecular pharmacological mechanisms.

Methods: We screened nearly 6,000 compounds and 16 classes of novel targets that synergize with the KRAS G12C inhibitor sotorasib to suppress KRAS G12C-mutant NSCLC cell lines. Drug synergy was scored using the HSA (Highest Single Agent) and Bliss independence models. Promising synergistic combinations were further validated through low-throughput assays to prioritize candidates with optimal Chou-Talalay combination indices (CI values). RNA-seq was employed to investigate the molecular output of combination therapy, and the nominated downstream pathways and targeted molecules were further interrogated via biochemical and cell biology methods.

Results: The GSK3 inhibitor LY2090314 emerges as a compound that sensitizes NSCLC cell lines to KRAS G12C inhibitors. LY2090314 and KRAS-G12C inhibitors synergized to induce the apoptosis of lung adenocarcinoma and squamous cell carcinoma cell lines, and suppressed the growth of lung tumor xenografts. Interestingly, LY2090314 played the tumor suppressive role by targeting GSK3β, but the mechanism was not dependent on Wnt/β-catenin signaling pathway. We uncovered multiple affected metabolic pathways promoting reactive oxygen species (ROS) that may at least partially account for the synergistic effect. Blocking ROS rescued the cancer cell lines from the KRAS-GSK3 combination therapy. We will employ CRISPR knockout to further validate the target.

Conclusions: We uncovered a GSK3 inhibitor LY2090314 that sensitized NSCLC to KRAS-G12C inhibitors, and proposed a new pharmacological mechanism for the combination therapy. Notably, LY2090314 previously went through a Phase-2 clinical trial for leukemia that had validated its safety. Therefore, our repurposing has potential to translate into clinical therapies that may benefit cancer patients harboring KRAS-G12C mutations.

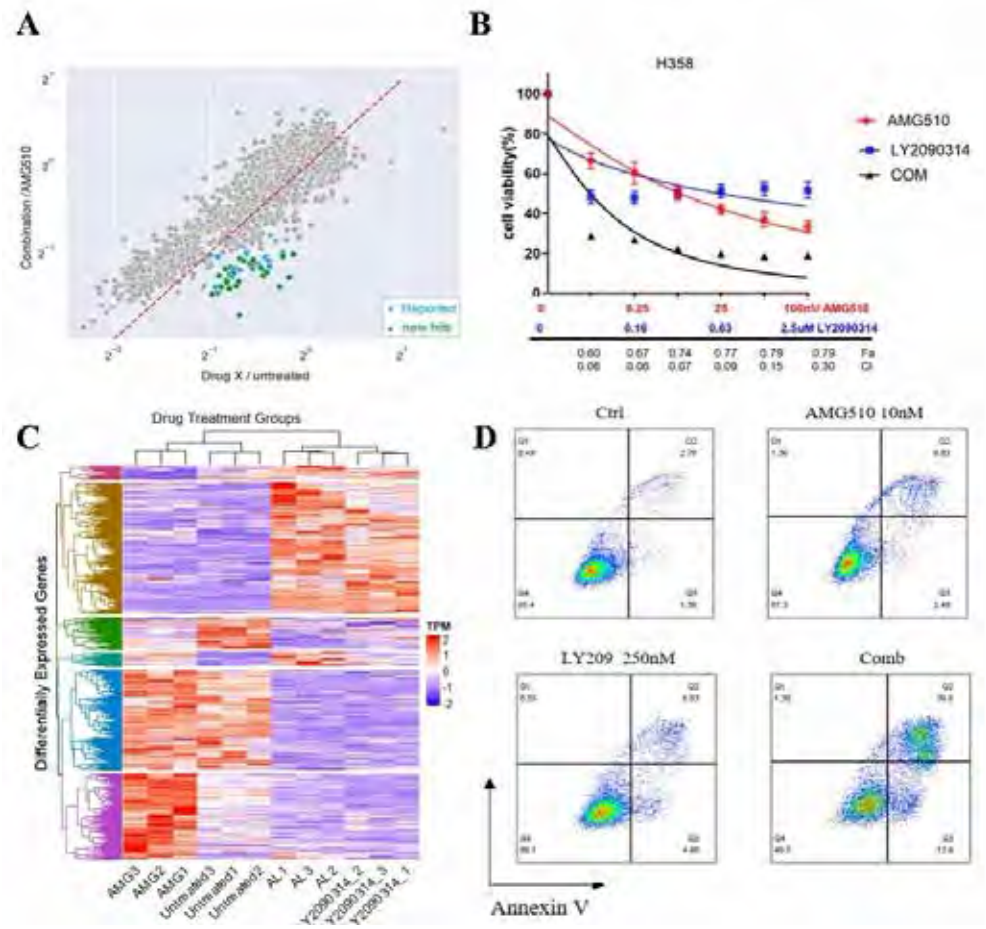

Figure. High-throughput drug screening reveals that GSK3 inhibition synergistically enhances the efficacy of KRAS G12C inhibitors in KRAS G12C-mutant lung cancer.

Keywords: KRAS G12C, high-throughput drug screening, drug combination

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.26 Ir-Metal Framework Loaded With Radiation-Responsive Anti-Angiogenic Prodrugs for Enhanced Radiotherapy Efficacy

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Introduction: The efficacy of radiotherapy is often hindered by radioresistance, particularly in tumor hypoxia and abnormal angiogenesis.

Methods: This study presents a novel approach using the iridium metal framework (Ir-MF), pazopanib prodrug (P), and SH-Polyethylene Glycol-NH2 (SH-PEG-NH2)-based Ir-MF@PP system to enhance the efficacy of radiotherapy. The Ir-MF serves as both a carrier and radiosensitizer, combined with a radiation-responsive anti-angiogenic pazopanib prodrug for targeted vascular delivery.

Results: The Ir-MF sensitizes tumor cells to radiotherapy by generating reactive oxygen species (ROS), allowing for effective treatment at lower doses while minimizing damage to healthy tissues. Furthermore, radiotherapy triggers the controlled release of pazopanib, a multi-targeted tyrosine kinase inhibitor primarily targeting vascular endothelial growth factor (VEGF), to normalize tumor vasculature, improving blood perfusion and oxygenation. This dual strategy not only increases local drug concentration and safety but also enhances the overall efficacy of radiotherapy by addressing the tumor hypoxia and abnormal blood supply.

Conclusions: Its effectiveness has been validated at both the cellular and animal levels, where it sensitizes tumors to radiotherapy either directly through Ir-MF or indirectly by inducing vascular normalization, thereby enhancing treatment efficacy and achieving superior tumor killing effects, paving the way for more precise and effective lung cancer treatments.

Keywords: lung cancer, radiation-responsive, Anti-Angiogenic Prodrugs

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.27 The TXNRD1-IGF2BP3 Axis Promotes EGFR-TKI Resistance and Identifies a Therapeutic Vulnerability in NSCLC

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Introduction: Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) remains a major challenge in non-small cell lung cancer (NSCLC). The thioredoxin reductase-1 (TrxR1) system plays a critical role in cellular redox homeostasis. Thioredoxin-1 (Trx1) encoded by the TXN1 gene, reduces reactive oxygen species (ROS), while TrxR1, encoded by the TXNRD1 gene, catalyzes the reduction of oxidized Trx1. Given the upregulation of the Trx1 pathway in cancer, the TrxR1 system may be a potential non-oncogene addiction target for overcoming acquired resistance.

Methods: Data-independent acquisition mass spectrometry (DIA-MS) was used for plasma proteomic profiling. Immunoprecipitation mass spectrometry (IP-MS) identified protein interactions, and RNA sequencing (RNA-seq) screened transcripts. Lentiviral transfection was employed to generate TXNRD1-overexpressing (oe) cell lines, mouse xenograft models were established to assess therapeutic efficacy. The HCC827 rezivertinib-resistant cell line (RR) was generated by continuous exposure to rezivertinib (BPI-7711) until reaching 100-fold of the initial IC50.

Results: Elevated Trx1 protein levels in plasma correlated with reduced sensitivity to BPI-7711, a third-generation EGFR-TKI, in NSCLC patients (Fig. 1A). Similarly, in resistant xenograft models, increased serum Trx1 expression was also associated with diminished EGFR-TKI efficacy (Fig. 1B). While Trx1 protein expression showed no significant difference between HCC827/RR and parental cells, TrxR1 protein levels were notably higher in HCC827/RR cells (Fig. 1C-D), indicating that TXNRD1 may be the key driver of resistance. Overexpression of TXNRD1 in HCC827 cell lines enhanced resistance to BPI-7711, decreased intracellular ROS levels, and attenuated EGFR-TKI-induced apoptosis (Fig. 1D-G). Transcriptomic profiling of HCC827 versus HCC827/RR cells (Group 1), and TXNRD1-oe versus control cells (Group 2), identified three differentially expressed genes through integrative analysis with IP-MS data from Group 2. Based on expression dynamics and specificity, IGF2BP3 was validated as a TXNRD1 downstream effector, whose upregulation was confirmed in both resistant and TXNRD1-oe cell lines via co-immunoprecipitation and Western blot (Fig. 1H-L). Mechanistically, IGF2BP3 mediates EGFR-TKI resistance by facilitating a metabolic shift from glycolysis to oxidative phosphorylation. Kaplan-Meier analysis of public datasets revealed that concurrent high expression of TXNRD1 and IGF2BP3 was associated with the poorest overall survival in NSCLC (Fig. 1M). Notably, combining the TrxR1 inhibitor Auranofin with BPI-7711 significantly enhanced anti-tumor efficacy and reversed drug resistance (Fig. 1N-O).

Conclusions: This study reveals a novel mechanism of EGFR-TKI resistance mediated by the Trx1/TrxR1 system and the TXNRD1-IGF2BP3 axis in NSCLC. Targeting TrxR1 with Auranofin could restore sensitivity to EGFR-TKI, highlighting a potential therapeutic strategy to overcome resistance.

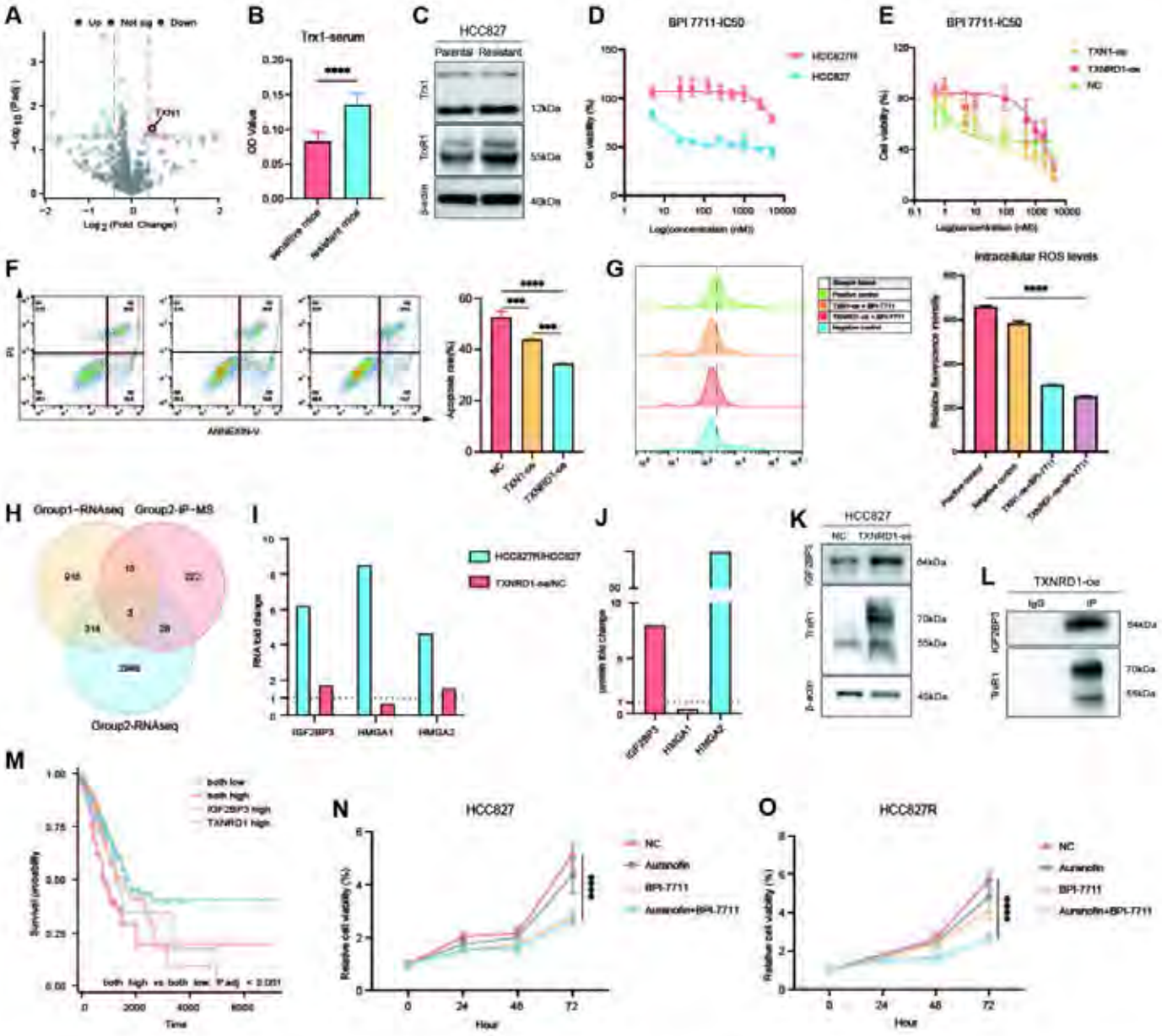

Figure 1. The TXNRD1-IGF2BP3 axis promotes acquired EGFR-TKI resistance in NSCLC
(A) Plasma Trx1 levels were negatively correlated with BPI-7711 sensitivity in NSCLC patients.
(B) Serum Trx1 expression was elevated in xenograft models resistant to BPI-7711 treatment.
(C) Western blot showed comparable Trx1 but elevated TrxR1 expression in HCC827/RR cells compared to parental HCC827.
(D) Cell viability curves indicated the successful generation of HCC827/RR.
(E) Cell viability curves indicated increased resistance to BPI-7711 in TXNRD1-oe but not TXN1-oe cells.
(F) Cell apoptosis analyses in TXNRD1-oe, TXN1-oe and control cells treated with BPI-7711(20nM) for 48 hours.
(G) Intracellular ROS levels detected by flow cytometry in TXNRD1-oe, TXN1-oe and control cells.
(H) The overlapping of RNA-seq and IP-MS data from Group1 and Group2, identified three genes potentially correlated with TXNRD1.
(I) RNA -seq validation of IGF2BP3 and HMGA2 upregulation in HCC827/RR and TXNRD1-oe cells.
(J) IP-MS validation of IGF2BP3 and HMGA2 upregulation in TXNRD1-oe cells.
(K) Western blot confirmed overexpression of TXNRD1 increased IGF2BP3 protein level.
(L) CO-IP assays demonstrated protein-protein interaction between TrxR1 and IGF2BP3.
(M) Concurrent high expression of TXNRD1 and IGF2BP3 correlated with the poorest overall survival in LUAD-TCGA database.
(N-O) Combination of Auranofin (TrxR1 inhibitor) and BPI-7711 significantly suppresses cell viability in both parental and HCC827/RR cells.

Keywords: EGFR-TKI resistance, TXNRD1-IGF2BP3 axis, NSCLC

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.28 Tumor Treating Fields (TTFields) Concomitantly With Anti-PD-1 and Cisplatin in a Mouse Model of Non-Small Cell Lung Cancer

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[1]Novocure Ltd, Haifa/IL ,[2]Novocure GmbH, Baar/CH

Introduction: Tumor Treating Fields (TTFields) are low-intensity, intermediate-frequency alternating electric fields that disrupt mitotic processes in cancer cells, promoting immunogenic cell death and enhancing antitumor immunity. TTFields therapy administered concomitantly with immune checkpoint inhibitors (ICIs) or chemotherapy is approved for metastatic non-small cell lung cancer (NSCLC) following progression on platinum-based treatment. The ongoing LUNAR-2 clinical trial (NCT06216301) is evaluating first-line TTFields administered concomitantly with pembrolizumab and platinum-based chemotherapy in metastatic NSCLC. The current study examines the efficacy of this concomitant treatment in preclinical models.

Methods: C57BL/6 mice were orthotopically implanted with LL/2 lung carcinoma cells. After 7 days, the mice received TTFields (150 kHz, continuous for 10 days) or sham (heat), and either vehicle or a treatment regimen consisting of anti-PD-1 (10 mg/kg), cisplatin (1 mg/kg), and pemetrexed (6 mg/kg), administered via intraperitoneal injection every 72 hours (three doses total), starting on day 2 of TTFields. Four groups were studied: control, TTFields alone, anti-PD-1/cisplatin/pemetrexed (PCP), and TTFields administered concomitantly with PCP. Tumor localization was confirmed at study start by MRI. Tumor volumes were measured at study end with calipers. Tumor-infiltrating lymphocytes (TILs) were assessed by flow cytometry. IFN-γ and Granzyme B expression in CD8+ T cells was evaluated following PMA/ionomycin restimulation.

Results: Mice treated with the concomitant TTFields plus PCP regimen had significantly smaller tumors compared to all other groups. PCP and TTFields plus PCP induced increased infiltration of CD3+ T cells, particularly CD8+ T cells. The TTFields plus PCP group showed a marked increase in IFN-γ-producing CD8+ T cells, alongside elevated Granzyme B expression compared to control and TTFields-only groups.

Conclusions: TTFields administered concomitantly with standard immunochemotherapy enhanced tumor control and augmented the cytotoxic immune response in a mouse model of NSCLC. These preclinical findings support the therapeutic potential of this approach.

Keywords: Tumor Treating Fields, NSCLC, anti-PD-1

P3.03.29 IAM1363 Is a Potent, Selective, and Irreversible HER2 and Pan-HER2 Mutant Small Molecule Inhibitor for the Treatment of HER2-Driven NSCLC

Z.J. Huang, K. Chen, A. Adams, L. Kulyk, C. Zhao, J. Park, H. Zhang, B. Liu, L. Gomez, M. Anderson, P. Harvey, F. Manby, P. Olson, T. Miller, N. Josephson
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Introduction: Alterations of HER2 have been identified in NSCLC, with ~3% of cases harboring HER2 amplifications and ~2% having activating mutations. Trastuzumab deruxtecan (T-DXd), a HER2-specific antibody-drug conjugate, is an approved therapy for relapsed NSCLC with HER2-activating mutations or protein overexpression (IHC3+). However, its clinical benefit is limited by suboptimal response durability in some patients and a notable risk of treatment-related toxicities, including interstitial lung disease. These challenges highlight ongoing unmet medical needs and opportunities for safer, more effective therapies in this population. Small molecule inhibitors to HER2 have the potential to treat HER2-driven NSCLC. However, due to structural homology between EGFR and HER2, many HER2 kinase inhibitors also inhibit EGFR, leading to dose-limiting toxicities.

Methods: IAM1363 was evaluated through a series of biochemical assays, cell-based studies, and animal models to comprehensively characterize its activity in NSCLC.

Results: IAM1363 is a potent, irreversible and selective Type II inhibitor of HER2, preventing phosphorylation and activation of wild-type HER2 and variants with activating mutations in the tyrosine kinase domain. It exhibited >500-fold biochemical selectivity for HER2 over EGFR and >400-fold cellular selectivity in HER2- versus EGFR-driven cell lines. This selectivity translated into potent activity in vitro, effectively inhibiting HER2-dependent cell growth and survival, while showing minimal impact on EGFR-driven cells. In vivo, IAM1363 is highly active in mouse models of HER2 amplified or mutant NSCLC, including CDX and PDX tumor models. In multiple NSCLC xenograft models tested, IAM1363 demonstrated equivalent or superior anti-tumor activity compared to T-DXd. Furthermore, IAM1363 showed synergistic activity in vitro and in vivo when combined with other anticancer agents, including T-DXd. Importantly, IAM1363 demonstrated robust anti-tumor activity in an intracranial model of HER2-amplified NSCLC, validating its ability to cross the blood brain barrier and achieve therapeutic effects in the CNS. IAM1363 treatment resulted in tumor regression across a wide range of pre-clinical models of HER2-driven cancers and it was well tolerated at therapeutic doses. Furthermore, IAM1363 demonstrated favorable PD and PK characteristics with sustained inhibition of HER2 phosphorylation in vitro and preferential enrichment within HER2-expressing tumors relative to plasma. As a result, anti-tumor activity was readily achieved with both standard QD and BID dosing, suggesting that substantial efficacy may be attainable with more flexible dosing schedules.

Conclusions: Based on its high selectivity, broad anti-tumor activity across biomarker-positive nonclinical models, and brain penetrance, IAM1363 is anticipated to be an effective treatment for HER2 amplified or mutant NSCLC patients, including for patients with CNS metastases. IAM1363 is currently being evaluated in a phase 1/1b clinical trial (NCT06253871).

Keywords: IAM1363, HER2/ERBB2, amplification/mutation

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.30 Activation of EGFR Signaling Mediated by PTPRR Methylation Causes Resistance to KRAS Inhibitor Sotorasib

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Introduction: KRASG12C inhibitors such as sotorasib have demonstrated clinical benefit in KRASG12C-mutant non-small cell lung cancer (NSCLC); however, primary and acquired resistance remains a major clinical challenge. The underlying mechanisms of resistance remain incompletely understood.

Methods: We established sotorasib-resistant NSCLC cell lines harboring KRASG12C mutations and analyzed molecular alterations using phospho-kinase arrays, immunoblotting, microarray, and next-generation sequencing. Functional validation was performed by siRNA-mediated knockdown, PTPRR overexpression, and colony formation assays. The impact of EGFR blockade was evaluated in vitro and in vivo using xenograft mouse models. DNA methylation of PTPRR promoter regions was assessed using bisulfite sequencing and TCGA datasets. Immunohistochemistry and clinical data were analyzed to assess the association between PTPRR expression and clinical outcomes in patients with KRASG12C- or EGFR-mutant NSCLC treated with sotorasib or osimertinib, respectively.

Results: Sotorasib-resistant clones displayed persistent ERK phosphorylation despite effective KRASG12C inhibition, accompanied by increased EGFR activation. Phospho-RTK arrays and western blotting identified the phosphorylation of tyrosine residues on EGFR, particularly Y1173. Expression profiling revealed marked downregulation of the tyrosine phosphatase PTPRR in resistant cells, which was linked to promoter hypermethylation. Co-immunoprecipitation confirmed direct interaction between PTPRR and EGFR. Functionally, PTPRR knockdown induced resistance and EGFR/ERK reactivation, whereas PTPRR re-expression suppressed EGFR phosphorylation and restored sotorasib sensitivity. Combined inhibition with cetuximab and sotorasib overcame resistance in vitro and in xenograft models without significant toxicity. Clinically, low PTPRR expression in tumor specimens was associated with shorter progression-free (median 4.3 vs. 7.5 months; HR 3.27, 95% CI: 0.76-14.0) and overall survival (median 7.5 months vs. not reached; HR 3.21, 95% CI: 0.70-14.7) in patients with KRASG12C-mutant NSCLC receiving sotorasib. When comparing patients with and without PTPRR expression at the time of EGFR TKI resistance, those with PTPRR expression exhibited a significantly shorter PFS on osimertinib (median of 91 days versus 372 days; HR not estimable), highlighting a broader role for PTPRR in modulating EGFR dependency across oncogenic contexts.

Conclusions: Our findings identify PTPRR as a critical regulator of EGFR phosphorylation and a key determinant of resistance to KRASG12C inhibitors. DNA methylation-mediated suppression of PTPRR leads to EGFR/ERK pathway activation and loss of sotorasib efficacy. Dual blockade of KRASG12C and EGFR is an effective therapeutic strategy, particularly in tumors with reduced PTPRR expression. Furthermore, PTPRR expression may serve as a biomarker to stratify patients who could benefit from EGFR inhibition in KRASG12C-mutant NSCLC. These insights support the rationale for incorporating epigenetic and phosphatase profiling into resistance monitoring and combination therapy strategies.

Keywords: KRAS, EGFR, Acquired resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.31 Transcriptomic Profiling Identifies a Prognostic and Predictive Inflammatory Signature in Patients With Lung Adenocarcinoma

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Introduction: Circulating inflammatory markers such as neutrophil-to-lymphocyte ratio are promising biomarkers in non-small cell lung cancer (NSCLC) patients. However, inflammatory transcriptomic biomarkers have not been well studied. Here, we constructed a transcriptomic-based inflammation signature and validated its prognostic and predictive value in LUAD.

Methods: We analyzed RNA-seq data from 507 lung adenocarcinoma (LUAD) patients and 59 normal controls from The Cancer Genome Atlas (TCGA). Inflammation-related genes (IRGs) were obtained from GeneCards, and differentially expressed genes (DEGs) were identified using DESeq2 with a threshold of |Log2FC| > 0.5 and adjusted p-value < 0.05. Prognostic biomarkers were selected using LASSO regression, followed by univariate and multivariate Cox proportional hazard models. We developed a risk score using significant genes, and patients were stratified into high- and low-score groups using the median as the cut-off value. Survival analysis for Overall Survival (OS) and progression-free Survival (PFS) was performed using Kaplan-Meier curves and log-rank tests. Functional enrichment analysis was conducted using Gene Ontology (GO). External validation was performed using independent GEO cohorts (GSE29013, GSE30219). Additionally, we used multiple machine learning models to assess the predictive value of inflammation-related genes for immune checkpoint inhibitor (ICI) response across four GEO datasets.

Results: We identified 3,083 DEGs between LUAD and normal samples, of which 872 were inflammation-related. LASSO regression and Cox analysis revealed three independent prognostic biomarkers: ADM, LOX, and NEFL, all associated with poor survival (P-value < 0.05). The risk score model effectively grouped patients into high-score and low-score groups. The high-score group had significantly worse PFS and OS than the low-risk group (P-value < 0.05). Functional enrichment analysis highlighted pathways related to neuronal signaling and extracellular matrix remodeling in tumor cells compared to normal tissue. Molecular analysis revealed distinct protein and gene expression profiles between risk groups, with proteins such as ERBB3 and MAPK9 overexpressed in the low-risk group. In contrast, SERPINE1 and SMAD3 were overexpressed in the high-risk group. External validation confirmed the prognostic utility of the risk model in independent cohorts. A machine learning model was developed using inflammation-related DEGs to predict ICI response based on transcriptomic data from four GEO cohorts. After training multiple models, LightGBM demonstrated the best performance when applied to a merged dataset of 68 patients and 42 genes, achieving an accuracy of 0.89 and an AUROC of 0.8. Using SHAP (Shapley Additive Explanations) analysis, we identified the key genes driving the model's predictions. The results showed that IL7 (SHAP Importance: 0.2722, p = 0.0018) and SLC2A1 (SHAP Importance: 0.2058, p = 0.0130) are significant predictors of ICI response, suggesting their potential as biomarkers in LUAD.

Conclusions: We constructed an inflammation score based on gene expression in LUAD patients. The signature depended on 3 inflammation genes significantly associated with survival. The high-inflammation group was associated with better OS, PFS, and DSS. Machine learning models demonstrated that inflammation-related genes could predict ICI response with high accuracy across multiple datasets.

Keywords: Inflmmation, biomarkers, Prognosis

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.32 Multi-Omic Characterization of ALK Fusion LUADs Reveals Overactivation of DNA Replication as a Contributor to ALK TKI Resistance

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Introduction: Lung adenocarcinomas (LUADs) driven by ALK gene rearrangements represent around 5% of LUADs and can be effectively treated with ALK-targeted therapies. However, resistance to these therapies inevitably develops in almost all cases, limiting long-term treatment success. While secondary mutations in ALK or other genes have been well studied as drivers of resistance, approximately 25% of cases exhibit resistance through non-genomic mechanisms. In this study, we have investigated the non-mutational mechanisms involved in ALK TKI resistance.

Methods: We performed a multi-omic analysis of ALK-fusion clinical samples (RNAseq, bisulfite sequencing, targeted mutational profiling) and patient-derived xenografts (PDXs) (RNAseq, single-cell RNAseq) before and after ALK TKI treatment.

Results: Mutational profiling of clinical samples revealed that approximately 50% of resistant ALK fusion-positive tumors harbor ALK mutations, with 24% of those showing ALK double mutations. Other significant genomic alterations observed in ALK TKI-resistant samples included MYC amplification and MET amplification. RNA sequencing analysis of resistant samples (n=27) revealed upregulation of DNA replication and cell cycle pathways, compared to TKI-sensitive clinical samples (n=24). Methylome characterization identified prominent hypermethylation of promoter regions in resistant samples. Integration of RNA sequencing and methylation data revealed few genes exhibiting concordant changes in both RNA and methylation levels, suggesting that the transcriptomic alterations associated with ALK resistance are not primarily regulated through methylation-driven epigenetic mechanisms. Characterization of 9 ALK-fusion PDXs confirmed upregulation of DNA replication and cell cycle pathways in resistant versus sensitive models. We next evaluated 3 highly sensitive PDXs before treatment and after relapse by scRNAseq. Resistant cells exhibited enrichment in a variety of pathways, including DNA replication, epithelial-to-mesenchymal transition (EMT), Hippo signaling, and TGF-β signaling, among others. These results suggest that TKI resistance mechanisms are complex and varied, with cells potentially relying on different molecular pathways to evade the effects of treatment. Given that the overactivation of the DNA replication pathway emerged as one of the most significant pathways associated with resistance in both clinical samples and patient-derived xenografts (PDXs), we next delved into the role of this pathway in driving ALK TKI resistance. We generated lorlatinib-resistant ALK cell lines (H3122 and H2228) through prolonged exposure of cells to lorlatinib. Resistant cells showed elevated expression of DNA replication-related proteins, including MYC, BRCA1, ORC1, and E2F1, and accumulated in the synthesis phase compared to wild-type cells. To target DNA replication and cell cycle pathways, we employed carfilzomib, an FDA-approved proteasome inhibitor. Combination of carfilzomib and lorlatinib strongly synergized, promoted cell death and induced cell cycle arrest in ALK-resistant cell lines by inhibiting DNA replication proteins. Ectopic overexpression of E2F1, CHEK1, ORC1 and EXO1 in wild-type cells increased lorlatinib IC50 and the number of drug-tolerant persister cells in vitro. In vivo experiments using ALK-driven PDXs confirmed that the combination of lorlatinib and carfilzomib significantly delayed tumor growth in TKI-acquired resistant PDXs (n=2), while showing a mild effect in models exhibiting primary mechanisms of resistance (n=2).

Conclusions: Overactivation of DNA replication contributes to ALK TKI acquired resistance and can be overcome with the proteasome inhibitor carfilzomib.

Keywords: ALK, LUAD, TKI resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.33 Clinical and Genomic Landscape of BRAF-Mutant NSCLC Patients From the AACR GENIE BPC Cohort

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Introduction: Activating mutations in BRAF occur in ~4% of NSCLC, and are classified into three functional classes based on kinase activity and signaling mechanisms. BRAF V600X mutations (Class I) are the most common and result in constitutive kinase activation, leading to cancer cell proliferation and survival. Non-V600 mutations (Class II and Class III) collectively account for ~50% BRAF mutations in NSCLC, in contrast to other malignancies that are predominantly driven by BRAF V600E. BRAF mutation classes might define different clinical and molecular features, and clinical outcomes.

Methods: Here, we describe the clinical and genomic landscape of BRAF-mutant (BRAFm) NSCLC patients from the AACR GENIE BPC cohort (v17, data accessed in March 2025).

Results: A total of 27,858 NSCLC patients were identified. BRAF mutations were observed in ~6% of patients (n=1,623). Patients with concurrent EGFR driver alterations (n=78) were excluded from subsequent analyses. The BRAFm NSCLC cohort included patients with Class I (24,6%, n=380), Class II (22%, n=341) or Class III (22%, n=340) mutations. Compound BRAF mutations (e.g., > 2 Class I, II or III mutation) were observed in ~6% of patients (n=64). Overall, 883 (57%) of BRAF mutations occurred at one of the following five residues: V600 (n=380; 24,6%); G469 (n=201; 13%); G466 (n=127; 8,2%); D594 (n=102; 6,6%) and N581 (n=73; 4,7%).No difference in the age, ethnicity or sex distribution across mutation classes was observed. Most patients in the three classes were white with lung adenocarcinoma. Patients with compound BRAF mutations presented comparable clinico-pathological characteristics.Median OS from the date of molecular diagnosis was s 46.3, 48.5 and 40.1 months for classes I, II and III, respectively. OS was not statistically significantly different between the groups. The date of diagnosis was not available in the database.Among patients with co-mutations (60,6%, 937/1,545), Class I patients harbored co-mutions in SETD2 (22.6%), ATM (11.5%), SMAD4 (9.3%) and PIK3CA (8.8%). Co-alterations in STK11 were observed in 23% and 20.4% of Class II and Class III patients, respectively. Concurrent mutations in KRAS were higher in Class III patients (27%), compared to Class II (18.4%). TP53 mutation was the most common co-alteration across all 3 classes.The median TMB was significantly higher in tumors with Class II (9.52 mt/MB, P<0.001) or Class III (10.4 mt/MB, P<0.001) mutations, compared to Class I (6.94 mt/MB). Notably, compound BRAF mt presented the highest mediant TMB (14.7 mt/MB).

Conclusions: The AACR GENIE BPC initiative provides annotated clinical and tumor genomic data for BRAF-mutant NSCLC patients, and depicts the molecular and clinico-pathological differences between BRAF-mutation classes, indicating that BRAF-mutant NSCLC is not a single entity.

Keywords: BRAF, Non-small cell lung cancer, co-mutation

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.34 Assessment of Minimal Residual Disease Using Liquid Biopsy in Patients With EGFR-Mutated Lung Cancer Treated With Osimertinib

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Introduction: Drug tolerance is one of the major mechanisms driving resistance to targeted therapies (TT), but the dynamics and molecular heterogeneity underlying the adaptive drug response in patients is still unknown. Here, we used iterative liquid biopsies from lung cancer patients to characterize minimal residual disease (MRD) and predict treatment outcome using circulating tumor DNA (ctDNA) and circulating tumor cells (CTC).

Methods: LUNG-RESIST (NCT04222335) is a prospective research study enrolling EGFR-mutant adenocarcinoma patients treated by osimertinib frontline. We collected blood samples at baseline, 1 month and every 3 months until progression. The initial EGFR mutation (EGFRm) was monitored in ctDNA by digital PCR. CTC were enriched and isolated based on their size, absence of leucocyte staining and viability, to perform single-cell transcriptomic.

Results: 40 patients were enrolled with a median progression-free survival (mPFS) of 14.5 months (95%CI, 8.5-24.5 months). 70% patients had detectable EGFRm in ctDNA at baseline, and complete clearance at 1 month was associated with a favourable mPFS. Clinical relapse could be anticipated 3 months ahead based on ctDNA increase for 9/20 patients. CTC-like cells were collected at baseline and MRD from respectively 31/40 and 29/40 patients, and at clinical progression for 12/22 patients who relapsed, for a total number of 1,510 cells. The single-cell transcriptomic data on CTC will be presented at the congress, and should provide a better insight into the dynamics of molecular events occurring throughout the adaptive response in patients.

Conclusions: We report the first molecular profiling of ctDNA and CTC during the adaptive response to osimertinib in lung cancer patients. Monitoring the response and predicting the clinical outcome for EGFR-mutant lung cancer patients undergoing TT treatment can be done using ctDNA level as a biomarker. The isolation of CTC-like cells represents a non-invasive approach to study drug tolerance and ultimately develop new combinatory treatments to prevent relapse.

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.35 Association of Intestinal Flora and Metabolites With Bone Metastasis in Patients With Non-Small Cell Lung Cancer

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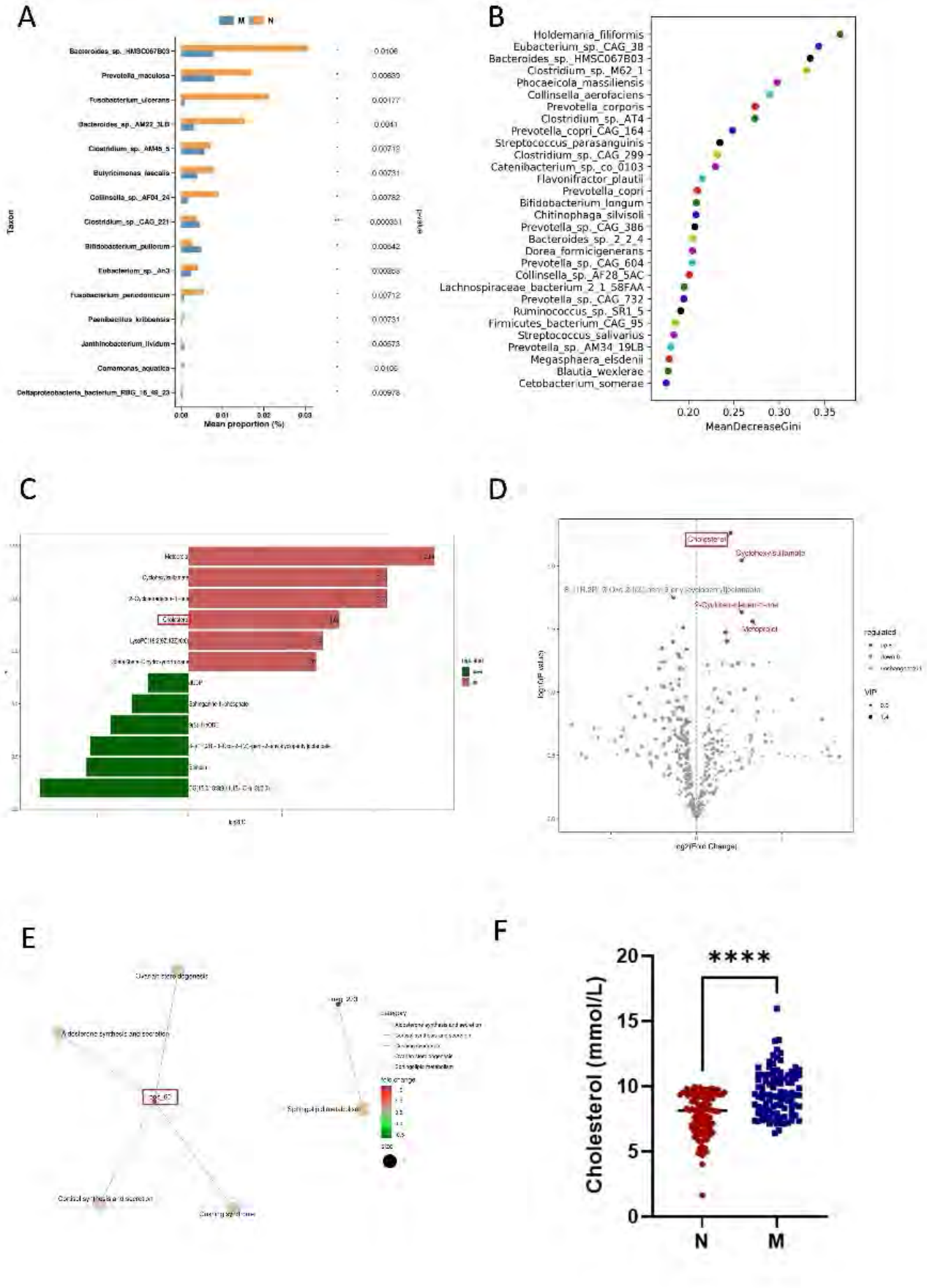
Introduction: Lung cancer is the most common cause of cancer-related death worldwide, and bone is a common site for lung cancer metastases, which occurs in up to 40% of patients with non-small cell lung cancer (NSCLC). Gut microbes are considered as the "second genome" of humans and are implicated in many diseases. However, the relationship between intestinal flora and bone metastasis of NSCLC remains unclear.

Methods: We collected baseline fecal samples from104 patients with newly diagnosed lung cancer, 61 patients with bone metastasis (M group), and 43 patients without bone metastasis (N group). We conducted metagenomic and metabolomic sequencing to compare the differences in gut microbiota and metabolites between the two groups. At the same time, we collected baseline serum samples from 112 NSCLC patients with bone metastasis and 151 NSCLC patients without bone metastasis. Serum cholesterol levels at baseline were quantified using ELISA.

Results: Our results showed that the abundance of bacteroides and prevotella in group N was significantly higher than that in group M. Metabolomic analysis showed that the cholesterol level in group M was significantly higher than that in group N ($P<0.05$). KEGG analysis revealed enrichment of cholesterol(pos_60) related pathways, such as ovarian steroid production, aldosterone synthesis and secretion, Cushing's syndrome, and cortisol synthesis and secretion. Serum cholesterol levels in patients with bone metastasis were higher than those without bone metastasis ($P<0.0001$), which was consistent with the trend of intestinal metabolites.

Conclusions: Dysregulation of intestinal flora and abnormal cholesterol metabolism may promote bone metastasis of NSCLC. Elevated serum cholesterol may be used as a predictor of NSCLC bone metastasis, and regulation of intestinal flora and cholesterol metabolism may be a potential therapeutic strategy.



Keywords: Non-small cell lung cancer, Gut microorganism, Bone metastases

P3.03.36 Whole Genome Doubling Drives Genomic Instability and Poor Postoperative Outcomes in Stage I Driver-Negative Lung Adenocarcinoma

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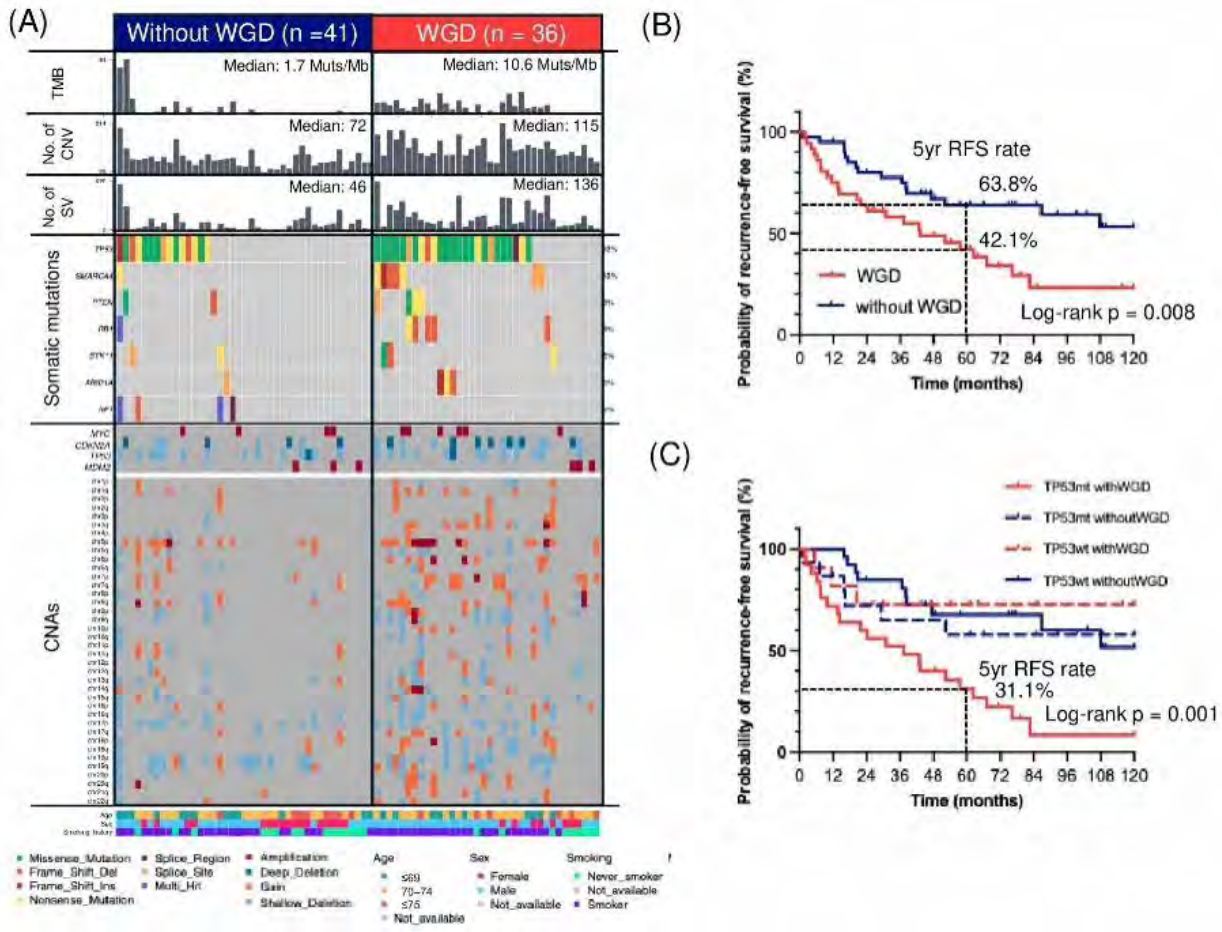
Introduction: Stage I driver-negative lung adenocarcinoma (DN-LUAD) patients without actionable genomic alterations are currently not aggressive candidates for perioperative chemotherapy. However, 30-40% of these patients can experience recurrence after surgery, highlighting the need for more accurate risk prediction. Whole genome doubling (WGD) is common in human cancers and leads to chromosomal instability, but its impact in patients with stage I LUAD remains poorly understood.

Methods: We performed deep whole genome sequencing (WGS; tumor depth: 100-120x, normal depth: 30x, paired-end reads: 150 bp) and transcriptome profiling on resected pStage I (UICC 8th) DN-LUAD specimens. Somatic mutations, copy number alterations (CNA), and structural variations (SV) were analyzed. Tumors were classified as WGD-positive when more than half of the autosomal tumor genome displayed at least two copies at the major somatic copy number. Tumor transcriptome profiles were evaluated using Gene Set Enrichment Analysis (GSEA).

Results: We analyzed 77 patients (stage IA: n = 42, stage IB : n = 35) with a median age of 67 years (range 32-83), 32% female, and 69% smokers. Median follow-up for censored patients was 67.7 months. WGD was detected in 46.8% (n = 36) of tumors and was significantly associated with higher tumor mutation burden, CNA, and SV loads (p < 0.0001) (Figure A). TP53 mutations were significantly more frequent in WGD patients (69.4% vs. 36.6%, p = 0.004), and CDKN2A copy number loss was numerically higher in WGD patients (19.4% vs. 9.8%, p = 0.36). GSEA revealed significant enrichment of DNA repair and cell cycle-related pathways (e.g., HALLMARK_DNA_REPAIR and G2M_CHECKPOINT) in WGD patients (q < 0.0001). Recurrent-free survival (RFS) was significantly shorter in WGD patients (median RFS: 43.3 months vs. not reached; HR 2.30, 95% CI: 1.21-4.37; p = 0.01), with 5-year RFS rates of 42.1% (95% CI: 25.4-58.0%) and 63.8% (95% CI: 46.5-76.8%), respectively (Figure B). Notably, patients with concurrent TP53 mutations and WGD had the poorest RFS (log-rank p = 0.001), while patients with TP53 mutations but without WGD had similar recurrence risk as those without TP53 mutations (Figure C).

Conclusions: WGD increases genomic instability in DN-LUAD, leading to cell cycle and DNA regulation abnormalities. The co-occurrence of WGD and TP53 mutations significantly increases the risk of postoperative recurrence even in stage I disease, suggesting the need for intensified perioperative treatment strategies for this high-risk subgroup.



Keywords: lung adenocarcinoma, stage I, whole-genome sequencing

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.37 Target Lipid Metabolism in Immune Microenvironment: Immunotherapy Sensitization and Combinatorial Strategies for NSCLC With Liver Metastases

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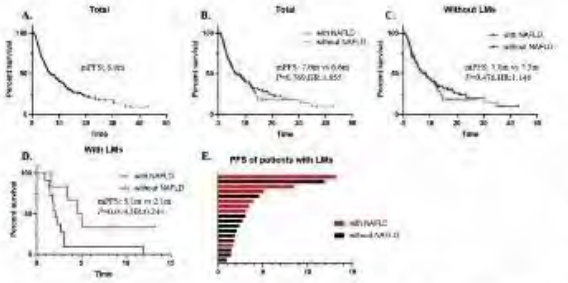
Introduction: Liver metastasis represents a critical factor contributing to immune therapy resistance in advanced non-small cell lung cancer (NSCLC), with its underlying mechanism closely associated with the unique hepatic lipid metabolism microenvironment. Prior clinical data indicate that NSCLC patients with liver metastasis and non-alcoholic fatty liver disease (NAFLD) exhibit a significantly higher response rate to PD-1 inhibitors (ORR: 38% vs 12%, p<0.01). Magl expression is markedly upregulated in Kupffer cells and tumor-associated macrophages (TAMs) of these patients. However, the molecular mechanisms underlying its regulation of the immune microenvironment remain elusive. This study aims to elucidate the cross-organ regulatory network that activates anti-tumor immunity through lipid metabolism reprogramming-mediated macrophage polarization via the MAGL-CB2/TLR4 axis.

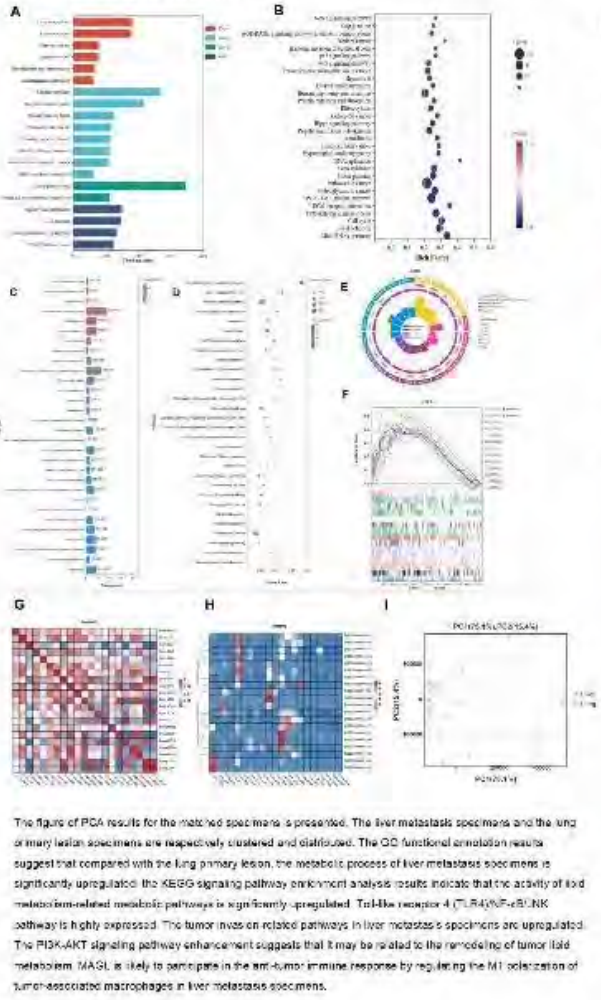
Methods: Collected paired biopsy specimens of primary lesions and liver metastases, and quantified the TAMs subgroups and T cell infiltration through mIHC (CD68/CD163/CD8). The in situ lung cancer liver metastasis animal model (C57BL/6-LLC) was established. By knocking out MAGL or using agonists to intervene in the CB2/TLR4 pathway, the phenotypic transformation of macrophages was analyzed through flow cytometry and spatial transcriptome analysis. Lipidomics (LC-MS) combined with transcriptomics (scRNA-seq) was employed to parse the co-variation network of fatty acid metabolites and immune gene modules in liver metastases.

Results: In the NAFLD+ group, MAGL expression in liver metastases was 3.2-fold higher than in primary liver lesions (p = 0.003). The proportion of lipid-laden macrophages (CD68+CD86+F4/80+Ly-6G+LipidTOX Deep-Red+) in tumor tissues significantly increased after immunotherapy (p = 0.001), particularly following synergistic immune sensitization, with a 2.7-fold increase in CD8+ T cell density (p = 0.008). MAGL hydrolyzes 2-AG into arachidonic acid, activating the dual CB2/TLR4 signaling pathway (50% reduction in phosphorylated ERK/NF-κB levels). This process induces Kupffer cells to polarize toward the M1 phenotype (the proportion of iNOS+ cells increasing from 12% to 41%) and recruits CXCL9+CD8+ T cells (a 2.3-fold increase in infiltration). Based on the metabolic-immune interaction network, the SREBP1-MAGL-CXCL9 axis was identified as a biomarker for predicting immunotherapy response (AUC = 0.83).

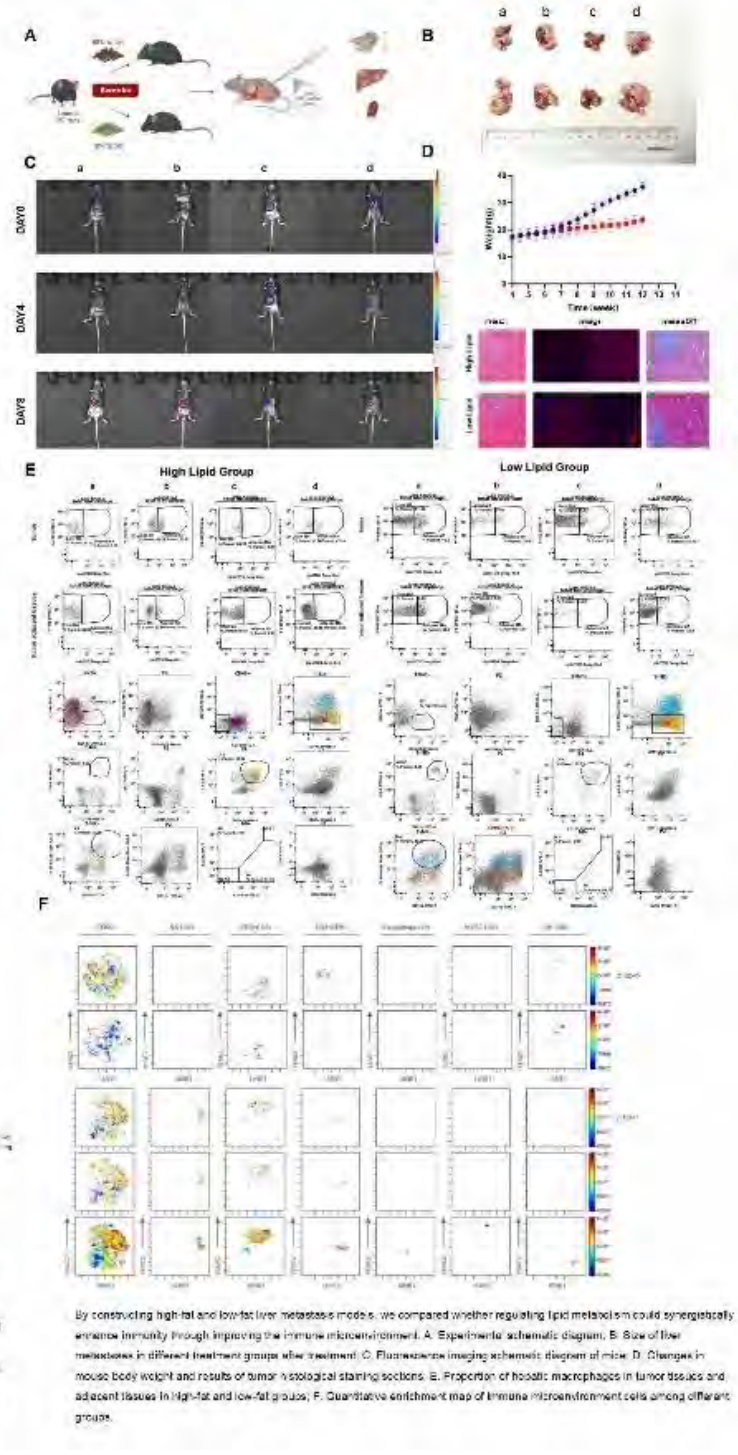
Conclusions: This study demonstrates that the hepatic lipid metabolism enzyme MAGL remodels the polarization of Kupffer cells/TAMs, thereby promoting the establishment of an anti-tumor immune microenvironment. Targeting the MAGL-CB2/TLR4 axis can reverse the immunosuppressive features of liver metastases and offers a novel “metabolic sensitization” strategy for patients resistant to PD-1 blockade therapy.



The median progression-free survival (PFS) for the entire group of patients with NSCLC receiving immunotherapy was 8.8 months. The median PFS for patients with NAFLD and those without NAFLD was similar (7.0 months vs. 6.5 months, P = 0.759, hazard ratio [HR]: 1.050, 95% confidence interval [CI]: 0.738 - 1.507) (Figure B). However, in the subgroup of patients with liver metastasis, the median PFS of patients with NAFLD was significantly longer than that of non-NAFLD patients (5.1 months vs. 2.1 months, P = 0.014, HR: 0.244, 95% CI: 0.078 - 0.813).



The figure of PCA results for the matched specimens is presented. The liver metastasis specimens and the lung primary lesion specimens are respectively clustered and distributed. The GO functional annotation results suggest that compared with the lung primary lesion, the metabolic process of liver metastasis specimens is significantly upregulated. the KEGG signaling pathway enrichment analysis results indicate that the activity of lipid metabolism-related metabolic pathways is significantly upregulated. Toll-like receptor 4 (TLR4)/NF-κB/NK pathway is highly expressed. The tumor invasion related pathways in liver metastasis specimens are upregulated. The PI3K-AKT signaling pathway enhancement suggests that it may be related to the remodeling of tumor lipid metabolism. MASL is likely to participate in the anti-tumor immune response by regulating the M1 polarization of tumor-associated macrophages in liver metastasis specimens.



By constructing high-fat and low-fat liver metastasis models, we compared whether regulating lipid metabolism could synergistically enhance immunity through improving the immune microenvironment. A. Experimental schematic diagram. B. Size of liver metastases in different treatment groups after treatment. C. Fluorescence imaging schematic diagram of mice. D. Changes in mouse body weight and results of tumor histological staining sections. E. Proportion of hostile macrophages in tumor tissues and adjacent tissues in high-fat and low-fat groups. F. Quantitative enrichment map of immune microenvironment cells among different groups.

Keywords: Immune microenvironment of liver metastasis, PD-1 enhances sensitivity, Metabolic-immune interaction

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.38 Oncolytic Virus Effectively Delivers CD47 Blockade to Suppress Tumour Growth in Preclinical NSCLC Models

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Introduction: CD47 regulates an innate immune checkpoint that inhibits the phagocytic function of macrophages and dendritic cells. Cancer cells exploit CD47 to prevent their destruction by phagocytes and subsequent activation of anti-tumour immunity. As such, CD47 is a promising immunotherapeutic target and numerous antibody-based therapeutics that inhibit CD47 are being investigated in clinical trials. CD47 is overexpressed in up to 60% of non-small cell lung cancers (NSCLC), highlighting the potential utility of CD47 blockade for treating lung tumours. We have found that genetic inactivation of CD47 within lung cancer cells significantly impairs the growth of orthotopic lung tumours in mice. Yet, monoclonal antibodies targeting CD47 (CD47-Ab), a common modality for delivering CD47 blockade in the clinic, did not affect tumour growth in mice. This result is consistent with the poor efficacy of CD47 blockade observed in lung and other cancer patients in clinical trials. We have also seen that CD47-Ab bind to various cells abundant in the blood (eg. erythrocytes, neutrophils and platelets), consistent with toxicities commonly seen in patients treated with CD47 blockade (ie. anemia, neutropenia, and thrombocytopenia). Taken together, results in our preclinical NSCLC models and patients in clinical trials suggest that alternative approaches for administering CD47 blockade are needed to harness its therapeutic effects. We suspect that the limited efficacy and toxicity of CD47 blockade in patients is attributable to the ubiquitous expression of CD47 and failure of intravenously delivered therapeutics to reach tumour tissues in amounts sufficient to elicit anti-tumour effects. We hypothesize that targeting CD47 blockade preferentially to lung tumour tissues is required to realize its therapeutic potential, and that oncolytic viruses (OVs) can be leveraged to do so. In this study, we evaluated the anti-tumour efficacy of a novel OV engineered to deliver CD47-targeted therapy in two syngeneic NSCLC models.

Methods: We synthesized an attenuated vesicular stomatitis virus encoding a mouse-specific fusion protein (VSV-FP) that blocks CD47 function. Subcutaneous LLC or CMT167 tumours grown in immunocompetent mice were treated with 3 doses of PBS (100uL), VSV-FP or a control OV encoding green-fluorescent protein (VSV-GFP; 1x106 pfu/dose) administered intratumorally. Tumour volume and body weights were monitored over the course of treatment to assess the therapeutic effects and tolerability of virotherapy.

Results: OVs were well tolerated in mice as no significant differences in body weight were observed across treatment groups over the course of the study. VSV-GFP (control) and VSV-FP significantly inhibited tumour growth in both models ($p<0.01$). Although there was no difference in the therapeutic effects of VSV-GFP and VSV-FP in the LLC model, VSV-FP elicited stronger tumour growth inhibition than VSV-GFP in the CMT167 model ($p<0.01$). Notably, VSV-FP abrogated CMT167 tumour growth for 12 days, with 2/8 mice appearing to have near complete responses.

Conclusions: VSV-FP effectively suppressed lung tumour growth in mice. Our results indicate that OVs can be used to harness the therapeutic potential of CD47 blockade in NSCLC. Future studies will focus on identifying combinatorial approaches to potentiate and prolong their anti-cancer effects.

Keywords: CD47, immunotherapy, oncolytic virus

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.39 Deep Learning Based Multiplex Imaging Platform for High Throughput ADC Targets Expression Quantification and Biomarker Discovery in NSCLC

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Introduction: Recent developments in cancer treatments have not only seen the emergence of multiple targeted therapies but also the emergence of immunotherapy, antibody- drug conjugates (ADCs) and multi-specific antibodies. To properly stratify patients for optimal treatment, novel paradigms of biomarker identification and quantification are needed, as neither targeted mutation calling nor immunohistochemistry fully captures the intra-tumor heterogeneity nor subcellular expression of target protein expression. Multiplex immunofluorescence (mIF) can capture the protein expression of a large number of proteins simultaneously, enabling parallel assessment of a large number of drug targets. Here we describe a high-plex spatial proteomics platform integrated with AI-driven data analysis to be used for evaluating and quantifying individual drug targets and their combinations in non-small-cell lung cancer (NSCLC).

Methods: 87 tumor microarray cores from NSCLC patients were stained with a 23-marker mIF panel, of which 16 are potential ADC targets. Utilizing Nucleai's deep learning (DL)-based analysis pipeline, marker positivity was determined by a DL-classifier for each segmented cell, followed by assignment to 9 cell types by known protein expression profiles. For each detected tumor cell, the membrane intensity of target proteins was quantified by calculating the mean intensity and five intensity quantiles (0.1, 0.25, 0.5, 0.9). Five clinically actionable markers (CD56, CEACAM5, EGFR, HER2, and MSLN) had their protein intensity levels annotated by expert mIF annotators into 4 intensity bins (0, +1, +2, +3) at both cellular (n=693) and core (n=87) levels. Using the membrane intensity quantiles and core-level intensity annotations, we trained a multiclass classifier to predict optimal intensity thresholds through 20-fold cross-validation. These thresholds were utilized to classify tumor-core intensity levels by applying them to the 0.75 quantile of tumor cells membrane target proteins intensity. Furthermore, tumor cell target protein expression levels were classified into four intensity bins using the predicted intensity thresholds.

Results: The predicted core target protein expression levels demonstrated excellent concordance with manual expert annotations, achieving nearly 100% accuracy across all intensity bins for CD56 and EGFR, and between 80-90% accuracy for MSLN and HER2. However, the model had difficulties distinguishing between 0 and 1+ core expression levels for CEACAM5, primarily due to nonspecific background staining, highlighting the necessity for rigorous antibody validation in mIF intensity quantification. We further evaluated the model's performance in single-cell intensity level classification, utilizing annotations not included in the model's training as a validation set. In this context, the model achieved over 90% accuracy for most intensity levels, with the exceptions being CEACAM5-1+ and HER2-1+, due to difficulties differentiating between low expression levels and high background stain

Conclusions: In this study, we present a novel method for quantifying membrane protein expression levels, enabling precise inference of cell- and patient-level intensities for ADC targets. This approach offers a cost-effective solution for screening for treatment eligibility and provides the capability to calculate intensity-based spatial features that can model protein expression distribution and heterogeneity across the tumor area. These advancements facilitate the development of intensity-based biomarkers, improving patient stratification and treatment outcomes.

Keywords: Biomarkers, antibody drug conjugates (ADC), deep learning

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.40 PRMT9 mRNA Stabilized by IGF2BP1 in an m6A-Dependent Manner Promotes Proliferation and Metastasis of Lung Adenocarcinoma Cells

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Introduction: PRMT9 is aberrantly expressed in various cancers, including lung adenocarcinoma (LUAD). This study aimed to investigate the expression pattern and functional role of PRMT9 in LUAD and explore its underlying mechanisms.

Methods: PRMT9 expression was analyzed in LUAD tissues, normal tissues, and cell lines. PRMT9 knockdown in A549 and H1568 cells assessed its effects on migration, invasion, and the RAS/MEK/ERK signaling pathway. The role of IGF2BP1 in PRMT9 mRNA m6A modification was examined. Functional assays were conducted with IGF2BP1 knockdown or overexpression, and pathway inhibition studies validated PRMT9's role. In vivo experiments further confirmed findings.

Results: PRMT9 mRNA and protein levels were significantly higher in LUAD tissues and cancer cell lines compared to normal tissues and cells. Knocking down PRMT9 in A549 and H1568 cells significantly reduced cell migration, invasion abilities, and the activation of the RAS/MEK/ERK signaling pathway. The abnormal expression of PRMT9 was associated with its mRNA m6A modification, which was regulated by IGF2BP1. The expression of IGF2BP1 was also higher in LUAD tissues and cancer cells. Knocking down IGF2BP1 reduced PRMT9 m6A modification and inhibited cell viability, migration, invasion, and RAS/MEK/ERK signaling pathway activation. Overexpression of IGF2BP1 promoted cell viability, migration, and invasion, which were reversed by PRMT9 knockdown. PRMT9 overexpression activated the RAS/MAPK signaling pathway, and blocking this pathway attenuated the effect of PRMT9 on LUAD metastasis. In vivo experiments confirmed that knocking down PRMT9 inhibited tumor growth and decreased the protein levels of RAS, pMek1/2, pErk1/2, and Ki67, while increasing caspase-3 levels.

Conclusions: PRMT9 is overexpressed in LUAD and promotes cancer progression by activating the RAS/MAPK signaling pathway. The abnormal expression of PRMT9 is associated with its mRNA m6A modification regulated by IGF2BP1. Targeting PRMT9 or the RAS/MAPK signaling pathway may provide new therapeutic strategies for LUAD.

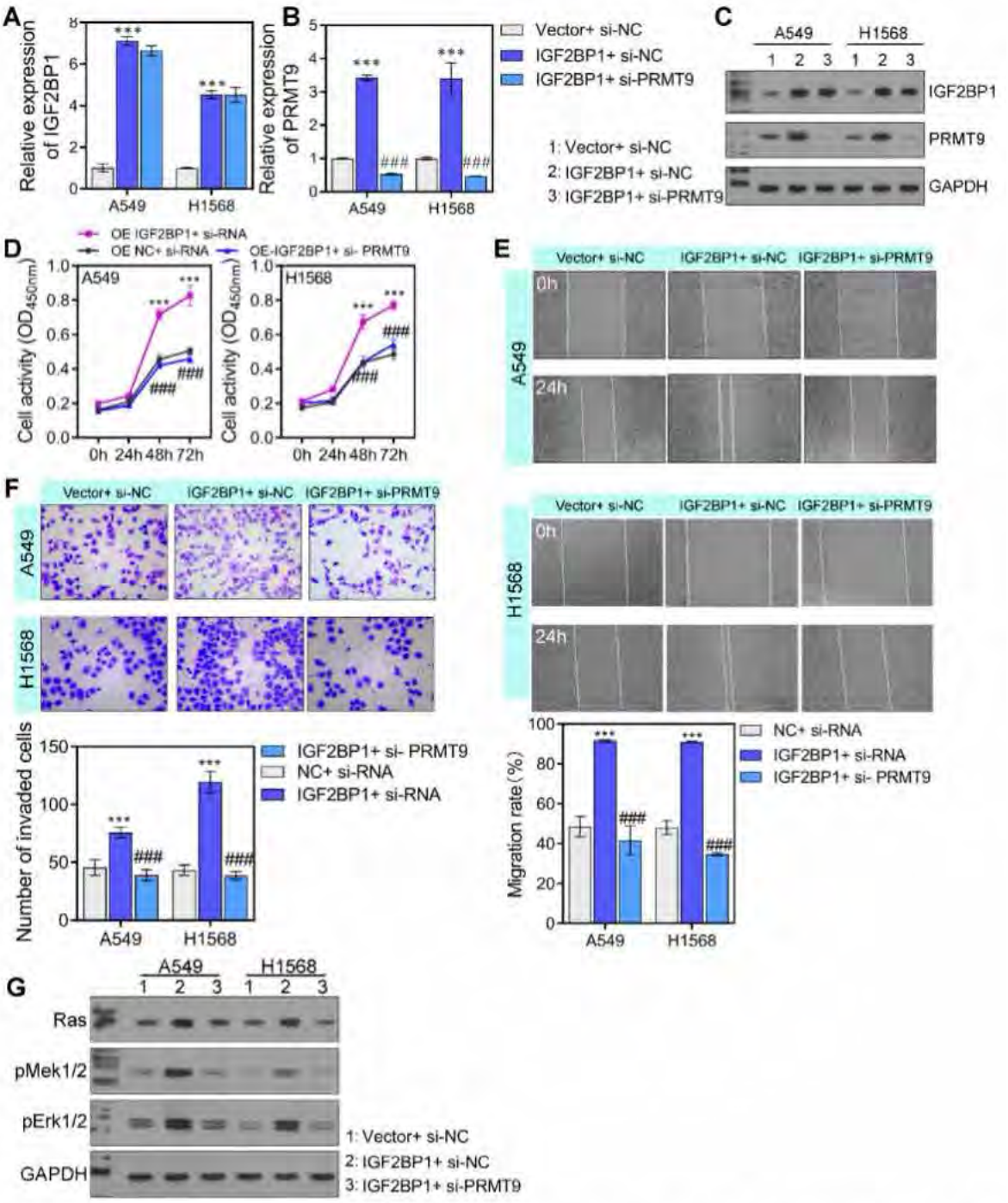

Figure 1 Knock-down of PRMT9 reversed the effect of IGF2BP1 overexpression on proliferation and metastasis

(A-C) QPCR and Western Blot methods for detecting IGF2BP1 and PRMT9 expression 48 hours after transfection. (D) Cell viability was detected by CCK8 assay. (E) Cell migration was measured by Scratch test. 40×magnification. (F) Cell invasion was measured by Transwell assay. 200×magnification. (G) Protein levels of RAS, pMek1/2 and pErk1/2 were showed by Western Blot analysis. ***P < 0.001, *vs.* Vector+ si-NC group; ###P < 0.001, *vs.* IGF2BP1+ si-PRMT9 group.

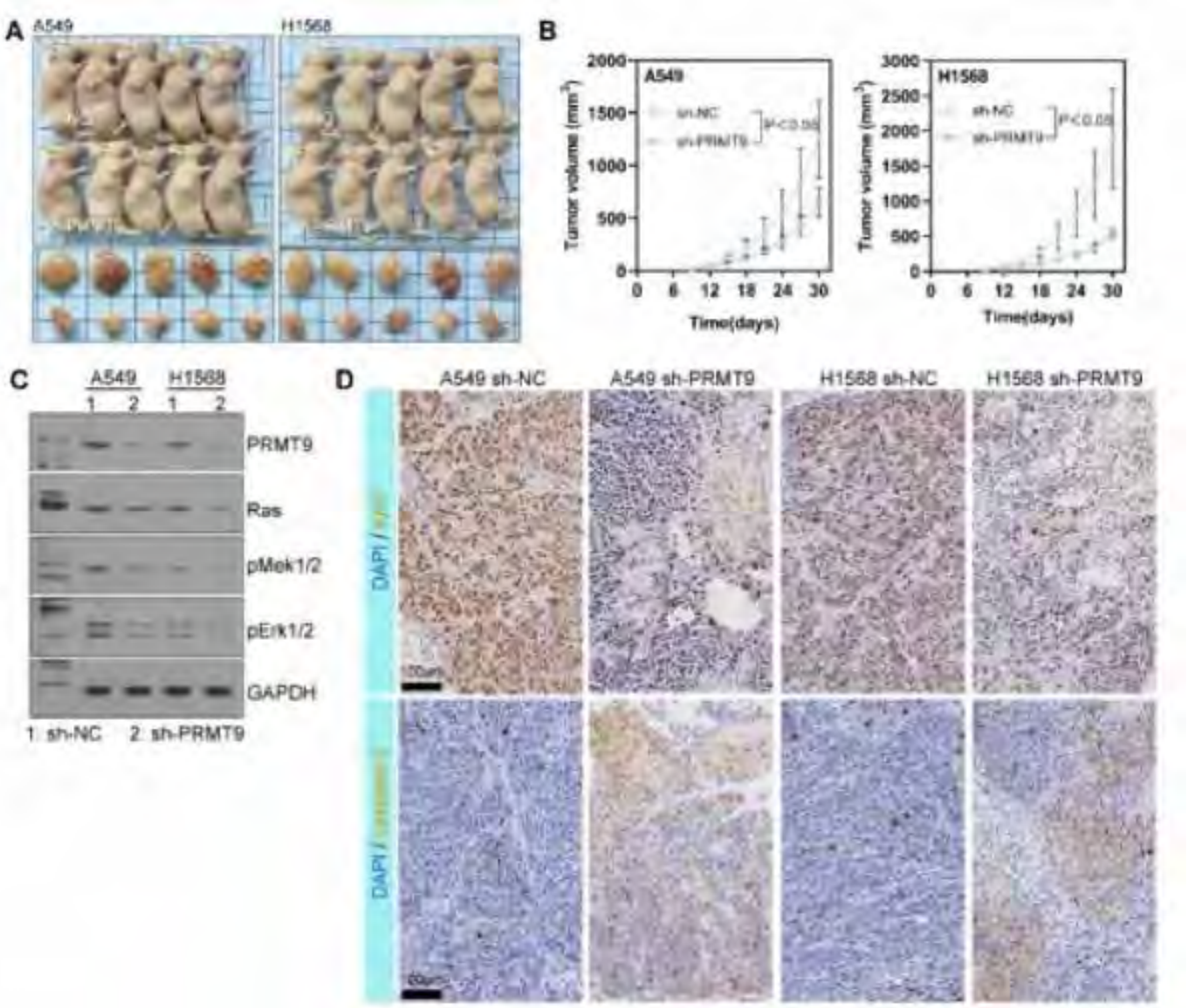

Figure 2 *In vivo* experiments confirmed that knocking down PRMT9 inhibits tumor growth

(A) Images of tumors in mice and that *in vitro* after excision. (B) Starting from the 9th day after injection, the calculated tumor volume was measured every 3 days. (C) Protein levels of PRMT9, RAS, pMek1/2 and pErk1/2 were showed by Western Blot analysis. (D) Expression levels and localization of Ki67 and Caspase-3 in tumors showed by IHC assay.

Keywords: Lung adenocarcinoma, IGF2BP1, PRMT9

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.41 FOXO3A Regulates NSCLC Radiotherapy Resistance Through PINK1/Parkin Pathway of Protective Mitophagy

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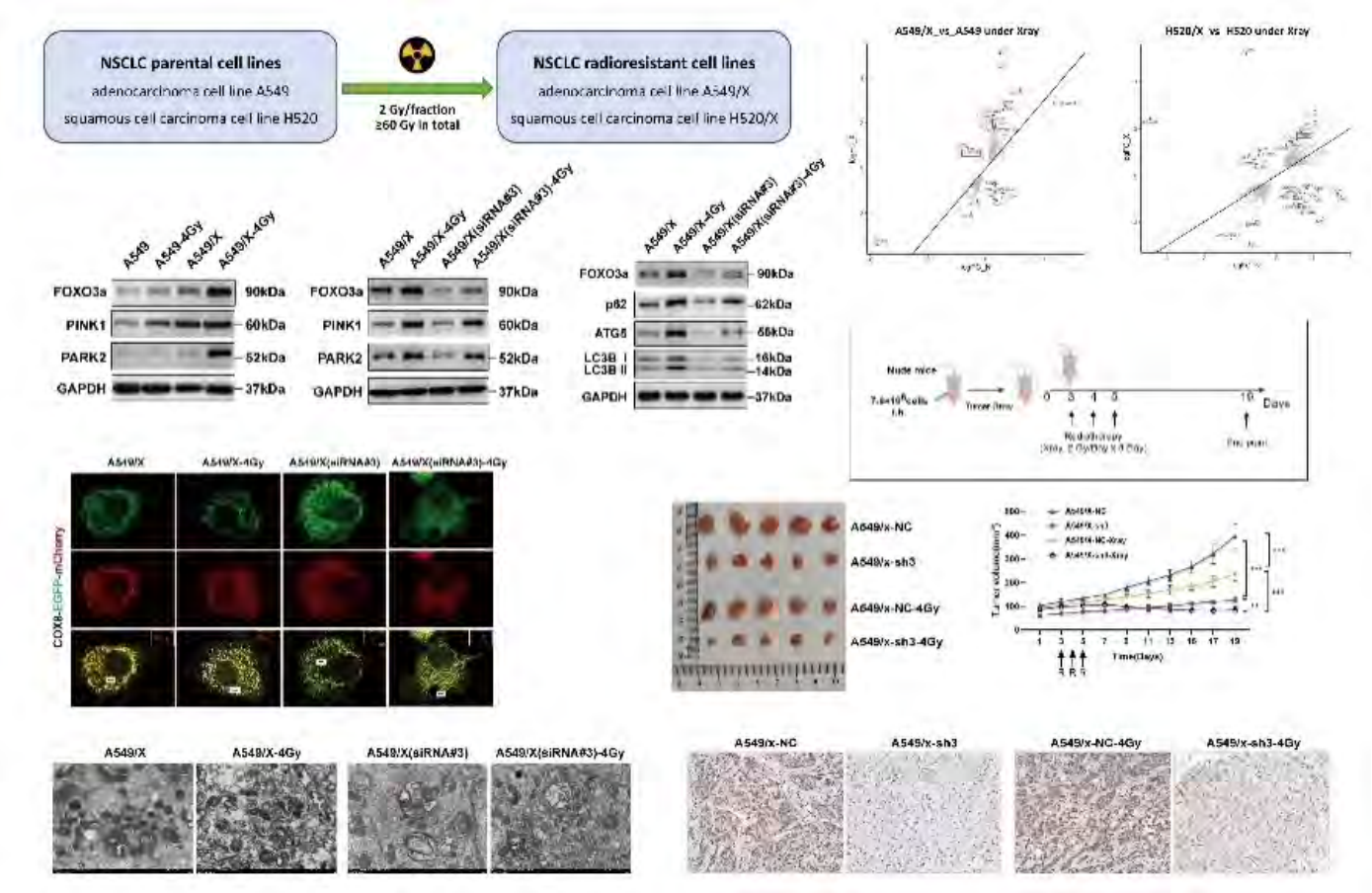
Introduction: Radiotherapy resistance has become one of the major causes of radiotherapy failure among patients with non-small cell lung cancer (NSCLC), and its underlying mechanism remains unclear. In recent years, the influence of cell mitochondrial autophagy on tumor radiotherapy resistance and its regulatory mechanism is one of the research hotspots.

Methods: We constructed stable radiotherapy-resistant NSCLC cell models A549/X and H520/X and the radioresistance of the cells was also verified. Subsequently, through high-throughput transcriptomic sequencing analysis and experimental verification, we found that the FOXO3a gene and mitochondrial autophagy PINK1/Parkin pathway in NSCLC radiotherapy-resistant cell lines were indeed consistent and upregulated more reactively than those of parental cells. The effect of gene expression status of FOXO3a-PINK1/Parkin pathway on the survival outcome of NSCLC was analyzed by TCGA database. Next, we inoculated nude mouse xenografts with siRNA to interfere with FOXO3a gene and shRNA to construct radiotherapy-resistant stable transtrains of NSCLC with stable knockdown of FOXO3a gene, and detected the association and regulation of FOXO3a gene expression levels with radioresistance and mitochondrial autophagy PINK1/Parkin pathway at the cellular and animal levels.

Results: The expression level of FOXO3a gene in NSCLC radioresistant cells was significantly positively correlated with the level of mitophagy and the expression level of PINK1/Parkin pathway. The gene expression status of FOXO3a-PINK1/Parkin pathway had an adverse effect on the survival outcome of NSCLC and was positively correlated with the radioresistance of cells. FOXO3a regulates radiotherapy resistance to NSCLC by regulating the PINK1/Parkin pathway of mitophagy.

Conclusions: FOXO3a regulates NSCLC radioresistance by regulating the mitochondrial autophagy PINK1/Parkin pathway, which may provide a new molecular intervention target and therapeutic entry point for intervening and improving the radioresistance of NSCLC in clinical practice.



Keywords: Radiotherapy Resistance, Mitochondrial Autophagy, Non-small Cell Lung Cancer

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.42 Immune-Related Gene Expression Profiling and ALK-TKI Efficacy for Patients With ALK-Rearranged Non-Small Cell Cancer

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Introduction: Anaplastic lymphoma kinase (ALK) rearrangements occur in 5-8% of non-squamous non-small-cell lung cancer (NSCLC) cases. While ALK tyrosine kinase inhibitors (TKIs) are effective first-line treatments, resistance inevitably develops. Immune checkpoint inhibitors (ICIs) have shown limited clinical benefits in ALK-rearranged NSCLC, necessitating novel salvage strategies post-ALK-TKI failure. Here, we analyzed the immune-related gene expression profiling (irGEP) in patients with ALK-rearranged NSCLC with the aim of evaluating the tumor microenvironment and identify potential therapeutic strategies.

Methods: This study utilized samples from the ALCURE trial (UMIN000038934), a prospective observational, multicenter study exploring the efficacy and resistance mechanisms of alectinib in patients with ALK-rearranged NSCLC. All patients were treated with alectinib as 1st line therapy, and pre-treatment tumor tissue receiving alectinib was analyzed using the NanoString nCounter PanCancer IO 360 Panel, which includes 750 immune-related genes with 20 housekeeping genes.

Results: Among the 249 patients who participated in the ACLURE trial, irGEP analysis was performed on 52 patients for whom residual nucleic acid samples of sufficient quality and quantity were available. The patient characteristics were consistent with those previously reported for patients with ALK-rearranged NSCLC. Programmed cell death-ligand 1 tumor proportion score (PD-L1 TPS) was available for 20 patients, of whom 12 had high (≥ 50%) and 8 had low expression (< 50%). In the high PD-L1 expression group, upregulation of genes associated with CD8+ TILs recruitment, such as CXCL9 and CXCL10, was observed. The genes encoding the inhibitory immune checkpoint molecules IDO1 and LAG3 were also highly upregulated, suggesting T cell exhaustion in the high PD-L1 expression group. Also, irGEP analysis revealed distinct immune profiles according to CD8A expression. The high CD8A expression group demonstrated decreased expression of CDH1, which encodes E-cadherin, and increased expression of SNAI1, indicative of epithelial-mesenchymal transition. Conversely, the low CD8A expression group upregulated the expression of ANGPT2, which encodes angiopoietin-2, and FLT1 (VEGFR1), suggesting enhanced tumor angiogenesis, which may contribute to the insufficient infiltration of T cells into the tumor. Progression-free survival of alectinib was tended longer in the high CD8A expression group compared with the low CD8A expression group (HR, 0.49 with 95% CI of 0.18-1.35).

Conclusions: High CD8 positive T cells infiltration in ALK-rearranged tumor might be associated with longer duration of alectinib efficacy. Anti-angiogenic therapies may enhance anti-tumor immunity and potentially augment the efficacy of alectinib in patients with ALK-rearranged NSCLC harboring low CD8 positive T cells infiltration.

Keywords: non-small cell lung cancer, ALK rearrangement, tumor microenvironment

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.43 Gut Klebsiella Pneumoniae Drives Lung Cancer Progression by Modulating Macrophage Hpgds and Suppressing the PGJ2-PPAR? Signaling Pathway

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Introduction: The mechanisms that the gut microbiota influences lung cancer remain to be elucidated. Klebsiella pneumoniae (KP), a gut conditional pathogen commonly causing disease after antibiotic-induced gut microbiota dysbiosis, whose impact on lung cancer remains to be investigated.

Methods: Gut microbiota dysbiosis was induced by a four-antibiotic cocktail on a mouse subcutaneous tumor model bearing Lewis Lung Carcinoma, while the gut KP colonization model was established by gavage after clindamycin treatment. 2bRAD-M sequencing was used to screen for bacterial species. Metabolomics and single-cell transcriptomics were employed to investigate the tumor microenvironment. In vitro, a co-culture model of KP-colon organoid epithelium-macrophages-tumor cells was constructed to validate cell proliferation assays and signaling pathways.

Results: Subcutaneous tumor-bearing mice treated with antibiotic cocktail exhibited distinct growth velocity, and were classified into ABXS (small tumors) and ABXB (large tumors) groups based on tumor size. 2bRAD-M sequencing revealed that gut KP was significantly enriched in the ABXB group. Metabolomic analysis showed that the arachidonate-PGJ2 pathway exhibited the most significant differences. Single-cell transcriptomics, immunofluorescence, and TCGA adenocarcinoma transcriptomics indicate that the key enzyme HPGDS, which regulates PGJ2 metabolism within tumors, is specifically localized to macrophages and is associated with prognosis. In vivo and in vitro experiments further validated that KP promoted PGJ2 metabolic reprogramming by influencing HPGDS expression in tumor-related macrophages, thereby accelerating tumor progression. Further analysis of mouse tumor transcriptomes and in vitro co-culture systems revealed that KP inhibits the synthesis and secretion of PGJ2 in macrophage. This subsequently suppresses the dephosphorylation of PPARγ at the Ser273 within tumor cells, affects the function of the transcription factor complex PPARγ-RXRα, and subsequently regulates downstream P53/P21 and cell cycle-related pathways to promote tumor cell proliferation.

Conclusions: Gut Klebsiella pneumoniae promotes lung cancer progression by modulating macrophage HPGDS and regulating the PGJ2-PPARγ signaling pathway. And further translational research is ongoing.

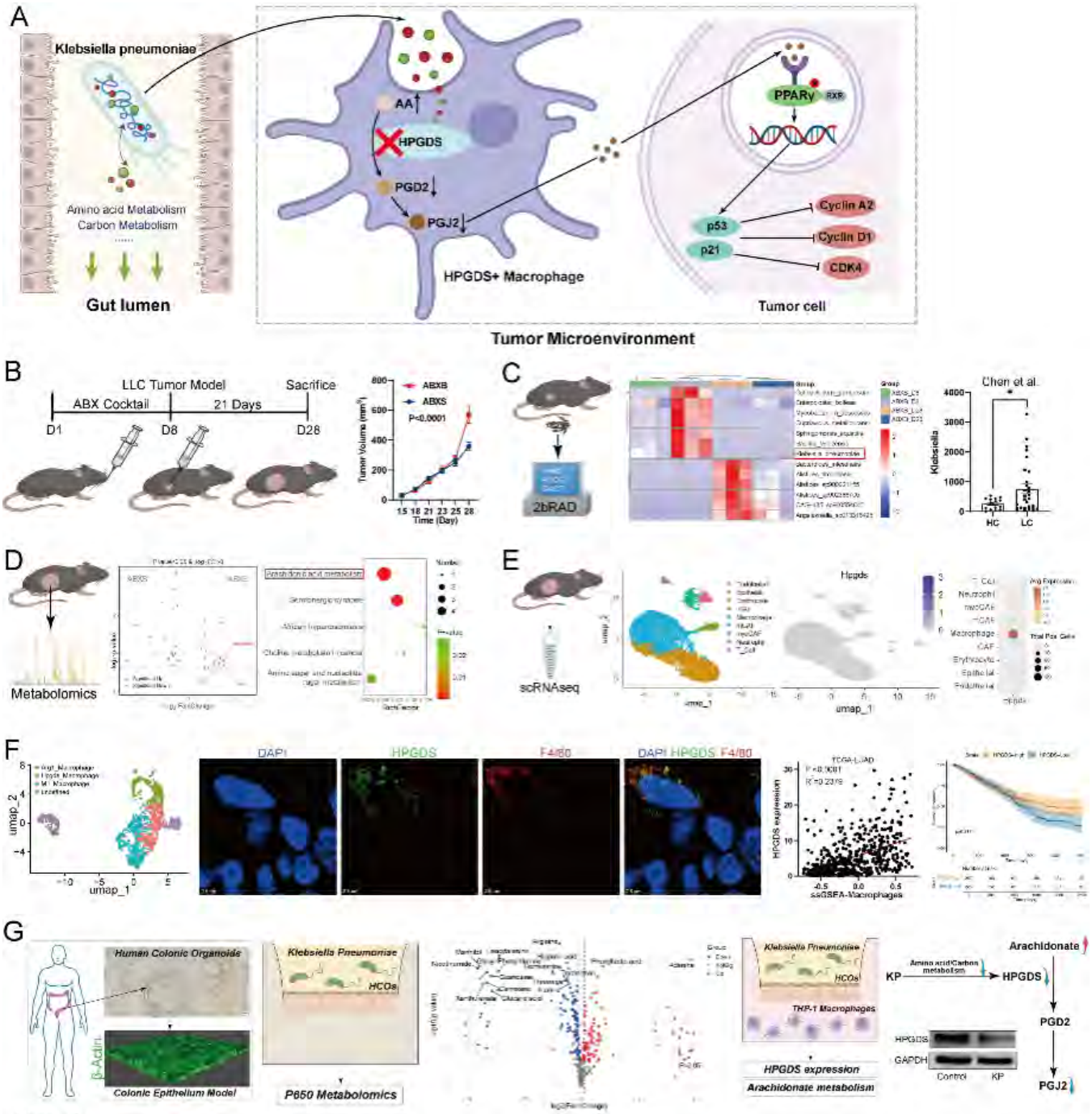

Figure 1

(A) Schematic diagram of the mechanism: Intestinal Klebsiella pneumoniae (KP) regulates amino acid metabolism and other mechanisms, affecting PGJ2 metabolic reprogramming in tumor-infiltrating HPGDS+ macrophages, thereby modulating the PGJ2-PPARγ signaling pathway in tumor cells to promote tumor progression.

(B) In a subcutaneous LLC cell tumor model after 7 days of antibiotic cocktail clearance, tumor progression exhibited obvious polarization. Samples were divided into the ABXS group (small tumors) and the ABXB group (large tumors) based on tumor size.

(C) 2bRAD-M sequencing revealed that KP was one of the significantly different microorganisms in the ABXB group, and this was validated in external datasets.

(D) Metabolomic analysis revealed that the levels of metabolites such as PGJ2 and the arachidonic acid metabolic pathway were the main differentially expressed metabolic pathways in tumor tissue.

(E) Single-cell transcriptomic analysis showed that the key enzyme HPGDS, which regulates arachidonic acid-PGJ2 metabolism in tumor tissue, was specifically expressed in a macrophage subpopulation, and this was validated in external data analysis.

(F) Single-cell analysis further clarified the characteristics of the HPGDS+ macrophage subpopulation. Immunofluorescence validation of tumor tissue confirmed the specific expression of HPGDS in macrophages. Simultaneously, TCGA data analysis showed that HPGDS expression levels were positively correlated with macrophage enrichment scores and were associated with patient prognosis.

(G) An in vitro colon organoid epithelial model was constructed using colon tissue extracts to achieve a co-culture system of intestinal KP and extra-intestinal macrophages. Metabolomic validation showed that KP mainly affects HPGDS expression and PGJ2 metabolic reprogramming in macrophages by consuming amino acids.

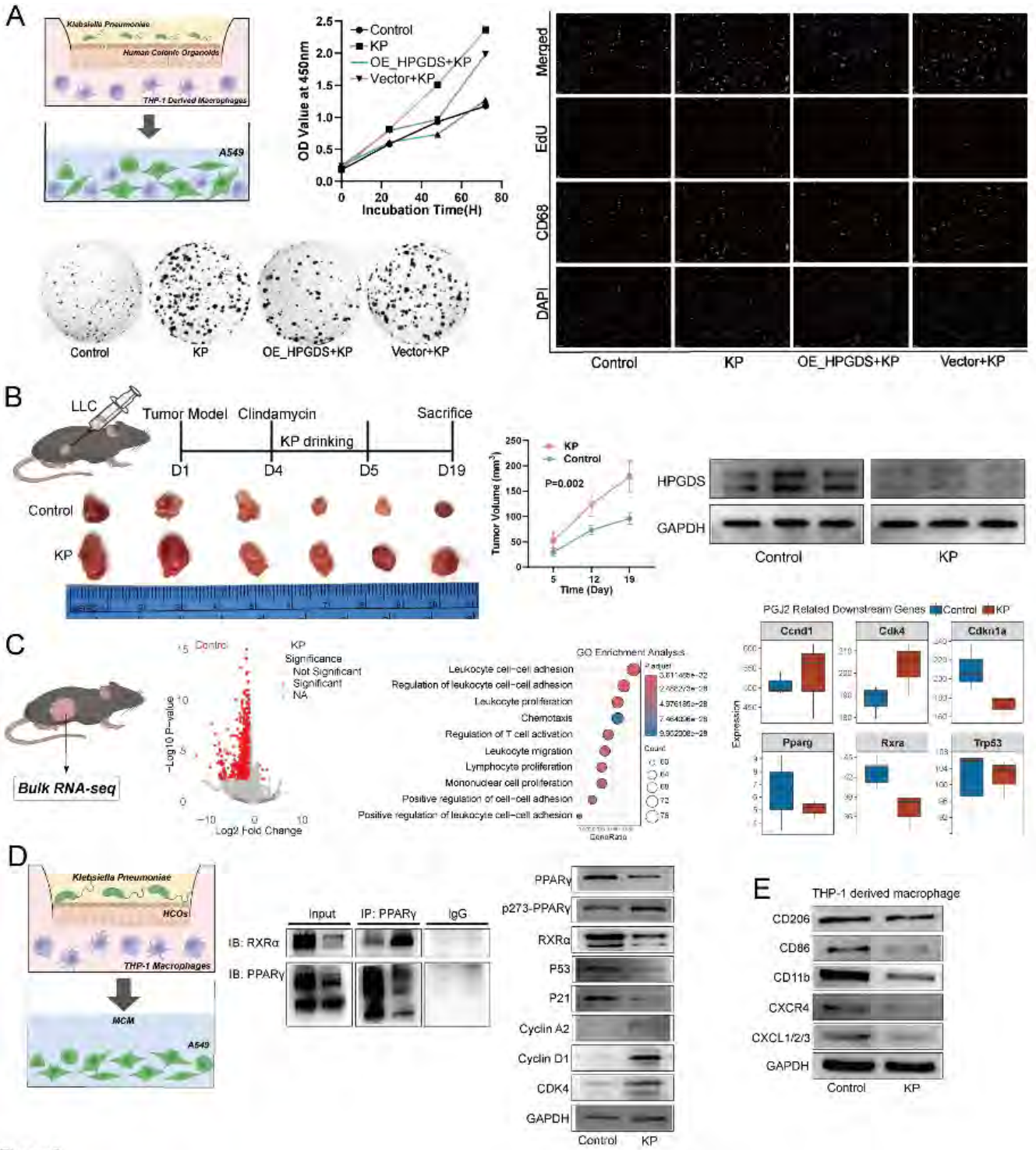

Figure 2
(A) In vitro co-culture experiments confirmed that intestinal Klebsiella pneumoniae (KP) promotes tumor cell progression by affecting HPGDS/PGJ2 metabolic reprogramming in macrophages.
(B) In vivo experiments revealed that KP can inhibit HPGDS expression in mouse tumor tissue and significantly promote tumor progression.
(C) Bulk RNA-seq analysis of mouse tumor tissue showed that intestinal KP can affect immune cell infiltration in tumor tissue and regulate the PGJ2 downstream receptor PPARγ signaling pathway.
(D) In vitro experiments, A549 cells treated with conditioned medium from KP-treated macrophages showed altered phosphorylation of the PGJ2 receptor PPARγ at Ser273 and its binding to RXRα in the cytoplasm, further regulating the activity of the downstream P53/P21/CyclinA2/CyclinD1/CDK4 signaling pathway.
(E) Discussion: Changes in the expression of macrophage surface markers CD11b, CD206, CD86, and CXCL, etc., after KP co-culture suggest that KP may also participate in tumor microenvironment regulation by affecting macrophage polarization and other functions.

Keywords: Gut microbiota, HPGDS/PGJ2-PPARγ signaling pathway, Tumor microenvironmen

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.44 High Frequency of SMARCA4 Inactivating Mutations in Advanced NSCLC and Their Association With Low PD-L1 Expressio

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Introduction: While immune checkpoint inhibitors (ICI) have significantly improved survival among patients with non-small cell lung cancer (NSCLC), the emergence of resistance mechanisms remains a challenge. We aim to elucidate the underlying resistance mechanisms by characterizing the genomic and molecular features of tumor immunogenicity in a cohort of NSCLC patients.

Methods: Patients diagnosed with NSCLC treated with ICI-based strategies at the Catalan Institute of Oncology-ICO Badalona, were prospectively enrolled (ImmunoLung PI-19-275). Samples were obtained through flexible bronchoscopy during diagnosis process. Comprehensive tumor genomic profiling was performed by whole-exome sequencing (WES) and RNA sequencing (RNA-seq), from those samples with enough quality material, conducted at the National Center for Genomic Analysis.

Results: Of 48 patient samples, 29 were available for deep genomic profiling. Patient characteristics included: mean age 66 years-old (range 43-85), 83% male, 17% female; 90% current or former smokers; ECOG PS 0/1: 83%, and ECOG PS 2: 17%. Histologic subtypes included 55% adenocarcinoma (ADC), 31% squamous cell carcinoma (SCC), and 14% NSCLC-NOS. At diagnosis, 60% were stage IV and 40% stage III. High PD-L1 expression (≥50%) was observed in 25% of tumors (IHC SP Ventana 263). All patients received anti-PD(L)1 based strategies either alone or in combination with chemotherapy or other ICI. Oncogenic drivermutations detected in primary lung tumors included KRAS (27%), SMARCA4 (17%), STK11 (14%), KEAP1 (10%), MYC amplification (7%), PIK3CA (7%), and ALK translocation (3%). Additionally, key alterations in the IFNγ signaling pathway were identified, including a splice site mutation in JAK2 (c.2131A>G, p.Ile711Val) and one polymorphism in TAP2 (c2059T>C, p.Ter687Gln). Notably, we detected a high prevalence (n=5, 17%) of truncating SMARCA4 mutations, a key regulator of chromatin remodeling associated with poor cancer prognosis. None of the SMARCA4-mutated tumors exhibited high PD-L1 expression, with a mean PD-L1 expression of 8%, compared to 27% in non-SMARCA4-mutated tumors (p=0.06). In our cohort, high PD-L1 expression (≥50%) correlated with improved median overall survival (OS) of 30.9 months (95% CI 0-89), compared to 14.5 months (95% CI 9.3-19.7) in tumors with PD-L1 <50% (p=0.37).

Conclusions: Our study reveals the genomic heterogeneity of NSCLC that contributes to tumor immunogenicity. Interestingly, we identified a high frequency of SMARCA4 mutations in advanced-stage NSCLC, and these alterations were associated with lower PD-L1 expression, potentially contributing to immune response capability in patients receiving ICI-based therapies. These results highlight the need to consider chromatin remodeling gene alterations as potential predictive biomarkers to ICI and warrants further investigation to expand and validate our results.

Keywords: SMARCA4, PD-L1, NSCLC

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.45 KRAS Mutations Shape an Oxidative, Immune-Cold Tumor Microenvironment Driving Chemo-Immunotherapy Resistance in Advanced NSCLC

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Introduction: Despite the improvement in precision medicine and the widespread use of checkpoint inhibitors (CPIs) combined with platinum-based chemotherapy (CIT), non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality globally. Approximately 30% of NSCLCs harbor KRAS mutations, with the G12C variant being the only one currently targetable in the second-line setting. However, beyond genomic alterations, the tumor microenvironment (TME) has emerged as a critical determinant of therapeutic response and resistance, particularly to CIT. Among the multifaceted mechanisms at play, oxidative stress has been shown to modulate CPI efficacy through altered PD-L1 expression and immune cell infiltration. Nevertheless, the precise immunometabolic interplay within the TME of KRAS-driven tumors remains insufficiently understood.

Methods: We prospectively collected tumor samples from 47 patients with treatment-naïve advanced NSCLC with an ECOG performance status of 0-1 and no significant comorbidities, candidates to receive CIT. Both KRAS wild-type and mutant tumors were included, while those harboring EGFR, ALK, or ROS1 alterations—identified via an extended molecular panel—were excluded. RNA was extracted from samples with ≥30% tumor cellularity and processed using the TruSeq RNA Access Kit (Illumina), followed by paired-end sequencing on the NovaSeq 6000 platform.Transcriptomic data were pre processed via nf-core/rnaseq. Differential gene expression analysis was conducted using DESeq2, with downstream gene set enrichment analysis (GSEA). The immune landscape was inferred using CIBERSORT and ESTIMATE algorithms. Associations between gene expression, immune composition, and clinical outcomes were evaluated using Spearman correlation, Cox multivariate modeling, and Kaplan-Meier analysis.

Results: Among the 47 analyzed cases (34 male, 13 female; median age 63.5 years, 46.8-81.5), 26 harbored KRAS mutations and 21 were KRAS wild-type. PD-L1 expression was broadly distributed (0-100%) and balanced between groups ($p = 0.355$). All the patients received a I line with CIT. Notably, KRAS-mutant tumors were associated with significantly shorter progression-free survival (PFS; $p = 0.01$). Transcriptomic analysis underlined 83 differentially expressed genes between KRAS-mutant and wild-type tumors, with 11 showing $|log2FC| > 1$. GSEA demonstrated a marked downregulation of immune-related pathways—including antigen processing, interferon signaling, and T cell-mediated cytotoxicity—in KRAS-mutant tumors. Conversely, genes associated with metabolism and oxidative stress were upregulated. Among them, EDN1 emerged as a potential key player. Overexpressed in KRAS-mutant tumors ($log2FC = 1.16$; $p = 0.026$), EDN1 was the gene most negatively correlated with CD8+ T cell infiltration and has known roles in ROS metabolism and TGFβ-mediated immunosuppression.

Conclusions: Our data suggest that KRAS mutations shape a metabolically reprogrammed and immunosuppressive TME that may drive resistance to CIT. Targeting oxidative stress and immunomodulatory pathways—such as those involving EDN1—may represent promising therapeutic strategies to overcome resistance and improve outcomes in KRAS-driven NSCLC.

Keywords: KRAS mutation, Immunotherapy resistance, Oxidative stress

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.46 Phenotyping Double Negative B Cells in Non-Small Cell Lung Cancer

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Introduction: The tumour microenvironment (TME) of NSCLC is complex, containing a variety of tumour infiltrating lymphocytes (TILs) including TIL-B cells which have been associated with favourable treatment responses. However, a subset of B cells characterised by the absence of IgD (naivety marker) and CD27 (activation marker), known as double negative (DN) B cells, have been associated with progression and adverse outcome in non-cancer diseases. We sought to characterise this DN population in NSCLC, including a sub-population (CD11c+, CD21-,CXCR5- DN cells) that may be precursors to short lived pathogenic auto-antibody secreting plasmablasts (PB).

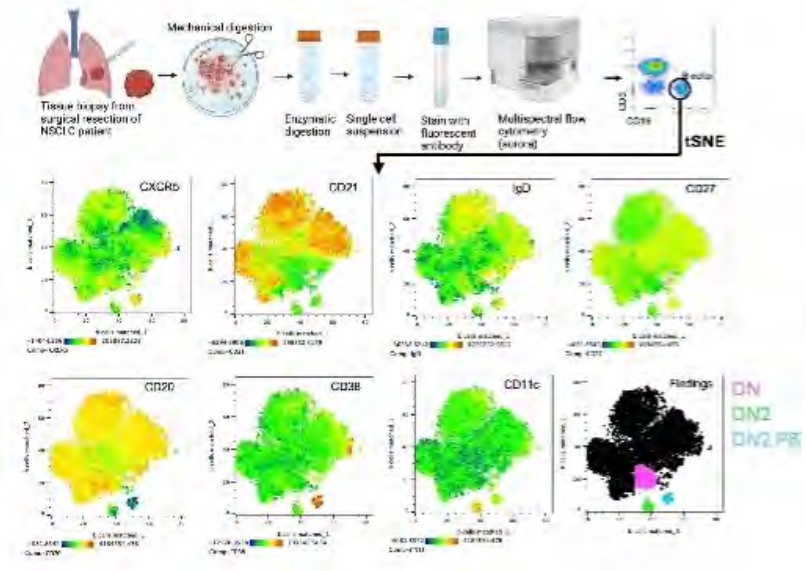
Methods: Tumour, adjacent non-cancerous lung (NCL) and PBMCs from treatment naïve early-stage NSCLC patients were dissociated to single cells and stained with a 32-colour multispectral flow cytometry panel (Figure 1A). B cells were gated, concatenated and a clustering algorithm explored DN populations (IgD-,CD27-); including the DN2 sub-population (IgD-,CD27-,CXCR5-,CD21-,CD38-,CD11c+) and a PB population (IgD-,CD27-/+,CXCR5-/+,CD21-,CD38 high,CD11c low) (1A).

Results: Using key markers (CD19,CD138,CD20,CD38,CD24,CD27,IgD/M/A/G and IL-10) we identified conventional B cell populations (plasma, memory, naïve, regulatory, etc.) across the NSCLC patient cohort. Focusing on DN B cells we observed 3 relevant populations: DN B cells, DN2 B cells and a subpopulation of DN2 PB expressing CD11c and highly expressing CD38, likely arising from the DN2 cells. DN B cells were more prevalent in both the tumour and NCL than in matched PBMC samples (20.5%,15.6%,10.8% respectively, n=5). Of the DN population, DN2 were significantly more prevalent in the tumour than in the NCL or the PBMCs (30%,13.5%, 4.7%, n=5) (1B). Interestingly, the CD11c+ PB population express FOX-P3 in flow cytometry data, indicating a regulatory phenotype (PCREG). As DN2 B cells can progress to autoreactive ASCs identifying the B cell receptor repertoire, and thus the antigen target, of the population we describe could provide insight to new therapeutic targets to exploit and improve NSCLC patient treatment response.

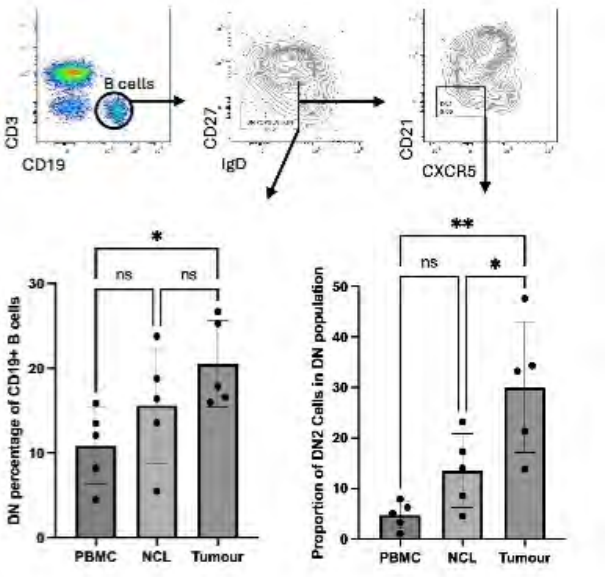
Conclusions: We found two TIL-B cell populations, previously undescribed in NSCLC. In non-cancerous pathologies these influence disease trajectory. Further work will integrate the flow data with sc-RNAseq data sets and tissue validation through a multiplex IFF panel on a tissue microarray set (>160 patients), linked to clinical outcome.

Figure 1

A- Processing protocol and matched sample concatenated tSNE cluster of NCL, PBMC, and Tumour to determine DN2 population (n=5)



B- DN2 percentage of population by tissue compartment



Keywords: Non-Small Cell Lung Cancer, TIL B cells, Double Negative B cells

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.47 Study of Genomic Intra-Tumor Heterogeneity and Acquired Resistance to Tyrosine Kinase Inhibitors in Lung Cancer

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Introduction: Precision-targeted therapies have been developed for lung cancer (LC) patients, focusing on specific tyrosine kinase inhibitors (TKIs) against membrane receptors with tyrosine kinase activity that are genetically activated in these tumors. However, despite an initial favorable response, tumors often develop resistance, leading to patient relapse. In LC, acquired resistance is associated with various molecular and genetic mechanisms, some of which have been studied and characterized. Here, we investigated the role and evolution of intratumoral genomic heterogeneity in acquired resistance to TKIs in LC cells.

Methods: We use the following LC cell models: 1) EGFR-mutant patient-derived cancer cells obtained before and after resistance to TKIs; 2) MET-activated cancer cells that developed resistance to TKIs following exposure to increasing drug concentrations; 3) RET-rearranged cancer cells that similarly acquired resistance through escalating TKI exposure. Comprehensive genetic (whole exome sequencing) and gene expression (bulk RNA sequencing) data from these cells were available from our previous studies. Single-cell analyses were performed at both RNA (scRNAseq) and DNA (scDNAseq) levels using the 10x Genomics and Tapestri (Mission Bio) platforms, respectively.

Results: Through whole exome sequencing and bulk RNA sequencing, we identified tumor-specific gene rearrangements (such as amplifications, deletions, fusions, and loss of heterozygosity [LOH]), as well as mutations and alterations in gene expression, some of them associated with resistance. These include, among others, alterations at MDM2, KRAS, FGFR3, and NF2. Using this information, we performed scDNA-seq and scRNA-seq to investigate cancer cell subpopulations before and after the development of acquired resistance. Our analysis revealed that some of these alterations were already present in the parental cells and expanded during treatment. Additionally, we observed the selection of distinct alterations among different resistant cancer cell populations. This highlights that intrinsic heterogeneity can drive clonal selection under the pressure of TKIs. Notably, however, the acquired alterations linked to TKI resistance were not always present in the parental cancer cells.

Conclusions: We have identified tumor heterogeneity present at both the DNA and RNA levels. The identification of tumor-specific gene rearrangements and mutations, some of which pre-existed in parental cells, suggests that intrinsic tumor heterogeneity plays a significant role in the emergence of resistance. These findings highlight the complexity of the drug resistance process and emphasize the need for more comprehensive approaches to target both pre-existing and emerging resistant subpopulations in order to improve cancer therapeutics. DeepL has been used to translate and modify the text formatting.

Keywords: Genomic intra-tumour heterogeneity, Acquired resistance to tyrosine kinase inhibitors, Single-cell sequencing (scRNA-seq / scDNA-seq)

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.48 Fluorescence Lifetime Imaging in Fixed NSCLC Samples Demonstrate Differences Between Tissue Compartments

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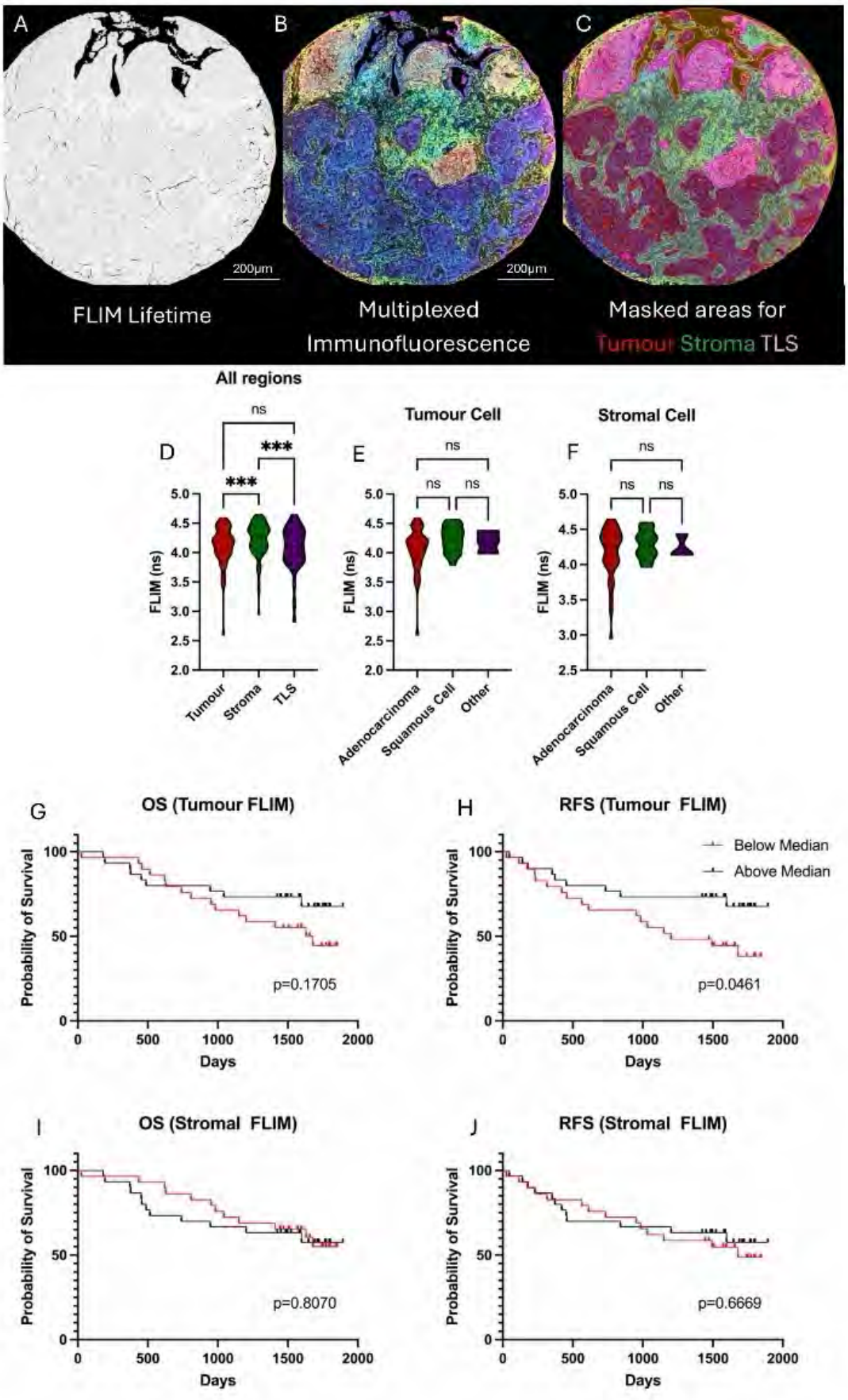
Introduction: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide. Fluorescence Lifetime Imaging (FLIM) measures the time-dependent decay from autofluorescent endogenous molecules. FLIM in formalin-fixed paraffin-embedded (FFPE) NSCLC has generated virtual H&E staining[1] and accurately predicts TTF-1 and P40 status[2]. Therefore, we characterised FLIM signals within FFPE cores across NSCLC tissue compartments.

[1] doi.org/10.1038/s44303-024-00021-7 [2] doi.org/10.48550/arXiv.2503.20817

Methods: Unstained TMA cores from NSCLC patients were FLIM imaged to capture lifetime using a Leica Falcon X microscope. FLIM images were reconstructed by exponential fitting to calculate lifetime values [A] and exported with a 0-5 nanosecond threshold. The same cores were stained in a multiplex Immunofluorescence assay using Akoya Opal dyes targeting CD3, CD20, PanCK, aSMA, and DAPI and imaged on an Akoya Vectra Polaris [B]. Regions for Tumour, tertiary lymphoid structures (TLS), and Stroma were determined within QuPath, and cell segmentation was performed [C]. These regions were exported to calculate the FLIM lifetime on a per-cell level, which was then averaged over each region for an individual patient core.

Results: We analysed 58 patient cores, calculating 652630 cells for tumour, stroma and TLS across the entire dataset. Using the average FLIM lifetimes for each core region, we found that tumour areas had significantly shorter lifetime values than stromal areas (p=0.0002). Stroma regions were also shorter than TLS regions (p=0.0001) and Tumour/TLS was non-significant [D]. No significant differences were found between adenocarcinoma and squamous cell carcinoma when comparing the compartments between cancer subtypes [E & F]. Similarly, FLIM was not different when stratified by smoking status (smoker vs ex or non-smoker) or Stage (I+II vs III+IV) across all compartments (all p>0.05). There was a trend to a poorer survival outcome in patients with lower tumour FLIM signal [G] and a significantly poorer outcome for recurrence-free survival (p=0.0461) [H]. This was not seen when assessing stromal compartments, suggesting this is tumour-cell driven [I & J].

Conclusions: We demonstrate that FLIM can distinguish between stroma and tumour compartments in NSCLC. While no significant differences were observed between cancer types, stages, or smoking status, lower FLIM lifetimes in tumour regions showed a significant correlation with poorer regression-free survival outcomes. This suggests FLIM has the potential as a prognostic tool in FFPE NSCLC, particularly in identifying more aggressive tumours by their characteristic fluorescence lifetimes. We plan to assess this within a broader cohort and more granular assessment of cell specific FLIM values.



Keywords: NSCLC, FLIM, Tissue compartment discrimination

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.49 Mechanisms of Resistance to Tyrosine Kinase Inhibitors in Lung Cancer Cells Harbouring RET Fusions

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Introduction: RET fusions are present in 1-2% of non-small cell lung cancer (NSCLC), with KIF5B-RET and CCDC6-RET being the most common. In recent years, two selective RET tyrosine kinase inhibitors (TKIs) have been approved by the Food and Drug Administration (FDA), selpercatinib and pralsetinib. However, the emergence of resistance limits the long-term effectiveness of these treatments. The aim of this study was to elucidate the mechanisms of resistance to these RET inhibitors in NSCLC cells and to identify new therapeutic targets to overcome the resistance.

Methods: Two lung cancer cell models harbouring RET fusions, LC-2/ad (CCDC6-RET) and PDC6 (KIF5B-RET), a patient-derived cell line established by our group, were used to generate resistant cell lines to selpercatinib and pralsetinib. We characterize these cells, at genetic and molecular level, by whole exome sequencing (WES), RNA-sequencing and analysis of signaling pathways.

Results: Resistance to both RET-TKIs involved morphological changes and differences in gene expression in all the resistant cells, along with a de novo activation or reactivation of AKT, ERK and mTOR in most of them. No on-target mutations were detected. In the LC-2/ad-resistant cells, different alterations of unknown significance were identified. In the PDC6-resistant cells, KRAS (p.Gly12Asp) and NRAS (p.Gln61Lys) mutations were found in two of the resistant cells, to selpercatinib and pralsetinib, respectively. As a potential resistance mechanism of three of the resistant cell lines, we observed the clonal expansion of a pre-existing novel gene fusion, associated to high expression of one of the fusion partners at both RNA and protein levels.

Conclusions: Here, we show that resistance to RET-TKIs frequently involves activation of the RAS/MAPK pathway through mutations in KRAS and NRAS and activation of ERK. In addition, the activation of AKT and the clonal expansion of a new gene fusion suggest the existence of multiple simultaneous resistance mechanisms to RET-TKIs. Altogether, these observations can help us to better understand the resistance processes in order to design future strategies for the treatment of these patients

Keywords: RET fusions, Tyrosine kinase inhibitors, Drug-resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.50 cIRCCAMSAP1 Induce Osimertinib Resistance in Lung Adenocarcinoma by Downregulating the Degradation Level of HSPA1A

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Introduction: Circular RNA (circRNA) is a special class of non-coding RNA with a covalently closed circular structure that exerts its biological function in the progression of a variety of cancers.The high expression of circCAMSAP1 in the osimertinib resistant NSCLC cell line was determined by RNA-seq sequencing analysis of the sensitive and resistant cell lines of lung adenocarcinoma, and the research mechanism of circCAMSAP1 in lung adenocarcinoma and osimertinib resistance is still unclear.

Methods: This study is the first to discuss the mechanism of osimertinib resistance of circCAMSAP1 in non-small cell lung cancer, and circCAMSAP1 exerts its biological role by inducing osimertinib resistance in non-small cell lung cancer by destabilizing HSPA1A.

Results: The stable expression of osimertinib-resistant lung adenocarcinoma cell lines PC9/OR and H1975/OR was successfully constructed by measuring IC50 values. The target gene circCAMSAP1 was screened by transcriptome sequencing analysis, and the cyclic structure and resistance to RNase R treatment of circCMSAP1 were further verified by characterization experiments. circCAMSAP1 was clearly distributed in the cytoplasm and nucleus of PC9/OR and H1975/OR cells by cytoplasmic and nuclear isolation experiments. The results of qRT-PCR assay showed that circCAMSAP1 expression was significantly increased in the more sensitive strains (PC9 and H1975) in lung adenocarcinoma osimertinib-resistant cell lines (PC9/OR and 1975/OR). The RNA pull-down assay based on the biotinylated circCAMSAP1 probe (nonsense sequence as a negative control) was used to screen out HSPA1A protein by mass spectrometry analysis, and its expression was verified to be significantly up-regulated in the more susceptible strains of lung adenocarcinoma osimertinib resistant cell lines (PC9/OR and H1975/OR). In vitro experiments showed that silencing of circCAMSAP1 inhibited cell proliferation, invasion, migration and cell clonal formation of osimertinib-resistant cell lines in lung adenocarcinoma, and silencing of circCAMSAP1 reversed osimertinib resistance by inhibiting autophagy. In vivo experiments showed that compared with the control group, the circCAMSAP1 silencing group significantly increased the sensitivity of nude mouse xenograft tumors to osimertinib and inhibited the tumor growth process. At the mechanistic level, RIP and CO-IP experiments were used to verify the mutual binding of circCAMSAP1 to HSPA1A protein, and the stability of HSPA1A protein was enhanced by inhibiting the E3 ubiquitin ligase SMURF1, and its ubiquitination degradation process was inhibited.

Conclusions: CircCAMSAP1 is associated with poor prognosis in lung adenocarcinoma and promotes osimertinib resistance in lung adenocarcinoma by inhibiting SMURF1-mediated HSPA1A ubiquitination.

Keywords: lung adenocarcinoma, ubiquitination, drug resistance

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.51 FLT3LG Improve Therapeutic Sensitivity to Anti-PD-1 Therapy by Modulating Immune Cell Infiltration in NSCLC

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Introduction: Immunotherapy, particularly anti-PD-1 therapy, has assumed a progressively significant position in the management of non-small cell lung cancer (NSCLC). Nevertheless, a subset of patients exhibit resistance to anti-PD-1 therapy, and the exploration of biomarkers for evaluating the responsiveness to anti-PD-1 therapy necessitates further investigation. FLT3LG is regarded as being associated with tumor diagnosis and immunotherapy in a variety of tumor types, but its function in NSCLC is uncertain.

Methods: Bioinformatics analysis was conducted to evaluate the clinical value, functional enrichment, genetic correlation, and immune infiltration of FLT3LG in NSCLC. We then used a mouse model to detect immune cell infiltration and relevant protein expression by flow cytometry and immunohistochemistry under anti-PD-1 treatment after overexpression of FLT3LG.

Results: In NSCLC patients, a better prognosis is linked to elevated FLT3LG expression. Among the genes strongly associated with FLT3LG, the majority were involved in immune-related processes and were predominantly enriched in immune-related pathways. Moreover, high expression of FLT3LG was significantly positively correlated with increased infiltration of multiple immune cells, including T cells and natural killer (NK) cells, in lung adenocarcinomas, as well with the expression of several immune cell markers, such as CD4 and CD8a. In a mouse model, overexpression of FLT3LG in mice xenograft elicited a pronounced immune response, thus leading to improved therapeutic efficacy following anti-PD-1 therapy.

Conclusions: FLT3LG could be considered as a diagnostic and prognostic marker for NSCLC and might play a role in enhancing the therapeutic response to immunotherapy in patients with NSCLC.

Keywords: Cancer immunotherapy, NSCLC, Immune cell infiltration

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.52 XPO1 Inhibition Reduces Tumor Growth Potential by Inhibiting Wnt Signaling Pathway in Lung Squamous Cell Carcinoma

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Introduction: Squamous cell carcinoma (LUSC) is the second most common histology of lung cancer after adenocarcinomas (LUADs). Molecular characterization of LUADs has defined distinct tumor subsets characterized by the presence of discrete driver alterations that predict sensitive to targeted inhibitors, leading to significant improvement in patient survival. However, for LUSCs, to date no specific drivers have been identified that are amenable for pharmacological targeting, and no targeted therapies are approved for treatment. Thus, identification of targetable vulnerabilities in this histological setting remains a critical unmet clinical need. Preliminary data from our lab has identified the nuclear exporter exportin 1 (XPO1) as a therapeutic vulnerability in small cell lung carcinomas. Importantly, XPO1 can be inhibited with selinexor, an FDA-approved drug for clinical use in hematological malignancies. Pharmacological inhibition of XPO1 with selinexor has shown promising results in several preclinical tumor solid models with negligible toxicity. Here, we explored the role of XPO1 as a therapeutic target in LUSC and the mechanism through which XPO1 inhibition induces tumor cell death in LUSC.

Methods: We performed a comprehensive histological and multi-omics analysis by Immunohistochemistry (IHC), targeted mutational profiling (MSK-IMPACT), methylation array, RNAseq and DIA- Mass spec characterization of a library of LUSC patient-derived xenografts (PDXs) (N=28) and matched clinical specimens (N=17)). To examine the potential of XPO1 inhibition as a therapeutic target in LUSC, we performed genetic and pharmacological inhibition experiments in LUSC cell lines and PDXs and functional in vitro experiments to study XPO1 as a druggable vulnerability in LUSC.

Results: Genomic characterization of our LUSC PDX platform identified frequent XPO1 gene gains (~30%) and amplifications (~4%). Other high prevalent genomic alterations included⋯ This observation was confirmed in the TCGA LUSC dataset with a 10.7% frequency for XPO1 amplification, which correlated with high XPO1 mRNA expression. XPO1 protein assessment by IHC revealed x% of PDXs exhibiting high expression of XPO1 and x% of LUSC clinical specimens in an in-house independent cohort. XPO1 genetic knockdown reduced the tumorigenic potential of LUSC cell lines, including proliferation and anchorage-independent growth. XPO1 inhibition with selinexor strongly synergized with the chemotherapeutic agent irinotecan in vitro. Similarly, selinexor induced a prominent tumor growth delay in LUSC PDXs (n=6) as monotherapy, which was further increased by the addition of irinotecan. Interestingly, squamous/ adenocarcinoma transformed PDXs showed the strongest response to XPO1 pharmacological inhibition across all models evaluated. Mechanistically, genetic and pharmacological inhibition of XPO1 downregulated WNT signaling pathway by disrupting the export of key players from nucleus to cytoplasm.

Conclusions: Our data suggest that XPO1 may exert a pro-oncogenic role in LUSC, and that its inhibition may represent a promising therapeutic approach for LUSC tumors, both as monotherapy or in combination with irinotecan. The clinical availability of selinexor will allow immediate clinical translation of the results generated in this project in a setting where no targeted therapies are available.

Keywords: Squamous, Lung, THERAPEUTIC VULNERABILITY

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.53 WISP3 Drives NSCLC Progression by Upregulating SDCBP via the TGF-? Signaling Pathway

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Introduction: Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases, constituting a significant global health challenge. Our previous research demonstrated that fibronectin promotes NSCLC angiogenesis and progression through upregulation of Wnt-inducible signaling pathway protein 3 (WISP3) and subsequent activation of Wnt signaling. The current study investigates the functional role and underlying molecular mechanisms of WISP3 in NSCLC progression.

Methods: We employed plasmid-mediated gene transfection to establish WISP3 overexpression and knockdown cell models. Functional characterization included tube formation assays, sphere formation assays, immunohistochemistry, western blot analysis, Transwell migration assays, and MTT viability assays. Proteomic profiling via mass spectrometry coupled with bioinformatics analysis identified differentially expressed proteins and associated signaling pathways in NSCLC cells. Furthermore, we established an NSCLC xenograft tumor model for in vivo validation.

Results: Clinical data analysis revealed that elevated WISP3 expression correlates with poor prognosis in NSCLC patients. Functional studies demonstrated that WISP3 enhances both angiogenic capacity and tumorigenic potential in NSCLC cells, findings that were corroborated in our xenograft tumor model. Mechanistically, WISP3 promotes NSCLC progression through activation of the TGF-β signaling pathway, as evidenced by increased phosphorylation of Smad2/3 (p-Smad2/3). Notably, WISP3 overexpression upregulated syntenin binding protein (SDCBP) expression both in vitro and in vivo. We identified a functional interaction between WISP3 and SDCBP that potentiates angiogenic and tumorigenic properties in NSCLC, effects that were reversible upon SDCBP silencing. These findings underscore the critical role of the WISP3-SDCBP axis in NSCLC progression.

Conclusions: Our study provides novel mechanistic insights into WISP3-mediated NSCLC progression, revealing its dual role in SDCBP upregulation and TGF-β pathway activation. These findings advance our understanding of NSCLC pathophysiology and highlight potential therapeutic targets for clinical intervention.

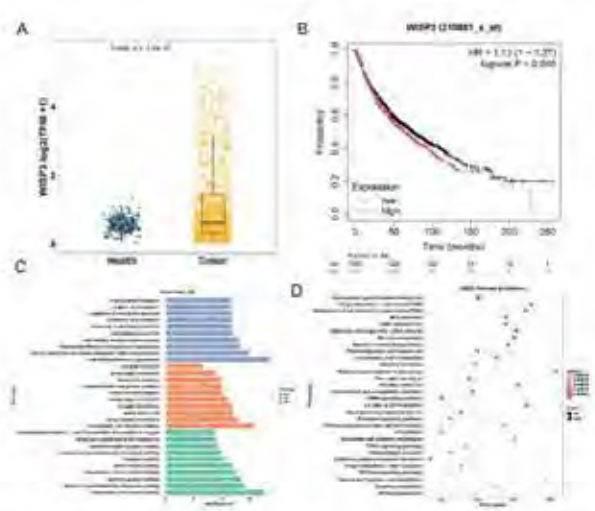

Figure 1. Analysis of WISP3 expression and its clinical significance in NSCLC. (A) A box plot showed WISP3 expression in 1025 LUAD vs. 108 normal tissues (TCGA data), with IQR and median indicated. (B) Kaplan-Meier analysis of 2167 lung cancer cases (stratified by median WISP3) revealed survival differences. (C-D) GO and KEGG analyses compared DEGs between high/low WISP3 groups in NSCLC.

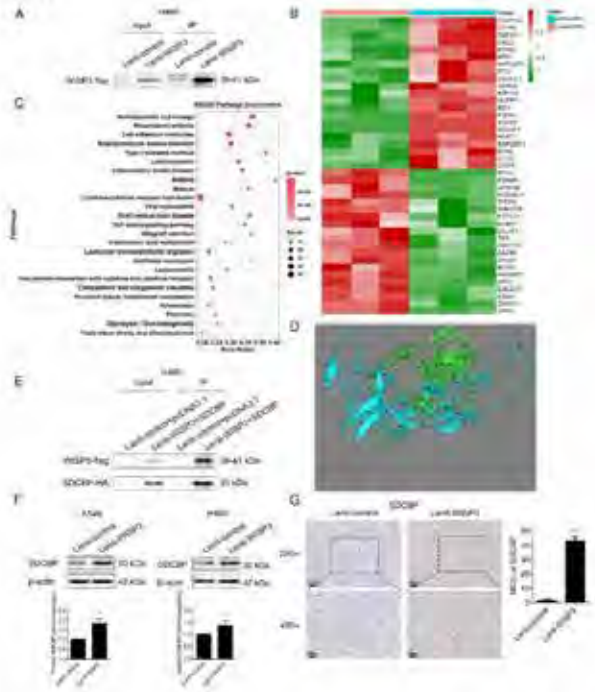

Figure 2. Comprehensive analysis of WISP3-associated proteins and their interactions in NSCLC. Panel A shows the IP assay enriching Flag-tagged WISP3 in overexpressing H460 cells. Purified proteins from WISP3-overexpressing and control cells were analyzed by mass spectrometry (B), followed by KEGG enrichment of WISP3-associated proteins in NSCLC (C). D displays protein docking between SDCBP (yellow) and WISP3 (blue), with hydrogen bonds (red) marking binding sites. E confirms their interaction via co-IP/WB in co-transfected H460 cells using Flag-WISP3 and HA-SDCBP antibodies. F shows upregulated SDCBP in WISP3-overexpressing H460/A549 cells (WB; *p<0.05, **p<0.01). G verifies elevated SDCBP in WISP3-driven tumors (IHC; 200×/400×; scale bars: 20/50 μm; **p<0.01).

Keywords: signaling pathway protein 3 (WISP3), syntenin binding protein (SDCBP), TGF-β signaling pathway

P3.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.03.54 Influenza'S Silent Warriors: Unveiling Lung Tumor Cell Assassination Through Macrophage Reprogramming via SAA4-MLKL Axis

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Introduction: Macrophages play a crucial role in maintaining balance in the body that goes beyond their known function in innate immunity. In particular, pro-inflammatory macrophages have anti-tumor properties, while anti-inflammatory macrophages tend to promote tumor growth. In diseases such as lung cancer or infections, the alveolar niche plays a crucial role in determining the macrophage phenotype. Since the mechanisms regulating this phenotype imbalance are still unclear, we hypothesized that tumor-inhibitory macrophage phenotypes and functions may be induced by infection stimuli. Our study aims to shed light on macrophage plasticity within a tumor-infection niche.

Methods: After exposure of pro-tumor macrophages to influenza A infection (IAV) bronchoalveolar lavage fluid (BALF), we observed an effective reprogramming of tumor-promoting macrophages to an anti-tumor state. Therefore, mass spectrometric analysis of IAV BALF was performed to identify the secretory factors responsible for this reprogramming. To decipher the transcriptomic signature of the reprogrammed macrophages, we performed RNA sequencing. In addition, we used lung organoids and precisely cut lung sections from tumors to mimic the niche of tumor and infection and demonstrate the inhibition of tumor cells by the regulated macrophage phenotype.

Results: Secretome analysis of IAV BALF revealed a significant upregulation of the SAA4 protein. Subsequent incubation of pro-tumor macrophages with recombinant SAA4 protein confirmed its ability to induce a tumor-inhibitory phenotype. RNA sequencing revealed an upregulation of the Mlkl gene in these reprogrammed macrophages. Silencing of the Mlkl gene resulted in a reduction of the pro-inflammatory and tumor-inhibitory macrophage phenotype, suggesting a regulatory role of MLKL in the reprogramming process.

Conclusions: Our results highlight that influenza A virus infection modulates macrophage plasticity and activates tumor-inhibitory responses through the SAA4-MLKL axis in the context of lung cancer.

Keywords: Lung cancer, Macrophage, Influenza infection

P3.09.01 Validation of Lung Specific-Graded Prognostic Assessment Score in NSCLC With Brain Metastases From India

S.M. S, A.R. Tibdewal, G. Maheshwari, G.R. Khatavkar, S.R. Pedapathi, S.B. Yewle, K. Prabhash, V. Noronha, J.P. Agarwal
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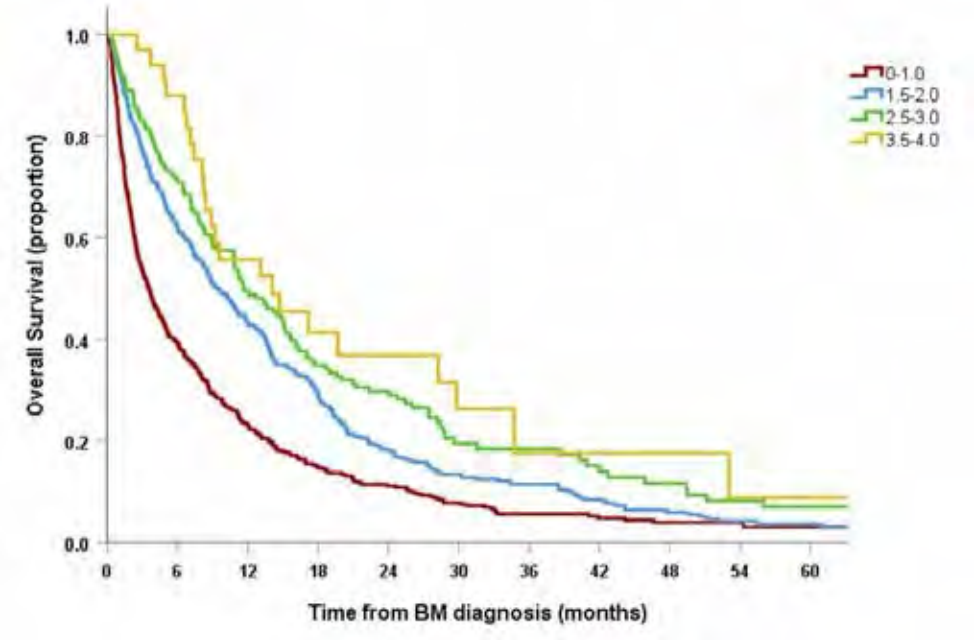
Introduction: Prognostication of brain metastasis (BM) aids in patient selection and optimal resource utilisation. We aim to validate the Lung Specific-Graded Prognostic Assessment (GPA) in patients with BM from Non-small cell lung cancer (NSCLC) at a tertiary cancer centre in India.

Methods: An ambispective analysis of 1197 NSCLC patients treated between May 2015 and May 2024 was performed. The GPA scores were calculated using age, Karnofsky Performance Status (KPS), number of BMs and extracranial metastasis status, and the log-rank test compared intergroup differences. Overall survival (OS) was estimated from the date of BM diagnosis till death or last known follow-up. The time-to-event analysis was performed by the Kaplan-Meier method, and a p-value of <0.05 was considered statistically significant. The study has been approved by the Ethics Committee and registered with the Clinical Trials Registry of India.

Results: The median age was 53 years (range, 19-86), and the majority were males (63%) with active tobacco use. Adenocarcinoma was 84% and squamous cell carcinoma (7%). EGFR mutation was seen in 37%, and ALK mutations in 16%. The majority received brain radiotherapy (RT) either in the form of whole brain RT (88%) or stereotactic radiosurgery (8%). The rest were offered observation or optimal supportive care. Systemic therapy was administered to 90% of the patients, which included chemotherapy (35%), TKI (41%), immunotherapy (2%), or a combination thereof. The median OS was 7.3 months (range, 0-78). The median follow-up of surviving patients was 42.1 months (range, 0.5-78). The median OS of various GPA subgroups are detailed in the table and represented in the figure.

Lung specific GPA [N (%)]	Median OS (months)	95% CI (months)
0 – 1 [482 (40.3)]	3.5	2.8 – 4.2
1.5 – 2 [509 (42.5)]	9.4	8.0 – 10.8
2.5 – 3 [172 (14.4)]	11.7	9.1 – 14.4
3.5 – 4 [34 (2.8)]	14.1	4.7 – 23.4
p-value	<0.001	



Conclusions: This is the largest study from India to validate lung specific-GPA in NSCLC patients with BM. Our study has shown the usefulness of lung specific-GPA in prognosticating, which helps in delivering tailored treatment and appropriate resource utilisation.

Keywords: Brain Metastasis, GPA, NSCLC

P3.09.02 Stereotactic Mr-Guided Adaptive Radiotherapy (SMART) for Ultracentral Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Stereotactic-ablative body radiotherapy (SABR) is a standard of care for early-stage lung cancer and thoracic oligometastatic and oligoprogressive disease. However, ultracentral lesions pose a challenge due to the safety concerns. Stereotactic MR-guided Adaptive Radiotherapy (SMART) permits daily adaptation, real-time tracking and automated-gating, allowing for sparing critical organs while potentially enhancing target coverage.

Methods: This retrospective analysis included SMART-based SABR for ultracentral located primary or metastatic lesions from histologically proven non-small cell lung cancer (NSCLC). Ultracentral location was defined as planning target volume (PTV) overlapping the proximal bronchial tree (PBT), oesophagus or pulmonary vessels. Endpoints included grade ≥3 SMART-related toxicity, freedom from local progression (FFLP), progression-free survival (PFS) and overall survival (OS). Additionally, the reduction in PTV volume and overlap with ultracentral OARs was estimated by comparing the SMART PTV to a simulated non-adaptive 4DCT SABR PTV.

Results: Between 2020 and 2023, twelve patients with 19 ultracentral NSCLC lesions underwent SMART. The median dose was 40Gy (30-60Gy) in 5-8 fractions. Online plan adaptation was performed in 100% of delivered fractions (86 fractions). No severe toxicity (grade 3+) was observed and G1-2 acute and late toxicity rates were 50% and 16.7%, respectively (Figure 1). Over a median follow-up of 15 months (range 4-38), one lesion recurred within the SMART field. FFLP at 1 year was 93%. Median-PFS was 6.15 months (1-38 months). Median and 1-year OS were not reached (range 4-38 months) and 92%, respectively. Median simulated conventional-SABR PTV was significantly larger than the SMART PTV (31.2cc vs 9.3cc, p< 0.001), with a significant increase in the median overlap with ultracentral OARs (4.6cc vs 0.75cc p < 0.001).

Conclusions: SMART, with daily online adaptation, achieved comparable LC to conventional non-adaptive SABR in ultracentral NSCLC, without severe toxicity. tumors.

Table. Key outcomes compared to the most relevant reports of ultracentral tumors

Platform/ RMM	Adaptive approach, MRI-Linac (MRIdian®) Tracking, Gating					Non- Adaptive approach, CT-based 4D-CT/ITV			
	Current cohort	SMART Phase I (10)	Sandoval (12)	Regnery (14)	Dana-Farber (13)	HILUS (6)	SUNSET (4)	Sunnybrook (5)	LUSTRE Phase 3** (7)
UC definition	PTV overlap/ touch PBT and/or esophagus and/or pulmonary vessels	GTV abutting mainstem bronchi, carina, or mediastinum	Per the HILUS trial definition	PTV overlap PBT or esophagus	GTV abutting PBT, esophagus and/or great vessels	1cm from PBT (Group A) ≤1cm from lobar bronchi (Group B)	PTV overlap/ touch PBT and/or esophagus and/or pulmonary vessels	CT-based/4D-CT/ITV	Central 1 cm of mediastinum or 2 cm of PBT (No provide UC definition)
Patients† (lesions)	12 (19)	5	26 (A) 12 (B)	16	18 (19)	29 (group A)	30	PTV overlap/ touch PBT and/or esophagus	45* (*central +SABR)
Histology	NSCLC (primary/metastasis)	NSCLC (OMD/inoperable)	Mix	Mix (OMD/primary NCLC	Mix (OMD/OPD)	Mix (78% NSCLC)	Primary NSCLC	154 (162)	Primary NSCLC (inoperable)
Dose regimens, Gy/#	40/8 (30-60/5-8) (BED_{10} 48-105)	50/5 (BED_{10} 100)	60/8 (50-60/5-15) (BED_{10} 75-105)	50-60/10 (BED_{10} 75-90)	50/5 (35-60/5)	56/8 (BED_{10} 95.2)	60/8 (BED_{10} 105)	Mix	60/8 (BED_{10} 105)
Survival Parameters *(calculated from SABR)*									
OS, Median, %	15m 1y: 80%	1y:60%	1&2y Group A: 89% Group B:81% & 76%	2y 63%	1y-75%, 2y-66% (no distinction central vs UC)	1y 81%; 2y 58%	3y 72.5%	44m 1y 78%; 2y 67%	1y 95%; 2y 78%
LC, %	94.7%	1y: 80%	2y:84%;3y:78% Group A: 2y:91%; 3y:81%	2y 93%	1y 94%; 2y 86%	85% (1y); 83% (2 and 3y)	89.6% at 3y	95.2% (2y 89%; 3y 86%)	87.6% 3y (no distinction central vs UC)
G3-5 toxicity, %	0%	20% (1 patient G3)	4.3% (G3)	19%	0%	33.8 (15.4% G5)	6.7 (3y)	1y 6.7%, 2y 8.4%; 3y 9.4%	13% (1 G5 in UC lesion)

BED: Biological Equivalent Dose (alpha/beta of 10);ITV: Interval Target Volume; LC: Local Control; Linac: linear accelerator; LPFS: Local Progression Free Survival; MRIdian®=6 MV 0.35T MRI-Linac ViewRay Systems' OS: NSCLC: Non-Small Cell Lung Cancer; Overall Survival; PBT: Proximal Bronchial Tree; PFS: Progression Free Survival; PTV: Planning Target Volume; RMM: respiratory motion management; SABR: Stereotactic Ablative Radiation Therapy; UC: Ultracentral
#: fractions, y: year(s)

† Only UCs number expressed
***LUSTRE trial no specified number neither definition nor stratified outcomes per UC lesions.*

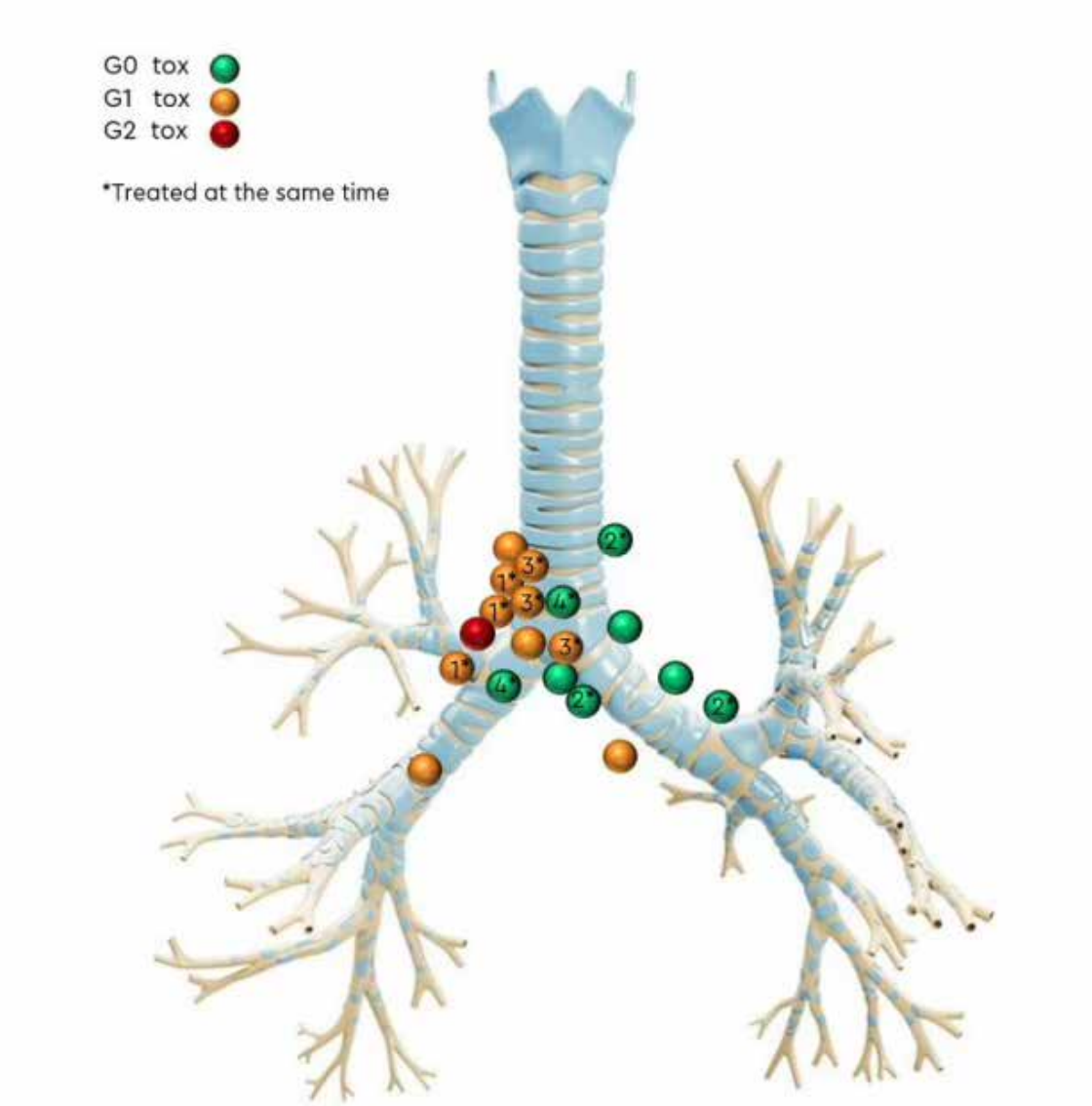

Figure 1. Distribution of each lesion location in relation to the PBT, graded by maximum reported toxicity and indicating those treated synchronously

Keywords: Adaptive Radiotherapy, SBRT, NSCLC

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.03 Efficacy of Radiotherapy in Patients With Oligo-Progressive Non-Small Cell Cancer - a Retrospective Analysis

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Introduction: Radiotherapy (RT) is well-established for treating oligometastatic non-small cell lung cancer (NSCLC), but its role in oligoprogression remains less defined. This study evaluates RT efficacy in oligoprogressive NSCLC and identifies factors associated with improved outcomes.

Methods: We retrospectively screened all patients with metastatic NSCLC at the Davidoff Cancer Center who were treated with first line systemic therapy (2018-2024) and identified patients who received RT to all progressing sites during first-line therapy. Primary endpoints included progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) from RT initiation. We assessed the impact of various factors, such as treatment type, initial disease state and RT sites.

Results: We identified 81 patients who received radiotherapy (RT) for oligoprogressive NSCLC, including 50 treated with immunotherapy with or without chemotherapy (immunotherapy cohort) and 31 treated with tyrosine kinase inhibitors (TKIs) (TKI cohort). The median age in both cohorts was 66 years, 67% had a history of smoking, and adenocarcinoma was the predominant histology (70%), followed by squamous cell carcinoma (16%). In the TKI cohort, EGFR common mutations were the most frequent driver alteration (77%), followed by ALK (13%), KRAS G12C (3%), ROS1 (3%), and BRAF V600E (3%). Overall, driver mutations were detected in 53% of cases, most commonly EGFR (30%). In the immunotherapy cohort, PD-L1 expression was positive (>1%) in 68% of patients. Oligoprogression was most frequently observed at new disease sites (53%), predominantly in the lungs (51%), but also in the primary tumor and pre-existing metastases. The median progression-free survival (PFS) and overall survival (OS) from RT initiation were 9 months and 34 months, respectively, with a median time to next treatment (TTNT) of 21 months. At 6 and 12 months, 81% and 63% of patients, respectively, remained on first-line therapy. PFS rates at 6 and 12 months were 62% and 50% in the immunotherapy cohort, compared to 52% and 29% in the TKI cohort (HR 0.8, 95% CI 0.48-1.35). Patients with oligometastatic disease at diagnosis (≤5 metastases) had longer PFS and OS at 6 and 12 months, although statistical significance was not reached (HR 0.77, 95% CI 0.45-1.32). RT to liver or bone metastases was associated with shorter PFS compared to RT to other sites such as the lungs and brain (HR 3.1, 95% CI 1.1-8.8 for liver; HR 2.2, 95% CI 1.01-4.7 for bone).

Conclusions: RT for oligoprogressive NSCLC demonstrates potential for prolonged disease control, with the potential of lengthening time on first line treatment. RT to bone and liver metastases were associated with shorter disease control compared to other sites. These findings suggest that patient selection is needed to optimize the therapeutic benefit of RT in oligoprogressive NSCLC.

Keywords: metastatic NSCLC, Oligoprogression, Radiotherapy

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.04 Macrophage CD38 Expression as a Predictive Biomarker for the Abscopal Effect in Lung Cancer Undergoing Radiotherapy-Immune Therapy

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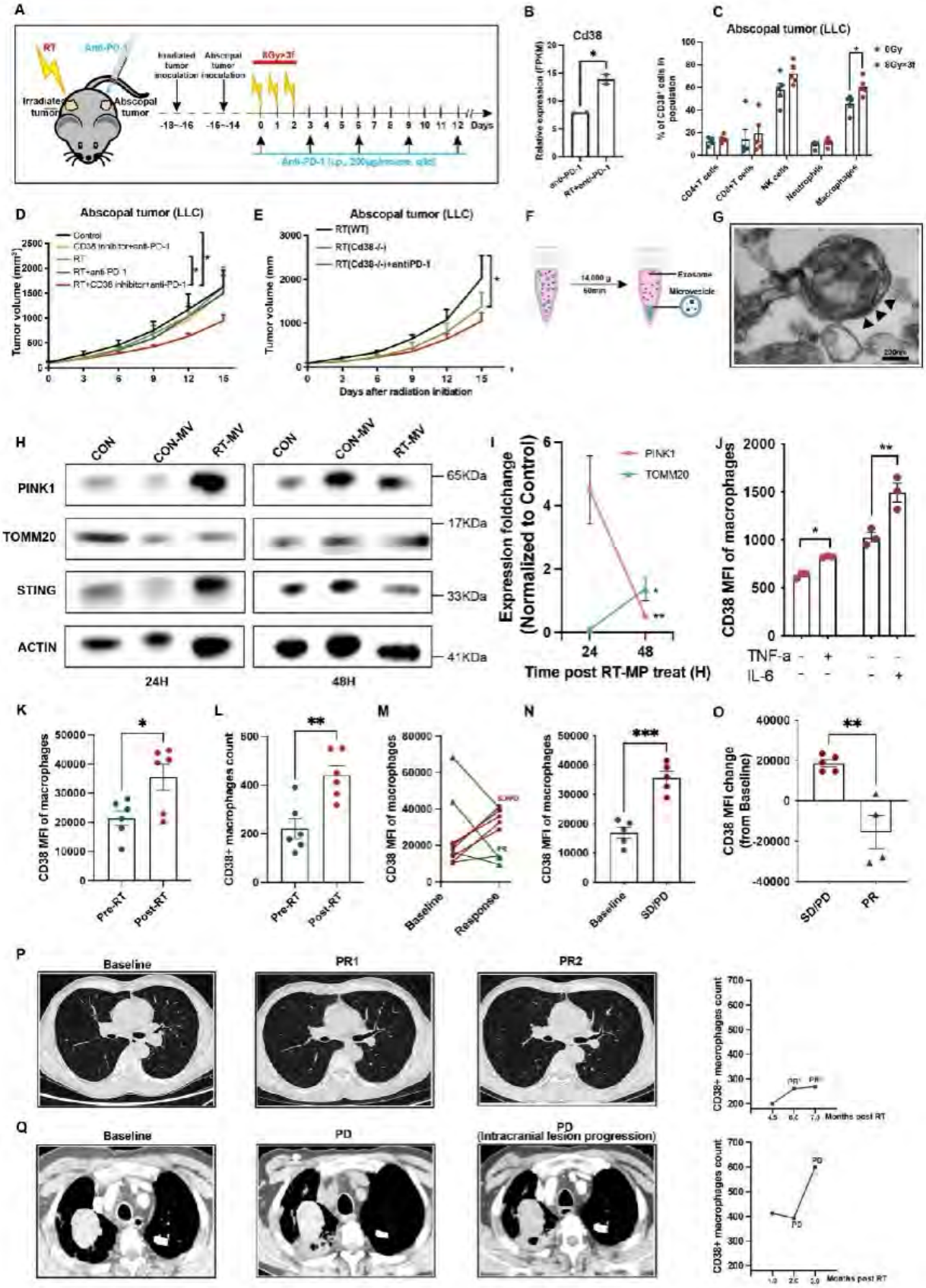
Introduction: The abscopal effect, where tumors outside the radiation field regress after radiotherapy, remains rare in lung cancer. Increasing the incidence of the abscopal effect and identifying its biomarkers are crucial. Bulk RNA sequencing and flow cytometry of distant tumors revealed significant CD38 upregulation in macrophages. We investigated its impact on the abscopal effect and its potential as a biomarker.

Methods: CD38 expression in distant tumors was analyzed by RNA sequencing and flow cytometry. For functional evaluation, we utilized a dual-tumor Lewis lung carcinoma (LLC) mouse model to assess the effects of CD38 inhibition and NAD+ supplementation on tumor regression. To investigate the underlying mechanism, EVs from irradiated tumors were isolated, characterized, and co-cultured with macrophages. TEM confirmed the presence of mitochondrial structures within EVs, while Western blot analysis evaluated signaling pathway activation in macrophages. For clinical validation, peripheral blood samples from lung cancer patients receiving radiotherapy were analyzed. CD38 expression on macrophages was assessed by flow cytometry and correlated with treatment response.

Results: Radiotherapy significantly increased CD38+ macrophages in distant tumors (34.3%, $P < 0.05$). CD38 inhibition enhanced T-cell infiltration (2.83.8-fold increase in GZMB T cells, $p < 0.01$) and tumor regression ($P < 0.05$).EVs from irradiated tumors induced CD38 expression in macrophages, with mitochondrial structures observed via transmission electron microscopy. EV uptake activated the stimulator of interferon genes (STING) pathway and induced macrophage senescence. Nicotinamide supplementation reversed CD38-mediated immunosuppression, restoring anti-tumor immunity ($p < 0.0001$). Clinically, radiotherapy increased macrophage CD38 MFI by 65.5% ($p < 0.05$), with CD38+ macrophages doubling ($p < 0.01$). CD38 MFI changes correlated with treatment response: in partial responders (PR), CD38 MFI decreased by ~40% ($p < 0.01$), while in stable/progressive disease (SD/PD), it increased by ~100% ($p < 0.01$). The percentage increase was significantly higher in SD/PD vs. PR ($p < 0.01$).

Conclusions: High macrophage CD38 expression correlates with poor response to radiotherapy and immunotherapy. Patients with disease progression showed increased CD38 expression on macrophages, while responders showed a decline. Irradiated tumor-derived EVs induced macrophage CD38 expression and senescence, highlighting CD38 as a predictive biomarker and therapeutic target.



Keywords: Radiotherapy, Abscopal effect, CD38

P3.09.05 Prognostic Value of TNM 9Th Lymph Node Classification and Pathological Node Count in NSCLC Patients

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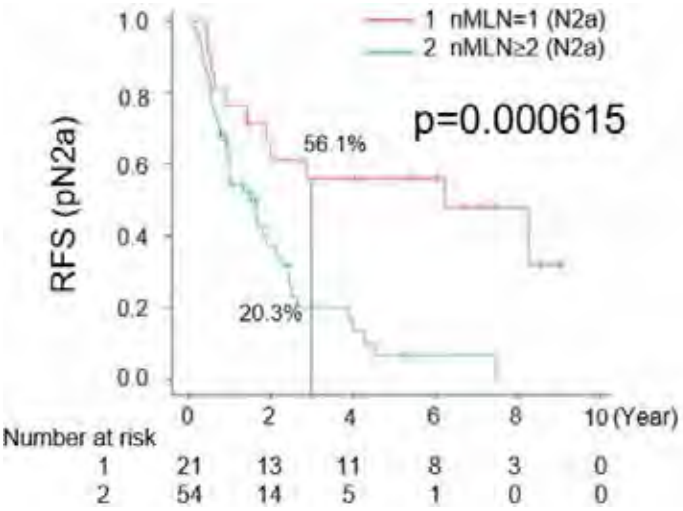
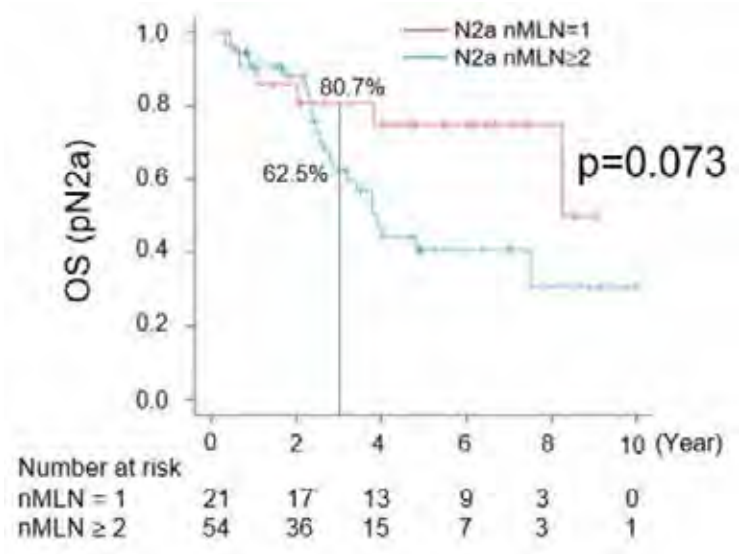
Introduction: The new TNM9th classification for non-small cell lung cancer (NSCLC) subdivided pN2 into pN2a (single) and N2b (multiple) based on the number of metastatic mediastinal lymph node (LN) stations. The number of metastatic LN (nMLN) has also been reported as a prognostic factor in NSCLC patients who underwent radical resection. However, their combined impact remains unexplored.

Methods: We investigated the clinical implication of pN status in NSCLC patients who underwent anatomical resection with systematic mediastinal nodal dissection and had N1/N2 disease from March 2012 to December 2022. Cox regression models were used for univariable and multivariable analyses.

Results: Among 216 patients enrolled, 101, 75, and 40 were classified as pN1, pN2a, and pN2b, respectively. The median nMLN was 2 (range, 1-30), and the patients were divided into two groups: 82 nMLN=1 or 134 nMLN≥2. Univariable analysis indicated that pN9th predicted recurrence-free survival (RFS) but not overall survival (OS), while nMLN predicted both RFS and OS. Multivariable analysis showed that nMLN, but not pN9th, was an independent factor for both RFS [hazard ratio (HR) of 2.283; 95% confidential interval (CI) of 1.513-3.446) and OS (HR of 2.165; 95%CI of 1.310-3.577). Subset analysis demonstrated that pN2a patients with nMLN≥2 had a worse prognosis than those with nMLN=1(Figures). Skip metastasis was present in 34% of pN2 disease while nMLN might impact prognosis more than skip metastasis.

Conclusions: The inclusion of nMLN, along with the pN9th factor, may be recommended for the upcoming TNM classification. Further research is needed to validate this finding.





Keywords: the TNM 9th lymph node classification, the number of pathological lymph node, skip metastasis

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.06 Primary Tumor Resection Confers Survival Benefit in cM0sM1a Lung Adenocarcinoma

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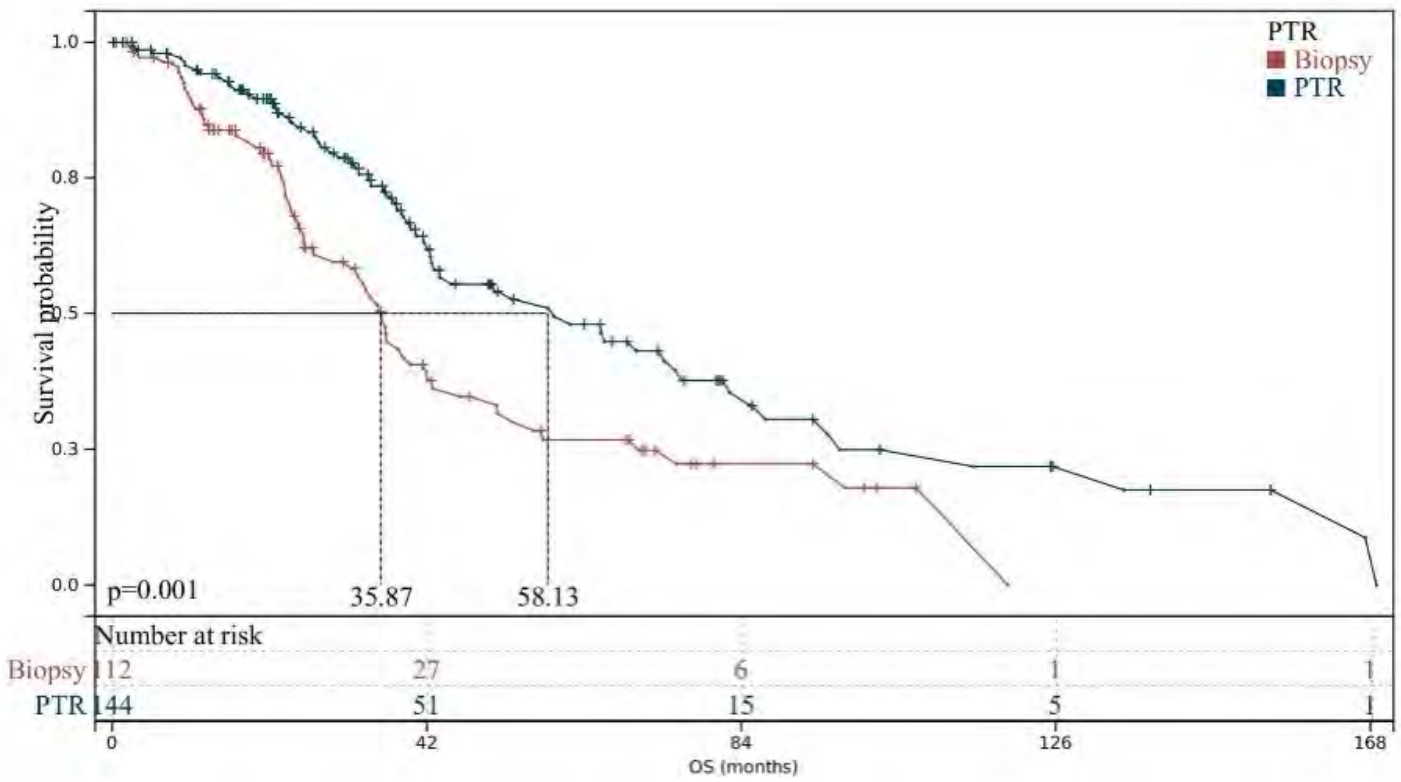
Introduction: The surgical management of lung adenocarcinoma (LUAD) with incidentally detected intraoperative pleural metastasis (cM0sM1a) remains a contentious dilemma. Current guidelines recommend aborting radical resection upon identification of pleural dissemination, prioritizing systemic therapy over locoregional intervention. The study aims to assess the prognostic impact of primary tumor resection (PTR), potentially providing evidence for intraoperative decision-making for cM0sM1a LUAD patients.

Methods: This retrospective study analyzed consecutive cM0sM1a LUAD patients without neoadjuvant therapy (November 2008 to December 2023) from Sun Yat-sen University Cancer Center. Clinicopathological characteristics, treatment patterns, and survival outcomes were extracted from electronic medical records. Overall survival (OS) was estimated using Kaplan-Meier analysis. Univariate Cox regression was applied to determine the prognostic factors, while multivariate Cox regression and propensity score matching (PSM) were used to address confounding. Subgroup analyses were performed to further explore the survival impact of PTR in various settings.

Results: The study included 310 cM1a LUAD patients (161 underwent PTR, 149 biopsy only). Multivariate Cox analysis revealed PTR (HR=0.68, p=0.021), adjuvant targeted therapy (HR=0.30, p<0.001), and adjuvant chemotherapy (HR=0.60, p=0.008) as independent protective factors, contrasting with smoking (HR=1.50, p=0.023) and intraoperative pleural effusion (HR=2.11, p<0.001) which demonstrated adverse prognostic significance. Notably, PTR demonstrated consistent survival benefits before (HR=0.57, p<0.001) and after PSM (HR=0.53, p=0.019), with marked survival advantage observed in cT1-2 subgroups (HR=0.56,p=0.001) and among patients without adjuvant targeted therapy (HR=0.47,p=0.007). Conversely, no significant survival advantages of PTR were observed in cT3-4 disease (HR=0.70,p=0.38) or among patients receiving adjuvant targeted therapy(HR=0.69,p=0.06). In terms of surgical resection extent, similar survival outcomes were maintained between sublobar resection and lobectomy (HR=1.00,p=0.99), while lymph node dissection demonstrated no significant impact on survival outcomes in patients with PTR(HR=0.70,p=0.19).

Conclusions: PTR significantly improved survival in cM0sM1a LUAD patients, emphasizing its pivotal role in the multidisciplinary framework. However, a broader resection did not confer survival benefits. This study provides high-quality evidence for optimizing decision-making and refining guidelines in the cM0sM1a LUAD management.



Keywords: Primary tumor resection, Pleural metastasis, cM0sM1a

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.07 Local MDT Improve the Survival of Leptomeningeal Metastasis in NSCLC With EGFR Mutation From the CLM-Tree Registry

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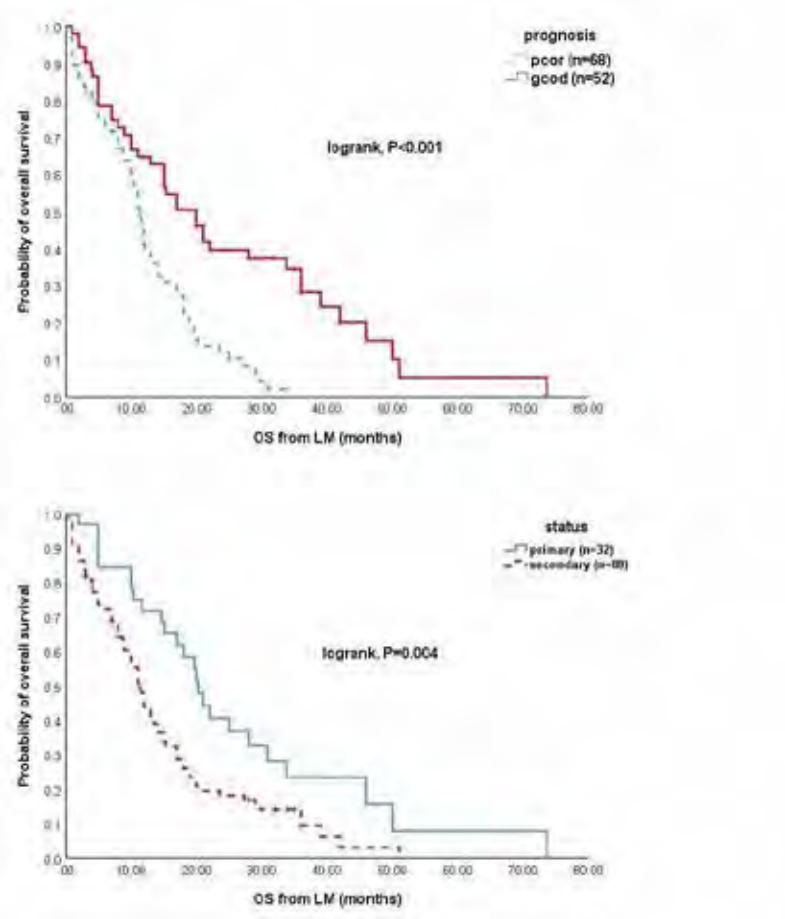
Introduction: Leptomeningeal metastasis (LM) in EGFR-mutant NSCLC has poor prognosis, even with TKI dose escalation. Recently, local multidisciplinary treatment (L-MDT) has been applied in China. This study analyzes survival outcomes using CLM-tree registry data (NCT06718972).

Methods: EGFR-mutant NSCLC patients with LM since 2018 were analyzed for clinical characteristics and survival based on CLM-tree registry data.

Results: Among 123 LM patients, 98.3% had adenocarcinoma, and 73.2% were diagnosed during treatment. Poor prognosis (NCCN-LM criteria) was observed in 55.3%. A total of 84.6% received L-MDT plus systemic treatment, including VP-shunt, intracranial chemotherapy, or cranial radiation. Dose escalation of third-generation TKIs was common (79.7%), including Osimertinib 160 mg (56.1%), Almonertinib 165/220 mg (27.6%), and Firmonertinib 160/240 mg (16.3%).Among 120 patients analyzed, median OS from LM diagnosis was 13 months, with a 1-year survival rate of 51.8%. Patients with good prognosis and primary LM had significantly longer OS (20.0 vs. 11.0 months, P<0.001; 20.3 vs. 11.3 months, P=0.004) (Figure). Firmonertinib showed a trend toward better survival (P=0.16). Multivariate analysis identified good prognosis (HR=0.39, P<0.001) and primary LM (HR=0.50, P=0.009) as significant prognostic factors.Due to widespread L-MDT application, OS improvement may be attributed to local treatment combined with TKI escalation. Median OS from LM diagnosis and L-MDT initiation was 12.1 and 10.0 months, respectively. Among 37 L-MDT patients with LM deterioration and neurological symptoms after systemic treatment failure, median OS from L-MDT was 11.0 months, with a 1-year survival rate of 33.8%. Neurological symptoms improved significantly (RANO-LM score: 5.3±0.5 vs. 2.0±0.4, P<0.001). No significant survival difference was observed between non-severe (LM≤4) and severe (LM score >4)) groups (12 vs. 10 months, P=0.19).

Conclusions: L-MDT combined with TKI escalation may improve survival in EGFR-mutant NSCLC patients with LM, especially those with severe neurological symptoms.



Keywords: Leptomeningeal metastasis, local multidisciplinary treatment, CLM-tree registry

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.08 Tumor Treating Fields for Patients With Metastatic Non-Small Cell Lung Cancer: Real World First Experience

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Introduction: Tumor Treating Fields (TTFields) are frequency-specific alternating electric fields that disrupt mitosis of cancer cells and may elicit an antitumor immune effect. TTFields concurrent with docetaxel or a PD-(L)1 inhibitor were FDA-approved in 10/2024 for the treatment of metastatic non-small cell lung cancer (mNSCLC) progressing on or after platinum-based therapy based on the overall survival benefit reported in the phase III LUNAR study. The objective of this analysis was to report demographics, treatment characteristics, and usage for patients treated in the United States post-FDA approval.

Methods: De-identified data from patients with mNSCLC that progressed on or after platinum-based therapy, and who were prescribed TTFields by a certified prescriber were collected from the device-manufacturer database. Baseline patient characteristics and treatment details were collated; usage was calculated for those who had used the device for at least one month, based on device-captured treatment time.

Results: 91 patients were prescribed TTFields and 62 patients (68%) were able to start the treatment within the data cutoff window for this analysis (March 7, 2025). The number of patients per month prescribed TTFields increased from 13 to 23 over the analyzed period (10/24-3/2025). Prescribing providers were medical oncologists for 67 patients (74%), radiation oncologists for 19 patients (21%), and other disciplines for 5 patients (5%). 70 patients (77%) were prescribed in a community hospital vs. 21 patients (23%) in an academic setting. For treated patients, the median age was 66 years (interquartile range [IQR]: 60-72) and 55% were female; 69% and 26% had adenocarcinoma and squamous cell carcinoma histology, respectively. Of 60 patients with available systemic therapy data, 33 (55%) were treated in the second-line setting, 15 (25%) in the third-line setting, and 12 (20%) in the fourth line and beyond. Concurrent systemic therapy consisted of docetaxel-based cytotoxic chemotherapy in 27 (44%), 32 (52%) with an immune-checkpoint inhibitor (ICI), and 3 (5%) with both; an ICI was included in at least one of previous lines of therapy for 94% of patients. Among 32 patients who used TTFields for at least 1 month, the median usage was 12 hours per day (IQR: 9.1-16.3).

Conclusions: Growth in TTFields uptake was observed after FDA-approval for patients with mNSCLC with the majority of patients being treated with an ICI. Usage patterns appear similar to those observed in the phase III LUNAR study. Further outcomes and toxicity data will be important to assess utility and benefit of TTFields with contemporary systemic therapies of mNSCLC in real life clinical practice.

Keywords: Tumor Treating Fields, Local therapy, NSCLC

P3.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.09.09 Frequency and Prognostic Impact of Local Ablation Therapy for Oligoprogression in Non-Small Cell Lung Cancery

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Introduction: During systemic treatment for patients with non-small cell lung cancer (NSCLC), oligoprogression (OP), a condition in which most lesions remain controlled while a few progress or develop, has recently attracted attention. Previous reports suggest that OP occurs in 20-40% of cases, with frequencies influenced by factors such as the presence of driver genes and the type of treatment. OP lesions are thought to represent populations resistance to systemic treatment. Eliminating these lesions by local ablation treatment (LAT) may prolong survival or the duration of systemic treatment. This rationale supports the application of LAT in managing OP. In fact, advancements in LAT, such as radiotherapy and surgery, have demonstrated clinical efficacy in some patients with OP. However, the characteristics of patients who may benefit from LAT or their genetic backgrounds remain unclear. This study evaluated the frequency of OP, clinicopathological characteristics, and efficacy of LAT as a treatment for OP.

Methods: This retrospective observational study was conducted at Hokkaido University Hospital. The inclusion criterion was patients aged 20 years or older who were diagnosed with NSCLC, experienced relapse after systemic treatment, and were diagnosed with OP between January 2015 and February 2024. OP was defined as those with three or fewer new or exacerbating lesions. LAT was defined as surgery or radiation therapy targeting OP lesions, whether performed for curative or palliative purposes. LAT did not require treatment of all OP lesions. Furthermore, we defined repeat OP as patients with recurrence of OP after treatment for OP and examined its frequency.The primary endpoint was to determine the proportion of patients with NSCLC who developed OP during systemic treatment. We also performed RNA sequencing (RNA-seq) to identify the genetic characteristics of OP.

Results: Overall, 106/510 (23.6%) patients exhibited OP; among these, six patients who received only the best supportive care after OP were excluded. Systemic treatment alone was administered to 79 patients (79.0%), whereas 21 patients (21.0%) received LAT. Median local progression-free survival (LPFS) was numerically longer in the LAT group than in the systemic treatment-only group (8.3 months and 6.7 months, respectively; p=0.38) without significance. In addition, overall survival (OS) was also numerically longer in the LAT group than in the systemic treatment-only group (78.1 months and 55.1 months, respectively; p=0.57) without significance. Next, of all progression events, 36 (45.0%) patients had repeat OP. When comparing the OP-OS between the repeat OP group and the non-repeat OP group, a numerically better trend was observed in the repeat OP group (HR 0.55, 95% CI: 0.29-1.04), with a median OP-OS of 64.1 months for the repeat OP group and 24.6 months for the non-repeat OP group (p = 0.06). RNA-seq showed an increase in extracellular matrix- and external encapsulating structure related gene expression after OP, suggesting potential molecular insights.

Conclusions: LAT showed better trend for LPFS and OS, but no significant prognostic benefit for patients with OP. Future research integrating clinical and molecular data may identify patients most likely to benefit from LAT.

Keywords: Oligometastasis, Oligoprogression, Local ablation therapy

P3.09.10 Safety and Efficacy of Co-Ablation System Therapy in Patients With Lung Cancer: A Single Arm Cohort Study

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Introduction: Co-ablation therapy, an emerging local treatment modality that integrates combined thermal and cryoablation techniques, has attracted growing clinical interest. However, its safety profile and therapeutic efficacy in lung cancer remain largely unknown.

Methods: From Feb 2023 to May 2024, the clinical data of 205 patients (212 lesions) treated with percutaneous co-ablation at Shanghai Pulmonary Hospital were prospectively collected and analyzed.

Results: Adverse events (grade ≥2) occurred in 26.83% (55/205) of patients, with pneumothorax (21.46%), pleural effusion (10.73%), and hemoptysis (6.34%). Grade 3 complications were rare (3.41%) with no procedure-related mortality. Multivariate analyses showed that severe emphysema (OR=3.14), tumor size (OR=1.09), and multiplicity (OR=4.60) as predictors of adverse events. Procedural success was achieved in 100% sessions, with complete ablation rates as 97.56% (200/205). With median follow-up of 6 months, local tumor control rates at 3, 6, and 12 months demonstrated significant advantage for smaller tumors (median diameter 13 mm). Progression-free survival (PFS) was markedly longer in tumors ≤3 cm versus >3 cm [NR vs. 6 months, 95%CI:4.1-7.9, P=0.004].

Conclusions: Co-ablation demonstrates high complete ablation rates (97.56%) and acceptable safety in patients with lung cancer. Tumor size less than 3 cm associated with long-term outcomes, suggesting co-ablation as a promising novel ablation strategy in patients with lung cancer.

Table 1 Characteristics of 205 patients received co-ablation system therapy

Characteristics	Value
Age, years	
Mean,IQR	66.00, CI: 45.50-79.00
Sex	
Female	90 (43.90%)
Male	115 (56.10%)
Smoking status	
Nonsmoker	95 (46.34%)
Current or former smoker	110 (53.66%)
ECOG PS	
0	81 (39.51%)
1	124 (60.49%)
Comorbidity	
Diabetes mellitus	27 (13.17%)
Hypertension	59 (28.78%)
Coronary heart disease	28 (13.66%)
TNM stage	
I	106 (51.71%)
II	5 (2.44%)
III	20 (9.76%)
IV	74 (36.10%)
Tumor diameter, mm	
Mean,IQR	15.00, CI:6.00-35.50
≤10mm	76 (37.07%)
10-20mm	85 (41.46%)
20-30mm	29 (14.15%)
>30mm	15 (7.32%)
Tumor location	
Central	38 (18.78%)
Periphery	124 (60.49%)
middle	43 (20.73%)
Tumor density	
GGN	7 (3.41%)
PSN	78 (38.05%)
SN	120 (58.54%)
Pathological type	
NSCLC	152(74.15%)
SCLC	4(1.95%)
Unknown lung	34(16.59%)
Metastatic carcinoma	15(7.32%)

Table 2 Hospitalization duration and adverse events

Characteristics	Value
Duration of post-treatment hospitalization, days	
Mean,IQR	5,CI:1.61-8.39
Adverse event	
Present	117(57.07%)
1	62 (30.24%)
2	48 (23.41%)
3	7 (3.41%)
(grade 2 or higher)	
pneumothorax	44 (21.46%)
Manual aspiration	2 (0.98%)
Chest tube insertion	41 (20%)
Chest tube insertion+ Pleural fixation	1 (0.49%)
hemoptysis	13 (6.34%)
Interventional hemostasis	1 (0.49%)
Pleural effusion	22 (10.73%)
Pleural hemorrhage	2 (0.98%)
pneumonia	8 (3.9%)
pulmonary abscess	1 (0.49%)
Phrenic paralysis	1 (0.49%)
Severe pain	1 (0.49%)
Hematoma	1 (0.49%)

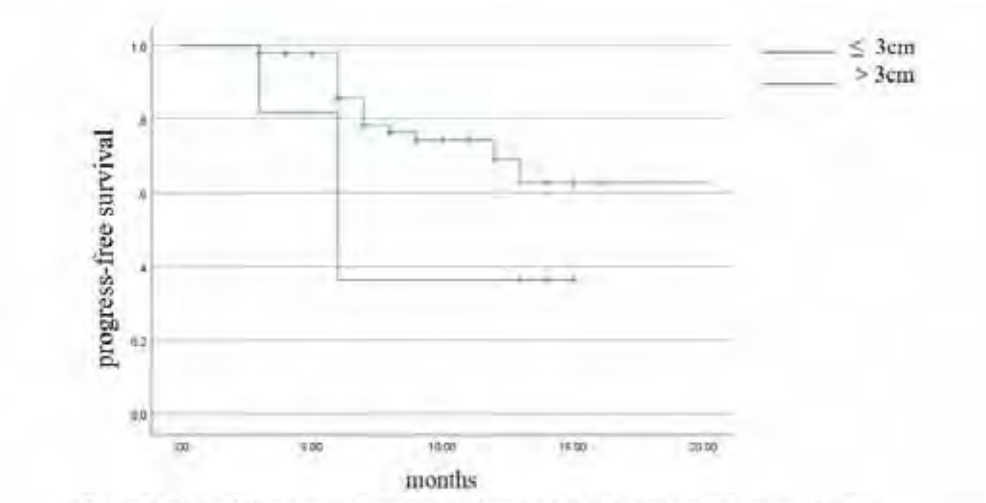

Figure 2. Kaplan-Meier curves of progression-free survival by tumor size (≤3 cm vs. >3 cm)

Keywords: co-ablation, lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.01 Phase II Trial of First-Line Double-Dose Firmonertinib in Locally Advanced or Metastatic NSCLC With EGFR L858R (FIRM Study)

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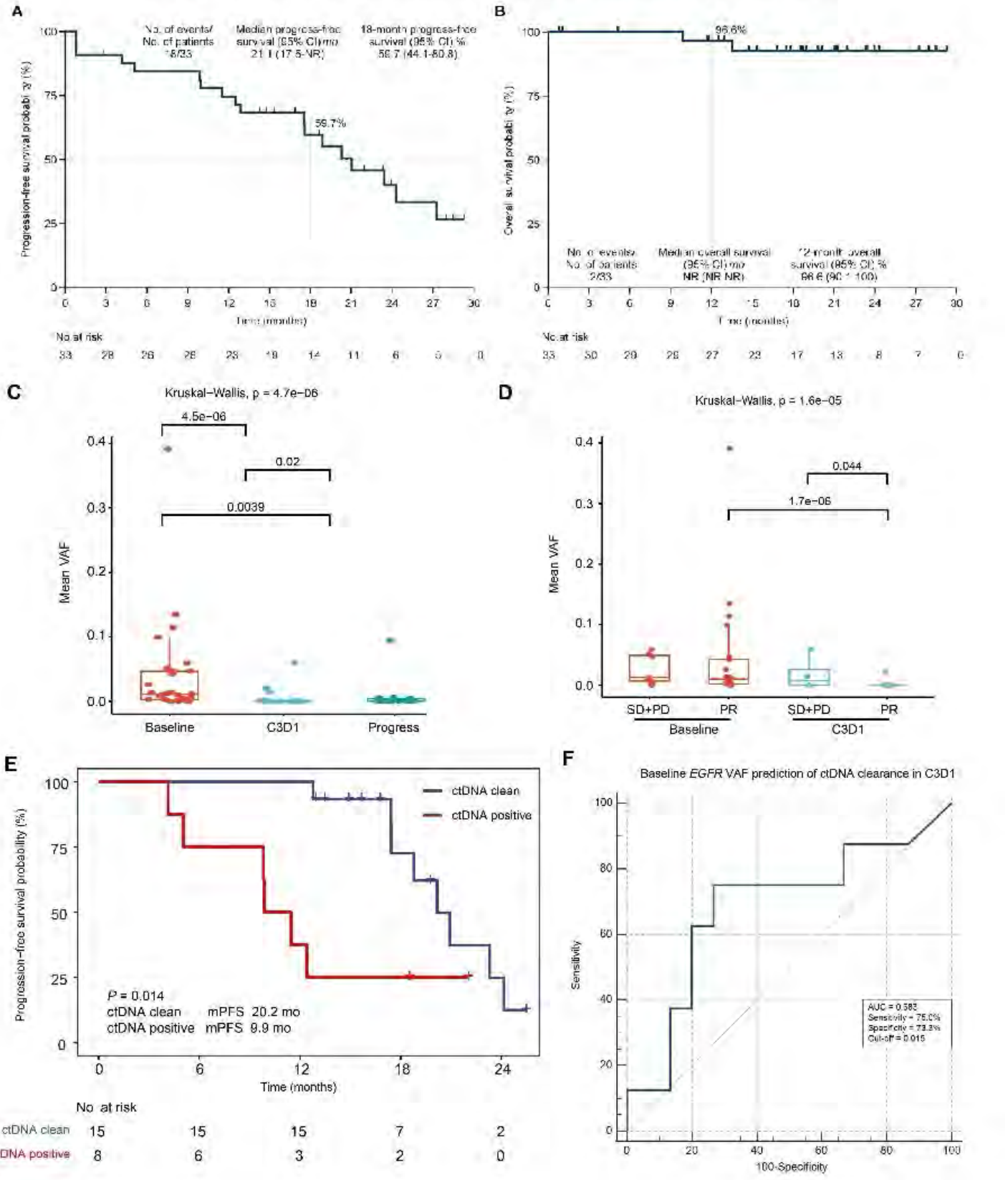
Introduction: Advanced non-small-cell lung cancer (NSCLC) with EGFR-L858R mutation had a shorter progression-free survival (PFS) compared to those with exon 19 deletions. This efficacy gap, compounded by the considerable toxicity, clinical complexity, and economic burden of current combination regimens, highlights the critical need for novel therapies. The FIRM study (ChiCTR2200060897) investigated double-dose firmonertinib as a therapeutic alternative.

Methods: This single-arm, multicenter phase II trial enrolled treatment-naïve adults (≥ 18 years) with locally advanced or metastatic NSCLC harboring EGFR-L858R mutation. Patients received firmonertinib 160 mg orally once daily in 21-day cycles until disease progression, death, intolerable toxicities, or withdrawal from the study. Circulating tumor DNA (ctDNA) was analyzed using a 158-gene panel at baseline, cycle 3 day 1 (C3D1), and upon disease progression. Primary endpoint was PFS. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), 18-month PFS rate, overall survival (OS), and safety. Exploratory endpoint assessed kinetics of the ctDNA profiles.

Results: As of February 2025, 33 patients received firmonertinib and were enrolled in efficacy and safety analyses with a median follow-up of 18.1 (range, 0.8-29.3) months. The median PFS (mPFS) reached 21.1 (95% confidence interval [CI], 17.5-not reached) months, with an 18-month PFS rate of 59.7% (95% CI, 44.1%-80.8%). Median OS was not reached with a 12-month OS rate of 96.6% (95% CI, 90.1%-100%). The ORR was 75.8% (95% CI, 57.7%-88.9%) with a median DoR of 18.5 (95% CI, 18.3-not reached) months, and DCR reached 90.9% (95% CI, 75.7%-98.1%). In the subgroup of patients with baseline brain metastases, ORR and DCR were 83.3% and 100%, respectively. Treatment was well-tolerated with only 6.1% grade ≥ 3 adverse events (anemia and hyponatremia), and no patients experienced dose reduction, discontinuation, or death. ctDNA dynamics revealed significant decreases in mean variant allele frequency (VAF) at C3D1 compared to baseline ($p<0.0001$), especially in the responders. Patients achieving ctDNA clearance at C3D1 showed significantly improved PFS (20.2m vs. 9.9m, P=0.014). Interestingly, baseline EGFR VAF, which was associated with total tumor diameter (R=0.426, P=0.042), emerged as a predictive biomarker for ctDNA clearance at C3D1 (Cut-off=1.5%, AUC=0.683).

Conclusions: Double-dose firmonertinib exhibited promising efficacy and safety in this trial, supporting its use as a first-line option for patients with EGFR-L858R mutation. ctDNA analysis demonstrates its significant clinical value for efficacy monitoring in FIRM and provides new insights for precise treatment strategies based on biomarker-driven stratification.

Figure 1. The efficacy estimation and biomarker exploration of FIRM study



Keywords: double-dose firmonertinib, EGFR exon 21 L858R, ctDNA dynamic monitoring

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.02 Real-World Outcomes in Patients With NSCLC and Leptomeningeal Disease

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Introduction: Historically, leptomeningeal disease (LMD) has had poor outcomes, but newer therapies may improve overall survival (OS). We examined factors affecting OS in a contemporary population of patients with NSCLC and LMD.

Methods: We retrospectively analyzed data from patients at MedStar Health who were diagnosed with NSCLC after December 1, 2017, and developed LMD at any point during their clinical course.

Results: Seventy-three patients met the inclusion criteria. LMD was diagnosed via: MRI alone (n=56, 78%), MRI and lumbar puncture (LP) (n=13, 18%), LP alone (n=2, 2%), and leptomeningeal involvement on pathology of a resected CNS metastasis (n=2, 2%). Twenty-two patients (30%) had LMD at their NSCLC diagnosis. Ten patients (14%) had no neurological symptoms at LMD diagnosis, and 16 patients (22%) had isolated LMD without parenchymal brain metastases. Median OS (mOS) following LMD diagnosis was 1.5 months (range: 1 day-43 months). Patients without neurological symptoms at LMD diagnosis had a mOS of 10 months (range: 1 day-32 months), compared to 1.2 months for those with symptoms (range: 6 days-44 months). Systemic treatment-naïve patients had a longer mOS (6.5 months, range: 1 day-43.8 months) than those with prior systemic therapy (1.3 months, range: 2 days-36 months, p=0.02). Patients who received treatment for LMD (n=48, 66%), such as radiation, intrathecal chemotherapy, or systemic therapy, had a longer mOS of 6.8 months (range: 11 days-43 months), compared to <1 month (n= 25, 34%, range: 1 day-5 months, p<.01) for those who did not. Similarly, patients with targetable mutations who received targeted therapy had a longer mOS of 8 months (n=23, range: 1-43 months) compared to those who did not (n= 21, mOS <1 month, range: 1 day-5 months, p<.01). Among patients who received 1 targeted therapy prior to LMD (n=23) diagnosis, those who received further targeted therapy (n=12) had improved OS (mOS 8 months, range 1-32 months), compared to those who did not (n=11, mOS <1 month, range 3 days-16 months, p <.01). Patients with PD-L1 ≥50% treated with immunotherapy had a mOS of 13 months (n=5, range: 1 day-35 months).

Conclusions: Treatment of LMD improves OS and can extend life by several years in a subset of patients, particularly those who are asymptomatic or treatment-naive. Targeted therapy was associated with improved OS in those with targetable mutations, regardless of prior exposure. High PD-L1 expression was linked to notable benefit from immunotherapy. Further investigation in a larger cohort is needed.

	N (%)	Median OS (months)	Minimum OS (months)	Maximum OS (months)
All patients	73 (100)	1.5	<1	44
Any Treatment for LMD	48 (66)	7	<1	44
Targetable mutation & LMD Treated with Targeted Therapy	23 (52)	8	1	44
PD-L1 ≥50% & LMD Treated with Immunotherapy	5 (7)	13	8	35

Keywords: leptomeningeal disease, non-small cell lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.03 Retrospective Analysis of Age, EGFR Mutation Type, and TP53 Co-Mutation on Survival Outcomes in EGFR-Mutant Non-Small Cell Lung Cancer

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Introduction: Young adults with non-small cell lung cancer (NSCLC) often have distinct clinico-genomic features compared to older adults. While targeted therapies for EGFR-mutant NSCLC primarily focus on 'classical' EGFR mutations, atypical EGFR mutations and TP53 co-mutations can negatively impact therapy response but remain understudied. This retrospective study evaluates the impact of patient age, EGFR mutation type (classical vs atypical), and TP53 co-mutation status on overall (OS) and survival from the initiation of osimertinib (Osi-OS) in patients with EGFR-mutant NSCLC.

Methods: 5,753 patients with EGFR-mutant NSCLC specimens were molecularly profiled at Caris Life Sciences (Phoenix, AZ) and distributed into two cohorts based on age at specimen collection: older adults (OA, >50 years, n=5404) and young adults (YA, ≤50 years, n=349). Classical mutations in EGFR include L858R, T790M and exon19 deletions, while all non-classical mutations were considered 'atypical'. Only pathogenic and likely pathogenic mutations were considered when determining TP53 mutation status. OS and Osi-OS were calculated using insurance claims data, with survival times measured from the date of specimen collection or osimertinib initiation to the date of last clinical contact using Kaplan-Meier estimates. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and p values were calculated using the log-rank test. To keep OS and Osi-OS distinct, patients treated with osimertinib were removed from OS calculations. Where applicable, p-values were corrected for multiple hypothesis testing with $q<0.05$ denoting statistical significance.

Results: Gender distribution and smoking history were comparable between the two groups. OA had a higher proportion of White and Non-Hispanic/Latino individuals (58 & 71%, respectively, vs 36 & 54% in YA; $q<0.05$); however, race and ethnicity were unknown for a greater proportion of YA. The distribution of classical/atypical EGFR mutations were similar between the two cohorts, while TP53 mutations were enriched in YA (76 vs 62%, $q<0.05$).Compared to OA with atypical EGFR mutations (OA-A), OA with classical mutations (OA-C) had a longer OS only in the absence of concurrent TP53 mutations (median OS: 39 vs 28m, HR=0.735, $p<0.0001$). However, OA-C (vs OA-A) had a longer Osi-OS only when co-mutated with TP53 (29 vs17m, HR=0.631, $p<0.001$). Additionally, YA with classical mutations (YA-C) had a longer median Osi-OS than both OA-C (40 vs 32m, HR=0.692, $p<0.01$) and OA-A (40 vs 21m, HR=0.47, $p<0.0001$), independent of TP53 mutation status.

Conclusions: In our study cohort, YA-C had the longest median Osi-OS, while OA-A had the shortest median Osi-OS. Our results highlight a significant role of TP53 mutation status, EGFR mutation subtype, and age in determining both OS and Osi-OS, particularly in OA. Further investigation is needed to explore the role of these factors in YA, where cohort sizes may limit conclusions.

Keywords: EGFR, Targeted Therapy, Non-small cell lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.04 Taletrectinib, a Next Generation Selective ROS1 Inhibitor, Exhibits a Differentiated Profile in ROS1 Fusion Models

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Introduction: ROS1 fusions, present in approximately 2% of non-small cell lung cancer (NSCLC) patients, drive cancer cell growth and survival. While FDA approved ROS1 inhibitors include crizotinib, entrectinib, and repotrectinib, patients are still in need of better treatment options that provide durable responses and prolonged progression-free survival (PFS), coupled with limited side effects. Taletrectinib is an oral, potent, central nervous system (CNS) active, selective, next-generation ROS1 inhibitor specifically designed for the treatment of patients with ROS1-positive NSCLC. Taletrectinib is being evaluated in patients with advanced ROS1-positive NSCLC, including tyrosine kinase inhibitor (TKI) naïve and TKI pretreated patients, in two Phase 2 single-arm pivotal studies: TRUST-I (NCT04395677) and TRUST-II (NCT04919811). Pooled results from the TRUST-I and TRUST-II studies of taletrectinib demonstrated a confirmed objective response rate (cORR) of 89%, an intracranial cORR of 77%, and a PFS of 46 months in patients with advanced ROS1-positive NSCLC that have not previously received a ROS1 TKI.

Methods: The kinase selectivity of taletrectinib was evaluated in comparison to approved ROS1 inhibitors. The in vitro and in vivo antitumor activity of taletrectinib was assessed against multiple ROS1 fusion models, including models with ROS1-G2032R fusions. Since ROS1 positive lung cancers have a high incidence of brain metastases, the intracranial activity and safety of taletrectinib was also compared to approved ROS1 inhibitors.

Results: Taletrectinib exhibits selectivity for ROS1 over tropomyosin receptor kinase (TRKB), the latter being associated with CNS-related side effects. At clinically relevant concentrations, taletrectinib inhibited growth of cell lines harboring various ROS1 wild type and ROS1-G2032R fusions. Taletrectinib treatment caused tumor regressions in several ROS1 fusion models regardless of fusion partner, including models resistant to crizotinib and entrectinib. Additionally, taletrectinib demonstrated CNS activity and a favorable toxicological profile in nonclinical safety studies.

Conclusions: In summary, our nonclinical data demonstrate that, at clinically relevant concentrations, taletrectinib exhibits activity in ROS1 wild-type- and mutant-driven cancers, including intracranial models, while maintaining selectivity against TRKB, resulting in an overall favorable profile. An NDA, based on the results from the pivotal TRUST-I and TRUST-II studies, has been accepted with Priority Review by the U.S. FDA for the treatment of patients with advanced ROS1-positive NSCLC.

Keywords: ROS1, NSCLC, TKI

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.05 Patterns of EGFR Mutations and Real-World Experience of Therapeutic Interventions - a Community Oncology Study

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Introduction: Epidermal Growth Factor Receptor (EGFR) mutations, the most commonly targeted mutations in lung cancer, have led to expanded treatment options in metastatic settings due to their heterogeneity. This study comprehensively summarizes the spectrum of EGFR mutations and co-mutations, clinical characteristics, treatment patterns, and survival outcomes in a real-world community oncology practice

Methods: This retrospective study included consecutive patients from community oncology centres diagnosed with EGFR mutant Non-small cell lung carcinoma (NSCLC) between March 2018 and September 2024

Results: Out of 2281 patients with Non-small cell lung carcinoma (NSCLC), 1592 were identified as adenocarcinomas, with EGFR mutations detected in 560/1592 (35.2%). The median age of the cohort was 64 years (IQR 55-72) with 17 patients presenting at less than 40 years of age and the M:F ratio being 1:1.07. The ECOG performance status scores were 0 in 54.4%, 1 in 38.6%, and ≥2 in 6.1% of patients, with the majority (80.5%) diagnosed with Stage IV disease most commonly metastasizing to the bone (270/451), brain (148/451), and lymph nodes (100/451). The prevalence of EGFR was higher in females compared to males (51.6% v/s 48.4 %, p=0.28).Detailed EGFR mutational testing records were available for 466 out of which comprehensive Next-generation sequencing (NGS) was done in 297/466 patients wherein 57.3% were tissue-based NGS, and 8.9% were liquid biopsy-based NGS while 281/466 patients were tested by Polymerase chain reaction (PCR). The frequency of co-mutations with EGFR was seen in 122/560 (21.8%) shown in Table 1. The majority of patients received tyrosinekinase inhibitors (TKIs) in the first-line (406/504, 80.6%) of which Gefitinib, Erlotinib, Afatinib, and Osimertinib were used in 32%, 7.8%, 13.3%, and 16.25% respectively while 21.67% received TKI in combination with chemotherapy. The TKI plus chemotherapy subgroup had a median age of 59 years (IQR: 52-67), with an ECOG PS of 0-1 in 97% and ≥2 in 3.3% of patients and 30.7% had brain metastases. Median overall survival m(OS) was 33 months (95% CI 29.3-36.7), with a median follow-up time being 29 months (95% CI 25.7-32.3). mOS was 33 months for Gefitinib/Erlotinib/Afatinib, 58 months for CT combined with TKIs, 38 months for Osimertinib, while moS for CT plus Osimertinib was not reached (P=0.078)

Conclusions: EGFR mutation testing is vital for optimizing NSCLC treatment outcomes, particularly in community oncology settings and developing countries, where access to targeted therapies and personalized treatment approaches can significantly improve patient care

EGFR with Exon details		EGFR with Co-mutants	
Exon records not available	179/ 560 (31.8%)	EGFR+ALK	8/381(2.1%)
Exon records available	381/560 (68.0%)	EGFR+ROS	9/ 381 (2.4 %)
Del 19	226/381 (59.3%)	EGFR+ALK+ROS	1/381 (0.3 %)
Exon 21 L858R	106/381 (27.8%)	EGFR+TP53	71 /381 (18.6 %)
20 insertion	39/381 (10.2%)	EGFR+MET	2 / 381 (0.5%)
T790M as baseline	23/381 (6.03%)	EGFR+BRAF	1/381 (0.3%)
EGFR rare mutation	16/381 (4.5%)	EGFR+KRAS	1 / 381 (0.3 %)
		EGFR+RET	1/ 381 (0.3 %)
		EGFR+ALK+TP53	2 /381 (0.5%)
		EGFR+MET+ATM	1/381 (0.3 %)
		EGFR+TP53+BRAF	1/381(0.3 %)
		EGFR+ KRAS+TP53	2/381(0.5 %)
		EGFR+ KRAS+PIK3Ca	1/381(0.3 %)

Keywords: EGFR Co-mutations, Western India, Survival Outcomes

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.06 Pralsetinib (Phase 1/2 ARROW Trial) Compared With Best Available Therapy (External Control) in Pretreated RET Fusion+ NSCLC

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Introduction: Pralsetinib, a highly potent, oral, selective inhibitor of rearranged during transfection (RET) receptor tyrosine kinase, received FDA approval in September 2020 for metastatic RET fusion-positive non-small cell lung cancer (NSCLC). Understanding pralsetinib's efficacy following front-line chemotherapy is key to optimizing treatment strategies and patient outcomes. This analysis used real-world (RW) data as an external control arm to compare outcomes of the subset of patients treated with pralsetinib as second-line or later (2L+) treatment in the Phase 1/2 trial ARROW (NCT03037385) vs best available therapy (BAT).

Methods: RW data on advanced RET fusion-positive NSCLC patients (2010-2020) were collected via retrospective medical chart review from 4 centers located in the US, France, Switzerland, and Italy. Eligibility criteria similar to ARROW were applied to obtain a comparable RW sample; the RW sample was limited to treatments initiated after RET fusion identification (i.e., "post-RET") to match trial patients. Objective response rate (ORR) was assessed using proportions. Average treatment effect of the treated (ATT) weights were calculated to balance baseline characteristics between ARROW and RW samples. Overall survival (OS) and progression-free survival (PFS) were evaluated using Kaplan-Meier methods and weighted Cox regression models, including variables that remained unbalanced after ATT-weighting (>10% standardized mean difference).

Results: The 2L+ post-RET analytical sample included 22 RW patients treated with BAT and 159 ARROW patients treated with pralsetinib in 2L+ (trial data cutoff Nov 18, 2019). Mean age was 58.3 and 59.1 years and 56.0% and 51.9% were female, among ARROW and the RW, respectively; 49.7% of ARROW and 37.0% of RW patients had received >1 prior lines of therapy. Most frequently received BAT were tyrosine kinase inhibitors (66.7%; 29.6% investigational agents, 25.9% cabozantinib, 7.4% vandetanib, 3.7% alectinib) and chemotherapy (25.9%). ORR (95% confidence interval [CI]) in ARROW was 61.4% (53.7, 69.2) and in the RW was 25.9% (9.4, 42.5). Median PFS was 16.8 and 3.5 months in ARROW and the RW, respectively. Median OS was not reached in ARROW and was 9.1 months in the RW. After adjustment, compared to BAT, patients treated with pralsetinib had significantly longer PFS and OS, with adjusted hazard ratios (95% CIs) of 0.13 (0.09, 0.20), p<0.001 and 0.28 (0.17, 0.46), p<0.001, respectively.

Conclusions: This RW, multi-center study found that 2L+ treatment with pralsetinib in advanced RET fusion-positive NSCLC was associated with higher ORR and significantly improved OS and PFS compared to BAT, even after adjusting for population differences. Limitations of RW data include missing data and potential unmeasured confounding, which this study aimed to mitigate through rigorous analytical methods.

Keywords: RET fusion-positive NSCLC, Pralsetinib, External control arm

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.07 Rezivertinib in EGFR-Mutated NSCLC Patients With Cns Metastases: Cns Efficacy From Phase 3 RAZOR Study

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Introduction: The RAZOR study (NCT03866499) randomized 369 treatment-naïve patients with EGFR-mutated (Ex19del or L858R) locally advanced or metastatic non-small cell lung cancer (NSCLC) into two double-blind groups at a 1:1 ratio, to receive either rezivertinib (180mg po QD) or gefitinib (250mg po QD). Previous results demonstrated that rezivertinib significantly prolonged progression-free survival (PFS) compared to gefitinib, with a favorable safety profile. This analysis updates the central nervous system (CNS) outcomes in patients with baseline CNS metastases.

Methods: In the RAZOR study, all patients received CT or MRI scans and brain MRI scan at baseline, and the following-up status until radiological disease progression. EGFR mutation testing was done on tissue or plasma samples. Patients with stable, asymptomatic CNS metastases were eligible for inclusion. The CNS full analysis set (cFAS) comprised patients with baseline CNS metastases by MRI scan, which was evaluated by blinded independent central review (BICR) per RECIST v1.1. Among them, those with measurable CNS target lesions formed the CNS evaluable-for-response set (cEFR). CNS efficacy was further assessed by BICR using RANO-BM criteria.

Results: By the data cut-off date on Nov 30, 2023, 159 patients with baseline CNS metastases were included in cFAS (rezivertinib: 81; gefitinib: 78) and 25 were included in cEFR (rezivertinib: 12; gefitinib: 13) assessed by BICR. In the cFAS, 59 CNS PFS events occurred (rezivertinib: 30; gefitinib: 29), and the median CNS PFS was significantly prolonged with 24.9 (95% CI, 16.5-NC) month in the rezivertinib group over 15.2 (95% CI, 10.5-NC) months in the gefitinib group (HR=0.58; 95% CI, 0.34-0.99; P=0.0473). Estimated CNS PFS rates at 12 and 18 months were 71.7% (95% CI, 59.2-81.0) and 60.3% (95% CI, 46.4-71.7) for the rezivertinib group, respectively, versus 60.4% (95% CI, 46.9-71.5) and 41.3% (95% CI, 24.1-57.8) for the gefitinib group. For 116 patients with baseline tissue EGFR mutation positivity in the cFAS (rezivertinib: 57; gefitinib: 59), the CNS PFS was 24.9 (95%CI, 16.0-NA) months for the rezivertinib group and 16.6 (95%CI, 12.6-NA) months for the gefitinib group, respectively (HR = 0.80; 95% CI, 0.40-1.58; P=0.5182); for 58 patients with baseline plasma EGFR mutation positivity in the cFAS (rezivertinib: 32; gefitinib: 26), the CNS PFS was NA (95%CI, 15.4-NA) months for the rezivertinib group and 8.5 (95%CI, 5.7-NA) months for the gefitinib group, respectively (HR = 0.34; 95% CI, 0.14-0.81; P=0.0142). In the cEFR, the confirmed CNS objective response rates (ORR) were 83.3% for the rezivertinib group and 76.9% for the gefitinib group (odds ratio=1.50; 95% CI, 0.220-11.0; P=0.6900). Estimated CNS PFS rates at 12 and 18 months were 73.3% (95% CI, 37.9-90.6) and 73.3% (95% CI, 37.9-90.6) for the rezivertinib group, respectively, versus 51.9% (95% CI, 22.5-75.0) and 41.5% (95% CI, 14.4-67.2) for the gefitinib group. No new safety findings were identified.

Conclusions: Rezivertinib exhibited superior CNS efficacy compared to gefitinib as a first-line treatment for EGFR-mutated advanced NSCLC with baseline CNS metastases. Safety profile was manageable.

Keywords: Rezivertinib, EGFR mutations, CNS efficacy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.08 Weight Gain Induced by Tyrosine Kinase Inhibitors in Oncogene-Addicted Non-Small Cell Lung Cancer: A Meta-Analysis and a Meta-Regression Study

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Introduction: For patients with oncogene-addicted (OA) non-small cell lung cancer (NSCLC) treated with tyrosine kinase inhibitors (TKIs), weight gain (WG) has recently gained attention as a relevant treatment-related effect. Identifying those TKIs more frequently associated with WG is crucial to characterize body composition-related modifications, deepen their metabolic impact and guide treatment decisions, considering the influence of WG on patients' quality of life (QoL) and long-term outcomes.

Methods: A systematic search was conducted across PubMed, Scopus, Cochrane and meeting resources (ESMO, ASCO, WCLC) using the following string: ("lung cancer" OR "NSCLC") AND ("TKI" OR "tyrosine kinase inhibitor" OR "target therapy") AND ("weight gain"). WG (calculated as the percent change from baseline) incidence and its association with demographic/clinical parameters were analyzed using meta-regression models.

Results: Among 7,596 identified studies (January 2009 - December 2024), 18 pivotal trials reporting WG data (7 randomized and 11 single-arm) were included in the final analysis, encompassing 25 arms. Table 1 reported the incidence of WG in patients receiving TKIs, according to the CTCAE grade. Lorlatinib showed the highest risk for treatment-induced WG [incidence 36%; 95% CI: 26%-46%; I2=92%], followed by alectinib [incidence 15%; 95% CI: 26%-46%; I2=52%] and crizotinib [incidence 5%; 95% CI: 0%-13%; I2=93%] [Figure 1]. Osimertinib and erlotinib showed the lowest incidence of WG. The meta-regression confirmed no significant correlation between WG and patient-specific factors, including gender (p=0.18), age (p=0.99), and ECOG PS (p=0.15), suggesting a drug-specific effect.

Conclusions: Our findings confirmed lorlatinib unique profile regarding WG, independently of patients' demographics or baseline ECOG PS. Considering the impressive prognostic horizons achievable with TKIs in OA NSCLC, adequate reporting of WG in clinical trials, as well as assessment/monitoring of WG, body composition modifications and impact on QoL should be prioritize, together with adequate lifestyle-based strategies for its management.

Table 1. Incidence of weight gain in patients receiving TKIs, according to the severity

Study	Drug	N ° Pts weight gain Any Grade (%)	Grade 1-2 N (%)	Grade 3 N (%)
Peters S, 2017	Alectinib	15 (10)	14 ((9)	1 (1)
Peters S, 2017	Crizotinib	0 (0)	0 (0)	0 (0)
Shaw AT, 2017	Lorlatinib	9 (17)	6 (11)	3 (6)
Yang JC, 2017	Alectinib	33 (15)	NA	NA
Solomon BJ, 2018	Lorlatinib	50 (18)	45 (16)	5 (2)
Shaw AT, 2019	Lorlatinib	16 (23)	11 (16)	5 (7)
Zhou C, 2019	Alectinib	23 (18)	19 (15)	4 (3)
Zhou C, 2019	Crizotinib	2 (3)	1 (1)	1 (2)
Camidge DR, 2019	Alectinib	14 (9)	NA	NA
Camidge DR, 2019	Crizotinib	0 (0)	0 (0)	0 (0)
Shaw AT, 2020	Lorlatinib	57 (38)	28 (21)	25 (17)
Shaw AT, 2020	Crizotinib	18 (13)	15 (10)	3 (2)
Wu YL, 2020	Osimertinib	0 (0)	0 (0)	0 (0)
Ou SI, 2020	Alectinib	19 (16)	15 (7)	4 (9)
Felip E, 2021	Lorlatinib	70 (24)	55 (19)	15 (5)
Lu S, 2022	Lorlatinib	35 (32)	28 (26)	7 (6)
Dagogo-Jack I, 2022	Lorlatinib	9 (39)	8 (35)	1 (4)
Piccirillo MC, 2022	Erlotinib	1 (1)	0 (0)	1(1)
Zhou Q, 2023	Lorlatinib	29 (49)	19 (32)	10 (17)
Zhou Q, 2023	Crizotinib	10 (17)	9 (15)	1 (2)
B.J. Sikkema, 2023	Alectinib	23 (22)	NA	NA
B.J. Sikkema, 2023	Alectinib	15 (16)	NA	NA
Solomon BJ, 2024	Lorlatinib	66 (44)	32 (21)	34 (23)
Solomon BJ, 2024	Crizotinib	18 (13)	15 (11)	3 (2)
John A, 2024	Lorlatinib	35 (81)*	15 (35)	4 (9)

Legend: NA, Not Available; N, Number. Weight gain was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) versions 4.0 and 5.0.
* Grade < G1 was reported in 37.2% of the pts

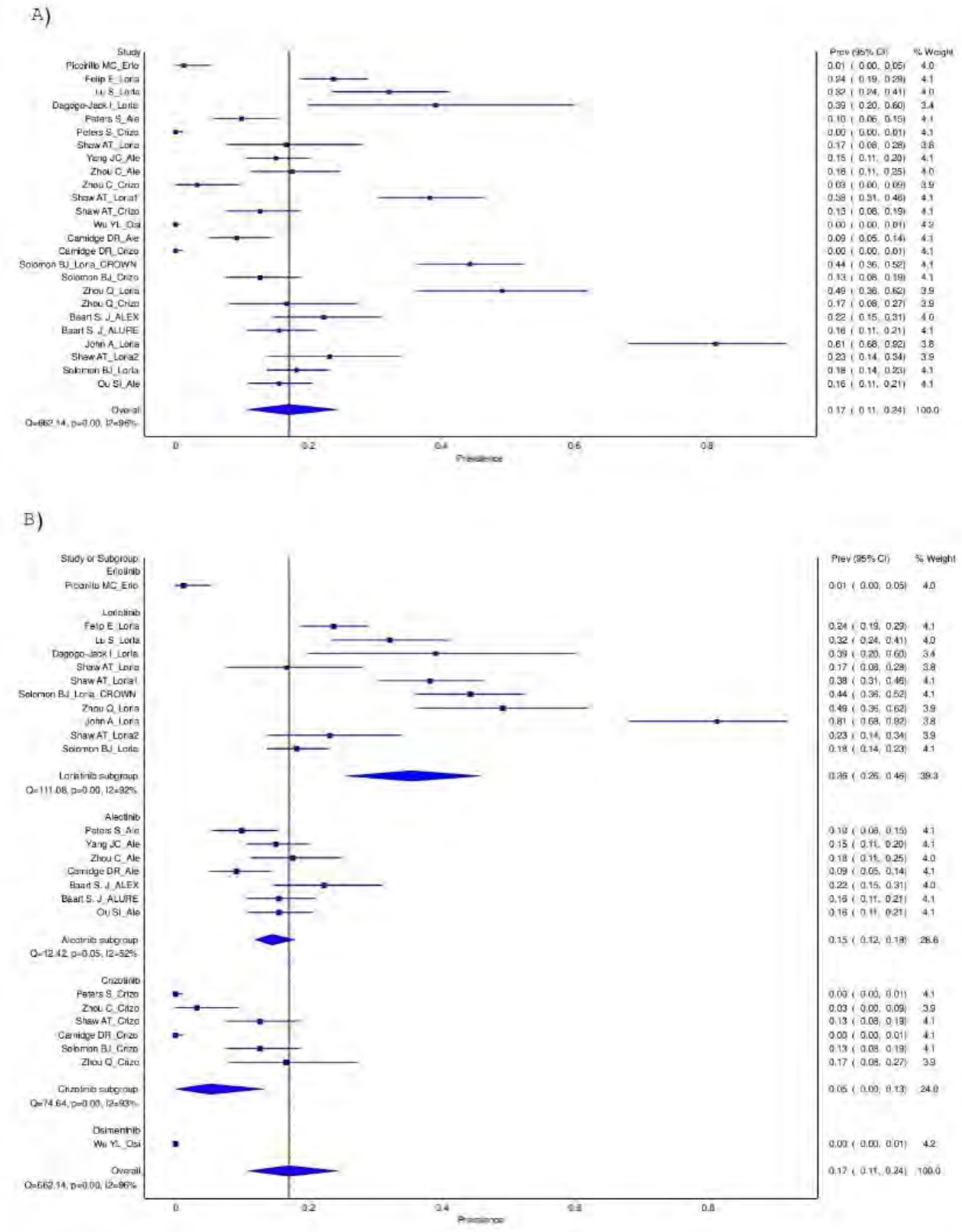

Figure 1. A. Forest plot of results of a meta-analysis evaluating % of patients with weight gain. Each square represents the hazard ratio (HR) for weight gain in individual studies. The horizontal line through each square indicates the 95% confidence interval (CI) for the HR, reflecting the range of uncertainty around the estimate of effect. The diamonds represent the estimated overall effect based on the meta-analysis random effects of the trials. B. Forest plot of analysis stratified by subgroups of TKIs.

Keywords: Weight Gain, Tyrosine Kinase Inhibitors, Meta-analysis

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.09 Efficacy of Tepotinib Against Non-Adenocarcinoma MET Exon 14 Skipping NSCLC: A Subanalysis of the REAL-MET Study

A Subanalysis of the REAL-MET Study

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Introduction: The VISION study demonstrated the efficacy of the MET inhibitor, tepotinib against non-small cell lung cancer (NSCLC) harboring MET exon 14 (METex14) skipping variants. However, the clinical efficacy and safety of tepotinib in histological subtypes other than the most common form of adenocarcinoma, such as squamous cell carcinoma and sarcomatoid carcinoma, have not been sufficiently evaluated.

Methods: We conducted herein a multicentric, retrospective study (the REAL-MET study) analyzing data on patient characteristics, treatment details, and the efficacy and safety of tepotinib in patients with METex14 skipping NSCLC diagnosed at any of six, Japanese hospitals between August 2020 and December 2024. Specifically, the clinical efficacy and safety of tepotinib were assessed in patients in this cohort with a histological subtype other than adenocarcinoma.

Results: In total, 79 patients were enrolled. Adenocarcinoma, squamous cell carcinoma, sarcomatoid carcinoma, adenosquamous carcinoma, and other subtypes occurred in 56 (70.9%), eight (10.1%), five (6.3%), four (5.1%), and six (7.6%) patients, respectively. Comparison of the baseline characteristics of the patients with non-adenocarcinoma histology (n=23) and those with adenocarcinoma (n=56) found that the former group had a higher proportion of females (47.8% vs. 35.7%), never-smokers (47.8% vs. 37.5%), and cases of high PD-L1 expression (60.9% vs. 37.5%). Median progression-free survival (PFS) and median overall survival (OS) after tepotinib therapy were superior in patients with adenocarcinoma than in those with non-adenocarcinoma histology although the difference was not significant (PFS: 10.4 months [95% confidence interval (CI): 8.0-12.8] vs. 5.3 months [95% CI: 3.8-6.8], hazard ratio [HR]: 0.77, 95% CI: 0.45-1.34, P = 0.35; OS: 24.4 months [95% CI: 15.2-33.5] vs. 16.0 months [95% CI: 10.9-21.2], HR: 0.60, 95% CI: 0.31-1.14, P = 0.12). The following were the median PFS and OS for specific, non-adenocarcinoma histological subtypes. Squamous cell carcinoma: PFS 4.7 months (95% CI: 2.7-6.8), OS 16.0 months (95% CI: 0.3-31.7); sarcomatoid carcinoma: PFS 5.3 months (95% CI: 0.0-12.9), OS 5.9 months (95% CI: 5.6-6.1); adenosquamous carcinoma: PFS 8.1 months (95% CI: 0.4-15.9), OS 30.8 months (95% CI: not achieved)(NOS); other subtypes: PFS 3.6 months (95% CI: 1.4-5.8), OS 13.4 months (95% CI: 10.6-16.1). Among the non-adenocarcinoma subtypes, patients with sarcomatoid carcinoma had the shortest, median OS. No significant difference was observed in the objective response rate or the frequency of adverse events among the histological subtypes.

Conclusions: The present, real-world analysis found that non-adenocarcinoma histology accounted for 29.1% of patients with METex14 skipping NSCLC, with squamous cell carcinoma, sarcomatoid carcinoma, and adenosquamous carcinoma being the most common subtypes. Although PFS and OS were shorter in patients with non-adenocarcinoma than in those with adenocarcinoma, tepotinib demonstrated clinical efficacy in the former subgroup, suggesting that the drug is effective against METex14 skipping NSCLC, including cases with a non-adenocarcinoma histology.

Keywords: Tepotinib, Non-adenocarcinoma MET exon 14 Skipping NSCLC

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.10 Adapting RECIST for Real-World Data: Independent Imaging Read Methodology Over Successive Treatments in a NSCLC Data Registry

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Introduction: Biomarker-defined drug-targetable subpopulations of NSCLC may be too small for classical Phase III confirmatory studies. In such cases, a post-authorization real-world cohort efficacy study, with independent tumor activity reads to assess activity endpoints, may be a practical alternative. However, such methodology has not previously been applied to solid tumors. Here we present an approach to independent read methodology, to guide and inform assessments in real-world data analyses for NSCLC. This methodology, modified from RECIST 1.1, was designed to evaluate treatment activity in the real-world NSCLC MOMENT registry, and was informally tested in a biomarker-defined subpopulation of NSCLC.

Methods: Images from the MOMENT registry were segmented into lines of treatment; baseline images for each line were identified. Read processes were developed to align with RECIST 1.1: two independent primary reviewers provide separate blinded assessments, with discrepancies resolved by an adjudicator, as required. Readers are informed of the date of dosing in relation to the dates of supplied images, and any change in the line of treatment. Measurable disease identified in one line of treatment does not determine measurable disease in subsequent treatment lines. Modified RECIST 1.1 criteria (Table 1) were developed. Key read testing refinements of this methodology include retrospective reselection of target lesions, to ensure the best assessment within the potentially incomplete real-world dataset. New lesions observed in previously unimaged areas are not automatically defined as progressive disease (PD). Brain lesions are followed as non-target lesions to avoid any impact from post-radiotherapy necrosis, and fluid collections do not define PD in the absence of other clear indications of progression.

Results: Application of this methodology was tested successfully on preliminary data from the MOMENT cancer registry database. It was also tested and found to be feasible in an informal analysis of data from a subset of clinical trial patients with NSCLC harboring MET exon 14 skipping; on a case-by-case basis, the results were consistent with independent review committee (IRC) assessments performed in the trial.

Conclusions: This methodology replicates the rigor of a clinical trial IRC-approach to tumor assessments using real-world imaging data. It may produce a more accurate estimate of overall response rate in real-world studies with prospective primary data collection, and could be considered an easy-to-implement alternative to classical Phase III confirmatory studies in small biomarker-defined subpopulations of patients with lung cancer. It may also be applicable to other orphan indications when randomized trials are not feasible.

Table 1. Modified RECIST 1.1 criteria

Topic	Read rule modifications
Technical Adequacy Review	All images reviewed for quality. Examples of technical inadequacies include: subject motion, artifacts, poor image quality, missing anatomical regions or entire imaging time points, and poor compliance with imaging guidelines
Measurable, Non-Measurable and New Lesions	Defined as per RECIST 1.1
Baseline	At baseline, independent reviewers will prospectively identify representative sites of disease present at the start of each treatment line, and characterize as target or non-target lesions
Target Lesions	Defined as per RECIST 1.1
Prior Radiation Therapy	Lesions known to have been previously irradiated will only be selected as target lesions if unavoidable
Lesion Measurement Procedures	Defined as per RECIST 1.1
Evaluation of Target Lesions	Defined as per RECIST 1.1
Non-Target Lesions	Defined as per RECIST 1.1
Fluid Collections	Pleural effusions, pericardial effusions and ascites may be considered, if felt to be a manifestation of malignant disease. If selected, they will be followed as a non-target lesion. A significant increase in existing effusions or ascites alone will not be considered sufficient evidence of progression
Evaluation of Non-Target Lesions	All non-target lesions to be considered together as either CR, non-CR/PD, unequivocal progression, or NE
Evaluation of New Lesions	Unequivocal appearance of new lesion(s) on CT/MRI will be considered PD. Ultrasound reports from the sites can be considered, but new lesions must show sequential enlargement to be considered PD if lacking CT/MRI confirmation
Pseudoprogression / pseudopseudoprogression	If tumor enlargement results in PD, but subsequent determinations result in a decrease in size, the initial tumor increase may be pseudoprogression or pseudopseudoprogression. Therefore, lesions will continue to be followed after PD so that this is noted
Re-Baselining Assessments for Subjects that Undergo Multiple Lines of Treatment	The time point closest to the new treatment date will be considered the new baseline by applying the following order of preference: 1) ≤4 weeks prior to the start of a new line of therapy; 2) ≤2 weeks after starting a new line of therapy; 3) 4–8 weeks prior to the start of a new line of therapy. If no images are available from any of these periods, then the line of therapy is not evaluable due to a lack of baseline
CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging; NE, not evaluable; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.	

Keywords: MOMENT, Non-small cell lung cancer, Imaging

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.11 Aumolertinib Plus Chemotherapy as First - Line for Ps 2 - 3 Advanced NSCLC With EGFR Mutations: A Phase 2 Subgroup Analysis

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Introduction: The ECOG performance status (PS) score rates from 2 to 3 with worse prognosis and tolerance, defined as advanced severe lung cancer. However, PS 2-3 patients(pts) were not included in most clinical trials and the efficacy of EGFR-TKIs for PS 2-3 pts were still unknown in the real world. Here, we report pre-specified, exploratory subgroup analyses of the efficacy and safety of aumolertinib combined with pemetrexed and carboplatin in the aforementioned PS 2-3 population.

Methods: In this phase 2 trial (NCT04646824), pts received aumolertinib 110 mg once daily plus pemetrexed (500 mg/m2) and carboplatin (area under curve=5) once every 3 weeks for 4 cycles, followed by maintenance aumolertinib (110 mg once daily) and pemetrexed (500 mg/m2 once every 4 weeks).The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Of the 34 patients involved in this prospective phase 2 study, 17 patients had a PS score of 2-3.

Results: From November 2020 to October 2021, 34 pts with EGFR Mutations were enrolled for overall analysis. The median PFS was 28.0 months (95% CI, 18.7 to 36.9) and the ORR was 91.2%. Of these 17 pts, 14 had a PS score of 2 and 3 had a PS score of 3. Among them, there were 8 male patients and 9 female patients. Nine had the 19del mutation, five had the L858R mutation, and three had other rare mutation types. The median PFS was 24.0 months(95% CI, 17.0 to 26.0). The ORR was 94.1% (16/17), and the DCR was 100%. The median OS was not reached. Among the 17 pts who underwent circulating tumor DNA (ctDNA) testing, 15pts (88.2%) demonstrated clearance of EGFR mutations after 2 or 4 cycles of treatment. Two pts had disease progression soon after ctDNA re-examination revealed EGFR-positive, with PFS 10 and 11 months respectively. The most common grade ≥ 3 treatment-related adverse event was decreased neutrophil count.

Conclusions: Aumolertinib plus chemotherapy shows benefits as first-line treatment for patients with PS 2-3 and EGFR-mutant NSCLC, which may be associated with a higher clearance rate of ctDNA.

Keywords: aumolertinib plus chemotherapy, PS 2-3, ctDNA clearance

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.12 Clinical Pharmacologic Characteristics of Taletrectinib

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Introduction: Taletrectinib is an oral, potent, central nervous system-active, selective, next-generation ROS1 inhibitor. In December 2024, the US FDA granted Priority Review of the New Drug Application for taletrectinib for advanced ROS1+ non-small cell lung cancer (NSCLC; Prescription Drug User Fee Act goal date, June 23, 2025). In a pooled analysis from TRUST-I and TRUST-II, taletrectinib demonstrated robust, durable efficacy and tolerable safety in patients with ROS1+ NSCLC. Here, we report key clinical pharmacologic findings of taletrectinib.

Methods: An integrated analysis from 10 phase 1 or 2 clinical trials was performed. Clinical pharmacology of taletrectinib (pharmacokinetics [PK], metabolism/elimination, and drug-drug interactions) was assessed as well as PK across populations to characterize exposure across patient groups.

Results: Taletrectinib PK exposure increases were roughly proportionate for 50-1200- mg doses once daily (QD). A steady state was reached by day 8 following 7-day QD dosing, with an accumulation ratio of 3.3-4.5 at 600 mg QD. Following oral administration, tmax was reached after ~2-6 hours. Taletrectinib had a terminal half-life (t1/2) of ~80-100 hours; effective t1/2 was ~66 hours, supporting QD dosing. Taletrectinib exhibited concentration-dependent protein binding; the estimated binding percentage in human plasma was 92.6%-96.5% for concentration levels 100-10,000 ng/mL. In vitro studies indicated that CYP P450 3A4 was the primary enzyme responsible for metabolizing taletrectinib. Per a clinical mass balance study, taletrectinib was eliminated primarily through hepatic metabolism (renal elimination, <5% of the total dose); 75.1% was excreted in feces, and 11.1% in urine. Plasma taletrectinib Cmax/AUCinf were increased by 76%/228% with administration of a strong CYP3A4 inhibitor and decreased by 42%/86% with administration of a strong CYP3A4 inducer; Cmax/AUCinf were decreased by 65%/40% with administration of a proton pump inhibitor (PPI). Pooled PK data from healthy participants (n=110) and patients with NSCLC (n=405) showed no clinically significant differences in PK based on age (≥65 years, 21%), sex (male, 55%), weight (median, 66 kg), hepatic impairment (mild impairment, 18%; not studied in patients with moderate or severe impairment), or renal impairment (mild impairment, 11%; moderate impairment, 1.4%; not studied in patients with severe impairment).

Conclusions: Taletrectinib demonstrated dose-proportional PK with a long terminal t1/2, enabling QD dosing. Metabolism primarily occurred through CYP3A4. Drug-drug interactions should be considered with CYP3A modulators and PPIs. No clinically significant PK changes were observed across demographics or with mild hepatic impairment or mild-to-moderate renal impairment.

Keywords: ROS1+, Non-small cell lung cancer (NSCLC), Taletrectinib

P3.12.13 Long-Term Real-World Outcomes of Sotorasib in Second-Line and Beyond Treatment of KRAS G12C-Mutated Advanced NSCLC

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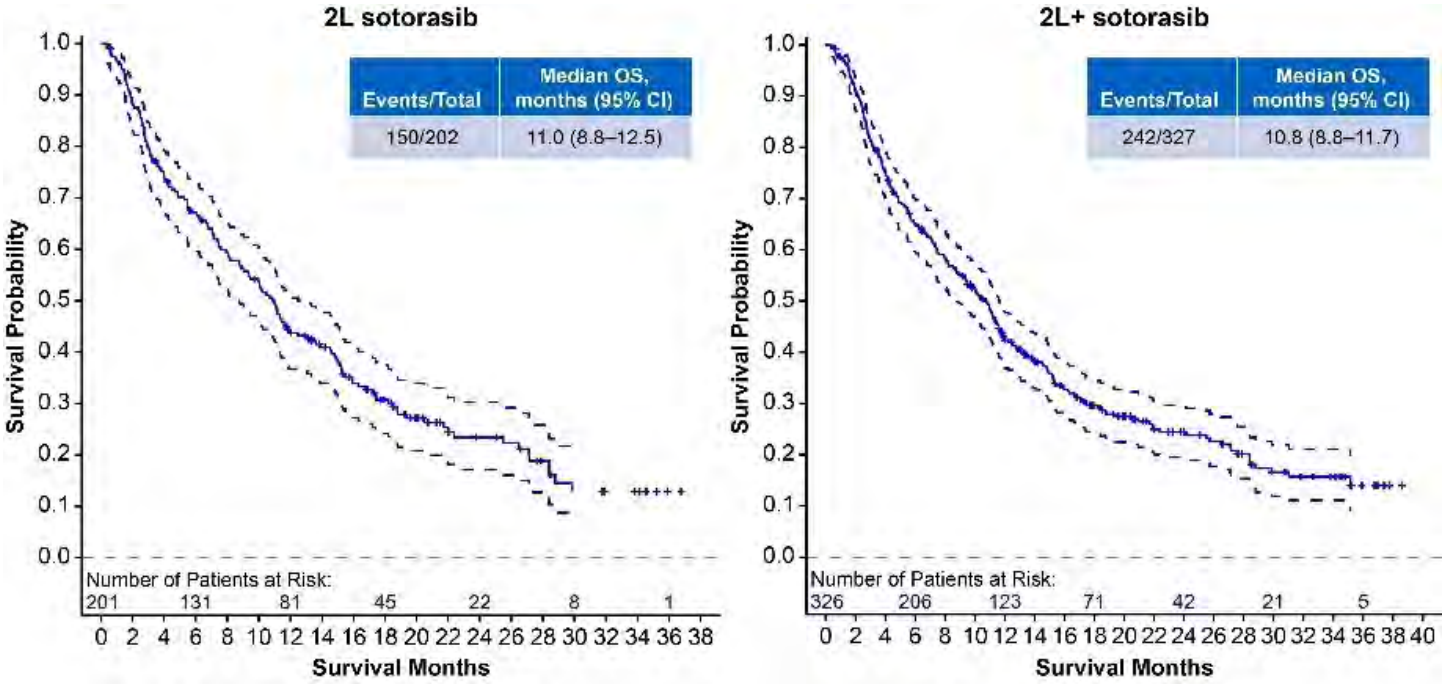
Introduction: In a previous study, the survival benefit of sotorasib was demonstrated in the second-line and beyond (2L+) real-world setting over a 1-year period in patients with KRAS G12C-mutated advanced non-small cell lung cancer (NSCLC; Johnson et al, Lung Cancer, 2024:197;107960). In the present study, we evaluate real-world clinicopathological characteristics and median overall survival (OS) of sotorasib in 2L and 2L+ settings from additional patients with a more recent data cutoff date thereby allowing for assessment of longer-term survival.

Methods: Patients from a US-based electronic health record-derived de-identified Flatiron Health Enhanced Datamart treated with 2L and 2L+ sotorasib between May 28, 2021, and September 30, 2023, and with a confirmed KRAS G12C mutation, were included in this analysis. The data cutoff date was September 30, 2024, allowing for a minimum of 12 months and up to 28 months opportunity for follow-up for outcomes from the initiation of treatment. Patient demographic and clinical characteristics were described. Median OS was the primary endpoint. Median OS and corresponding 95% confidence intervals (CIs) were calculated by line of therapy (2L and 2L+) using Kaplan-Meier estimates.

Results: A total of 210 patients received 2L sotorasib and 338 received 2L+ sotorasib. Overall, baseline demographics and disease characteristics of patients were similar across 2L and 2L+ analysis sets. Most patients included in the 2L and 2L+ analysis sets were female (56.7%; 57.4%); ≥65 years old (73.8%; 68.9%); White (73.3%; 73.7%); were from the community practice setting (74.8%; 73.7%); had a history of smoking (96.2%; 97.3%); an initial diagnosis of advanced disease (72.9%; 72.5%); with a histology of non-squamous cell carcinoma (96.2%; 95.9%); and had prior anti-PD-(L)1 treatment (75.2%; 78.4%). Most patients in the 2L and 2L+ analysis sets had an Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 (53.8%; 55.6%). Of note, 19.0% and 17.8% of patients had ECOG PS 2 and 3.8% each had ECOG PS ≥ 3 in 2L and 2L+ analysis sets, respectively; ECOG PS data were not available for 23.3% and 22.8% of patients. The median OS (95% CI) for 2L and 2L+ sotorasib was 11.0 months (8.8-12.5) and 10.8 months (8.8-11.7), respectively (Figure).

Conclusions: Sotorasib in 2L and 2L+ settings demonstrated long-term survival in a real-world population of patients with KRAS G12C-mutated advanced NSCLC, including those with poor ECOG PS.



Keywords: Sotorasib, KRAS G12C-mutated advanced NSCLC, Overall survival

P3.12.14 Clinical Effectiveness and Safety of Tepotinib in Patients From Germany With MET Exon14 Skipping NSCLC: A Case Series

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Introduction: MET exon 14 (METex14) skipping is a primary oncogenic driver observed in 2% (range: 0.5% to 6.8%) of patients with non-small cell lung cancer (NSCLC). Tepotinib, a highly selective MET tyrosine kinase inhibitor (TKI), is approved to treat METex14 skipping NSCLC in multiple countries/regions, including the EU, where it was approved for use after immunotherapy and/or chemotherapy in February 2022. We report clinical effectiveness and safety outcomes from a cohort of patients with METex14 skipping NSCLC in Germany, who gained early access to tepotinib via compassionate use requests prior to its EU approval.

Methods: Patients received tepotinib 500 mg (450 mg active moiety) once daily in clinical practice in Germany. Physicians provided data on patient characteristics, response (per the treating physician's assessment), and tepotinib-related adverse events (AEs) as of November 2024.

Results: The cohort included 25 patients with stage IIIA-IVB NSCLC, who initiated tepotinib between January 2021 and February 2022. Patients were aged 58-91 years, 14 were female, 15 had a smoking history, and 18 had adenocarcinoma histology. ECOG PS was 0 in seven patients, 1 in 15 patients, and 2 in three patients. METex14 skipping was detected in tissue biopsies by next-generation sequencing in 24 patients and polymerase chain reaction in one patient. Programmed death-ligand 1 status was positive in 18 patients. Twelve patients received tepotinib as first-line, eight as second-line, four as third-line, and one as fourth-line treatment. Tepotinib treatment duration was 0.8-34.4 months. At the time of data collection, treatment was ongoing in one patient. Per the treating physician's assessment in patients with available data, 12/23 patients had a partial response, and duration of response was 3-32.9 months. Detailed outcomes will be presented during the meeting. The most common tepotinib-related AE was edema, which was reported in 17/25 patients (Grade 1/2, n=14; Grade 3, n=3), followed by pleural effusion (n=4), and fatigue (n=2). AEs led to dose reduction in three patients and discontinuation in six patients (mostly due to edema). Conservative management of edema included compression stockings, diuretics, and fluid restriction.

Conclusions: In this case series from Germany, tepotinib demonstrated clinical effectiveness and manageable safety in patients with METex14 skipping NSCLC in real-world practice.

Keywords: Tepotinib, MET inhibitors, Non-small cell lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.15 Activity and Tolerability of MET Tkis in METex14 NSCLC: Updated Real-World Data From the Italian Biomarker Atlas Database

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Introduction: Capmatinib and tepotinib have been incorporated into the treatment algorithm for patients with advanced non-small cell lung cancer (NSCLC) with MET exon 14 skipping mutations (METex14). Here, we report updated data on disease and patient characteristics, as well as on efficacy and tolerability of MET tyrosine kinase inhibitors (TKIs) in advanced METex14 mutated NSCLC patients from the Italian real-world registry ATLAS.1

Methods: Clinical data, treatment efficacy and tolerability were retrospectively collected from patients' medical and electronic healthcare records. Treatment-related adverse events (TRAEs) were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: From July 2020 to February 2025, a total of 185 patients with advanced METex14 NSCLC were included across 45 Italian centers. The median age was 74 years, most patients were female (53.5%), with an Eastern Cooperative Oncology Group performance status < 2 (83.8%). Most patients were current or former smokers (53%) with adenocarcinoma histology (82.7%). 166 (89.7%) received at least one line of systemic anticancer therapy. 130 patients (70.3%) received targeted treatment, 78 (42.2%) were treated with capmatinib and 52 (28.1%) with tepotinib. Among patients treated with MET TKIs, the response rate (RR) was 54.8% in 42 treatment-naïve patients and 40.9% in 88 patients who had received one or more lines of therapy previously. With a median follow-up of 18 months, median progression-free survival (mPFS) was 8.1 months (95% confidence interval [CI] 6.5-9) and median overall survival (mOS) of 13.1 months (95% CI, 9.9-16.2). In patients with measurable brain metastases (17 cases), the intracranial RR was 41.1%. In the cohort of 78 patients treated with capmatinib, the RR was 62.5% among the 24 patients who received capmatinib as first-line therapy and 38.9% among the 54 patients treated with capmatinib in second or further treatment line. mPFS was 7.5 months(95% CI, 5.8-9.2) and mOS was 14.8 months (95% CI, 10.6-19.0). Grade > 3 TRAEs were reported in 16.7% of the patients, including peripheral edema in 10.3%. A fatal adverse reaction occurred in one patient due to pneumonitis. Adverse events led to dose reduction in 30.8% of patients and to permanent discontinuation in 1.3%. In the cohort of 52 patients treated with tepotinib, the RR was 44.4% among the 18 patients who received tepotinib as first line and 44.1% among 34 patients treated with tepotinib in second or later lines. mPFS was 8.7 months (95% CI, 5.5-11.9) and mOS 11.5 months (95% CI, 8.1-14.8). Grade > 3 TRAEs were reported

in 25% of patients, including peripheral edema in 19.2%. A fatal adverse reaction occurred in one patient, also in tepotinib cohort, due to pneumonitis. Adverse events led to dose reduction in 21.2% of patients and to permanent discontinuation in 7.7%.

Conclusions: Conclusion: This updated real-world analysis confirmed the good clinical activity of MET TKIs, particularly in the treatment-naive setting, supporting the implementation of this therapeutic approach in a challenging patient population.1 Reale ML, et al. ESMO Open. 2024 Sep;9(9):103680.

Keywords: MET exon 14 skipping, capmatinib, tepotinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.16 Reduced Survival in Black Patients With EGFR-Mutant NSCLC

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Introduction: Despite improvements in survival for patients with non-small cell lung cancer (NSCLC), disparities persist in outcomes of patients with EGFR-mutant disease. Lack of representation across racial and ethnic groups in clinical trials limits the understanding of treatment effectiveness and safety across populations. This study aims to investigate the impact of race on the efficacy of first-line osimertinib in treating EGFR-mutant NSCLC within two large metropolitan hospitals in the United States.

Methods: In this observational study, data from the electronic medical records of consecutive patients with EGFR-mutant NSCLC from Cedars-Sinai Medical Center (Los Angeles, CA) and Henry Ford Hospital (Detroit, MI) were evaluated. The cohort included patients with metastatic diease at the time of diagnosis who received single-agent osimertinib as first-line therapy. Patient characteristics were compared by race using Fisher's exact test or the Kruskal-Wallis test. Progression-free survival (PFS), time on osimertinib treatment (TOT), and overall survival (OS) were analyzed across racial groups using Kaplan-Meier curves and the log-rank test. Multivariable logistic regression models were applied to assess factors associated with PFS exceeding 18 months.

Results: A total of 337 patients met the inclusion criteria across both sites: 204 (60.5%) White, 71 (21%) Asian, and 62 (18.5%) Black. The groups were balanced for gender and EGFR mutation type. However, Black patients were younger (p<0.01), and Asian patients had lower smoking rates (p<0.001) and higher TP53 co-mutation (p-0.002). The median PFS was significantly lower among Black patients compared to Asian and White patients (p<0.0001), as was the TOT (p<0.0001). OS was also lower in Black patients and highest among Asian patients (p=0.013) (Table 1). In a multivariable logistic regression model assessing PFS>18 months, Asian patients had 16.6 times the odds of remaining progression-free >18 months compared to Black patients (p<0.001), and White patients had 14.5 times the odds (p<0.001).

Conclusions: This study presents survival outcomes in the largest cohort of Black patients with EGFR-mutant NSCLC to date. Black patients exhibited poorer PFS, TOT, and OS compared to Asian and White patients. These findings underscore the urgent need to address inequalities in care to ensure high quality treatment access and outcomes across all racial groups. Further research is necessary to better understand the underlying factors contributing to these results, identify modifiable challenges, and implement targeted interventions to optimize therapeutic strategies in first line treatment to improve outcomes for all patients with EGFR-mutant NSCLC.

Table 1:

	Black (months)	Asian (months)	White (months)	P value
PFS	7.8	21.6	24.2	<0.0001
TOT	13.3	25.3	35.1	<0.0001
OS	31.4	68.4	59.5	0.013

PFS – Progression free survival, TOT – Time on treatment, OS – Overall survival

Keywords: NSCLC, EGFR mutaion, Racial disparities

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.17 A Phase II Study of Firmonertinib Combined With Apatinib as First-Line Therapy in NSCLC Patients With EGFR Uncommon Mutations

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Introduction: Firmonertinib is an oral, highly CNS-penetrant epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). Although afatinib or osimertinib as preferred first-line therapy options have been recommended for the treatment of non-small cell lung cancer (NSCLC) with EGFR uncommon mutations, patients' therapeutic demands are far from being met. The purpose of this study is to investigate the efficacy and safety of the combination of firmonertinib and apatinib as firs-line therapy for metastatic NSCLC with EGFR uncommon mutations.

Methods: Metastatic NSCLC patients with EGFR uncommon mutations received oral firmonertinib 80 mg plus apatinib 250 mg once daily until disease progression, intolerable toxicity, or death. The primary endpoint was the investigator-assessed objective response rate (ORR).

Results: Between June, 5, 2023 and April, 1, 2025, 18 patients were enrolled. 8 (44.4%) presented brain metastases, and 8 (44.4%) had ECOG scores of 1 or 2. EGFR uncommon mutations included EGFR 18 exon G719X (12/18,66.7%), followed by EGFR 21 exon L861Q (4/18,22.2%) and EGFR 20 exon S768I (2/18,11.1%). As of April, 1, 2025, the median follow-up was 8.2 (range, 2.2-22.2) months. The investigator-assessed ORR was 61.1% (11/18), and the disease control rate (DCR) was 100% (18/18). The median progression-free survival (PFS) was 13.5 (95% CI, 8.7 to 18.3) months, and overall survival was not reached. The most frequent grade 1 or 2 treatment-related adverse events included rash (29.4%), oral ulcers (17.6%) and diarrhea (11.7%), with one patient presenting with a grade 3 rash. No treatment-related deaths were reported.

Conclusions: Firmonertinib combined with apatinib demonstrated promising antitumor activity and a manageable safety profile for metastatic non-small cell lung cancer with EGFR uncommon mutations.

Keywords: NSCLC, EGFR uncommon mutations

P3.12.18 Vebreltinib Plus EGFR-TKI in EGFR-Mutated NSCLC With MET Amplification And/Or Overexpression After Failure on EGFR-TKI: A Retrospective Study

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Introduction: Combination therapy with MET inhibitors and EGFR tyrosine kinase inhibitors (EGFR-TKIs) can overcome acquired MET-mediated resistance to EGFR-TKIs. Vebreltinib is a potent and highly selective c-MET inhibitor. This retrospective study investigates the efficacy and safety of the combination of Vebreltinib and EGFR-TKI, and explores criteria to identify patients most likely to respond.

Methods: Between November 2023 and January 2025 in our center, we reviewed data from patients(pts) with EGFR-mutant NSCLC and MET driven who had received Vebreltinib plus EGFR-TKI combination therapy. Eligibility criteria included advanced NSCLC, initial treatment with EGFR-TKI, MET overexpression was detected by IHC (3+ in ≥50% of tumor cells [IHC50+]) or MET amplification was detected by NGS(regardless of copy number value). The primary endpoint was objective response rate (ORR), secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and safety profile.

Results: As of the data cut-off (March 20, 2025), a total of 26 patients were retrospectively enrolled and evaluated. Median age 56 years; 62% female; 23% brain metastases. Regarding treatment, 100% pts received third-generation EGFR-TKI as first-line (1L) treatment,58% received dual-target therapy in the 3L-7L treatment, while 42% received it as 2L treatment. The most common dual-target regimen was Furmonertinib plus Vebreltinib (54%), followed by Osimertinib plus Vebreltinib (31%) at study entry. The ORR was 50.0 % (95%CI, 32.0,68.0). The DCR was 92.3% (95%CI, 75.9,97.9). The median PFS was 6.2 months (95%CI, 4.7,8.0). The efficacy was particularly impressive in the MET amplified population. The ORR was 57.1 % (95%CI, 32.6,78.6). The DCR was 92.9% (95%CI, 68.5,98.7). The median PFS was 8.3 months (95%CI, 5.3,11.0)(Table). Overall, treatment was well tolerated and no severe adverse reactions (SAEs) were observed.

Conclusions: Vebreltinib combined with EGFR-TKI is a promising treatment for EGFR-mutated advanced NSCLC pts with MET amplification and/or overexpression after EGFR-TKI failure, especially in MET-amplified pts. In our study, pts were eligible if MET gene amplification was detected by NGS, without a threshold limit. The manageable adverse events further support its use in clinical practice.

Table

	All Pts; MET IHC 3+/≥50% or MET amplification by NGS	Pts with MET amplification by NGS
Endpoint	Tatal(N=26)	Tatal(N=14)
ORR,%(95%CI)	50.0 % (95%CI, 32.0，68.0)	57.1 % (95%CI, 32.6，78.6)
DCR,%(95%CI)	92.3% (95%CI, 75.9，97.9)	92.9% (95%CI, 68.5，98.7)
Median PFS, months(95%CI)	6.2 months (95%CI, 4.7，8.0)	8.3 months (95%CI, 5.3，11.0)

CI, confidence interval; IHC, immunohistochemistry; NGS, Next-generation sequencing ; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival.

Keywords: MET oversxpression and/or amplification, EGFR-TKI resistance, Vebreltinib

P3.12.19 Optimizing Treatment Sequencing to Maximize Survival in ALK+ Advanced Non-Small Cell Lung Cancer: A Modeling Study

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Introduction: The European Society for Medical Oncology and National Comprehensive Cancer Network 2024 guidelines recommend either alectinib, brigatinib or lorlatinib anaplastic lymphoma kinase inhibitors (ALKis) as first-line (1L) treatment options for ALK-positive advanced non-small-cell lung cancer (aNSCLC). Second-line (2L) recommendations include lorlatinib or chemotherapy. Additional ALKis, such as NVL-655 is under investigation. Currently there are no head-to-head comparisons to aid in selection of different sequences of ALKis. Moreover, real-world evidence comparing observed treatment sequences has not had sufficient follow-up time to interpret findings. This study uses modeling methods to identify the longest likely progression-free survival (PFS) and overall survival (OS) across sequencing strategies for recommended ALKis.

Methods: Disease state models were informed from clinical trials of recommended therapies for ALK+ aNSCLC by line of therapy (LoT). Parametric survival curves for PFS and OS were fit to published Kaplan-Meier curves. Patients experiencing disease progression on a treatment were assumed to initiate the next treatment in the sequence, up to 2 ALKis then chemotherapy. An area under the curve (AUC) approach was used to account the long "tails" of observed PFS to estimate cumulative progression-free life years across all LoTs.

Results: 1L lorlatinib sequences yielded the longest PFS overall, with ~5 years of additional PFS vs 1L therapy with alectinib or brigatinib (Table and Figure). Results were sensitive to assumptions around long-term extrapolation of PFS. An important limitation is that due to the prolonged PFS observed for patients treated with 1L lorlatinib, minimal information is available to characterize PFS on 2L therapy. OS analyses are ongoing.

Conclusions: Based on current evidence and modeling assumptions, initial treatment with 1L lorlatinib may yield the longest PFS vs 2nd gen TKIs, regardless of types of subsequent treatments. This highlights the importance of initiation of 1L treatment with the longest demonstrated PFS upfront.

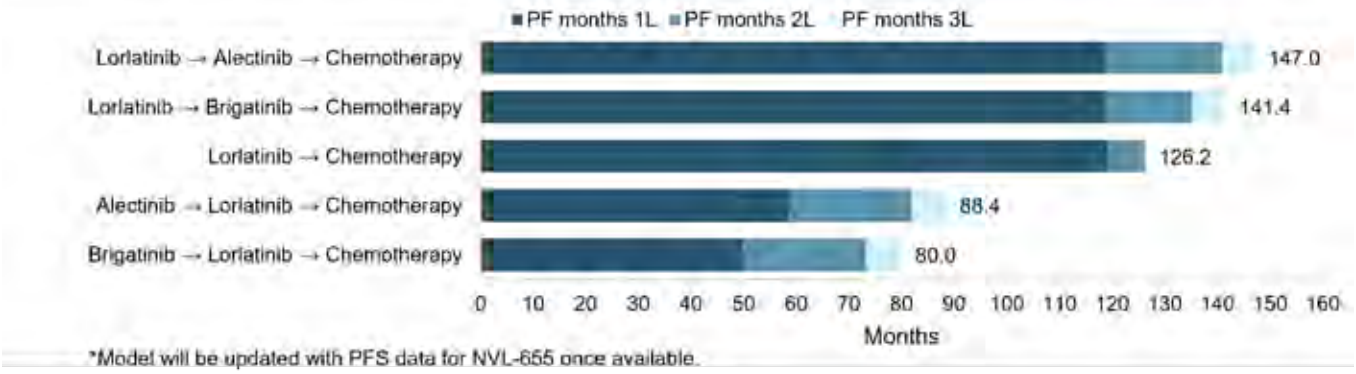
Comparison of Sequences*

Sequence	1L Median PFS, Months (Source)	2L Median PFS, Months (Source)	3L Median PFS, Months (Source)	Cumulative Progression-Free Years Across LoTs Based on AUC Approach
Lorlatinib → alectinib → chemotherapy	93.6 (CROWN)	10.9 (ALUR)	4.3 (Lin 2020)	12.3 years
Lorlatinib → brigatinib → chemotherapy		12.9 (ALTA)		11.8 years
Lorlatinib → chemotherapy		4.3 (Lin 2020)	N/A	10.5 years
Alectinib → lorlatinib → chemotherapy	34.8 (ALEX)	12.2 (NCT01970865 [1027 Study] EXP2-3A)	4.3 (Lin 2020)	7.4 years
Brigatinib → lorlatinib → chemotherapy	30.8 (ALTA-1L)			6.7 years

†Model will be updated with PFS data for NVL-655 once available.

*Median estimated based on extrapolation of PFS curve fitted to patient-level data, as median PFS for lorlatinib had not yet been met at time of analysis.

PFS Months (Estimated Based on AUC Approach) Across LoTs*



*Model will be updated with PFS data for NVL-655 once available.

Keywords: lorlatinib, ALK+ aNSCLC, sequencing

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.20 VAF of EGFR Mutations in Relation to Early Tumor Shrinkage or Deepness of Response During Osimertinib in NSCLC Patients

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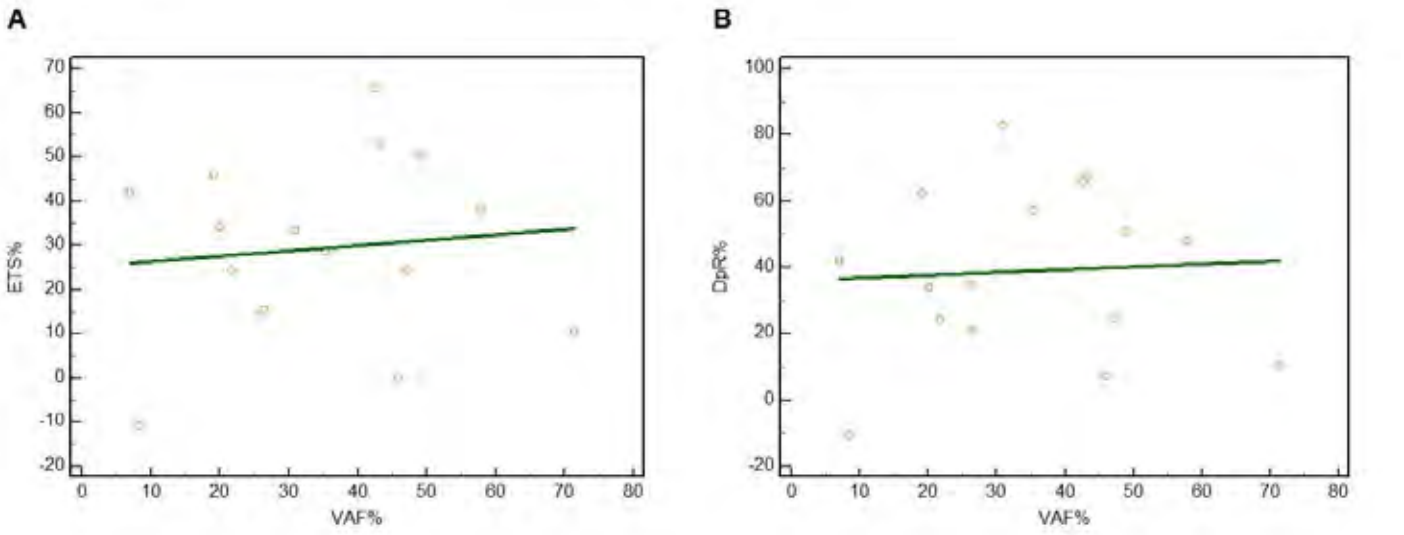
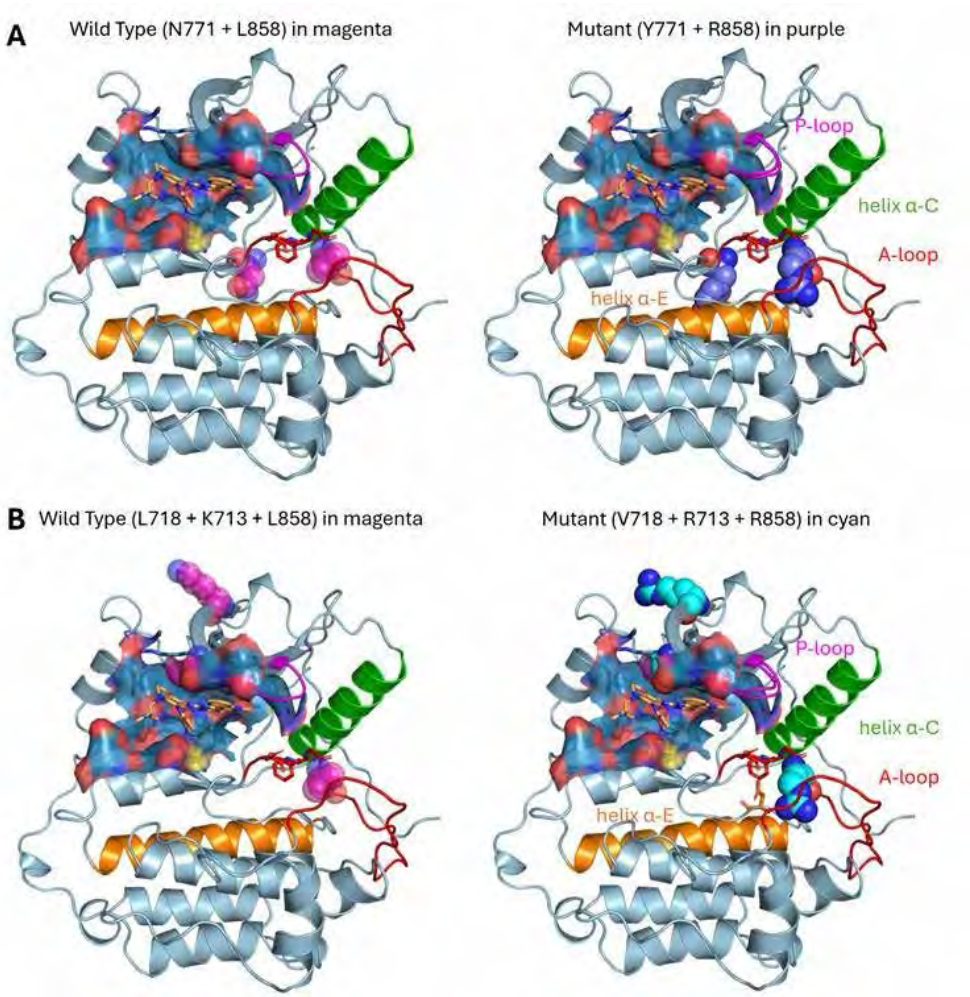
Introduction: This study investigates the impact of variant allele frequency (VAF) of EGFR mutations on osimertinib effectiveness in mNSCLC. Despite NGS provides extensive genomic data, VAF is poorly used in clinical practice. This research explores the relationship between VAF and ETS or DpR.

Methods: We retrospectively analyzed mNSCLC patients treated with an EGFR-TKI; VAF was determined by NGS. The primary goal was to explore the relationship between VAF and ETS or DpR, according to RECIST-1.1 criteria. Secondary objectives included assessing associations between VAF and best tumor response (BTR), progression-free survival (PFS), and overall survival (OS). Molecular modeling was performed for compound uncommon mutations, never described before in literature. Statistical analyses included Spearman correlation, chi-squared test, and log-rank test.

Results: Sixteen patients were included. No significant correlation between VAF and ETS (r = 0.11, p = 0.69) (Figure 1A) or DpR (r = 0.06, p = 0.83) (Figure 1B) were found. A VAF percentage equal to or greater than the median (33%) showed a trend toward longer median PFS (29 months vs. 9 months; HR: 0.55, p = 0.42) and OS (36 months vs. 26 months; HR: 0.29, p = 0.11), though not statistically significant. We found undescribed compound uncommon EGFR mutations: N771Y + L858R and L718V + K713R + L858R. These mutations do not prevent osimertinib binding and function, as suggested by molecular modeling (Figure 2).

Conclusions: VAF of EGFR mutations does not significantly influence tumor size reduction (ETS/DpR) in osimertinib-treated patients. Higher VAF showed a not statistically significant trend toward improved PFS and OS.





Keywords: EGFR, variant allele frequency, osimertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.21 Biomarker Analysis and Final Efficacy of Lorlatinib in Patients With ALK-Positive Advanced Non-Small Cell Lung Cancer

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Introduction: Lorlatinib is a brain-penetrant, third-generation anaplastic lymphoma kinase (ALK) and ROS1 tyrosine kinase inhibitor (TKI) approved for patients with ALK-positive advanced non-small cell lung cancer (NSCLC) in the first line as well as in those previously treated with a second-generation ALK TKI. In patients treated with lorlatinib after failure of a second-generation ALK TKI, ALK mutations were identified as a potential marker of response. To identify other correlates, we evaluated ALK fusion subtypes and comutations to predict clinical outcomes with lorlatinib and identify potential resistance mechanisms.

Methods: Plasma samples were prospectively collected at baseline and end of treatment from patients enrolled in the following expansion cohorts (EXPs) in the global phase 2 study (NCT01970865): EXP1 (treatment naive), EXP2-3A (prior crizotinib ± chemotherapy), and EXP3B-5 (≥1 prior ALK TKI ± chemotherapy). Circulating tumor DNA (ctDNA) was analyzed using Guardant360. ALK fusion subtypes and mutation and TP53 mutation status were correlated with clinical outcomes. Tumor tissue samples collected at baseline were also analyzed by next-generation sequencing.

Results: Thirty patients were enrolled in EXP1, 59 in EXP2-3A, and 139 in EXP3B-5. Baseline ctDNA samples were available for 28 patients in EXP1, 55 in EXP2-3A, and 129 in EXP3B-5. In EXP2-3A cohort, patients with short EML4-ALK fusion variant 3 (v3) had shorter overall survival (OS) or lower survival probability at 72 months than those with long variants (v1 and v2), while similar OS benefit was observed regardless of the variant type in EXP1 and EXP3B-5 (Table). Presence of TP53 mutation led to shorter OS or lower survival probability at 72 months in EXP1, EXP2-3A, and EXP3B-5 cohorts. Confirmation of these results in tumor tissue is ongoing. In patients with matched paired ctDNA samples, none had acquired ALK single or compound mutations in EXP1; however, these mutations were detected in patients in EXP2-3A and EXP3B-5 cohorts.

Conclusions: After a minimum follow-up of 5 years, final analyses from this phase 2 study confirmed substantial activity and prolonged OS with lorlatinib in treatment-naive and previously treated patients with ALK-positive advanced NSCLC, regardless of the ctDNA-based biomarker groups. Resistance mechanisms in treatment-naive patients did not include emergence of ALK mutations, while new single and compound mutations emerged in a small number of patients who previously received an ALK TKI.

Survival probability at 72 months and median OS by ctDNA-based molecular biomarker subgroups

Biomarker subgroup	EXP1 (n=28)		EXP2-3A (n=55)		EXP3B-5 (n=129)	
	n	Probability (%) or median OS (months) (95% CI)	n	Probability (%) or median OS (months) (95% CI)	n	Probability (%) or median OS (months) (95% CI)
***EML4-ALK* fusion variant type**						
v1 and v2	8	58.3 (18.0–84.4) mOS: NE (30.7–NE)	10	50.0 (18.4–75.3) mOS: NE (37.1–NE)	29	NE (NE–NE) mOS: 14.7 (6.5–20.4)
v3	3	100.0 (100.0–100.0) mOS: NE (NE–NE)	9	26.7 (4.1–57.9) mOS: 28.1 (12.1–NE)	23	NE (NE–NE) mOS: 14.4 (8.0–18.0)
***TP53* status**						
Detected	10	50.0 (18.4–75.3) mOS: NE (22.8–NE)	19	43.5 (20.3–64.8) mOS: 45.2 (12.1–NE)	44	NE (NE–NE) mOS: 15.1 (8.6–19.2)
Not detected	15	79.4 (48.8–92.9) mOS: NE (NE–NE)	28	64.3 (42.8–79.6) mOS: NE (52.5–NE)	59	28.7 (17.2–41.2) mOS: 22.7 (14.8–41.4)

Summary of resistance mechanisms (ctDNA-based paired baseline and end-of-treatment samples)

	EXP1 (n=8)	EXP2-3A (n=17)	EXP3B-5 (n=64)
Resistance mechanisms at EOT, n (%)			
New single *ALK* mutation	0	1 (5.9)	1 (1.6)
ALK compound mutation	0	1 (5.9)	4 (6.3)
Bypass mechanism, n (%)			
MAPK pathway aberration	0	0	1 (1.6)
PI3K/MTOR/PTEN pathway aberration	0	0	2 (3.1)
RTK pathway aberration	0	0	5 (7.8)
Cell cycle pathway aberration	0	0	2 (3.1)
Other gene aberration, n (%)	2 (25.0)	6 (35.3)	15 (23.4)
Unknown, n (%)	6 (75.0)	10 (58.8)	40 (62.5)

ctDNA, circulating tumor DNA; EOT, end of treatment; EXP, expansion cohort; mOS, median overall survival; NE, not evaluable; OS, overall survival

Keywords: non-small cell lung cancer, biomarker, lorlatinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.22 A Phase II Study of Sunvozertinib Combined With Anlotinib in Treatment-Naïve NSCLC With EGFR Sensitive Mutations and Co-Mutations (WU-KONG32)

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Introduction: EGFR mutations are key drivers in non-small cell lung cancer (NSCLC), but when accompanied by co-mutations such as TP53, the efficacy of EGFR-tyrosine kinase inhibitors (TKIs) is significantly reduced, leading to shorter survival.The molecular mechanism of vascular endothelial growth factor (VEGF) inhibitors combined with EGFR inhibitors in the treatment of NSCLC suggests synergistic anti-tumor effects and drug resistance alleviation. Sunvozertinib is a novel EGFR-TKI targeting EGFR-sensitive mutations (e.g., 19del, L858R, T790M), while Anlotinib is a multi-target TKI with anti-angiogenic effects. This combination may enhance efficacy in NSCLC patients with EGFR mutations and co-mutations.

Methods: This phase II, single-arm, open-label study evaluated Sunvozertinib (300 mg or 200 mg once daily) plus Anlotinib (8 mg once daily, days 1-14 of a 21-day cycle) in treatment-naïve patients with advanced NSCLC harboring EGFR-sensitive mutations (19del, L858R, T790M) and co-mutations (e.g., TP53, CTNNB1,PIK3CA). In the safety un-in phase, the first 10 patients received 300 mg of Sunvozertinib to observe dose-limiting toxicities (DLTs). If more than 3 DLTs are observed in these patients, the dose for subsequent patients will be reduced to 200 mg. Treatment continued until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS) per RECIST 1.1. Secondary endpoints included objective response rate (ORR), duration of response (DoR), disease control rate (DCR), overall survival (OS), and safety. Planned enrollment was 52 patients.

Results: Sixteen EGFR-sensitive mutation patients were enrolled and 9 with TP53 mutations. In the safety run-in, 1 DLT (grade 2 interstitial lung disease) occurred among the first 10 patients, leading to 300 mg p.o. daily Sunvozertinib in combination with Anlotinib 8 mg p.o. daily from day 1 to day 14 (21 days per cycle) for subsequent patients. Of 9 evaluable patients, 7 achieved partial response (PR) and 2 had stable disease (SD), yielding an ORR of 77.8% (95% CI: 40.0-97.2) and DCR of 100% (95% CI: 66.4-100). The common (≥30%) TEAEs were diarrhea, rash, and anorexia. Grade ≥3 TEAEs occurred in 5 patients (31.3%), with no discontinuations or treatment related deaths.

Conclusions: Sunvozertinib combined with Anlotinib demonstrated promising efficacy and manageable safety in treatment-naïve NSCLC patients with EGFR mutations and co-mutations. This combination therapy holds promise to meet the unmet clinical needs of this population, offering new regimen for patients and warranting further investigation.

Keywords: EGFR Sensitive Mutations, Co-Mutations, Sunvozertinib+Anlotinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.23 Tepotinib Efficacy in Poor Performance Status and Elderly Patients With MET Exon 14 Skipping NSCLC: A RELA-MET Subanalysis

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Introduction: While the VISION study demonstrated tepotinib's efficacy against MET exon 14 (METex14) skipping non-small cell lung cancer (NSCLC), the data on its clinical effectiveness and safety in subgroups frequently managed outside the clinical trial setting are scarce. Specifically, the utility of tepotinib in patients with poor performance status (PS) and in the elderly population warrants further investigation.

Methods: We conducted a multicenter retrospective study (REAL-MET) using data on patient characteristics and treatment details, including its efficacy and safety, in patients with METex14 skipping NSCLC receiving tepotinib therapy at six Japanese hospitals between August 2020 and December 2024. The analysis focused on evaluating the clinical efficacy and safety of tepotinib in patients in the cohort with a poor PS or advanced age. Poor PS was defined as Eastern Cooperative Oncology Group (ECOG) PS 2 or 3, and advanced age was defined as age ≥ 75 years.

Results: In total, 79 patients were enrolled. Their median age was 75 years (range: 55-90), 53.2% were aged ≥75 years, and 24.1% (n=19; PS 2: n = 14; PS 3: n = 5) had a poor PS. Compared to patients with a good PS (PS 0-1; n=60), those with a poor PS were more often aged < 75 years (57.9% vs 43.3%) and had programmed death ligand-1 ≥ 50% (26.3% vs 50.0%). The characteristics of the elderly patients resembled those of the overall cohort. The median PFS and OS were significantly shorter for patients with poor PS (PFS: 7.6 months [95% CI: 2.5-12.7] vs. 10.8 months [95% CI: 5.6-16.0], hazard ratio [HR]: 2.26, 95% CI: 1.27 to 4.02, P = 0.01; OS: 13.4 months [95% CI: 6.6-20.1] vs. 25.8 months [95% CI: 19.7-31.8], HR: 2.30, 95% CI: 1.13 to 4.70, P = 0.02). Within the poor PS group, the median PFS and OS was 8.5 months [95% CI: 5.6-11.4] and 16.4 months [95% CI: 11.8-21.0] for patients with PS 2, respectively. The outcomes were notably poor for patients with PS 3 (PFS: 1.8 months [95% CI: 0.01-3.5]; OS: 3.2 months [95% CI: 0.0-7.8]). After stratification by age, the median PFS and OS were shorter for elderly (≥ 75 years) patients than for younger (< 75 years) patients, but the difference was not significant (PFS: 8.1 months [95% CI: 6.9-9.3] vs. 10.4 months [95% CI: 8.0-12.8], HR: 1.14, 95% CI: 0.69 to 1.90, P = 0.6; OS: 16.4 months [95% CI: 14.2-18.5] vs. 25.8 months [95% CI: 18.7-32.8], HR: 1.66, 95% CI: 0.87 to 3.16, P = 0.13) Among patients with a poor PS (n=19), treatment discontinuation was mainly due to progressive disease (57.9%), adverse events (21.1%), and PS deterioration (10.5%). The frequency of adverse events was comparable across PS and age groups.

Conclusions: This real-world analysis included a substantial cohort of elderly (53.2%) patients and those with a poor PS (24.1%). While age had minimal impact, poor PS significantly limited the efficacy of tepotinib. Nonetheless, the discernible benefit to patients with PS 2 supports the use of this drug for this subgroup.

Keywords: Tepotinib, MET exon 14 Skipping, non-small cell lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.24 Real-World Treatment of Osimertinib Monotherapy Versus Combination Therapy in Stage IV Non-Small Cell Lung Cancer Patients

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Introduction: In February 2024, the Food and Drug Administration approved osimertinib in combination with chemotherapy given the results of the FLAURA-2 trial showing a progression-free survival benefit. We evaluated stage IV non-small cell lung cancer (NSCLC) pts who received osimertinib in the real world, and what clinical and demographic factors may impact the choice of osimertinib monotherapy (osi-mono) versus osimertinib plus chemotherapy (osi+chemo).

Methods: Using the Integra Connect PrecisionQ's de-identified database, pts were identified with an ICD-10 diagnosis of C34, age >=18, who were stage IV and started first treatment on or after February 19, 2024 to December 31, 2024, with osi-mono or osi+chemo. Pts were assessed as to whether age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, provider volume based on attributed NSCLC pts, stage, treatment with radiation, or brain/central nervous system (CNS) metastases (mets) may have impacted treatment with monotherapy versus combination therapy. Descriptive statistics were used for proportions and chi-squared analyses to assess for significance.

Results: A total of 235 pts were identified for the analysis, median age 71 (IQR 62 - 79), 67% were female. Among 235 pts, the use of osi+chemo was 29%. In Q1 2024, the use of osi+chemo was 21% (N = 28) to a high of 37% in Q2 2024 (N = 71) that decreased to 18% (N = 65) in Q4 2024. There were no differences in treatment by gender with 29% of both male and female pts receiving osi+chemo. Osi+chemo was higher in pts <65 years of age at 42% (N = 71) compared to pts >=65 at 23% (N = 164) (p <0.01). Osi+chemo by ECOG performance status was as follows: 0 at 33% (N = 87), 1 at 30% (N = 83), >=2 at 23% (N = 39). Osi+chemo by race was as follows: White at 23% (N = 110), Black/African American at 24% (N = 21), Asian at 17% (N = 12), and all other at 38% (N = 92). Based on stage, use of osi+chemo was 20% in Stage IVA (N = 94) and 34% in stage IVB (N = 127) (P <0.05). Among pts with CNS/Brain mets the use of osi+chemo was 37% (N = 38). Among pts who receive radiation therapy the use of osi+chemo was 32% (N = 34). For physicians who had <200 NSCLC attributed pts, the use of osi+chemo was 24% (N = 94) vs. 31% (N = 141) for those who had treated >=200 attributed NSCLC pts.

Conclusions: Since the approval of FLAURA-2, real-world data suggests that among pts who received osimertinib, only 29% of pts are being treated with osi+chemo. The data also suggest pts who are younger and have a more advanced stage are more likely to receive osi+chemo compared to the osi-mono and other factors such as race, gender, performance status, and provider volume of pts managed with NSCLC did not seem to play as much of a factor.

Keywords: Targeted Therapy Utilization, Stage IV, Osimertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.25 First-Line HLX07 Plus Serplulimab With or Without Chemotherapy in Squamous Non-Small Cell Lung Cancer: A Phase 2 Study

Y. Wu[1], Z. Wang[1], X. Dong[2], J. Li[3], L. Wu[4], L. Han[5], X. Li[6], A. Zang[7], W. Li[8], G. Wen[9], W. Lin[10], X. Hu[11], F. Yang[11], H. Yu[11], J. Li[11], Q. Wang[11], J. Zhu[11]
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Introduction: This was a randomized, multicenter phase 2 study comparing the efficacy and safety of HLX07, a novel humanized anti-EGFR antibody, plus serplulimab (anti-PD-1 antibody) ± chemo versus serplulimab plus chemo as first-line option for advanced sqNSCLC.

Methods: This study consisted of 4 parts that assessed varied combinations of HLX07 (at different doses), serplulimab, and chemotherapy. Part 3 evaluated the preliminary efficacy of the three-drug combination and is presented below. Patients with stage IIIB/IIIC or IV sqNSCLC that was not amenable to surgery or radiation therapy and high tumor expression of epidermal growth factor receptor (H score≥150) and no prior systemic therapy were randomized 1:1 to receive intravenous HLX07 at 800 mg (group A) or 1000 mg (group B), in combination with serplulimab (300 mg) and chemotherapy (carboplatin and nab-paclitaxel), once every three weeks. The primary endpoints were the independent radiological review committee (IRRC)-assessed objective response rate (ORR) and progression-free survival (PFS) per RECIST 1.1.

Results: As of 05 March 2025, 27 patients were enrolled and randomly assigned to group A (n=13) and group B (n=14) in part 3. 15 (55.6%) patients had metastatic disease. With a median follow-up of 18.6 months (95% CI 17.2-23.4), IRRC-assessed confirmed ORR per RECIST 1.1 was 69.2% (95% CI 38.6-90.9) in group A and 71.4% (95% CI 41.9-91.6) in group B. Disease control rate was 92.3% (95% CI 64.0-99.8), and 100% (95% CI 76.8-100.0), respectively. Median PFS was not reached (95% CI 4.1-not evaluable [NE]) in group A and 17.4 months (95% CI 8.1-NE) in group B. The median overall survival and duration of response were still not reached in either group. All the patients in both groups reported treatment-emergent adverse events (TEAEs); most common TEAEs of any grade included neutrophil count decreased (92.3% vs. 71.4%), white blood cell count decreased (84.6% vs. 85.7%), anemia (84.6% vs. 78.6%), platelet count decreased (76.9% vs. 71.4%), hypokalemia (53.8% vs. 64.3%), rash (46.2% vs. 57.1%), alopecia (46.2% vs. 50.0%) and hypocalcemia (53.8% vs. 50.0%). 6 (46.2%) patients, and 8 (57.1%) in group A, and B reported immune-related adverse events, respectively.

Conclusions: First-line HLX07 plus serplulimab and chemotherapy showed promising preliminary efficacy with a manageable safety profile in patients with advanced sqNSCLC which warrants further investigation.

Keywords: squamous NSCLC, HLX07, serplulimab

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.26 Adding Gefitinib to Target Acquired C797S Mutation After Progression on First-Line Osimertinib in EGFR-Mutant Advanced NSCLC

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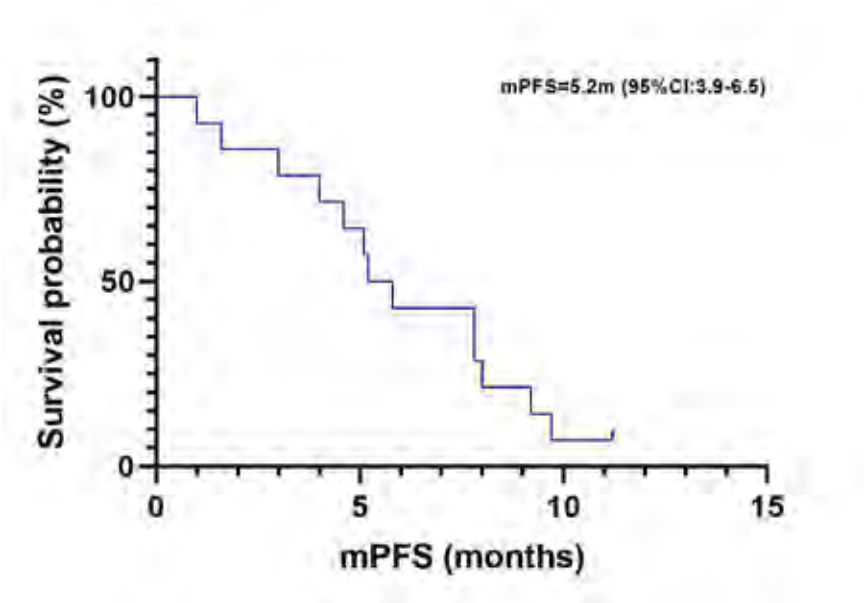
Introduction: Acquired epidermal growth factor receptor (EGFR) C797S mutation accounts for approximately 7% of resistance mechanism after first-line osimertinib. Few data reported that the first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) showed efficacy in overcoming such resistance. This study aims to investigate the efficacy of gefitinib for non-small-cell lung cancer (NSCLC) patients with acquired C797S mutation after first-line osimertinib.

Methods: Totally 14 patients with acquired C797S mutation were included in the study. A retrospective review of medical records was performed in Guangdong Provincial People's Hospital to analyze EGFR-mutant advanced NSCLC patients who developed acquired C797S mutation after first-line osimertinib. Objective response rate (ORR) and progression-free survival (PFS) were assessed. Clinical characteristics and adverse events (AEs) were documented. Next-generation sequencing (NGS) was performed upon progression to gefitinib plus osimertinib.

Results: Up to Jan 10, 2025, 13 (92.9%, 13/14) patients had progressed or died, and one (7.1%, 1/14) patient was still on treatment. Following gefitinib plus osimertinib/savolitinib therapy, the ORR and disease control rate (DCR) was 42.9% and 78.6%. The median PFS was 5.2 months (95% CI: 3.9-6.5) . One patient with cellular mesenchymal-epithelial transition factor (c-MET) amplification and EGFR C797S subsequently received gefitinib plus savolitinib and the other 13 patients received gefitinib plus osimertinib. One patient stopped osimertinib due to Grade 2 diarrhea(CTCAE 5.0). Other patients did not discontinue the treatment due to serious AEs, and all other AEs observed were mild and manageable. Resistance mechanisms of the gefitinib plus osimertinib have been analyzed in 5 patients, including T790M/C797S in-cis, EGFR C797S disappearance, no change and new unknown mutations.

Conclusions: Gefitinib therapy may be an optional strategy to overcome resistance of acquired C797S mutation in EGFR-mutant advanced NSCLC treated with first-line osimertinib.



Keywords: EGFR C797S, Targeted therapy, Non-small cell lung cancer

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.27 Resistance Mechanisms of Novel Targeted Therapies to EGFR Exon 20 Insertion Mutation-Positive Non-Small Cell Lung Cancer

B-C. Liao[1], N-J. Chiang[2], C-L. Lai[3], W-Y. Liao[4], S-G. Wu[1], C-J. Yang[5], M-H. Lee[5], I-W. Chong[5], C-I. Shen[2], Y-H. Luo[2], W-H. Hsu[4], C-L. Hsu[4], Y-T. Lin[1], C-F. Hsiao[6], C-C. Ho[4], J-Y. Shih[4], J.C-H. Yang[1]
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Introduction: Amivantamab is the only approved targeted therapy for metastatic EGFR exon 20 insertion mutation-positive (EGFR exon 20+) NSCLC. Many novel oral EGFR inhibitors are under clinical development for this patient population. The resistance mechanisms of these drugs are not known.

Methods: We enrolled patients with metastatic EGFR exon 20+ NSCLC who received amivantamab, mobocertinib or other novel EGFR inhibitors targeted on EGFR exon 20 insertion mutation. We also enrolled patients with tumor harboring EGFR p.A763_Y764insFQEA mutation who received first- or second-generation EGFR tyrosine kinase inhibitors. We collected tissue samples before and after treatment. We conducted comprehensive tissue-based next-generation sequencing (NGS) testing (ACTOnco+).

Results: We enrolled eighteen patients with various types of EGFR exon 20 insertion mutations. Ten (56%) patients had paired tumor tissue samples. Two patients with p.A763_Y764insFQEA who received afatinib therapy developed EGFR T790M as the resistance mechanism. Among 10 patients who received mobocertinib (n = 7), sunvozertinib (n = 2) or furmonertinib (n = 1), baseline EGFR mutations preserved in post-treatment tissue samples in 9 (90%) patients, EGFR amplification was detected in 5 (50%) patients. One patient who received sunvozertinib and another one who received furmonertinib developed MET and MYC amplification, respectively. Two patients who received mobocertinib developed MDM2 and CDK4 amplifications. Three patients received amivantamab monotherapy in this cohort, but NGS analysis did not disclose potentially actionable resistance mechanisms.

Conclusions: EGFR amplification is the most common resistance mechanism of novel EGFR inhibitors targeted on EGFR exon 20 insertion mutation. The resistance mechanisms of amivantamab therapy warrant further study.

Keywords: EGFR exon 20 insertion, resistance mechanism, mobocertinib

P3.12.28 Association of PD-L1 Expression With Clinical Outcome in Advanced NSCLC With ALK Rearrangement

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Introduction: ALK-rearrangement is the second common oncogenic-driver (7-10%) in Thailand. ALK-inhibitors accessibility in Thailand is limited. We conducted this study to evaluate clinical outcomes and the correlation between PD-L1 expression and survival in ALK-rearranged patients.

Methods: Patients with ALK-rearranged advanced-NSCLC, identified by either D5F3-IHC or FISH between January 2019 and October 2024 at Ramathibodi Hospital were enrolled. PD-L1 expression by tumor proportion score was tested using 22C3-IHC. Categorical variables were compared using the chi-square test and Fisher's exact test. Survival analysis was performed using the Cox regression method.

Results: Eighty-seven patients were enrolled, of whom 82 received ALK-inhibitors. Majority of patients were female (57%), non-smokers (47%), had M1b disease (39%), and 16% had intracranial metastases. Sixty-six patients had adequate tissue for PD-L1 testing with positive expression of 77% (51 out of 66). CNS metastases were found in 14 out of 87 patients and majority of them (9 patient) were PD-L1-positive expression. Among the 87 patients, 65 received ALK-inhibitor as first-line (1L) treatment (Crizotinib: 6; Ceritinib: 37; others 2nd/3rd generation ALK-inhibitors: 22), 17 patients received chemotherapy. Sixty percent of patients received only one line of ALK-inhibitor. The overall response rate was 80-85% across all generations of ALK-inhibitors. The 5-year overall survival (OS) rate and progression-free survival (PFS) rates in 87 patients were 52% and 16%. The 5-year PFS rate was extremely high (38.5%) in patients whom taking 2nd/3rd generation ALK-inhibitors as the first-line treatment compared to other types of first-line treatment (Table 1). Univariate analysis showed that de novo metastasis, extra-thoracic metastasis, and PD-L1 positivity tended to be associated with poorer prognosis, although the results were not statistically significant. Patients receiving ALK-inhibitors (65 patients) as first-line treatment had significantly higher PFS compared to those receiving chemotherapy (median PFS: 1.8 VS 0.3 years, HR: 0.24, P < 0.01). The median chemotherapy-free survival was 2.1 years. Patients whom receiving ≥ one line of ALK-inhibitors (17 patients) had significantly longer chemotherapy-free survival (3.8 vs 1.6 year, HR: 0.33, P = 0.001) and tend to have longer OS (5.4 vs 3.1 year, HR: 0.66, P = 0.35), compared to whom received only one ALK-inhibitor (48 patients).

Conclusions: ALK-inhibitors demonstrated a certain benefit in survival outcomes, especially with the use of higher-generation drugs. High PD-L1 co-expression was found in ALK-positive patients and tended to be associated with a poorer prognosis. Treating patients with first-line and with more than one ALK-inhibitor demonstrated the significant longer survival.

First-line treatment	Median PFS (Years)	Hazard ratio	3-years PFS rate (%)	5-years PFS rate (%)
Chemotherapy without pemetrexed	0.3	Ref.	8.3	0
Chemotherapy with pemetrexed	1.35	0.55 (95% CI 0.19, 1.60) *P* = 0.27	0	0
Crizotinib	0.63	0.44 (95% CI 0.26, 1.21) *P* = 0.11	16.7	0
Ceritinib	1.87	0.21 (95% CI 0.10, 0.44) *P* = < 0.01	34.5	0
Others 2nd-3rd generation ALK-TKIs	1.91	0.13 (95% CI 0.05, 0.33) *P* = < 0.01	48.1	38.5

Table 1 : Progression free survival categorized by types of first-line treatment in all patients

P3.12.29 Effectiveness and Treatment Patterns in Patients With First-Line 2G ALK TKI Across the Esme French Real-World Cohort

G. Nicolas[1], S. Eltaief[2], D. Debieuvre[3], Y. Le Guen[4], H.H. Le[5], N. Rifi[6], C. Audigier Valette[7], J. Remon-Masip[8], L. Bosquet[2], C. Chouaid[9], M. Pérol[10]
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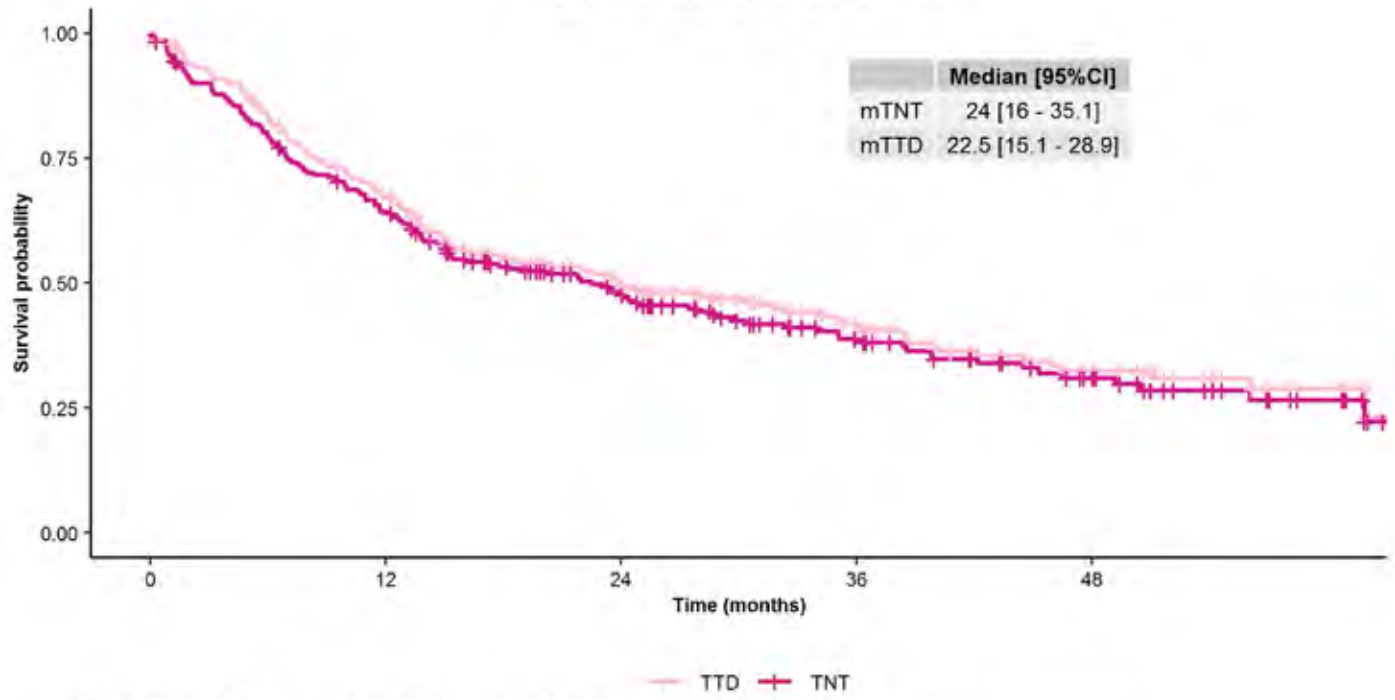
Introduction: The ESMO guidelines recommend alectinib, brigatinib (second-generation [2G]) or lorlatinib (third-generation [3G]) anaplastic lymphoma kinase inhibitors (ALKis) as the preferred first-line (1L) treatments for ALK+ advanced non-small-cell lung cancer (aNSCLC). As around 35% of patients in this population have baseline brain metastases (BM) and additional 20% on 2G ALK tyrosine kinase inhibitors (TKI) will develop new BM within 5 years, intracranial efficacy is also of interest. Since ALK+ aNSCLC is rare, real-world evidence of 1L ALK TKIs are limited. This study aims to describe treatment patterns and real-world outcomes in patients initiated with 1L 2G ALK TKIs for aNSCLC in France.

Methods: This retrospective chart review study utilized the ESME LC Database, encompassing a group of 38 oncology centers in France. The study included adults (aged ≥18 years) with a histologically confirmed diagnosis of ALK+ aNSCLC treated with 2G ALK TKIs in 1L between June 2017 and March 2023, followed until September 2024. The primary outcomes were effectiveness by BM status.

Results: 239 patients who received 1L 2G ALK TKIs were included in this study; 92 (38%) of them had baseline BM. Patients had median age of 63 years (52-73), 46% were male and 82% had ECOG score of 0-1. Most patients (83%) received alectinib in 1L, 12% received brigatinib. With the median follow-up time of 41 months (95%CI 35.3-45.6), treatment discontinuation during 1L was 53.6% (n=128), majority due to progression (73.4%) and 112 patients (47%) went on to receive 2L, with majority (78.6%) receiving ALK TKI. For patients with progression during 1L (n=141), 32 (23%) did not receive 2L. Median time to discontinuation (mTTD) and median time to next treatment (mTNT) were about 2 years (Fig1). mTTD in patients with/without baseline BM were similar, 21.8 [12.9-34.0] vs 22.5 [14.8-35.1] months. Same trend was observed with mTNT, 23.4 [13.9-36.1] vs 25.1 [15.3-38.5] months respectively. Median OS was 55.8 months [44.5-NR], and was 46.1 [32.7-NR] vs 65.1 [46.4-NR] months respectively in patients with/without baseline BM. BM incidence in overall cohort were 7.4% within 1 year, 13.6% within 2 years, 15.1% within 3 years and 18.8% within 4 years from 1L start date among patients who were alive.

Conclusions: Results of this study are consistent with previous results, highlighting the unmet need with 2G ALK TKIs. This supports thoughtful consideration of 1L treatment with the longest systemic and intracranial efficacy upfront to provide the greatest benefit for patients with ALK+ aNCSLC.

Figure 1: TNT and TTD - 2G ALK TKi cohort



TNT is the time from the 1L start date to the start date of subsequent line of therapy (2L)
TTD is the time from the date of initiation of 1L ALK TKI to the stop date of ALK TKI received as per the first-line treatment or date of death wichever occured first.
mTNT and mTTD are proxies of mrwPFS.

Keywords: Tyrosine kinase inhibitors, Real-world data, Brain metastases

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.30 Histological Transformation as Resistance Mechanism in NSCLC: A Multicenter Study Exploring Clinico-Pathological and Molecular Features

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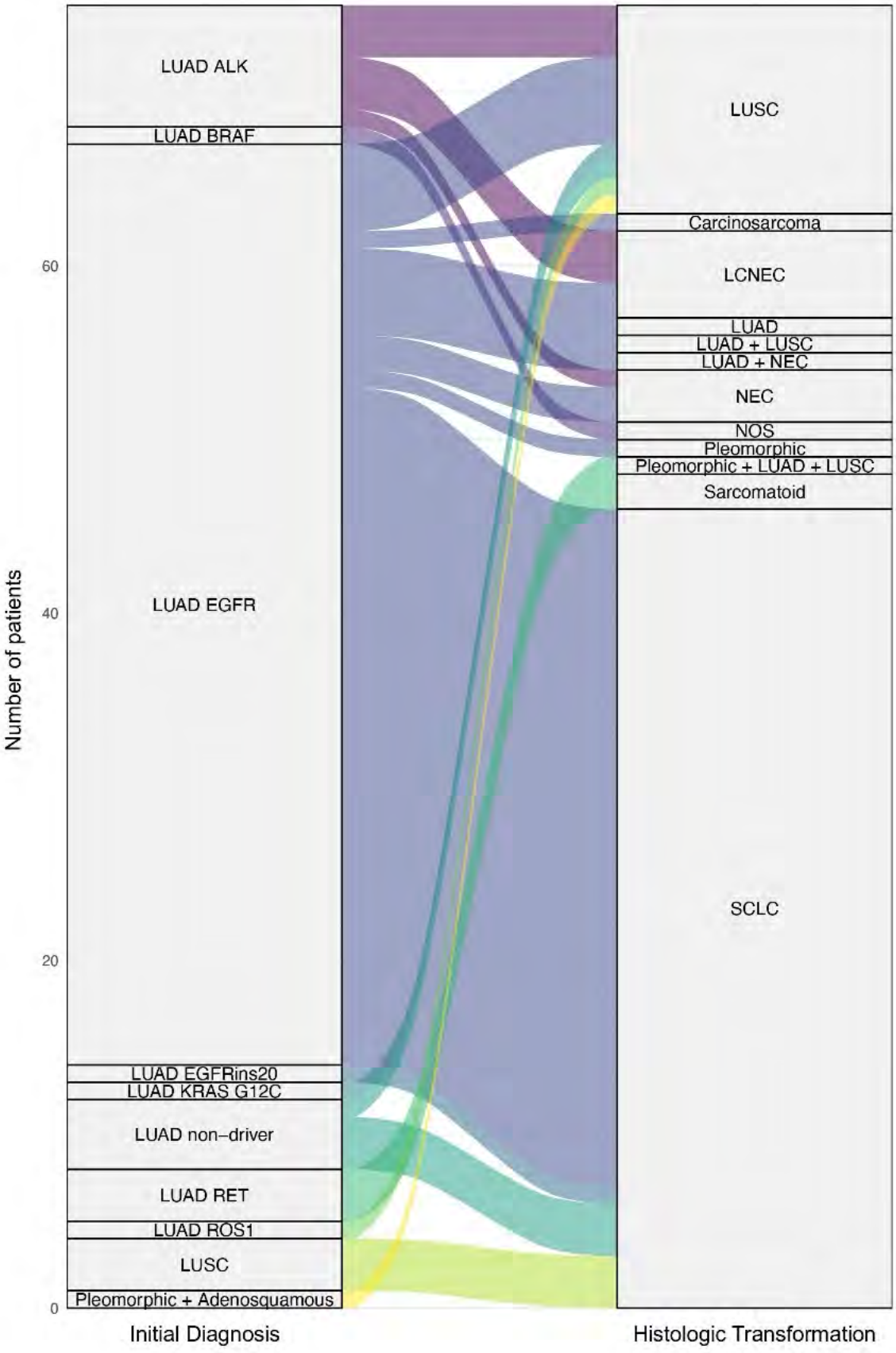
Introduction: Histological transformation (HT) is recognized as a resistance mechanism to systemic therapies in non-small cell lung cancer (NSCLC). However, the clinico-pathological and molecular determinants driving this shift remain poorly characterized.

Methods: We conducted an international, retrospective, multicenter study across 15 European centers. Clinical, pathological, treatment response and molecular data at diagnosis and at the time of HT were collected for patients with proven HT. Here we present the preliminary results based on the clinico-pathological and the available molecular data.

Results: A total of 75 patients were enrolled, with median age 59.5 years (17-88). The majority (69.3%) were women and 54.7% never-smokers. Among former-smokers (26.7%), median time since smoking cessation was 10 years. The majority (82.7%) of patients presented with stage IV disease and 34.7% had central nervous system (CNS) metastases at diagnosis. Molecular profiling revealed: 70.7% of tumors harbored EGFR mutations (EGFRdel19 or EGFRex21), 9.3% ALK rearrangements, and 1.3% each an EGFR ex20ins, a RET/ROS1 translocation or BRAF V600E and KRAS G12C mutation. An actionable genomic alteration lacked in 10.7% of cases.At the time HT was demonstrated, 73.3% of patients were receiving targeted therapy, 8% chemotherapy, 6.7% chemo-immunotherapy, 5.3% immunotherapy, and 2.7% an antibody-drug conjugate. The median number of lines of therapy before HT was 1 (0-6). At HT, 62.7% of tumors had transformed into SCLC, while 16% showed squamous histology. In few cases, we observed a shift towards large cell neuroendocrine carcinoma (8%), sarcomatoid (2.7%), pleomorphic (2.7%), neuroendocrine carcinoma (2.7%), carcinosarcoma (1.3%), and combined histologies (4%). CNS metastases were present in 42.7% of patients after HT. Among patients with available matched NGS (before and after HT, n=30), all retained their original driver mutations. After HT, 14.7% of patients received targeted therapy, while 68% of patients received chemotherapy, either alone (34.7%) or combined (with target therapy 9.3%, with immunotherapy 24%). The median time from diagnosis to HT was 30.8 months (3.0-134.3), while median survival after HT was 10.8 months (0.3-60.1).

Conclusions: This work represents the largest reported cohort of HT, beyond EGFR-mutated NSCLC and SCLC transformations. HT is an underexplored phenomenon that may occur more commonly and more heterogeneously than previously recognized. Further molecular analyses are needed to uncover potential biomarkers that may predict or better characterize this phenomenon.



Keywords: NSCLC, histological transformation, SCLC

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.31 Rezivertinib in Advanced NSCLC Patients With EGFR T790M Mutation via Tissue/Plasma Samples: Pooled Analysis of 2 Clinical Studies

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Introduction: Rezivertinib (BPI-7711) is a novel third-generation EGFR-TKI. During the phase I and phase IIb studies, patients were allowed to detect with tissue or plasma samples for EGFR mutations status at screening. The results revealed that patients with tissue positive sampling at baseline showed higher ORR, DCR and prolonged median PFS over those with plasma EGFR T790M positive sampling, while patients with both positive tissue and plasma EGFR T790M mutation were associated with the worst efficacy. Here we further analyzed the efficacy and safety results of rezivertinib, at the dosage of 180 mg orally once daily, for advanced NSCLC patients with EGFR T790M mutation detected with both tissue and plasma samples at baseline.

Methods: Eligible patients were included from rezivertinib phase I and IIb studies. Patients with EGFR T790M detected in both tissue and plasma samples (at least one positive result) after progressing on first- or second-generation EGFR-TKIs and treated with rezivertinib 180mg once daily were included in full analysis set (FAS). Patients with stable, asymptomatic baseline CNS lesions (measurable/non-measurable) formed the CNS full analysis set (cFAS). Blinded independent central review (BICR) assessed ORR, DCR, PFS, OS, and CNS-PFS.

Results: 89 patients were included in the FAS, while 32 patients in the cFAS. The ORR was 55.0% (95% CI: 34.2-74.2%) and 78.3% (95% CI: 67.2-86.4%) for patients detected with both positive tissue and plasma EGFR T790M sampling (group A) and for patients with only tissue-positive but plasma-negative EGFR T790M sampling (group B). The DCR was 90.0% (95% CI: 69.9-97.2%) and 100.0% (95% CI: 94.7-100.0%) for group A and group B (P=0.0485). The BICR-assessed median PFS was 6.5 (95% CI: 3.8-12.4) months in group A and 16.7 (95% CI: 13.9-27.7) months in group B (hazard ratio [HR]=0.26, 95% CI: 0.13-0.50, P<0.0001; Figure 1). The BICR-assessed median CNS-PFS was 18.3 (95% CI: 1.3-NC) months in group A months versus 16.7 (95% CI: 8.3-NC) months in group B. 84.3% (75/89) patients in the FAS experienced TRAEs.

Conclusions: Rezivertinib demonstrated encouraging systematic and CNS efficacy among EGFR T790M-mutated advanced NSCLC patients detected with both tissue and plasma samples. Patients with tissue-positive but plasma-negative EGFR T790M mutation showed better efficacy than those with both tissue and plasma EGFR T790M positivity. Plasma EGFR T790M positivity at baseline might predict the worse treatment outcome for rezivertinib in this patient population.

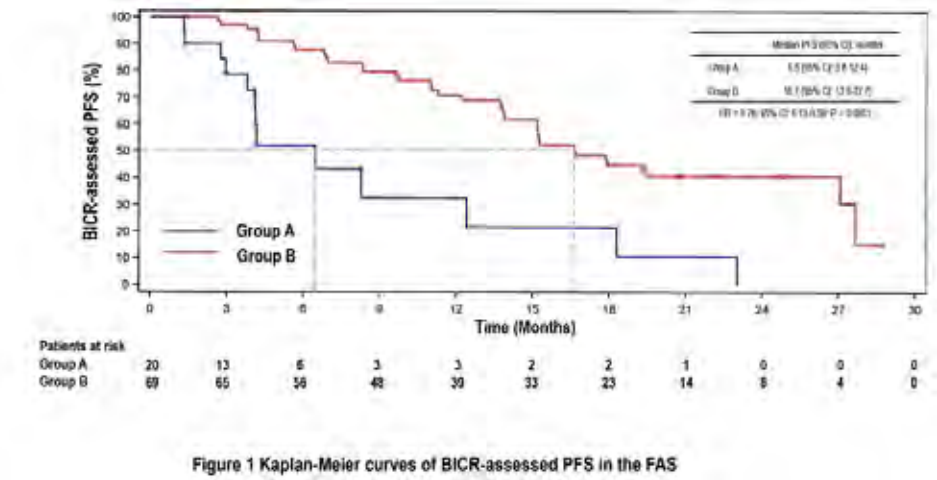

Figure 1 Kaplan-Meier curves of BICR-assessed PFS in the FAS

Keywords: Rezivertinib, EGFR T790M mutation, Plasma

P3.12.32 Long-Term Survival Outcome After First-Line Osimertinib Monotherapy in Advanced/Metastatic NSCLC: Results From LC-SCRUM-Asia

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Introduction: Osimertinib, a 3rd-generation EGFR tyrosine kinase inhibitor, is the common first-line treatment for EGFR-mutated advanced non-small cell lung cancer (NSCLC). However, few real-world studies have investigated long-term survival outcome with osimertinib in Japan. We assessed overall survival (OS) following first-line osimertinib using a large-scale clinico-genomic database of LC-SCRUM-Asia.

Methods: LC-SCRUM-Asia was a real-world patient registry established in Feb 2013 as a nationwide genomic screening project for developing individualized medicine of lung cancer in Japan. It enrolled NSCLC patients with stage II or higher, ECOG<2, with adequate organ functions, without serious complications, and have >3 months life expectancy. This retrospective, observational cohort study included patients who met additional eligibility criteria: i) age≥18 years at enrollment; ii) diagnosed with EGFR-mutated (exon19 deletions or exon21 L858R) advanced/metastatic NSCLC, and iii) initiated first-line osimertinib monotherapy on or after 21-August-2018 (osimertinib approval date in Japan). Index date was first osimertinib initiation date. The latest enrollment date available was 31-March-2022. Patients were followed-up until death, loss to follow-up, or data cut-off. OS and 95% confidence intervals (CIs) were estimated using Kaplan-Meier method. Real-world overall response rate (rwORR) was reported.

Results: A total of 809 patients were included. At enrollment, the median age was 71 years (IQR: 63, 77), 65% were female and 59% having never smoked. ECOG performance status was 0 in 42% of patients, 95% were stage IV, 97% had adenocarcinoma and 52% had exon19 deletions. Baseline metastases were noted in 31% of patients for brain, 11% for liver, and 40% for bone. The median OS following first-line osimertinib was 33.4 months (95% CI: 30.8, 37.3), with a rwORR of 65%. Of 608 patients who discontinued osimertinib, 203 (33%) did not receive subsequent treatments. Among patients who received second-line treatments (n=405), 34% received chemotherapy, 24% received EGFR TKIs, 19% received combination of chemotherapy and immune-oncology agents, and 12% received combination of chemotherapy and VEGF inhibitors. Older age (≥75 years), brain metastases, liver metastases, bone metastases and exon21 L858R were associated with significantly shorter median OS (P<0.01; Table).

Conclusions: First-line osimertinib was found to have a lower median OS (33.4 months) from LC-SCRUM-Asia database, when compared to that reported in pivotal trials (median OS of 38.6 months in FLAURA trial). Majority of patients (86%) had risk factors associated with poor survival. Approximately one-third of patients who discontinued osimertinib did not receive second-line therapy. These results highlight the pressing need to improve outcomes in first-line treatment.

Table Prevalence of risk factors for poor survival

Risk factors	Prevalence (%)	Median OS (95% CI) with vs. without risk factors	P-value*
≥75 years of age	35%	29.2 (26.3, 33.1) vs. 36.8 (31.2, 45.3)	0.0022
Brain metastases	31%	30.1 (27.3, 35.4) vs. 36.9 (31.9, 41.5)	0.0095
Liver metastases	11%	22.4 (18.6, 29.2) vs. 36.2 (32.8, 39.4)	<0.0001
Bone metastases	40%	29.8 (25.9, 33.1) vs. 37.3 (33.4, 42.3)	<0.0001
EGFR exon21 L858R	48%	29.1 (27.2, 33.1) vs. 38.2 (34.0, 46.1)	<0.0001
Patients who had ≥1 risk factors above	86%	31.9 (29.8, 35.4) vs. 46.1 (41.5, NA)	0.0003

*P-values are obtained from the log-rank test.

Keywords: EGFR NSCLC, Survival outcome, First-line treatment

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.33 The Primary Endpoint Analysis of RELAY-Effusion; a Phase II Study of Ramucirumab Plus Erlotinib in EGFR-Mutated NSCLC With Pleural Effusion

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Introduction: The treatment efficacy of patients with EGFR-mutated non-small cell lung cancer (NSCLC) and malignant pleural effusion (MPE) is considered poor. Efficacy of ramucirumab plus erlotinib in EGFR-mutated non-squamous (non-Sq) NSCLC with MPE has not been investigated.

Methods: In this single-arm, phase II study, treatment-naïve, advanced non-Sq, NSCLC patients with EGFR common mutation and MPE were enrolled. Participants were treated with ramucirumab 10 mg/kg, intravenously every 2 weeks plus oral erlotinib (150 mg) until disease progression or unacceptable toxicity. The primary end point was investigator-assessed progression-free survival (PFS). The secondary endpoints were overall response rate (ORR), overall survival (OS), drainage-free survival without thoracic drainage, and safety. Regarding statistical consideration, the threshold and the expected PFS were set as 9 and 14 months, respectively with one-sided $\alpha = 0.2$, and $\beta = 0.2$, the required sample size was 38 cases. A total of 40 cases was planned to take into account the possibility of a few dropped or ineligible cases. This study was funded by Eli Lilly and Trial identification no. is jRCT051210138.

Results: Between Dec 2021 and Dec 2023, 40 patients were enrolled from 15 institutions in Japan. All patients were analyzed for safety and efficacy. Of those, median age was 73 (41-85), male/female: 18/22, never-/smoker/unknown: 21/18/1, ECOG performance status: 0/1/2 8/30/2, stage IVa/IVb: 26/14 and EGFR mutation:19del/L858R 23/17. Baseline brain metastases were 10% of the patients. The median duration of follow-up was 24.2 months (6.5-37.7 months). Median PFS of the primary endpoint was 12.9 months (95% CI, 7.3-17.0 months) and PFS rate at 12 months was 55.0%. Median OS was 33.0 months (95% CI, 28.5-NA months) and OS rate at 12 months was 87.5%. Median drainage-free survival was 31.8 months (95% CI, 22.8-NA months). The ORR and disease control rate were 77.5% (95% CI, 61.5-89.2%) and 85.0% (95% CI, 70.2-94.3%), respectively. Any grade and grade 3-4 adverse events (AEs) occurred in 67.5% and 22.5%, respectively. Most common AEs were dermatitis acneiform (47.5%), anorexia (25.0%), elevated AST (25.0%) and anemia (22.5%). Pneumonitis occurred in 5.0% (grade2, n=2). Grade 3-4 AEs were dermatitis acneiform (7.5%), anorexia (5.0%), hypertension (5.0%) and elevated AST and ALT (5.0%), but no treatment-related death occurred. T790M mutation rate at disease progression was 27.8% (5 of 18 patients).

Conclusions: Median PFS of the primary endpoint was 12.9 months in patients with advanced non-Sq NSCLC harboring EGFR mutation and MPE, and it did not exceed the expected PFS of 14 months. MPE control was favorable. The safety profile of ramucirumab plus erlotinib was consistent with the established profiles of the individual agents for patients with MPE.

Keywords: EGFR mutation, Malignant pleural effusion, Ramucirumab

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.34 Real-World Study in Patients With ALK+ Metastatic Non-Small Cell Lung Cancer (mNSCLC) Treated With First-Line (1L) Lorlatinib

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Introduction: Lorlatinib, a brain-penetrant, third-generation ALK tyrosine kinase inhibitor (TKI), was approved by the FDA for the 1L treatment of ALK+ mNSCLC on March 3, 2021. Evidence for real-world 1L lorlatinib patient and provider experience is limited. We conducted a retrospective pilot study to describe 1L lorlatinib patient and provider characteristics and the real-world starting dose.

Methods: In this multi-site, physician-led chart review, adult patients diagnosed with ALK+ mNSCLC in the US on or after January 1, 2021, and treated with 1L lorlatinib on or after March 3, 2021, were included. Patients who received lorlatinib in a randomized clinical trial (RCT) were excluded. The target sample size was 50, with a maximum of 5 patients recruited per provider. The primary objective was a descriptive assessment of real-world demographics and clinical characteristics of 1L lorlatinib recipients. Data were collected through February 6, 2025.

Results: Fifty patient charts were abstracted by 15 providers. Providers practiced for a median of 17 years and treated a median of 10 patients with ALK+ mNSCLC during the study period. Overall, 12 (80%) practiced in a community setting, 6 (40%) were from the South, 6 (40%) were from the West, and 10 (67%) were from urban settings. Patient characteristics are presented in the Table. The median time between mNSCLC diagnosis and ALK testing date was 2.5 days, and the median time between ALK testing date and 1L lorlatinib initiation was 14 days. Most patients (31 [62%]) initiated 1L lorlatinib in 2024. Overall, 39 (78%) patients had ≥1 comorbidities at treatment initiation, and 20 (40%) had baseline brain metastases. Lorlatinib was initiated at 100 mg in 41 (82%) patients, 75 mg in 8 (16%), and 50 mg in 1 (2%). No patient had a dose increase during a median follow-up period of 7.8 months; 9 (18%) patients had ≥1 dose reduction, and 5 (10%) had ≥1 dose interruption or delay. By the end of follow-up, 41 (82%) patients remained on 1L lorlatinib treatment.

Conclusions: This study characterized the real-world demographics, clinical and provider characteristics, and starting dose in 50 patients with ALK+ mNSCLC treated with 1L lorlatinib. In this pilot study, most patients started lorlatinib at 100 mg, which was the starting dose assessed in the CROWN RCT. A larger real-world study with expanded patient counts and longer-term follow-up is ongoing. A genAI tool (3/05/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility.

Table. Patient demographics and clinical characteristics of 50 1L lorlatinib patients in real-world setting	
Patient demographics	
Female, n (%)	24 (48)
Age at mNSCLC diagnosis, median (Q1, Q3), years	59.4 (54.4, 69.0)
Never smoked, n (%)	28 (56)
Race/ethnicity, n (%)	
White	30 (60)
Asian	8 (16)
Black or African-American	6 (12)
Hispanic or Latino	5 (10)
American Indian or Alaska Native	1 (2)
Employment status, n (%)	
Retired	16 (32)
Full-time employed	14 (28)
On disability	6 (12)
Part-time employed	5 (10)
Unemployed	4 (8)
Short/long-term leave	1 (2)
Unknown	4 (8)
BMI at mNSCLC diagnosis, n (%)	
18.5 to 24.99 kg/m² (normal)	20 (40)
25 to 29.99 kg/m² (overweight)	21 (42)
≥30 kg/m² (obese)	8 (16)
Unknown	1 (2)
Clinical characteristics	
Tissue sample used for *ALK* genetic testing, n (%)	48 (96)
Broad next-generation sequencing used for *ALK* genetic testing, n (%)	45 (90)
Adenocarcinoma histology, n (%)	49 (98)
ECOG performance status 0-1, n (%)	40 (80)
Comorbid conditions,[a] n (%)	
Comorbid hypertension	28 (56)
Hyperlipidemia	10 (20)
Diabetes	7 (14)
Myocardial infarction-history	3 (6)
Psychiatric disorders (anxiety, depression, post-traumatic stress disorder, other)	3 (6)
Renal disease	3 (6)
Cerebrovascular disease	0
Concomitant medications,[a] n (%)	
Antihypertensive medications	24 (48)
Statins	9 (18)
Metformin	6 (12)
Psychotropic medications[b]	4 (8)
Glucose-dependent insulinotropic polypeptide or glucagon-like peptide-1 receptor agonist	0

ALK, anaplastic lymphoma kinase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; mNSCLC, metastatic non-small-cell lung cancer; Q1, first quartile; Q3, third quartile.

[a]Not mutually exclusive.

[b]Antipsychotics, antidepressants, mood stabilizers, anxiolytics, sedatives, antiepileptics.

Keywords: non-small cell lung cancer, real world, lorlatinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.35 Real-World Clinical Outcomes of Osimertinib in Patients With Recurrent EGFR Mutated Lung Adenocarcinoma: A Multicenter Study

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Introduction: The 9th edition of the TNM classification for lung cancer introduced a new subdivision of M1c status into M1c1 (multiple extra-thoracic metastases in a single organ system) and M1c2 (multiple extra-thoracic metastases in multiple organ systems) under the category of stage IVB. This refinement is also reflected in the IASLC staging manual and can more accurately predicts prognosis; however, their clinical implications, especially in relation to the efficacy of molecular targeted therapies, remain unclear. Furthermore, although recurrent lung cancer under the postoperative monitoring can be generally detected with lower tumor burden than those with de novo stage IV, there are no prior studies that have examined whether this distinction influences the clinical efficacy of EGFR-TKIs. To address the therapeutic outcomesbased on the 9th edition of TNM classification, we analyzed that the clinical efficacies of 3rd generation EGFR-TKI,Osimertinib, for patients with recurrent EGFR-mutant lung adenocarcinoma in comparison with those for patients with de novo stage IV in a real-world cohort.

Methods: We retrospectively analyzed clinical data from 275 patients with de novo stage IV or recurrent sensitizing EGFR-mutant lung adenocarcinoma treated with first-line osimertinib from six institutions. Disease stages of de novo stage IV were assigned according to the 9th edition of the TNM classification. Patients with postoperative recurrence were subclassified as follows: r-M1a (recurrence within the thorax), r-M1b (single extra-thoracic metastasis), r-M1c1 (multiple extra-thoracic metastases in a single organ system), and r-M1c2 (multiple extra-thoracic metastases in multiple organ systems) based on recurrence pattern. Progression-free survival (PFS) and overall survival (OS) were compared between these classifications.

Results: Among the 183 patients with de novo stage IV disease, the distribution was as follows: M1a (26.8%), M1b (13.1%), M1c1 (28.4%), and M1c2 (31.7%). In the 92 patients with postoperative recurrence, recurrence patterns were: r-M1a (63.0%), r-M1b (12.0%), r-M1c1 (12.0%), and r-M1c2 (13.0%). Patients with postoperative recurrence had significantly better PFS and OS compared to those with de novo stage IV (PFS: 34.6 vs. 17.9 months, $P < 0.0001$; OS: 53.4 vs. 35.2 months, $P = 0.0030$). In multivariate analysis, recurrence status remained an independent prognostic factor. Furthermore, in the patients with de novo stage IV, patients with M1c2 showed significantly shorter PFS and OS compared to those with M1b and M1c1. A similar trend was observed in the patients with postoperative recurrence, indicating multiple extra-thoracic metastases in multiple organ systems were associated with the poorest outcomes in the cases treated by osimertinib.

Conclusions: Our real-world cohort study demonstrates that postoperative recurrence is associated with more favorable survival compared to de novo stage IV in patients with EGFR-mutant lung adenocarcinoma, who were treated by osimertinib. Moreover, the subclassification of M1c1 and M1c2 in the 9th edition of the TNM classification can reflect clinically meaningful differences in the therapeutic response and prognosis.

Keywords: postoperative recurrence, EGFR-mutated NSCLC, M1c2

P3.12.36 Multicenter Retrospective Study of Selpercatinib Treatment for Advanced or Recurrent RET Fusion-Positive NSCLC in Japan

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Introduction: Based on the results of the LIBRETTO-431 trial, selpercatinib has become the standard first-line treatment for recurrent or advanced non-small cell lung cancer (NSCLC) with RET fusion gene alterations. However, RET fusion-positive recurrent or advanced NSCLC is rare, accounting for only 1-2% of all lung cancers, and real-world data (RWD) on the use of selpercatinib remain extremely limited, particularly in the Japanese population. Therefore, we conducted a multicenter retrospective study to evaluate the efficacy and safety of selpercatinib in patients with recurrent or advanced RET fusion-positive NSCLC.

Methods: This retrospective multicenter study enrolled 27 patients, who were pathologically diagnosed with advanced or recurrent RET fusion-positive NSCLC and started administration of selpercatinib between September 2021 and June 2024.The median follow-up period was 12.0 months (range 0.5-31.5 months). From the perspective of efficacy, we evaluated the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in both previously systemically treated and treatment-naive groups. Additionally, PFS was analyzed based on PD-L1 status, separately in the tumor proportion score (TPS)-high (TPS≥50%) and TPS-low groups. From the perspective of safety, we summarized all reported adverse events of any grade and those of Grade 3 or higher in all 27 cases.

Results: The ORR was 80% (8 of 10 cases) in the previously treated group and 76% (13 of 17 cases) in the treatment-naive group, with no significant difference between the two. The median PFS was not reached (95% confidence interval [CI] 0.5-Not Evaluable [NE]) in the previously treated group and 23.5 months (95% CI 5.7-NE) in the treatment-naive group, no significant difference was observed. Given that a majority of patients have not experienced an event, the median PFS should be interpreted with caution. The median OS was 25.4 months (95% CI 0.5-NE) in the previously treated group and not reached (95% CI NE-NE) in the treatment-naive group, no significant difference was observed. The median PFS was 23.5 months (95% CI 8.0-NE) in the TPS-low group (TPS<50%) and not reached (95% CI 2.9-NE) in the TPS-high group (50%≤TPS), no significant difference was observed. The most frequent Grade3 adverse event (AE) was increased ALT (n=11,41%), followed by increased AST (n=7,26%). Grade 3 hypertension was observed in 5 patients (19%), Grade 3 QT prolongation was observed in 1 patient (4%).

Conclusions: Compared to the LIBRETTO-001 trial, this study showed a trend toward lower ORR and PFS in the treatment-naive group, whereas the previously systemically treated group exhibited a trend toward higher ORR and PFS. Regarding adverse events, this study reported a higher frequency of severe liver dysfunction compared to the LIBRETTO-001 and LIBRETTO-431 trials, while the incidence of hypertension and QT prolongation remained relatively similar. These findings suggest that liver dysfunction may be more severe in the Japanese population, highlighting the need for careful dose management strategies.

Keywords: RET Fusion-Positive NSCLC, Selpercatinib

P3.12.37 First-Line Lazertinib With or Without Local Ablative Radiotherapy in Oligo-Metastatic EGFR-Mutant NSCLC

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Introduction: Lazertinib, a blood-brain barrier penetrant, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has demonstrated significant improvement in progression-free survival (PFS) in treatment-naïve, EGFR-mutant advanced non-small cell lung cancer (NSCLC), as a single-agent or in combination with amivantamab. In this study, we aimed to investigate whether the addition of local ablative therapy (SBRT) to lazertinib would improve PFS in oligo-metastatic, EGFR-mutant NSCLC compared to lazertinib alone (NCT05167851).

Methods: This is a multi-center, randomized, non-comparative, phase II study of patients with oligo-metastatic NSCLC harboring activating EGFR mutations (ex19del or L858R). Synchronous oligo-metastatic disease was defined as metastatic lesion < 5 and involved organs < 3. All lesions were deemed amenable for SBRT at the discretion of radiologist. Patients were stratified by EGFR mutation status (Ex19del vs. L858R), and randomized to receive 240 mg of oral lazertinib monotherapy with or without the addition of SBRT. The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety.

Results: A total of 67 patients (lazertinib monotherapy, n=34; lazertinib plus SBRT, n=33). were enrolled from 4 centers in Republic of Korea between January 2022 and May 2023. At the data cutoff (December, 2024), the median follow-up duration was 23 months (range 20.3-24.0 months). The median PFS were 24.8 months (90% CI, 15.7-NA months) and 34.0 months (90% CI, 26.6-NA months) for lazertinib and lazertinib plus SBRT groups, respectively. In the lazertinib monotherapy group, the median PFS was 24.8 months (90% CI, 14.5-NA) for Ex19del (n=16) and 20.3 months (90% CI, 10.8-25.7 months) for L858R (n=18). In the lazertinib plus SBRT group, the median PFS was not reached (90% CI, 15.7-NA) and 27.6 months (90% CI, 18.2-NA) for Ex19del (n=17) and L858R (n=16), respectively. OS data remain immature with 3 death events at the time of data cutoff. The ORR was similar between both treatment groups (lazertinib, 62%; lazertinib + SBRT, 58%). Sites of progression were mainly the original sites in lazertinib group (n=11/14, 78%) and new sites in lazertinib plus SBRT group (n=12/13, 92%). In terms of toxicity profile, no new safety signals were seen in lazertinib plus SBRT arm, and no grade 3 or higher radiation pneumonitis was seen. There were no grade 4 or 5 adverse events in both arms. Additionally, whole exome sequencing and bulk RNA sequencing analyses using baseline tissue samples and tissues obtained at the time of progression are ongoing to reveal mechanisms of acquired resistance.

Conclusions: In patients with EGFR-mutant, oligo-metastatic NSCLC, the addition of SBRT to lazertinib is a feasible approach, leading to clinically meaningful improvement in terms of PFS, compared to historical data. The addition of SBRT was well-tolerated with previously reported safety profile.

Keywords: EGFR-mutant NSCLC, lazertinib, SBRT

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.38 Updated Clinical Results From FURTHER: A Study of Firmonertinib in TKI-Naive, Advanced NSCLC With EGFR PACC Mutations

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Introduction: Firmonertinib (also known as furmonertinib) is a once-daily oral, highly brain-penetrant EGFR inhibitor with broad activity and selectivity across EGFR mutations. Firmonertinib has FDA breakthrough therapy designation and is being tested in a global, Phase 3 study in first-line (1L) EGFR ex20ins mutant NSCLC. P-loop and αC-helix compressing (PACC) mutations represent approximately 12% of EGFR mutations and are similar to ex20ins mutations in narrowing the drug-binding pocket of ATP competitive EGFR inhibitors. We report updated FURTHER trial clinical and translational results.

Methods: FURTHER (FURMO-002; NCT05364073) is a global, Phase 1b study. Stage 2, Cohort 4 (PACC cohort) enrolled NSCLC patients with EGFR PACC mutations randomized to two dose levels of firmonertinib (160 mg or 240 mg, QD). Key eligibility criteria include documented EGFR PACC mutation, measurable disease per RECIST 1.1, and no prior EGFR TKI. Patients with untreated but clinically stable brain metastases were eligible. Primary endpoint is confirmed ORR per RECIST 1.1 by BICR. Key secondary endpoints include PFS and duration of response (DoR).

Results: Updated efficacy results for 1L NSCLC patients (n=45 patients) with EGFR PACC mutations include ORR by BICR which was 81.8% (18/22; 95% CI, 59.7% - 94.8%) at 240 mg, and 52.2% (12/23; 95% CI, 30.6% - 73.2%) at 160 mg. Confirmed ORR by BICR were 68.2% (15/22; 95% CI, 45.1% - 86.1%) at 240 mg, and 43.5% (10/23; 95% CI, 23.2% - 65.5%) at 160 mg, and median DoR was 14.6 months at 240 mg and not reached (NR) at 160 mg. Median PFS by BICR was 16.0 months (95% CI, 12.5, NR) at 240 mg QD and 11.1 months at 160 mg (95% CI, 6.6, NR) with a hazard ratio of 0.728 (95% CI, 0.305, 1.736) and a median follow-up of 12.5 months for both dose levels. Antitumor activity was observed in both single PACC mutation (confirmed ORR by BICR of 60% [6/10; 95% CI, 26.2% - 87.8%] at 240 mg and 25% [3/12; 95% CI, 5.5% - 57.2%] at 160 mg) and compound PACC mutation (confirmed ORR by BICR of 75% [9/12; 95% CI, 42.8% - 94.5%] at 240 mg and 63.6% [7/11; 95% CI, 30.8% - 89.1%] at 160 mg) subgroups. In patients with brain metastases, CNS confirmed ORR by BICR was 50% (7/14) per modified RECIST. A rapid decrease in EGFR mutation variant frequency in ctDNA was overall consistent with radiographic responses. The adverse event profile was consistent with prior firmonertinib studies with dose reductions due to TRAEs occurring at 22.7% and 12.0% at 240 mg and 160 mg dose levels, respectively. Treatment discontinuation due to TRAE occurred at 0% and 4.0% at the 240 mg and 160 mg dose levels, respectively. Additional updated efficacy and safety data will be presented at the conference.

Conclusions: Updated FURTHER trial results demonstrate promising antitumor activity in 1L EGFR PACC mutant NSCLC patients treated with firmonertinib including prolonged DoR and PFS with a tolerable and manageable safety profile. Further investigation of firmonertinib in this patient population is planned, including future registrational studies.

Keywords: Firmonertinib or furmonertinib, EGFR uncommon mutations, EGFR PACC mutations

P3.12.39 Long-Term Overall Survival in Advanced EGFRm NSCLC Treated With 1L Osimertinib: Results From the US, Japan, Germany and China

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Introduction: Osimertinib is a third-generation, irreversible, central nervous system-active epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that selectively targets EGFR-TKI sensitising and EGFR T790M resistance mutations. It is the global preferred first-line (1L) treatment for advanced EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). We present data on long-term real-world overall survival (rwOS) from a global retrospective cohort, examining outcomes in patients with advanced EGFRm NSCLC who received 1L osimertinib.

Methods: Adults with stage IIIB-IV EGFRm NSCLC who initiated 1L osimertinib between April 2018 and December 2020 were identified through deidentified electronic health records from country-specific registries and hospitals. Participating countries included the US and Japan (via chart reviews), Germany (CRISP registry), and China (China Precision Medicine Registry). Median rwOS estimates were reported for the overall cohort and a subset of patients meeting the FLAURA trial (NCT02296125) inclusion criteria (ECOG 0/1 with EGFR Ex19Del/L858R, with or without other co-occurring EGFR mutations), referred to as the FLAURA-like cohort.

Results: Baseline patient characteristics are summarised in the Table. The median age at treatment initiation ranged from 62 to 71 years. Most patients were female, diagnosed with stage IV adenocarcinoma, and had classical EGFR mutations (Ex19Del or L858R). The proportion of patients with brain metastases at baseline ranged from 37% to 51%. Median follow-up times were 52.6 months in the US, 41.4 months in Japan, 35.1 months in Germany, and 35.5 months in China. Median rwOS in the overall cohort was 34.1 months (95% CI 25.6, 52.1) in the US, 39.7 months (95% CI 31.6, 51.8) in Japan, 30.1 months (95% CI 23.9, 35.8) in Germany, and 36.5 months (95% CI 27.6, NE) in China. For FLAURA-like patients, median rwOS was 37.2 months (95% CI 28.5, NE) in the US, 42.7 months (95% CI 37.8, NE) in Japan, 34.1 months (95% CI 27.0, NE) in Germany, and 36.5 months (95% CI 24.4, NE) in China.

Conclusions: The outcomes for patients in our study were consistent with the OS findings from the FLAURA trial (NCT02296125). Our results support the rwOS benefits of 1L osimertinib monotherapy in patients with EGFRm advanced NSCLC, including those who may not have qualified for the FLAURA trial.

Table 1. Baseline Characteristics

	US (N=88)	Japan (N=141)	Germany (N=222)	China (N=92)
Median age (Q1, Q3), years	70 (61, 77)	71 (65, 76)	69 (58, 77)	62 (54, 68)
Gender, n (%)				
Female	63 (72)	99 (70)	148 (67)	53 (58)
Male	25 (28)	42 (30)	74 (33)	39 (42)
Stage at treatment initiation, n (%)				
IIIB–IIIC	0 (0)	9 (6)	5 (2)	1 (1)
IV	88 (100)	132 (94)	217 (98)	89 (97)
Unknown	0 (0)	0 (0)	0 (0)	2 (2)
History of smoking, n (%)				
Never	50 (57)	85 (60)	105 (47)	69 (75)
Former/current	38 (43)	37 (26)	98 (44)	17 (18)
Unknown	0 (0)	19 (14)	19 (9)	21 (23)
Histology, n (%)				
Adenocarcinoma	82 (93)	127 (90)	214 (96)	84 (91)
Other	6 (7)	14 (10)	8 (4)	6 (7)
Unknown	0 (0)	0 (0)	0 (0)	2 (2)
ECOG score at treatment initiation, n (%)				
0	28 (32)	55 (39)	69 (31)	0 (0)
1	30 (34)	59 (42)	92 (41)	50 (54)
≥2	12 (14)	18 (13)	30 (14)	21 (23)
Unknown	18 (20)	9 (6)	31 (14)	21 (23)
EGFRm subtype, n (%)				
Ex19Del/L858R	71 (80)	136 (97)	162 (73)	71 (77)
Uncommon	9 (10)	5 (3)	27 (12)	19 (22)
Unknown	8 (10)	0 (0)	33 (15)	2 (1)
Site of metastases, n (%)				
Brain/CNS	35 (40)	53 (37)	82 (37)	47 (51)
Bone	31 (35)	53 (37)	105 (47)	62 (67)
Liver	3 (3)	10 (7)	37 (17)	11 (12)
Median follow-up time (Q1, Q3), months	53 (44, 56)	41 (29, 55)	35 (33, 41)	36 (23, 43)

Keywords: Real-world, EGFR mutations, Osimertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.40 Safety and Patient-Reported Outcomes With Tepotinib in Patients With METex14 Skipping NSCLC: =3-Years Follow-Up of VISION

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Introduction: Patients with non-small cell lung cancer (NSCLC) harboring MET exon 14 (METex14) skipping are typically elderly with a poor prognosis, and therefore treatments with a manageable safety profile are especially relevant. Tepotinib is an oral, once-daily, and highly selective MET-tyrosine kinase inhibitor (TKI), approved in multiple countries for the treatment of advanced/metastatic NSCLC with METex14 skipping based on the outcomes from the VISION study. Safety outcomes and health-related quality of life (HRQoL) patient-reported outcomes (PROs) of tepotinib in VISION have previously been reported from earlier data cuts (safety: data cut-off: July 1, 2020 [Clin Lung Cancer 2022;23(4):320-332]; HRQoL PROs: data cut-off: February 20, 2022 [Poster 9060 presented at ASCO 2023]). Here, we report long-term safety outcomes and HRQoL PROs from VISION in patients with ≥3-years follow-up (data cut-off: May 20, 2024).

Methods: Patients with advanced EGFR/ALK wild-type NSCLC and METex14 skipping received tepotinib 500 mg (450 mg active moiety) once daily until disease progression, intolerable toxicity, or withdrawal of consent. Secondary endpoints included safety and HRQoL, which was assessed using the EORTC QLQ-C30 Global Health Score (GHS), EQ-5D-5L visual analog scale (VAS), and EORTC QLQ-LC13 cough, dyspnea, and chest pain scores. Mean change from baseline across all visits was evaluated by linear mixed model regression in patients with baseline and ≥1 post-baseline score.

Results: 313 patients were evaluated for safety. Median age of the patients was 72.0 years (range: 41-94), 50.8% were female, and 73.8% had an Eastern Cooperative Oncology Group performance status of 1. Patients had a median treatment duration of 7.5 months (0.03-83.12). All-cause any grade adverse events (AEs) occurred in 310 (99.0%; Grade ≥3: 68.4%) patients, while any grade treatment-related AEs (TRAEs) occurred in 287 patients (91.7%; Grade ≥3: 36.1%) patients. Any grade serious TRAEs were observed in 50 (16.0%) patients. The most common TRAEs were peripheral edema in 212 patients (67.7%; Grade ≥3: 11.8%), hypoalbuminemia in 79 patients (25.2; Grade ≥3: 3.8%), and nausea in 73 patients (23.3%; Grade ≥3: 0.6%). TRAEs led to permanent discontinuation in 49 (15.7%) patients. At the end of treatment, in patients analyzed for HRQoL, the mean change (±standard deviation) from baseline for EORTC QLQ-C30 GHS was −7.1 (26.66) (n=174) and for EQ-5D-5L VAS was −10 (23.7) (n=172), with positive values indicating an improvement. Mean change (±standard deviation) from baseline in EORTC QLQ-LC13 symptom scores for cough, dyspnea, and chest pain were −6.1 (28.16) (n=175), 7.1 (21.05) (n=175), and −2.3 (28.13) (n=174), respectively, with negative values indicating improvement. Median time to deterioration of EORTC QLQ-LC13 symptom scores was 36.5 months for cough, 30.4 months for chest pain, and 5.5 months for dyspnea. Overall, HRQoL PROs remained stable during treatment with tepotinib.

Conclusions: In patients with ≥3-years follow-up, tepotinib demonstrated a continued manageable safety profile with no new safety signals, as well as stability in HRQoL PROs, consistent with earlier findings. These considerations support maximizing clinical benefits for this elderly patient population while maintaining their quality of life.

Keywords: Tepotinib, MET inhibitors, MET exon 14 skipping

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.41 Factors Associated With Clinical Outcomes in Patients With HER2-Mutant NSCLC Treated With Sevabertinib (BAY 2927088)

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Introduction: Mutations in HER2 occur in about 2-4% of patients with non-small cell lung cancer (NSCLC) and are associated with unfavorable outcomes. Sevabertinib is a potent, oral, reversible HER2 tyrosine kinase inhibitor that has demonstrated durable responses and a manageable safety profile in patients with advanced NSCLC having HER2 mutations. Our exploratory analysis assessed the impact of baseline clinical characteristics and molecular alterations on treatment outcomes.

Methods: Patients from expansion Cohort D of the SOHO-01 Phase I/II study (NCT05099172) were included in this analysis. All had advanced NSCLC with a HER2-activating mutation and experienced disease progression after at least one systemic therapy, but were naïve to HER2-targeted therapy, and received treatment with sevabertinib 20 mg twice daily. Plasma ctDNA was assessed using the Thermo Fisher Scientific Oncomine™ Precision Assay. HER2 variant information and co-alteration data were used to assess the correlation with investigator-assessed treatment response and outcomes.

Results: Of the 44 patients treated in expansion Cohort D, 43 patients who had a post-baseline tumor assessment were included. At baseline, median age was 62.0 years, 65.1% were female, 72.1% had never smoked, and 46.5% had received <2 prior lines of therapy. Treatment with <2 vs ≥2 prior lines of therapy was associated with a higher objective response rate (75.0% vs 69.6%), longer median duration of response (DoR: not reached vs 5.2 months), and improved median progression-free survival (PFS: not reached vs 6.7 months). TP53 mutations were the most frequently observed co-alterations, found in 13 out of 37 patients (35.1%) with detectable HER2 ctDNA. The HER2 Y772_A775dup (YVMA) variant appeared to be associated with enhanced treatment efficacy, whereas the presence of a TP53 co-alteration was not. Multivariate analysis indicated that both TP53 and HER2 YVMA provide independent prognostic information. Patients lacking TP53 co-alterations and having the YVMA variant showed favorable responses and outcomes, similar to those who had received only one prior therapy.

Conclusions: This exploratory analysis of clinical and molecular factors in patients with HER2-mutant NSCLC indicates favorable DoR and PFS among those who had received only one prior line of therapy or who had specific molecular characteristics. The findings underscore the importance of integrating clinical and molecular features to identify potential prognostic or predictive markers. As part of an ongoing study, these preliminary results emphasize the need for validation in a larger sample size to confirm these insights and further explore therapeutic strategies for patients with HER2-altered cancers.

Keywords: Phase I/II, HER2, Tyrosine kinase inhibitor

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.42 Concurrent KRAS Mutations Render Single-Agent EGFR Inhibitors Futile in Advanced NSCLC

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Introduction: Anti-EGFR tyrosine kinase inhibitors (TKI) are transformational drugs for patients with advanced NSCLC and EGFR alterations. Osimertinib, a third generation TKI, is considered first line for metastatic EGFRmut(+) NSCLC, among other TKIs. While rare, some tumors with EGFR alterations have concomitant KRAS mutations, and may have an activated oncogenic pathway not inhibited by current TKIs. We hypothesized that patients with EGFR-mutant NSCLC receiving current generation anti-EGFR targeted therapy will have reduced clinical benefit when there are co-occurring KRAS alterations.

Methods: Following a prespecified analysis plan, this study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB), with data originating from approximately 280 US cancer clinics (~800 sites of care). The prevalence cohort included patients with NSCLC treated in the advanced setting with first-line and had both EGFR and KRAS status assessed via tissue NGS obtained prior to treatment initiation. The outcome cohort included patients in the prevalence cohort treated with single-agent anti-EGFR TKIs and were EGFRmut(+). Differences in outcomes between groups were assessed via Kaplan-Meier plots and multivariable Cox PH models additionally adjusting for clinical factors: age, sex, ECOG performance score, pre-therapy [IA1] opioid prescription, presence of brain or bone metastases, socioeconomic status, histology, stage at diagnosis, and specific TKI. We additionally explored similar outcome associations on standard chemotherapy regimens.

Results: Prevalence cohort: among 10,740 1st line treatment decisions, 1359 (12.6%) were EGFRmut(+), and among these, 36 (2.5%) had EGFR and KRAS co-mutations. Outcome cohort: of 859 patients with EGFR-alterations meeting selection criteria, 11 (1.2%) had co-alteration of EGFR and KRAS, with the rest being KRAS wild-type. Among the 11 co-altered, 2 had EGFR exon 19 deletion, 2 had L858R, 6 had other EGFR alterations, and 1 had multiple EGFR alterations. Among co-altered, 4 received afatinib, 1 received getfitinib, and 6 received osimertinib. Compared to those with wild-type KRAS, co-altered patients had shorter median PFS (4.2 vs. 12.4 months, adjusted HR: 2.41, 95%CI: 1.24 - 4.65, p = 0.009) and directionally consistent OS (17.7 vs. 26.2 months, adjusted HR: 1.5, 95%CI: 0.71 - 3.17, p = 0.284). Evaluating patients who received chemotherapy and not anti-EGFR TKIs, we additionally saw less favorable PFS (HR: 2.66, 95%CI: 1.47 - 4.81, p = 0.001) and directionally consistent OS (HR: 1.24, 95%CI: 0.57 - 2.66, p = 0.59). Additional associations of specific concurrent KRAS alterations and prior treatment exposure will be presented at conference.

Conclusions: While rare, co-alteration of EGFR and KRAS appears to be a poor prognostic marker and compromises anti-EGFR treatment efficacy with numerically lower PFS (statistically significant) and OS for current generation TKIs. The results are consistent with our biologically informed hypothesis. We also saw similar associations with standard chemotherapy, underscoring the challenge of treating this subgroup Recently, the FLAURA2 (chemotherapy/Osimertinib) and MARIPOSA: Amivantamab/Lazertinib trials showed improved PFS as compared to osimertinib but with increased toxicity. In the setting of approved treatment-intensification strategies, co-alteration of KRAS should be further evaluated as a biomarker of aggressive disease that may warrant more aggressive frontline treatment.

Keywords: EGFR, KRAS, Osimertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.43 A Phase II Study of Sunvozertinib Combined With Anlotinib in NSCLC Patients Harboring EGFR Ex20Ins and Uncommon EGFR Mutations

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Introduction: Sunvozertinib is an oral, potent, highly selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has been approved in China for ≥second-line treatment of advanced NSCLC with EGFR exon 20 insertion mutation (exon20ins). In previous reports, sunvozertinib monotherapy has demonstrated promising and durable anti-tumor activity in EGFR exon20ins and uncommon mutation. Preclinical studies indicated that the combination of an EGFR-TKI plus a VEGF inhibitor (VEGFi) resulted in a synergistic effect. This is the first report about sunvozertinib combination therapy with anti-angiogenic drug in EGFR exon20ins and uncommon EGFR mutations.

Methods: This open-label, single arm, phase II study is planned to enroll 40 patients into two groups. Cohort 1 was defined as previously untreated patients with EGFR exon20ins. Cohort 2 was defined as previously treated patients with uncommon EGFR mutations. This study has two parts. Part A adopted the dose-reduction safety run-in design to assess the tolerability and safety of sunvozertinib combined with anlotinib. The initial dosing of sunvozertinib was 300 mg p.o. daily in combination with anlotinib 8 mg p.o. daily from day 1 to day 14 (21 days per cycle). Part B is an expansion period at the recommended combination dose (RCD). The primary endpoint of this study is objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression free survival, overall survival and safety profile.

Results: As of the 31th, March 2025 (DCO), 10 patients had successfully passed dose reduction safety run-in part and 2 patients was enrolled in dose expansion part. Sunvozertinib in combination with anlotinib was well tolerated, no DLT event occurred, and the RCD was sunvozertinib 300 mg p.o. daily in combination with anlotinib 8 mg p.o. daily from day 1 to day 14 (21 days per cycle). Overall, 10 patients completed first assessment. The ORR was 100%. These 10 cases include 9 previously untreated patients with EGFR exon20ins and one patient harboring with EGFR uncommon mutation (G719S and L861Q). In this uncommon EGFR mutation case, we also observed complete remission of the intracranial lesions. As of the DCO, all patients remained on treatment. The common (≥10%) TEAEs were diarrhea, rash, hypertension, hepatic dysfunction and oral ulcer. Only one patient required dose reduction of sunvozertinib due to diarrhea. No sunvozertinib-related discontinuations and no treatment related deaths were observed.

Conclusions: Sunvozertinib in combination with anlotinib is well tolerated and has demonstrated encouraging antitumor activity in NSCLC patients with EGFR exon20ins and uncommon EGFR mutations. Enrollment is currently ongoing and results will be updated in the meeting.

Keywords: EGFR ex20ins, uncommon EGFR mutation, sunvozertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.44 A Retrospective Study of the Effect of Cumulative Smoking Dose on Clinical Course in People With EGFR-Mutated NSCLC Treated With Osimertinib

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Introduction: Non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations are more common in people with non-smoking (NS). In analyzing the impact of smoking history on anticancer therapy, smoking history is usually stratified into two groups, NS versus smokers. However, it is controversial whether it is correct to divide smoking into only these two groups. Previous reports have shown that cumulative smoking dose (CSD) had significant impacts on clinical outcomes in first- and second-generation EGFR-tyrosine kinase inhibitors (TKIs), but there has been no study for osimertinib, which is the most frequently used agent recently. Thus, in this study, we investigated the impact of CSD on progression free survival (PFS), objective response rate (ORR), overall survival (OS), and type of genetic mutation other than EGFR in treatment with osimertinib.

Methods: We retrospectively reviewed people with NSCLC treated with osimertinib at our institution from October 2016 to June 2024. Primary endpoint was designated as PFS, and secondary endpoints were ORR, OS and genetic mutation. CSD was classified into three groups: NS, light-smoking (<20 pack-year (PY), LS) and heavy-smoking (≥20 PY, HS).

Results: There were 109 eligible participants, 64 with NS, 20 with LS, and 25 with HS, respectively. The overall median age was 74 years, with a larger proportion of women overall (64.2%) but a larger proportion of men among LS (60.0%) and HS (80.0%). The proportion of osimertinib administered as the first-line therapy was not significantly different between the groups. Median PFS was 14.3 months (mo.) for NS, 9.0 mo. for LS, and 3.7 mo. for HS, with a statistically significant difference (p=0.031 estimated by the Log-rank test). ORR was 73.4% for NS, 65.0% for LS, and 72.0% for HS (p=0.765). Median OS was 30.8 mo. for NS, 31.9 mo. for LS, and 24.5 mo. for HS (p=0.329). Cox proportional hazard model for PFS showed a trend of decreasing the efficacy of osimertinib with increasing CSD [hazard ratio (HR), 1.17; 95% confidence interval (CI), 0.65-2.09; p=0.596 for LS, HR, 1.93; 95% CI, 1.17-3.18; p=0.010 for HS], but the model for OS showed no significant difference (HR, 0.93; 95% CI, 0.49-1.78; p=0.838 for LS, HR, 1.46; 95% CI, 0.85-2.52; p=0.173 for LS). The frequency of gene mutations other than EGFR was 18.8% in NS, 15.0% in LS, and 20.0% in HS, showing no significant difference (p=0.331).

Conclusions: As with first- and second-generation EGFR-TKIs, PFS of osimertinib shortened significantly with increasing CSD. Osimertinib monotherapy may have insufficient efficacy on EGFR-mutated NSCLC for those with high CSD.

Keywords: Cumulative Smoking Dose, EGFR mutations, Osimertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.45 Aumolertinib for Treatment-Naïve EGFR-Mutant NSCLC Patients With Brain Metastases: Updated Efficacy Data From the ARTISTRY

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Introduction: Brain metastases (BMs) represent the most prevalent site of distant metastasis in non-small cell lung cancer (NSCLC). Patients with BMs generally have a poor prognosis. Notably, the incidence of BMs is significantly higher, ranging from 44% to 63% in EGFR mutant NSCLC patients. Thus, investigating the optimal treatment for BMs in EGFR mutant NSCLC patients has substantial clinical significance. Results from the FLAURA and AENEAS trials demonstrated that third -generation EGFR-TKIs exhibit superior efficacy and safety compared to first-generation EGFR-TKIs in patients with BMs harboring EGFR mutations. The BLOOM study indicated that high-dose EGFR-TKIs are highly effective in treating leptomeningeal metastases. ARTISTRY (NCT04778800) is an ongoing dose-escalation study. It evaluates the third-generation EGFR-TKI aumolertinib in three cohorts of EGFR-mutated NSCLC patients with brain or leptomeningeal metastases. Here, we report updated efficacy and safety data from cohort 1, which focuses on patients with brain parenchymal metastases.

Methods: Treatment-naïve EGFR-mutant NSCLC patients with brain parenchyma metastases received aumolertinib 110mg orally once daily. The dose was then escalated to 165mg in case of only intracranial progression. Assessments were performed every 4 weeks and then every 8 weeks after 2 consecutive disease control until extracranial progression as per RECIST v1.1. The primary endpoint was progression free survival (PFS), which included PFS1 during the standard-dose phase for all patients and PFS2 during the subsequent dose-escalation phase for patients with intracranial progression as the initial progression. Other endpoints were intracranial objective response rate (iORR), intracranial disease control rate (iDCR), ORR, DCR and safety.

Results: At data cut-off (January, 2025), a total of 30 patients were enrolled. The median age was 59.5 years, and 20% of the patients were male. In the 110mg period, the ORR was 90% and the DCR was 96.7%. The median PFS1 was 17.1 months (95% CI:15.0-26.40). Eight patients achieved intracranial complete remission during the treatment with the standard dose of aumolertinib. The iORR was 86.7% and the iDCR was 96.7%. The median iPFS1 was not reached (95% CI: 19.10-NR). Seven patients had intracranial metastasis as the initial lesion in progression. One withdrew from the study, while the remaining six underwent dose escalation to 165 mg/day of aumolertinib. During 165mg treatment, the iORR and iDCR were 33.3% (2/6) and 100% (6/6), respectively. The iPFS2 was 12.8m (95% CI: 4.40-12.80). The mPFS2 was 8.7 months (95% CI: 2.00-17.10). The most common grade 1-2 adverse events (AEs) in all patients were elevated creatine kinase, alanine aminotransferase increased, glutamic aminotransferase increased.

Conclusions: Aumolertinib showed superior antitumor activity with a manageable safety profile as first-line therapy in EGFR-mutant NSCLC patients with brain metastases, and patients with brain metastases progression still benefit from high dose Aumolertinib. Enrollment for this trial will continue, and further analyses are warranted to determine longer-term outcomes.

Keywords: Brain Metastases, dose-escalation, Aumolertinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.46 Enhanced vs Standard Dermatologic Management With Amivantamab-Lazertinib in EGFRm Advanced NSCLC: The COCOON Global RCT

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Introduction: First-line amivantamab-lazertinib significantly prolonged overall survival (OS) versus osimertinib among participants with EGFR-mutant advanced NSCLC in MARIPOSA (P<0.005). The phase 2 COCOON study (NCT06120140) demonstrated early success (median follow-up: 4.2 months), showing a significant reduction in grade ≥2 dermatologic adverse events (AEs) with enhanced (COCOON) vs standard-of-care (SoC) dermatologic management (P<0.0001). Here, we report results from the fully-enrolled population.

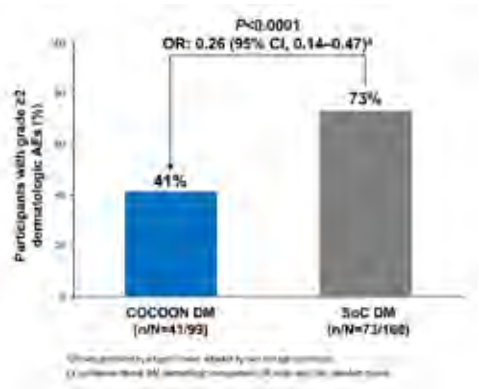
Methods: Eligible participants with previously-untreated, EGFR-mutant (Ex19del/L858R) locally advanced or metastatic NSCLC were randomized 1:1 to receive COCOON dermatologic management (DM), described below, or only SoC DM. All participants received standard-dose IV amivantamab plus oral lazertinib and SoC DM. Prophylactic anticoagulation was mandatory for the first 4 months of anticancer treatment. COCOON DM included oral doxycycline or minocycline 100 mg (twice daily, Weeks 1-12), chlorhexidine 4% on fingernails/toenails daily for 12 months, clindamycin 1% lotion on the scalp (daily, Weeks 13-52), and ceramide-based moisturizer for the face/body for 12 months. Primary endpoint was incidence of grade ≥2 dermatologic AEs of interest in the first 12 weeks of anticancer treatment

Results: As of 12-Mar-25 (median follow-up: 7.1 months), 199 participants received COCOON DM (n=99) or SoC DM (n=100) with amivantamab-lazertinib. Median age was 63 years; 59% were female, and 77% remain on anticancer treatment as of clinical cutoff.

Based on full trial enrollment, the COCOON DM regimen demonstrated a significant reduction in grade ≥2 dermatologic AEs in the first 12 weeks vs SoC DM (41% vs 73%; OR, 0.26 [95% CI, 0.14-0.47]; P<0.0001; Figure 1). By Week 12, the largest benefit with COCOON DM was observed in face/body dermatologic AEs (excludes paronychia; 26% vs 59%; P<0.0001) and scalp dermatologic AEs (10% vs 26%; P=0.005); paronychia incidence was comparable (20% vs 21%). Discontinuations of amivantamab or lazertinib due to any AE were lower with COCOON DM vs SoC DM (16% vs 20%). The COCOON regimen was well-tolerated, with only 2 participants discontinuing doxycycline or minocycline due to treatment-related AEs.

Objective response rate (investigator-assessed) was 81% in the COCOON DM arm and 76% in the SoC DM arm, consistent with prior reports for first-line amivantamab-lazertinib. Additional results will be reported at the meeting.

Conclusions: An easy-to-use, widely available, prophylactic regimen (COCOON DM) reduced the incidence and severity of dermatologic AEs with amivantamab-lazertinib. New approaches focusing on a simplified regimen with early intervention are being investigated. This optimization, along with an OS improvement, further enhances the benefit-risk profile for first-line amivantamab-lazertinib.



Keywords: Non-small cell lung cancer, EGFR mutation, amivantamab

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.47 A Phase II Study of Sunvozertinib Combined With Chemotherapy in EGFR-TKIs Resistant EGFRm Advanced NSCLC Patients(WU-KONG36)

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Introduction: Sunvozertinib is a highly selective EGFR tyrosine kinase inhibitor (TKI) targeting various EGFR mutations. In previous reports, Sunvozertinib monotherapy has demonstrated promising and durable anti-tumor activity in EGFR sensitizing mutations (EGFRm), who failed standard EGFR TKI treatment. Preclinical studies also shown that the combination of Sunvozertinib and chemotherapy resulted in a synergistic effect. This is the first report about sunvozertinib in combination with chemotherapy in EGFRm NSCLC.

Methods: Methods: This open-label, single arm, phase II study is planned to enroll 40 patients, which harbored EGFR sensitizing mutations and failed standard EGFR-TKI treatment. This study has two parts. Part A adopted the dose-reduction safety run-in design to assess the tolerability and safety of Sunvozertinib combined with chemotherapy. The initial dosing of Sunvozertinib was 200 mg p.o. daily in combination with pemetrexed plus cisplatin or carboplatin, followed by pemetrexed maintenance and Sunvozertinib 200 mg. Part B is an expansion period at the recommended combination dose (RCD). The primary endpoint of this study is objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression free survival, overall survival and safety profile. In this study, we also explored the potential resistance mechanisms based on NGS testing.

Results: As of the 23th, March 2025 (DCO), 9 patients had successfully passed dose reduction safety run-in part. Sunvozertinib in combination with chemotherapy was well tolerated, with no DLT event. Overall, 9 patients completed first assessment. The ORR was 33.3%, and DCR was 77.8%. The common (≥30%) TEAEs were anemia, neutrophil count decreased, alanine aminotransferase increased, white blood cell count decreased, platelet count decreased, and aspartate aminotransferase increased. No Sunvozertinib-related discontinuations or reductions and no treatment related deaths were observed.

Conclusions: Sunvozertinib in combination with chemotherapy is well tolerated and has demonstrated encouraging antitumor activity in NSCLC patients with EGFR mutations who failed prior EGFR-TKIs therapies. Enrollment is currently ongoing and results will be updated in the meeting.

Keywords: NSCLC, TKI failure, sunvozertinib

P3.12.48 Efficacy and Safety of Savolitinib in Advanced or Metastatic METex14 NSCLC Patients With or Without Prior Immunotherapy

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Introduction: For treatment-naïve, biomarker-driven, gene-positive, advanced or metastatic non-small cell lung cancer (NSCLC), the recommended first-line regimen is gene-targeted therapy with or without chemotherapy; but few patients (pts) would receive immunotherapy (IO). We previously reported the primary results of savolitinib (savo, a highly selective oral MET inhibitor) in advanced or metastatic MET exon 14 mutation (METex14) NSCLC in a phase 3b confirmatory study (data cut-off date: Oct 20, 2023; Shun L, et al. ELCC 2024). Herein, we evaluated whether prior IO potentially impacted the efficacy and safety of savo in this phase 3b study.

Methods: Eligible pts with advanced or metastatic METex14 NSCLC received savo once daily at 600 mg (≥50 kg) or 400 mg (<50 kg). Previously treated (≥2L) pts were included in the post-hoc analysis, which examined baseline characteristics, efficacy, and safety variables, in populations who had been treated with prior IO (prior IO-treated) and had not (prior IO-naïve).

Results: As of Nov 30, 2024, in 79 previously treated pts, 19 pts were prior IO-treated, and 60 were prior IO-naïve. The median follow-up was 21.2mo. No notable differences in baseline characteristics were observed between the two populations. Among the prior IO-treated population (n=19), the Independent Review Committee-assessed objective response rate (ORR), disease control rate (DCR), and median progression-free survival (PFS) were 31.6%, 94.7%, and 9.7mo, respectively; median overall survival (OS) was 18.0mo. A trend toward improved response and survival was observed in prior IO-naïve population (n=60), with corresponding efficacy variables of 45.0%, 91.7%, 13.7mo, and 25.3mo, respectively (Table 1). A more favorable safety profile was also identified in prior IO-naïve population. The incidence of grade ≥3 treatment-related adverse events (TRAEs) was 63.2% vs 51.7%, the incidence of TRAEs leading to dose interruption or reduction was 89.5% vs 60.0%, and the incidence of TRAEs leading to discontinuation was 15.8% vs 5.0%, in prior IO-treated vs prior IO-naïve populations, respectively.

Table 1 Efficacy Summary

	IRC		Investigator	
	Prior IO-treated (N = 19)	Prior IO-naive (N = 60)	Prior IO-treated (N = 19)	Prior IO-naive (N = 60)
ORR (95%CI), %	31.6 (12.6, 56.6)	45.0 (32.1, 58.4)	31.6 (12.6, 56.6)	53.3 (40.0, 66.3)
DCR (95%CI), %	94.7 (74.0, 99.9)	91.7 (81.6, 97.2)	94.7 (74.0, 99.9)	91.7 (81.6, 97.2)
mDoR (95%CI), mo	33.1 (2.9, -)	11.2 (6.6, 20.7)	- (6.9, -)	11.0 (8.2, 16.6)
mPFS (95%CI), mo	9.7 (4.2, -)	13.7 (7.9, 17.9)	- (3.5, -)	11.0 (6.8, 16.6)
mOS (95%CI), mo	Prior IO-treated vs Prior IO-naive: 18.0 (8.0, -) vs 25.3 (21.6, 30.7)			

Keywords: MET exon 14 mutation, NSCLC, savolitinib

P3.12.49 Clinical Significance of a Genomic Screening Platform of Non-Small Cell Lung Cancer in Asia-Pacific: LC-SCRUM-AP

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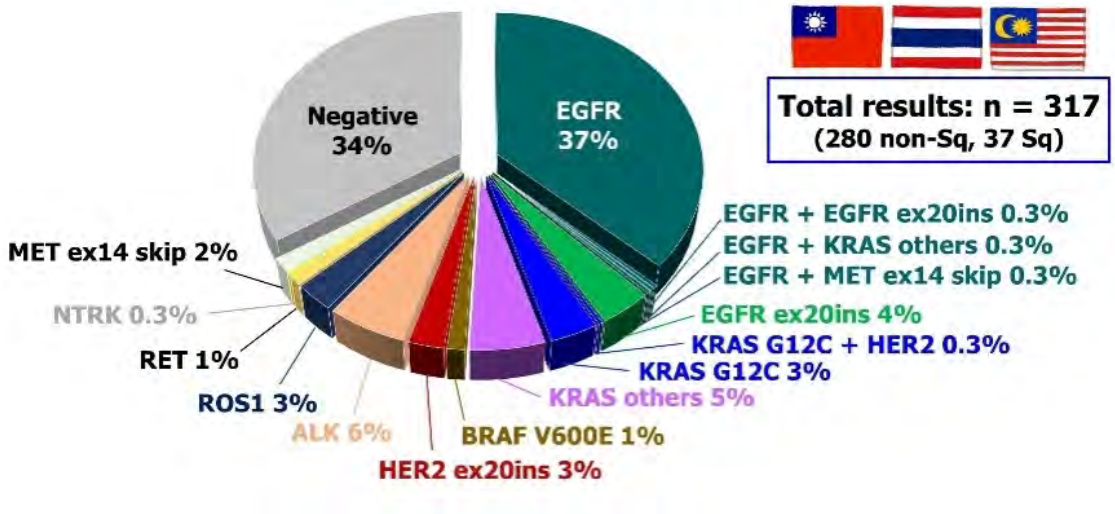
Introduction: The lung cancer genomic screening platform (LC-SCRUM-Asia) started in Japan, which expanded to other Asia-Pacific countries (LC-SCRUM-AP). The objective of this study is to elucidate the clinical significance of genomic screening in Asia-Pacific countries and to compare the current situation of targeted therapies in Asia-Pacific countries with that in Japan.

Methods: 14 institutions in Taiwan, Thailand, Malaysia, and Vietnam are participating in the LC-SCRUM-AP. Samples are analyzed by a rapid multi-gene PCR assay, AmoyDx® Pan Lung Cancer PCR Panel, and a high-spec next-generation sequencing assay, Oncomine™ Precision Assay. Clinical, pathological and genomic data are stocked as a clinical-genomic database in each participating country, which was compared with that of 6753 Japanese-cohort with matched clinical characteristics (LC-SCRUM-Asia data from June 2019 to March 2024).

Results: From January 2023, a total of 345 non-small cell lung cancer (NSCLC) patients has been enrolled from 3 countries (Taiwan/Thailand/Malaysia = 149/102/94 pts). A multi-gene PCR assay data was available in 317 cases. The median turn-around time (TAT) was 5 days, and the genomic analysis successful rate was 99.7%. The frequency of driver alterations in the Taiwan/Thailand/Malaysia cohort (AP-cohort) were shown in Figure 1. The information regarding treatment history was available in 222 cases of the AP-cohort, which was compared with that of the Japanese-cohort. In the AP-cohort, oncogenic driver alteration was detected in 154 patients, of which 117 (76%) received targeted therapies. Proportion of patients received targeted therapies were similar between the AP-cohort and Japanese-cohort in the EGFR mutations excluding ex20ins (AP-cohort vs. Japanese-cohort = 95% vs. 90%), ALK fusions (AP-cohort vs. Japanese-cohort = 100% vs. 91%), and ROS1 fusions (AP-cohort vs. Japanese-cohort = 78% vs. 84%). Meanwhile, proportion of patients received targeted therapies for BRAF V600E tended to be lower in the AP-cohort (AP-cohort vs. Japanese-cohort = 0% vs. 70%). For the patients with EGFR ex20ins, while no patient received targeted therapy in the AP-cohort, 20% of the Japanese-cohort enrolled in the clinical trials for targeted agents.

Conclusions: LC-SCRUM-AP enables the efficient detection of driver alterations in NSCLC with a short TAT. This screening platform highly contributed to deliver targeted therapies in Asia-Pacific countries with a high implementation rate. Proportion of patients received targeted therapies depended on the approval and insurance reimbursement status in each country. For BRAF V600E and EGFR ex20ins mutations, it was shown that patients in Asia-Pacific countries tended to have less access to targeted therapies than those in Japan.

Figure 1. Genomic alterations detected by multiplex PCR



Keywords: genomic screening, Asia Pacific, targeted therapy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.50 A Prognostic Model Based on a Concurrent Gene Mutational Signature for EGFR Mutant NSCLC With TKI Treatments

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Introduction: EGFR-TKIs significantly improved the survival and the quality of life of NSCLC patients with EGFR mutations. Understanding specific concurrent genetic changes and how they influence the efficacy of EGFR-TKI therapy is necessary to optimize clinical outcomes.

Methods: Using next-generation sequencing (NGS), 82 individuals who harbored EGFR mutations and received TKI treatment were included. The K-M curve and log-rank test analyzed survival significance. SelectKBest was conducted 100 times to screen the concurrent genetic alterations (score > 20; select_num ≥ 80) that were crucial to predict PFS, and t-SNE was used to establish a co-mutational gene signature. Straightforward data augmentation was used to introduce 1000 new data samples as the training group, and the original 82 data served as the testing group. A multivariate model was developed using random forests and a bootstrap resampling method (n = 100) to predict the PFS of EGFRMT NSCLC treated with TKIs.

Results: Based on the univariate Cox regression, age (P = 0.023), M-stage (P = 0.037), the line of TKI treatment (P = 0.018), and the single nucleotide variation (SNV) of GSTM1 (P = 0.029) were independent predictors for PFS. Moreover, a remarkably shorter PFS was observed in GSTM1MT patients than in GSTM1WT patients. Six concurrent gene mutations were screened, and based on them, a concurrent gene mutational signature was established. The combination of age, M stage, the line of TKI treatment and the concurrent gene mutational signature demonstrated an accurate prediction for 6 month-PFS (Accuracy = 0.868 ± 0.021, F1-score = 0.924 ± 0.011) and 9 month-PFS (Accuracy = 0.807 ± 0.029, F1-score = 0.854 ± 0.023). There was also a dramatic improvement of the combinational model to the predictive ability of age, M-stage, the line of TKI treatment, and GSTM1 mutation status (all P < 0.001 for 6-month-PFS and 9-month-PFS).

Conclusions: This is the first study to report that SNV of GSTM1 reduces TKI responsiveness and worsens prognosis in patients with EGFRMT NSCLC. In addition, we developed a prognostic model based on a concurrent gene mutational signature for EGFR mutant NSCLC treated with TKIs.

Keywords: GSTM1, epidermal growth factor receptor (EGFR), concurrent gene mutation

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.51 Patient-Derived Organoids as Preclinical Models for Drug Resistance in NSCLC

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Introduction: Precision medicine has introduced targeted therapies for patients with non-small cell lung cancer (NSCLC) harboring molecular alterations in EGFR, ALK, ROS1, RET, NTRK, HER2, MET, and KRAS. However, at least 25% of NSCLC patients lack targetable drivers, and even those who initially respond to TKIs eventually develop drug resistance, making resistance a major cause of death. Available preclinical models like 2D cell lines fail to capture the heterogeneity and complexity of NSCLC, while patient-derived organoids (PDOs) offer a promising alternative by preserving key histologic and molecular traits and allowing rapid drug screening. Unlike patient-derived xenografts (PDXs), PDOs are scalable and can be established within weeks. Our group has developed a research pipeline at Princess Margaret Cancer Centre to generate and screen PDO models efficiently. Our project aims to assess whether molecular profiling and drug screening of PDO models, generated at the time of acquired TKI resistance, can guide the selection of optimal subsequent therapies for NSCLC patients.

Methods: PDO models were generated from patients with advanced, treatment-resistant lung adenocarcinoma at the time of resistance to initial TKIs. Long-term, renewable PDO models underwent quality control testing, including STR profiling, mycoplasma testing, and histological analysis. Additionally, whole-exome sequencing (WES) and RNA sequencing (RNA-seq) were used to profile genomic alterations in the PDOs. PDO models underwent drug screening to assess correlation with patient's response to TKI therapy. Organoids were plated in 384-well drug plates, treated with TKI drugs at different concentrations, and cell viability was measured after six days. Drug sensitivity curves were generated for individual compounds using a 21-point dose-response assay.

Results: We processed 52 biopsies and 61 pleural fluid samples from patients with advanced, TKI-resistant NSCLC to generate organoid models. Organoid initiation rates (any growth in P0) were 29% for biopsies and 36% for pleural fluid samples, while establishment rates (expansion for ≥10 passages) were 2% and 10%, respectively. We successfully developed seven long-term patient-derived organoid models with oncogenic mutations in ERBB2, KRAS, MET, and EGFR genes. These patients were resistant to TKI inhibitors, including Afatinib, Capmatinib, Gefitinib, Amivantamab, and Trastuzumab. Histopathological and genomic analyses confirmed that PDO models accurately reflected tumor biology, with sequencing verifying driver mutations from original patient tissues. PDO drug screening demonstrated high concordance with patient responses and proved amenable to high-throughput and synthetic lethality screening.

Conclusions: We demonstrate that patient-derived organoids (PDOs) can be successfully generated from treatment-resistant NSCLC patients and serve as a valuable preclinical model for studying TKI resistance. The high concordance between PDO drug screening and patient responses highlights the potential of these models to guide personalized treatment decisions. Additionally, the scalability and rapid establishment of PDOs make them well-suited for high-throughput and synthetic lethality screening, offering a promising platform for identifying novel therapeutic strategies in TKI-resistant NSCLC.

Keywords: NSCLC, Patient-Derived Organoids, Targeted Therapy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.52 Aumolertinib Plus Anlotinib in Advanced EGFR-Mutant NSCLC With TP53 Co-Mutation: A Single-Arm, Phase II Study

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Introduction: Based on the AENEAS study, aumolertinib has superior efficacy as the first-line standard treatment. However, its efficacy against concurrent mutations remains unclear, especially for the high incidence (up to 55%-65%) of TP53 co-mutation. In recent RELAY and ACTIVE studies, subgroup analysis has shown particular benefits for patients receiving dual inhibition of EGFR and angiogenesis. Herein, we conduct a prospective study to explore aumolertinib combined with anlotinib as a first-line treatment option for advanced NSCLC harboring EGFR mutation and TP53 co-mutation. (NCT05778149)

Methods: Treatment-naïve EGFR-positive NSCLC pts with TP53 co-mutation were enrolled including pts with at least one assessable lesion (RECIST 1.1). All pts received aumolertinib (110mg, orally QD) plus anlotinib (12mg, orally QD, day 1 to 14 of a 21-day cycle) until disease progression or intolerable adverse reactions or death. The primary endpoint is progression free survival (PFS). Secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results: At data cut-off (February, 2025), we recruited 15pts in this trial, of which 14 pts were evaluable. All pts underwent NGS testing, and various types of exon mutations were identified. The baseline characteristics were presented in Table 1. The mPFS was 25 months (95%CI 11.0-NA), with a median follow-up time of 23 months (95%CI 8.0-31.0). The ORR and DCR were 57.1% (5/14) and 100% (14/14), respectively. Total pts were divided into two subgroups according to gene type, ORR was 66.7% (4/6) in the 19del group and 50% (4/8) in 21L858R group. Hypertension was the most common adverse reaction (64.2%), majority of the AEs were <Grade 3. No new safety signals were identified.

Table 1 Baseline Characteristics(n=15) p class="MsoNormal">

Conclusions: This represents the first prospective study evaluating aumolertinib plus anlotinib in NSCLC patients with TP53 co-mutations, demonstrating promising efficacy and favorable safety profile. Enrollment for this trial will continue, and further analyses are warranted.

Table 1 Baseline Characteristics(n=15)

Age, years	
Median	59(45-66)
Sex, n (%)	
Male	9(60.0%)
Female	6(40.0%)
Smoking, n (%)	
Never smoker	7(46.7%)
Ever smoker	8(53.3%)
ECOG performance status	
1	14(93.3%)
2	1(6.7%)
Number of organs with metastases	
≤1	5(33.3%)
≥2	10(66.7%)
EGFR mutation type, n (%)	
Exon 19 del	6(40.0%)
p.L858R	9(60.0%)
TP53 mutation, n(%)	
Exon 5	4(26.7%)
Exon7	4(26.7%)
Non-exon 5/7	7(46.7%)

Keywords: TP53 Co-Mutation, Aumolertinib, Anlotinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.53 High-Dose Furmonertinib Plus Bevacizumab in EGFR-Mutant NSCLC With CNS Metastases After Resistance to Third-Generation EGFR-TKIs

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Introduction: Third-generation EGFR tyrosine kinase inhibitors (TKIs) have significantly improved outcomes in EGFR-mutant non-small cell lung cancer (NSCLC), but acquired resistance inevitably occurs, especially in patients with central nervous system (CNS) metastases. Antiangiogenic therapy (eg, bevacizumab) can transiently normalize the tumor vasculature and blood-brain barrier, potentially enhancing CNS drug delivery and efficacy of EGFR-TKIs. This research aimed to evaluate the efficacy of high-dose furmonertinib (a third-generation EGFR-TKI) combined with bevacizumab in EGFR-mutant NSCLC patients with CNS metastases who progressed after prior third-generation EGFR-TKI therapy.

Methods: A single-center retrospective study was performed focusing on EGFR-mutant NSCLC patients with CNS metastases (including leptomeningeal metastases and/or brain parenchymal) who had disease progression after at least one prior third-generation EGFR-TKI. All patients received furmonertinib 160 mg once daily plus bevacizumab 7.5 mg/kg every 3 weeks until progression or unacceptable toxicity. Intracranial progression-free survival (iPFS) and overall progression-free survival (PFS) were the primary endpoints; secondary endpoints included intracranial and systemic objective response rates (ORR) and safety. Kaplan-Meier methods were used to estimate survival outcomes, and Cox proportional hazards regression was employed for univariate and multivariate analysis of prognostic factors.

Results: As of February 2025, a total of 78 patients were included with a median follow-up of 8.75 months (Q1-Q3, 6.03-14.70), the median iPFS was 7.63 months (95% confidence interval [CI]: 0.95-not reached [NR]), and median overall PFS was 6.37 months (95% CI: 0.95-NR). The intracranial ORR was 29.5%, and the systemic ORR was 42.3%. Median overall survival data were not yet mature. In patients with both brain parenchymal and leptomeningeal metastases (n = 47), median iPFS was 7.63 months (95% CI: 0.95-NR) and PFS 5.80 months (95% CI: 0.95-NR), with an intracranial ORR of 31.9% and systemic ORR of 53.2%. In patients with brain-only metastases (n = 31), median iPFS was 7.20 months (95% CI: 0.95-NR) and PFS 6.70 months (95% CI: 0.95-NR), with iORR 25.8% and ORR 25.8%. Multivariate Cox analysis showed that EGFR exon 19 deletion (19del) mutation (hazard ratio [HR] = 0.24, 95% CI: 0.08-0.70, P = 0.009) and the use of intracranial radiotherapy during treatment (HR = 0.36, 95% CI: 0.15-0.87, P = 0.023) were independently associated with prolonged PFS.

Conclusions: High-dose furmonertinib combined with bevacizumab demonstrated notable intracranial and systemic activity in EGFR-mutant NSCLC patients with CNS metastases after third-generation TKI resistance. The combination yielded meaningful clinical benefit with manageable toxicity in this difficult-to-treat population, supporting its consideration as a therapeutic option pending further prospective validation.

Keywords: Furmonertinib, EGFR-TKI resistance, CNS metastases

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.54 Predicting Osimertinib-Induced Pneumonitis in EGFR-Mutated NSCLC Using Multi-Modal Machine Learning Model

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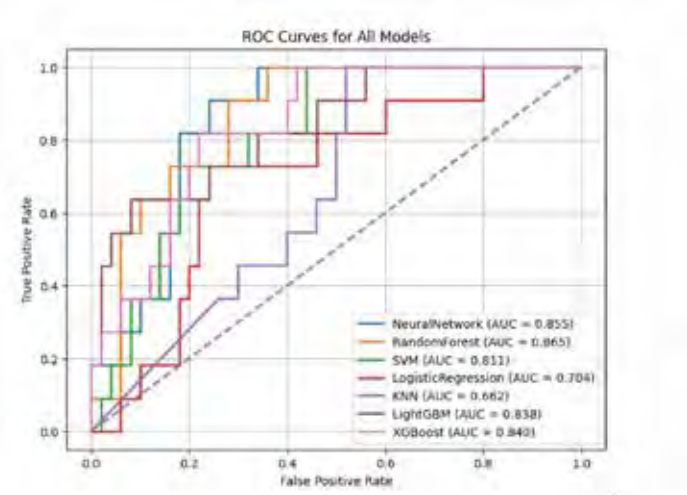
Introduction: Osimertinib improved overall survival in EGFR-mutated non-small cell lung cancer (NSCLC), but drug-induced interstitial lung disease (DILD) remains a significant concern, particularly among Asian patients. Existing clinical risk factors alone offer limited predictive accuracy, highlighting the need for integrated risk models.This study aims to develop and validate a machine learning model integrating clinical and computed tomography (CT) imaging features to predict DILD risk in NSCLC patients initiating osimertinib.

Methods: We retrospectively analyzed EGFR-mutated NSCLC patients treated with osimertinib. Patients were randomly split into training (70%) and test (30%) sets. Clinical features included demographics, laboratory values, prior therapies, and radiologic history. Pretreatment CT images were processed with a 3D ResNet for imaging feature extraction. All clinical and imaging features were initially considered, and relevant features were selected using the SelectKBest method. These selected features were used to train six machine learning models: Neural Networks, SVM, LightGBM, XGBoost, KNN, Random Forest, and logistic regression. Performance was evaluated on the test set using AUC-ROC. The Youden Index identified the optimal threshold for risk stratification. Kaplan-Meier curves compared DILD incidence between high- and low-risk groups.

Results: Among 203 patients, 32 (15.8%) developed pneumonitis: Grade 1 (n=14), Grade 2 (n=10), and Grade 3 (n=8). Significant clinical predictors included prior thoracic surgery, thoracic radiotherapy, and pre-existing interstitial lung disease. After feature selection, all models were trained and tested using the same optimized feature set. Random Forest yielded the highest AUC (0.865). Using the optimal threshold of 0.3, the test set was stratified into high- and low-risk groups. Kaplan-Meier analysis revealed a significantly higher pneumonitis incidence in the high-risk group (p=0.0075). Sensitivity and specificity at this threshold were 0.75 and 0.82.

Conclusions: A Random Forest model accurately predicts pneumonitis risk using clinical and imaging features. Further validation in multicenter cohorts is needed.



Keywords: Machine learning, Osimertinib, Interstitial lung disease

P3.12.55 Efficacy of Vebreltinib in Advanced NSCLC Patients With MET Exon 14-Skipping: Post-Hoc Analysis of KUNPENG Study

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Introduction: Vebreltinib (PLB1001), a potent and highly selective c-MET inhibitor, demonstrated superior objective response rate (ORR) benefits in locally advanced or metastatic non-small-cell lung cancer (NSCLC) patients (pts) with MET exon 14 (METex14) skipping mutations in the previous analysis of the phase II KUPENG study. Here we present results from post-hoc analysis of KUNPENG study.

Methods: In this Phase II, open-label, multicenter, and multi-cohort study, tumor tissue was assessed for METex14 skipping mutation using next-generation sequencing (NGS) from CAP or CLIA certificated local or central laboratories. Pts in Cohort 1 received 200 mg of vebreltinib twice daily (28 days per cycle) until discontinuation criteria were met. The primary endpoint was ORR assessed by blinded independent review committee (BIRC).

Results: Between Jan 17, 2020 and Feb 09, 2021, 52 pts were enrolled in Cohort 1. In the Per-Protocol Set (PPS) of 46 patients, 21 were treatment-naïve, and 25 were previously treated. For this set, we conducted a post hoc analysis. As of the data cut-off (Nov 14, 2024), the median duration of follow-up was 21.4 months (range, 3.7-58.0) and the median duration of treatment was 12.5 months (range, 1.0-58.0). Per BIRC assessment, the ORR was 80.4% (95% CI: 69.0-91.9), the disease control rate (DCR) was 97.8% (95% CI 93.6-100.0), the median duration of response (DoR) was 19.1 months (95% CI 12.0-NE), the median progression-free survival (PFS) was 17.5 months (95% CI 6.4-31.3), and the median overall survival (OS) was 22.5 months (95% CI 17.9-44.3). The 3-year OS rate was 39.7%. Subgroup analyses showed the ORR of pts with any baseline brain metastases (N=5), treatment-naïve (N=21) and pre-treated (N=25) were 100.0%, 85.7% and 76.0%; mPFS were 6.4, 25.8 and 12.0 months and mOS was 17.9, 44.3 and 20.7 months, respectively.

Conclusions: Vebreltinib provided remarkable tumor response for locally advanced or metastatic NSCLC pts with exon 14 skipping, which can translate into long-term survival benefits, especially in treatment-naïve patients.

Summary of efficacy assessed by BIRC in Per-Protocol set

Variables	Treatment-naïve (n=21)	Pre-treated (n=25)	PPS (n=46)
ORR (%)	18(85.7)	19(76.0)	37(80.4%)
95% CI	70.7-100.0	59.3-92.7	69.0-91.9
DCR (%)	21(100.0)	24(96.0)	45(97.8)
95% CI	100.0-100.0	88.3-100.0	93.6-100.0
mDoR, months (95% CI)	30.4(12.0-NE)	16.7(5.5-NE)	19.1(12.0-NE)
mPFS, months (95% CI)	25.8(6.3-NE)	12.0(6.4-20.3)	17.5(6.4-31.3)
mOS, months (95% CI)	44.3(18.2-NE)	20.7(15.2-29.7)	22.5(17.9-44.3)

Keywords: vebreltinib, MET exon 14-skipping, NSCLC

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.56 Medication Adherence to Osimertinib in Patients Diagnosed With Metastatic Non Small Cell Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer-related death in the United States. Guidelines currently recommend osimertinib as first-line therapy for metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R mutations. Oral oncolytics allow for more patient autonomy; however, medication adherence has been a concern due to the various barriers patients may encounter. A previous study determined that adherence to oral oncolytics among patients with lung cancer is 64.7%, while a study comparing pharmacy type found that 83% of internal pharmacy users and 69% of external pharmacy were adherent. Non-adherence to these therapies has been associated with increased rates of physician visits, hospitalization, and longer hospital stays. The purpose of this study is to assess medication adherence to osimertinib in a diverse patient population receiving treatment at a comprehensive cancer center.

Methods: A retrospective chart review was performed at a large multi-site community cancer center with an affiliated specialty pharmacy who received osimertinib between January 1, 2018 and December 31, 2023. Inclusion criteria included patients 18 years and older with EGFR-mutated advanced NSCLC. Exclusion criteria included patients who received osimertinib with concurrent chemotherapy, and patients who received medication through a patient assistance program. Data were collected from electronic medical records and prescription refill history. Medication adherence was defined as having a proportion of days covered (PDC) of 90% or higher over a span of the first six months of therapy. A two-sample t-test was conducted to compare medication adherence, measured by the PDC, between patients using internal and external pharmacies. All statistical analyses were conducted using Stata/BE 18, and results were considered statistically significant at $p < 0.05$.

Results: Of the 150 patient medical charts reviewed, 38 patients were included. The mean age was 63.2 years (SD = 10.5). The majority of patients were female (71.05%), married (57.89%), privately insured (68.42%), and non-smokers (71.05%). The study population included 42% Hispanic, 18% Black, 29% White, and 10% Asian. The majority of patients (65.79%) used an external pharmacy, while 34.21% used an internal pharmacy. Overall, 94.74% of patients were adherent to osimertinib with a PDC of 90% or higher. The combined mean PDC across all patients was 96.19%, with a mean PDC of 96.85% for internal pharmacies and 95.83% for external pharmacy users. (p= 0.53).

Conclusions: The findings from our study highlight that the majority of patients maintained high adherence rates regardless of where they filled their medications, reflecting the comprehensive approach to medication management within our healthcare system. This supports the efforts of the Memorial Healthcare System in ensuring appropriate coordination and execution of prescription refills when collaborating with both internal and external pharmacies, as demonstrated by the high adherence observed in both pharmacy types.

Keywords: Medication Adherence, Proportion of Days Covered, Lung Cancer

P3.12.57 Phase I/II Study of FHND9041 in T790M-Positive Advanced NSCLC Patients Progressed After Prior EGFR-TKI Therapy

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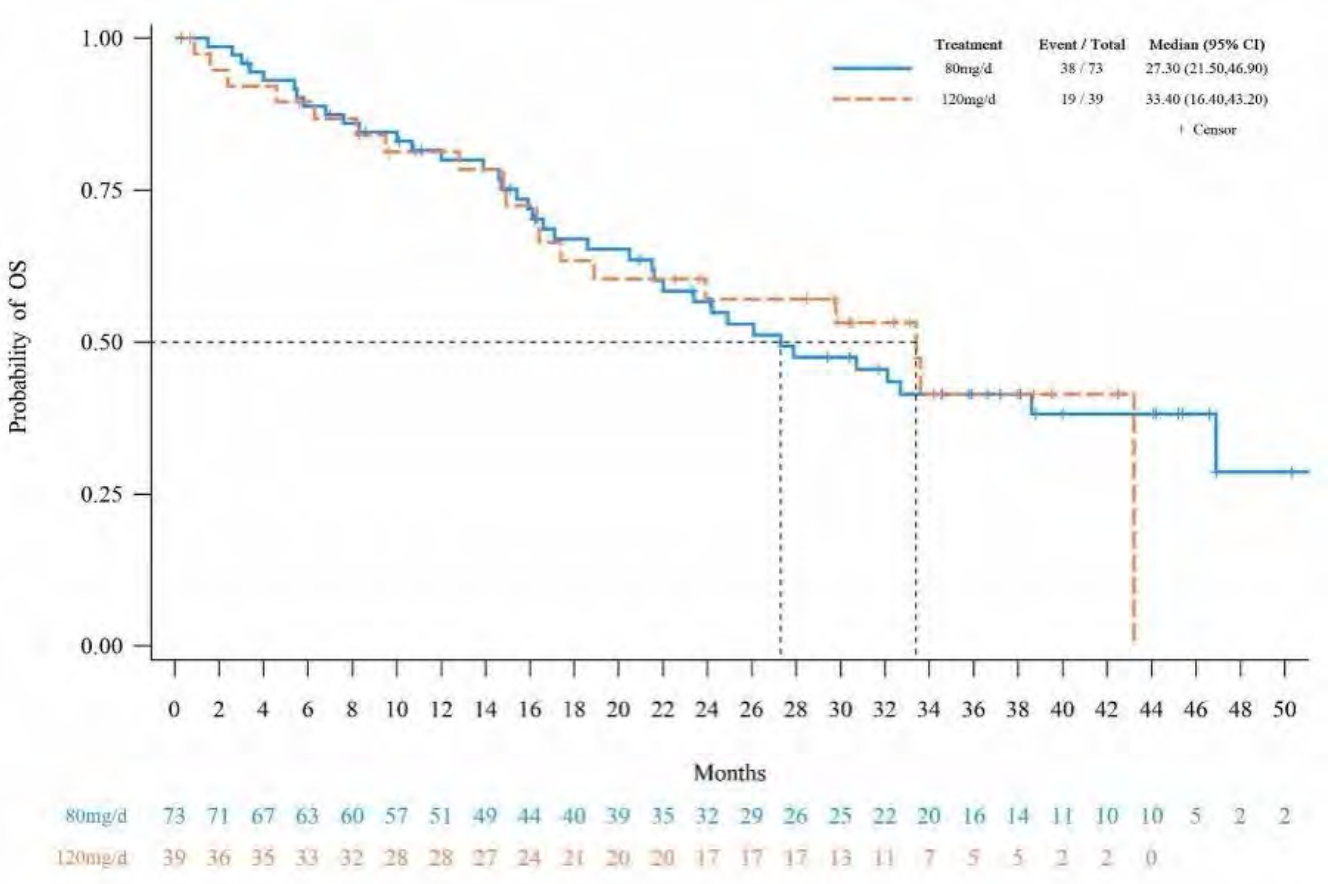
Introduction: FHND9041 is a novel third-generation EGFR-TKI developed for the treatment of patients with EGFR T790M-positive non-small cell lung cancer (NSCLC) who have progressed on prior EGFR-TKI therapy.

Methods: The study included dose-escalation and dose-expansion phase for patients with locally advanced or metastatic EGFR T790M-positive NSCLC. In the dose-escalation phase, 12 patients received oral FHND9041 at 40 mg (n=3), 80 mg (n=3), 120 mg (n=3), and 180 mg (n=3) once daily (QD). In the expansion phase, 112 patients were enrolled to receive FHND9041 at 80 mg (n=73) or 120 mg (n=39) QD. The primary endpoints were safety/tolerability and objective response rate (ORR) according to RECIST v1.1. Secondary endpoints included progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and overall survival (OS).

Results: A total of 112 patients were treated in Phase II. The confirmed ORR (N=109) was 49.5% (54/109; 95% CI: 39.8-59.3), and the disease control rate (DCR) was 96.3% (95% CI: 90.9-99.0). The median PFS in the overall population (N=112) was 15.1 months (95% CI: 11.1-16.6), with censored patients of 36 patients (32.1%). The P75 was 27.6 months (95% CI: 23.4-NE). The mean PFS was 18.5 months (SE: 1.4). Median DoR was 19.4 months (95% CI: 13.8-26.3). The median OS was 29.8 months (95% CI: 21.6-43.2), with 55 patients (49.1%) censored. These results suggest a promising duration of disease control with FHND9041.

In the dose-escalation phase, one dose-limiting toxicity (DLT) of elevated alanine aminotransferase (ALT) was observed at the 180 mg dose level. In the 80 mg (the Phase III dose) expansion cohort, grade ≥3 treatment-related adverse events (TRAEs) occurred in 8.2% (6/73) of patients, with no TRAEs leading to dose reduction. Across both 80 mg and 120 mg expansion cohorts, no treatment-related deaths were reported and grade ≥3 TRAEs were observed in 14.3% of patients (16/112).

Conclusions: FHND9041 showed durable efficacy and a favorable safety profile in patients with EGFR T790M-positive NSCLC who progressed after EGFR-TKI treatment, supporting its further development as a potential treatment option.



Keywords: EGFR T790M, NSCLC, FHND9041

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.58 Initial Results From Phase 1/2 Study of the RET-Selective Inhibitor Vepafestinib in Patients With RET-Aberrant Solid Tumors

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Introduction: Cancers with RET alterations have limited next-generation targeted therapeutic options. Vepafestinib (TAS0953/HM06), a RET-selective inhibitor, is being evaluated in patients with locally advanced or metastatic solid tumors harboring RET alterations in MARGARET (NCT04683250), an open-label, single-arm, phase 1/2, first-in-human study. Here, we present the preliminary phase 1 safety and antitumor-activity results (data cutoff date: November 15, 2024).

Methods: Phase 1 consists of dose escalation (DE; for patients with solid tumors harboring RET alterations) and dose expansion (EX; for patients with locally advanced or metastatic RET-fusion-positive non-small-cell lung cancer [NSCLC]). In EX, patients naïve to RET-selective inhibitors and systemic anticancer treatment were enrolled in cohort 1 (C1), and patients pretreated with RET-selective inhibitors were enrolled in cohort 2 (C2). The initial dose in DE was 20 mg BID, and accelerated titration was performed. The primary endpoints were the maximum tolerated dose (MTD) for DE and the recommended phase 2 dose in EX. The secondary endpoints included safety, tolerability, antitumor activity, pharmacokinetics, and predictive biomarkers.

Results: As of November 15, 2024, 32 patients were enrolled for DE (Asian: 41%, White: 50%, other: 9%), and 14 patients (C1: 4, C2: 10 patients) for EX (Asian: 100%). The DE tumor types were lung (n=23), thyroid (n=8), and pancreatic (n=1) cancer. The vepafestinib dose was escalated to 650 mg BID. Dose-limiting toxicities (DLTs) occurred in two of the three patients at 650 mg BID, and 500 mg BID was deemed the MTD. The DLTs were grade 3 headache (n=1) and grade 3 back pain (n=1). The most common treatment-emergent adverse events (TEAEs) in DE (any grade, grade ≥3) were headache (25%, 6%), nausea (25%, 0%), and malaise (19%, 3%). Confirmed/unconfirmed partial responses (PRs) in DE were reported in four of 32 patients: a patient with RET-fusion-positive NSCLC who was pretreated with an RET-selective inhibitor, a patient with RET-fusion-positive thyroid cancer who was pretreated with an RET-selective inhibitor, and two patients who were naïve to RET-selective inhibitors and had fusion-positive NSCLC. In EX, 500 mg vepafestinib was administered BID. The most common TEAEs (any grade, grade ≥3) in EX were headache (79%, 7%), nausea (29%, 0%), and malaise (21%, 0%). In C1, PRs were observed in two of four patients; the disease control rate (DCR) and median time to response (mTTR) were 50% and 1.3 months, respectively. On C2, PRs were observed in three of 10 patients, and the DCR and mTTR were 80% and 1.4 months, respectively.

Conclusions: Vepafestinib was well tolerated and displayed preliminary antitumor activity in patients with solid tumors harboring RET alterations, both in treatment-naïve and RET-selective inhibitor-pretreated cancers, indicating encouraging therapeutic potential. Enrollment in this trial continues.

Keywords: Vepafestinib, RET-selective inhibitor, RET-aberrant solid tumors

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.59 A Phase Ib/Ii Study of Vebreltinib Plus Tislelizumab in Patients With MET-Amplified and PD-L1-Positive Locally Advanced or Metastatic NSCLC

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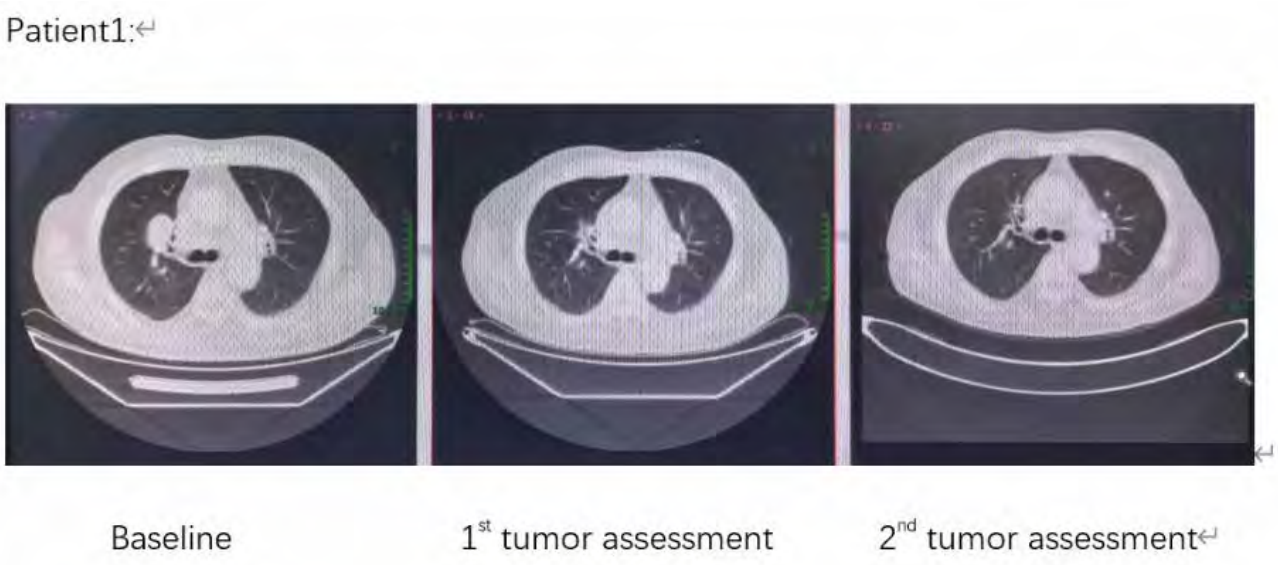
Introduction: For patients with de novo MET amplification who lack driver mutations, treatments remain limited. The standard treatment for driver-negative patients offers only modest survival benefits. Moreover, MET-targeted monotherapy yields suboptimal outcomes in primary MET-amplified NSCLC. Given that MET aberrations are frequently associated with high PD-L1 expression, combining MET inhibitors with immune checkpoint inhibitors may confer enhanced clinical benefit. In this investigator-initiated trial, we evaluated the safety and efficacy of combining Vebreltinib-a highly selective MET-TKI with Tislelizumab in patients with MET-amplified and PD-L1-positive locally advanced or metastatic NSCLC.

Methods: Eligible patients with locally advanced or metastatic NSCLC demonstrating primary MET-amplified and positive PD-L1 expression received Vebreltinib and Tislelizumab every 21 days (Q21d). Tumor assessments were conducted every six weeks from the initiation of administration.

Results: To date, two patients have been enrolled. Patient 1: A 65-year-old male was diagnosed stage IVC NSCLC with primary MET amplification confirmed by fluorescence in situ hybridization (FISH; GCN of 10.8, MET-to-CEP7 ratio ≥2.40), and a PD-L1 tumor proportion score (TPS) of 60%. After six cycles of combined treatments, computed tomography (CT) scans demonstrated a marked reduction in the target lesions, achieving a partial response (PR). A subsequent assessment revealed further tumor shrinkage-70.9% reduction-confirming PR. At manuscript submission, the patient maintained a sustained response with a progression-free survival (PFS) exceeding six months. One serious adverse event-SAE (immune-related colitis), attributable to Tislelizumab, was reported; no SAE were related to Vebreltinib. Patient 2: A 68-year-old male with stage IIIC NSCLC exhibited primary MET amplification which was confirmed by FISH (GCN of 8.15, MET-to-CEP7 ratio ≥2.80), with a PD-L1 TPS of 60%. Following two cycles of treatments, CT scans indicated a significant reduction in the target lesions, reaching a PR. At manuscript submission, the patient continued to experience a sustained response with a PFS of more than five months, and treatments was well tolerated with no SAE.

Conclusions: In this study, first-line treatment with the combination of Vebreltinib and Tislelizumab resulted in rapid and durable antitumor activity in two patients with MET-amplified and PD-L1-positive locally advanced or metastatic NSCLC. However, clinicians should remain vigilant regarding immune-related adverse events. Notably, although both patients exhibited low-level MET amplification by NGS, FISH analysis revealed GCN exceeding 10, suggesting that the optimal cut-off for MET amplification merits further investigation. Larger studies are warranted to validate the efficacy and safety of this combined regimen.



Keywords: MET-amplified, PD-L1 postive, Vebreltinib

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.60 The Combination of USP24-i-101-Astemizole Sensitizes the Cytotoxicity of Taxol and Gefitinib in Drug-Resistant Lung Cancer

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Introduction: Cancer is one of the major causes of death worldwide. Genomic instability is the primary reason that triggers gene mutation and induces cancer progression. Genes such as Kras, EGFR and p53 are highly mutated, leading to hyperplasia and metastasis of tumors. Various treatments, including surgery, radiotherapy, chemotherapy, target therapy, and immune therapy, have been employed to treat cancer. However, genomic heterogeneity causes drug resistance and cancer recurrence after treatment. Overcoming drug resistance following therapies is important to prevent from cancer-led deaths in the future.

Methods: In this study, we created a gene signature for drug discovery utilizing the Connectivity Map (CMap). This strategy involves repurposing drugs by identifying those with genetic effects that counteract the USP24 signature, thereby potentially reversing or alleviating drug resistance. After rigorous screening and analysis, we identified several promising candidates, excluding those previously tested in lung cancer trials to maintain novelty in our research.

Results: In this study, we employed the yeast two-hybrid system to screen for proteins interacting with USP24. Among 250 such proteins, functional enrichment analysis using MetaCoreTM revealed that 33 of them were involved in lung cancer progression. Subsequently, we investigated gene expression and survival rates of these 33 proteins in lung cancer patients and cell lines utilizing TCGA databases, Kaplan-Meier Plotter databases, and RNA-seq profile from A549/A549-T24 cells. Our findings indicated high expression of genes like FEN1 and NEK2, coupled with low expression of MOAP1 and PIAS2, was associated with poor prognosis in lung cancer patients. Based on these gene signatures, we identified 10 potential drugs for inhibiting lung cancer progression or drug resistance through the Connectivity Map (CMap) database via drug repurposing strategy. Of these 10 drugs, six showed similar indicators in Clinical_Trials, while the other four candidates (15-delta prostaglandin J2, Astemizole, Trifluoperazine, and 1,4-chrysenequinone) were chosen to evaluate their effect on re-sensitizing cytotoxicity of Taxol and Gefitinib in drug-resistant cancer cells. Experiments demonstrated that treatment with USP24-i-101 and Astemizole alone significantly inhibited drug resistance and re-sensitized the cytotoxicity of Taxol and Gefitinib in drug-resistant lung cancer cells (Fig.1).

Conclusions: In this study, we combined global USP24-interacting proteins, gene expression profiles from TCGA and lung cancer drug sensitive and resistant cells, along with clinical survival rate to screen for drug repurposing. Several approved clinical drugs, including 15d-PGJ2, Trifluoperazine, 1,4-Chrysenequinone and Astemizole, were found to inhibit chemotherapy-induced and target therapy-induced cancer drug resistance.

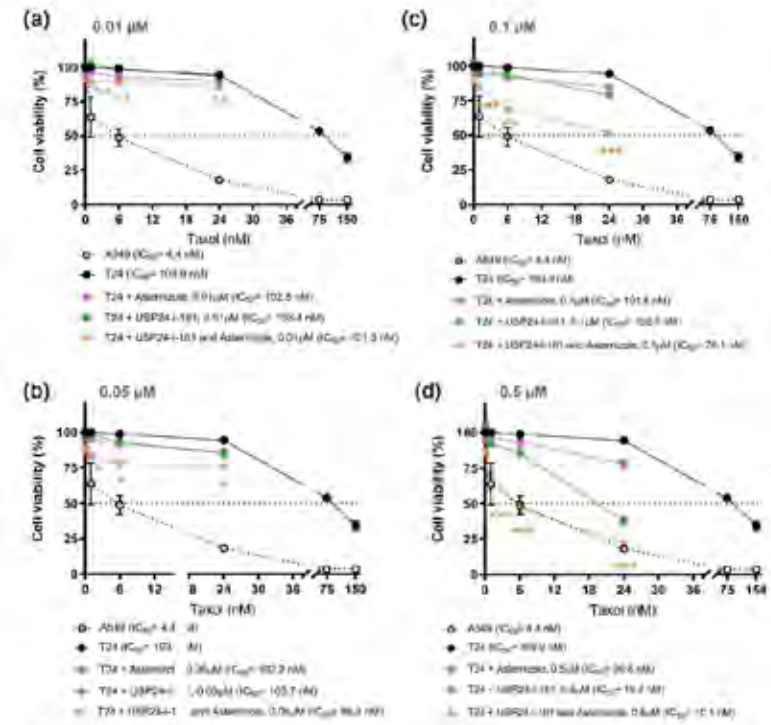

Fig. 6. USP24-i-101 and Astemizole cocktail treatment induced synergistic effect on resensitizing the cytotoxicity of Taxol. Taxol-induced drug-resistant lung cancer cells (T24 cells) were treated with various doses of Taxol combined with 0.01 μM (a), 0.05 μM (b), 0.1 μM (c), and 0.5 μM (d) USP24-i-101 and Astemizole for 48 h, and cell viability was measured by cell counting assay.

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.61 Retrospective Multicenter Study Within the German Network Genomic Medicine Lung Cancer on RET Fusions as Resistance in EGFR-Mutant Lung Cancer

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Introduction: EGFR mutations occur in between 15% and 50% 1,2 of non-small cell lung cancer cases (NSCLC), with third-generation tyrosine kinase inhibitors (TKI) providing clinical benefit until resistance emerges. Recent advancements in sequencing have identified RET-fusions as a potential resistance mechanism3-6. Emerging evidence suggests that combining EGFR- and RET-TKIs may overcome this resistance 7,8. Creating personalized assays, such as digital droplet - based ctDNA analysis allows for a dynamic assessment of tumor genetics over time, providing early insight into treatment efficacy. This study aimed to retrospectively evaluate the occurrence of RET fusions as a resistance mechanism in EGFR-mutated NSCLC patients within the national Network Genomic Medicine (nNGM) in Germany and analyse responses to different treatment approaches.

Methods: A multicenter retrospective analysis across all nNGM centers analysed EGFR-mutant NSCLC patients with concurrent RET fusions. Clinical data, treatments, and outcomes were evaluated, with PFS and OS as primary endpoints. In one patient, tumor and liquid biopsies were assessed and an individualized EGFR and RET-specific assay was developed using digital droplet PCR technology. Tissue and circulating tumor DNA were analyzed longitudinally and correlated with the clinical trajectory

Results: Nine nNGM centers contributed one patient each with an EGFR and concurrent RET fusion. Patients had a median age of 54; most were female (77%) and never-smokers (66%). Two patients (22%) harboured rare EGFR (Exon 20 insertion) mutations with KIF5B-RET fusions and received a selective RET-TKI as first-line monotherapy. The others (n=7) had common EGFR mutations (66% Del19, 11% L858R), with fusion partners including CCDC6 (57%) and NCOA4 (29%).In one case, the fusion partner could not be reported. Patients received an EGFR-TKI as first-line therapy and developed RET-mediated resistance in median 11.4 months after initial diagnosis (range: 6.3-19.7 months). For three patients, a combination of RET (Pralsetinib) and EGFR-TKIs (Osimertinib) was chosen, yielding a PFS of 3.9 months, 6.0 months (ongoing) and 10.5 months (ongoing). The results of the EGFR and RET-specific assay in the latter patient closely correlated with the clinical course: both alterations were identified during oligoprogression and again subsequently at systemic progression (Fig. 1). However, following treatment with Osimertinib and Selpercatinib, neither alteration was detectable.

Conclusions: RET fusions constitute a rare yet clinically significant resistance mechanism in EGFR-mutated NSCLC. Early detection via individualized EGFR and RET-specific cDNA-assay may enhance therapeutic decision-making. While combinatorial EGFR- and RET-TKI therapy holds promise, further research is essential to refine treatment strategies and evaluate long-term efficacy.

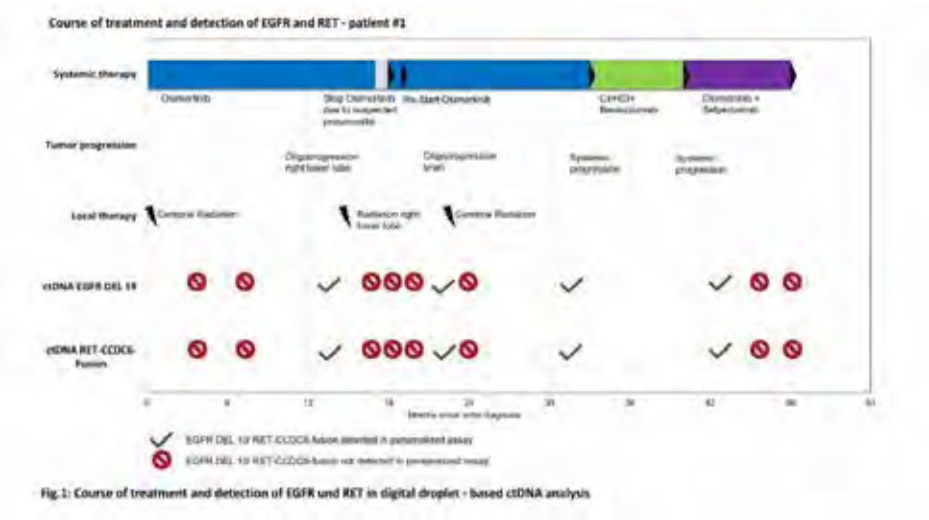

Fig. 1: Course of treatment and detection of EGFR und RET in digital droplet - based ctDNA analysis

Keywords: RET fusion as resistance in mEGFR NSCLC, individualized EGFR and RET-specific assay, combined EGFR and RET- targeted therapy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.62 First-Line Osimertinib ± Platinum-Pemetrexed Chemotherapy for EGFR-Mutated Advanced NSCLC: FLAURA2 Non-Asian Country Cohort

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Introduction: In FLAURA2 (NCT04035486), first-line osimertinib (a third-generation, CNS-active EGFR-tyrosine kinase inhibitor) + chemotherapy showed a statistically significant progression-free survival (PFS) benefit versus osimertinib monotherapy in patients with EGFR-mutated advanced NSCLC. We report data from the non-Asian country cohort, defined as the full analysis set minus the Asian cohort.

Methods: In the global, Phase III, open-label FLAURA2 study, eligible patients were ≥18 years with EGFR-mutated (Ex19del/L858R) locally advanced/metastatic NSCLC, WHO PS 0/1 and no prior systemic treatment for advanced NSCLC; stable CNS metastases were permitted. Patients were randomised 1:1 to osimertinib 80 mg QD + chemotherapy (4 induction cycles: osimertinib + pemetrexed with cisplatin or carboplatin Q3W; then osimertinib + pemetrexed Q3W maintenance) or osimertinib monotherapy until progression/discontinuation. Stratification was by race (Chinese Asian/non-Chinese Asian/non-Asian), EGFR mutation test method (local/central) and WHO PS (0/1). Primary endpoint: PFS by investigator per RECIST 1.1. Secondary endpoints included overall survival (OS) and safety. PFS and OS hazard ratio (HR) analyses in the non-Asian country cohort were performed by stratified log-rank test. Data cut-off: 3 April 2023 (updated interim OS analysis [regulatory authority request]: 8 January 2024).

Results: In the non-Asian country cohort, 110 and 114 patients were randomised to osimertinib + chemotherapy and osimertinib monotherapy, respectively. Baseline characteristics were generally balanced between arms (osimertinib + chemotherapy/osimertinib monotherapy: median age, 61/62.5 years; male, 37%/33%; Ex19del, 72%/60%; L858R, 25%/39%; Ex19del + L858R, 3%/1%; CNS metastases, 34%/36%; median baseline target lesion tumour size, 64.5/71 mm). PFS and OS were improved with osimertinib + chemotherapy versus osimertinib monotherapy (Table). In the osimertinib + chemotherapy (safety analysis set; n=109) versus osimertinib monotherapy (n=111) arms, grade ≥3 adverse events (AEs) were reported in 64 (59%) versus 36 (32%) patients, and AEs led to osimertinib discontinuation in 14 (13%) versus 6 (5%) patients (further safety data will be presented).

Conclusions: First-line osimertinib + chemotherapy resulted in clinically meaningful benefits versus osimertinib monotherapy in patients from non-Asian countries with EGFR-mutated advanced NSCLC, consistent with the global FLAURA2 results (Planchard NEJM 2023); top-line safety results were also similar to the global data. These data support osimertinib + chemotherapy as a first-line treatment option for this patient population.

Efficacy endpoint	Osimertinib + chemotherapy n=110	Osimertinib monotherapy n=114
Median PFS by investigator, months (95% CI)*	26.0 (21.9, NC)	14.1 (13.6, 22.1)
PFS HR (95% CI) [maturity, %†]	0.53 (0.36, 0.78) [49]	
Median PFS by blinded independent central review, months (95% CI)*	29.4 (22.3, NC)	16.4 (13.8, 25.3)
PFS HR (95% CI) [maturity, %†]	0.51 (0.34, 0.77) [44]	
Median OS, months (95% CI)‡	Not reached (37.1, NC)	32.6 (28.8, NC)
OS HR (95% CI) [maturity, %†]	0.66 (0.43, 1.01) [39]	

*Data cut-off, 3 April 2023. †Overall, across both arms. ‡Data cut-off, 8 January 2024.
CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; PFS, progression-free survival.

Keywords: Osimertinib, EGFR-mutated NSCLC, EGFR-TKI

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.63 MTAPloss Is Frequent and Potentially Targetable With PRMT5 Inhibitors in Oncogene-Driven NSCL

M. Aldea[1], M. Locquet[1], L. Liao[1], K. Ngo[1], E. Garbo[1], S. Laaksonen[2], P. Gokhale[1], N. Mahadevan[3], S. Nakazawa[1], E. Ivanova[1], F. Pecci[1], J. Huang[2], F. Paoloni[1], E. Gariazzo[1], V. Santo[1], B. Ricciuti[1], J. LoPiccolo[1], J. Luo[1], J.K. Rotow[1], C. Paweletz[1], L. Sholl[2], A. Shaw[1], P.A. Janne[1]
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Introduction: Homozygous loss of MTAP (methylthioadenosine phosphorylase) defines a new therapeutic vulnerability based on emerging clinical data with MTA-cooperative PRMT5 (protein arginine methyltransferase 5) inhibitors. We report the frequency of MTAP loss in oncogene-driven NSCLC and evaluate the preclinical activity of PRMT5 inhibitors, alone or combined with tyrosine kinase inhibitors (TKIs), in patient-derived models of oncogene-driven NSCLC.

Methods: This retrospective study included NSCLC patients at Dana-Farber Cancer Institute whose MTAP status was assessed by next-generation sequencing (NGS) using Oncopanel v3-3.1. MTAP loss was defined as a homozygous deletion; samples with tumor purity <40% were excluded. MTAP status was assessed in patient-derived models by immunohistochemistry (IHC) and/or NGS (PDX), and by Western blot and Sanger sequencing (cell lines). MTAP was knocked out using CRISPR-Cas9 in MTAP-intact, EGFR+ or ALK+ cell lines to evaluate impact on TKI sensitivity via a 5-day viability assay. The efficacy of the MTA-cooperative PRMT5 inhibitor BMS-986504 (MRTX1719) was tested alone or with a TKI in patient-derived and commercial cell lines using a 10-day viability assay. Synergistic activity was assessed using Combenefit software.

Results: Among 2,027 NSCLC patients, MTAP loss was observed in 11.9% (242/2027), with highest prevalence in ALK$^+$ (28.3%, 17/60), followed by EGFR$^+$ (16.7%, 86/516), RET$^+$ (15.4%, 4/26), MET$^+$ (13.3%), ROS1$^+$ (12.5%, 2/16), KRAS$^+$ (9.9%, 58/584), HER2$^+$ (7.1%, 3/42), and BRAF$^+$ (7.1%, 7/99). Among patients without a targetable oncogene, MTAP loss was identified in 9.2% (59/639). Compared to MTAP-intact samples, MTAP-deleted tumors were significantly enriched for CDKN2A loss (100% vs. 5.7%, p<0.001), EGFR mutations (37% vs. 26%, p<0.001), and ALK fusions (7.5% vs. 2.7%, p<0.001). In patients with metastatic disease and unpaired biopsies collected before (N=229) or after TKI (N=238), the frequency of MTAP loss was similar between baseline and progression samples (14.8% vs. 21%, p=0.37 across all drivers; EGFR$^+$: 15.9% vs. 22.5%, p=0.37; ALK$^+$: 29.2% vs. 30%, p=1.00). MTAP deletion was detected in 19.4% (27/139) of patient-derived models of oncogene-driven NSCLC, including 20.6% (13/63) EGFR$^+$, 44.4% (4/9) ALK$^+$ and 15.8% (3/19) KRAS$^+$ models. CRISPR-engineered MTAP knockout in EGFR$^+$ (HCC827) and ALK$^+$ (DFCI76) cell lines did not alter sensitivity to respective TKIs, with IC_{50} values of 0.01 µM for osimertinib (HCC827sgMTAP) and 0.01 µM for alectinib and lorlatinib (DFCI76sgMTAP), all comparable to parental controls. MRTX1719 monotherapy showed IC_{50} <0.5 µM in 5/7 EGFR$^+$ MTAP-deleted models, and <0.16 µM in all 5 ALK$^+$ MTAP-deleted lines. Combination with osimertinib or lorlatinib demonstrated synergistic activity in 3/7 EGFR$^+$ and 3/5 ALK$^+$ MTAP-deleted models. In TKI-sensitive lines, 10-day treatment followed by drug washout and live-cell imaging showed delayed regrowth with combination compared to TKI alone (final confluence: 30-50% with TKI vs. <10% with combination).

Conclusions: MTAP loss occurs in nearly one-third of ALK+ NSCLC and one-sixth of EGFR+ NSCLC regardless of prior TKI treatment. Preclinical data suggest that oncogene-driven tumors with MTAP loss are sensitive to single agent PRMT5 inhibitors and that combination TKI and PRMT5 inhibitors may have additive or synergistic antitumor activity. These findings support clinical testing of combined TKI and PRMT5 inhibitors in oncogene-driven MTAP deleted NSCLC.

Keywords: MTAP loss, driver, PRMT5 inhibitor

P3.12.64 Frontline Treatment Duration in MET-Amplified NSCLC After Third-Generation EGFR-TKI Failure: SACHI Study Insights

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Introduction: MET amplification is an important mechanism of acquired resistance to third-generation (gen) EGFR-TKIs, which are widely used in treating advanced EGFR-mutated non-small cell lung cancer (NSCLC) patients. However, MET amplification testing is not routinely performed for all patients who fail first-line EGFR-TKI treatment. Consequently, data on characteristics of the acquired MET amplification patients is still being explored.

Methods: We evaluated all screened MET-amplified patients who had been previously treated with third-gen EGFR-TKIs from the SACHI study, which is a randomized, open-label, phase 3 study of savolitinib plus osimertinib versus chemotherapy, targeting MET-amplified advanced NSCLC patients who progressed on first-line EGFR-TKIs. MET amplification was assessed in a central laboratory using tumor samples collected after disease progression. Patients who had been previously treated with third-gen EGFR-TKI were required to have MET copy number ≥10 verified by Fluorescence In Situ Hybridizatio (FISH). In these population, the disease characteristics and prior treatments of this defined group were collected and analyzed.

Results: Among 307 patients who had been previously treated with third-gen EGFR-TKI, and provided valid tissue samples, 99 were verified to have MET copy number≥10. Among these patients, 96 (97.0%) were initially diagnosed with adenocarcinoma. EGFR mutation types were mainly 19Del (47.5%, 47 patients) and L858R (51.5%, 51 patients). Brain metastases were reported in 44 patients (44.4%), while the remaining patients had no brain metastases, except for 2 missing reports; 68 patients (68.7%) had metastases in three or more sites. The median duration of therapy (DoT) for previous therapy was 12.7 months among 93 patients with available start and end dates for front-line EGFR-TKI treatment. Of these patients, 68 (73.1%) received osimertinib, with a median treatment duration of 12.8 months, while the rest were mainly treated with almonertinib (19.4%) and furmonertinib (6.5%). Treatment durations were shorter than the median DoT reported in FLAURA study and other phase 3 studies of third gen EGFR-TKIs (15.2-18.3 months; Soria J et al, New Engl J Med; Lu S et al, J Clin Oncol; Shi Y et al, Lancet Respir Med).

Conclusions: NSCLC patients with MET amplification who failed first-line third-gen EGFR TKI treatment demonstrated a high disease burden, affecting their exposure to prior therapy. These data suggested that MET amplification might accelerate disease progression during prior therapy as an early resistance mechanism.

Table

Characteristic	*MET* Copy Number ≥ 10 (N=99)
Initial pathological diagnosis of adenocarcinoma, n (%)	96 (97.0)
EGFR mutation type at initial diagnosis, n (%)	
Exon 19 Deletion	47 (47.5)
L858R	51 (51.5)
Other	1 (1.0)
Clinical stage of IV at baseline, n (%)	99 (100.0)
Brain metastasis at baseline, n (%)	44 (44.4)
Number of metastasis sites, n (%)	
< 3	31 (31.3)
≥ 3	68 (68.7)
Duration of Previous EGFR-TKI Therapy (months)	
n	93
Median (range)	12.7 (2.7, 35.7)
Osimertinib	
n	68
Median(range)	12.8 (3.0, 30.6)

Keywords: EGFR-mutant, MET-amplified advanced NSCLC, savolitinib plus osimertinib, duration of therapy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.65 First-Line Osimertinib ± Platinum-Pemetrexed in EGFR-Mutated Advanced NSCLC: FLAURA2 Clinical Outcomes by EGFRm Subtype

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Introduction: Osimertinib is a third-generation, CNS-active, EGFR-TKI that potently and selectively inhibits EGFR-TKI sensitising and EGFR T790M resistance mutations and is a preferred first-line treatment for EGFR-mutated advanced NSCLC. In the Phase III FLAURA2 study (NCT04035486), osimertinib plus platinum-pemetrexed chemotherapy significantly improved PFS versus osimertinib monotherapy as first-line treatment of EGFR-mutated advanced NSCLC (investigator-assessed median PFS, 25.5 vs 16.7 months, respectively; HR 0.62, 95% CI 0.49, 0.79; p<0.001) and is now a recommended treatment option in this setting. The PFS benefit of osimertinib plus chemotherapy was consistent across pre-specified subgroups, including those associated with a poor prognosis, such as patients with L858R mutations. To better understand the impact of EGFR mutation subtype, we evaluated outcomes in the relevant patient subgroups from FLAURA2.

Methods: Eligible patients were randomised 1:1 to receive osimertinib plus platinum-based chemotherapy, or osimertinib monotherapy until progression or a discontinuation criterion was met. Primary endpoint was investigator-assessed PFS per RECIST 1.1. Secondary endpoints included OS and safety. Exploratory analyses by baseline EGFR mutation type (L858R and Ex19del) were performed, including baseline characteristics, clinical outcomes and safety. Data cut-off: PFS and safety, 03 April 2023; second interim analysis of OS, 08 January 2024.

Results: 557 patients were randomised to osimertinib plus chemotherapy (overall, n=279; L858R subgroup, n=106; Ex19del subgroup, n=172) or osimertinib monotherapy (overall n=278; L858R subgroup, n=107; Ex19del subgroup, n=169). Baseline characteristics by EGFR mutation subgroups were similar between treatment arms. In the L858R subgroup, osimertinib plus chemotherapy/osimertinib: median age, 63/65 years; male, 41%/41%; CNS metastases, 43%/47%. In the Ex19del subgroup, osimertinib plus chemotherapy/osimertinib: median age, 60/60 years; male, 36%/38%; CNS metastases, 40%/35%. PFS favoured osimertinib plus chemotherapy compared with osimertinib alone, in both the L858R subgroup and the Ex19del subgroup, with a trend towards improvement in OS (Table). The adverse event (AE) profiles in the two treatment arms were consistent between subgroups and with the global analysis. All causality grade ≥3 AEs: L858R, osimertinib plus chemotherapy 68%/osimertinib 27%; Ex19del, 61%/28%, respectively. AEs that led to treatment discontinuation: L858R, osimertinib plus chemotherapy 47%/osimertinib 6%; Ex19del, 48%/7%, respectively.

Conclusions: These data show a clinically meaningful PFS benefit with osimertinib plus chemotherapy compared with osimertinib monotherapy, and a trend towards an OS benefit at the second interim analysis for OS, irrespective of EGFR mutation subtype.

	L858R subgroup (n=213)		Ex19del subgroup (n=341)*	
	Osi + CTx (n=106)	Osi (n=107)	Osi + CTx (n=172)	Osi (n=169)
PFS events, n (%)	55 (52)	70 (65)	65 (38)	94 (56)
mPFS, months (95% CI)	24.7 (19.5, 27.4)	13.9 (11.1, 19.4)	27.9 (25.1, NC)	19.4 (16.5, 27.6)
HR (95% CI)†	0.63 (0.44, 0.90)		0.60 (0.44, 0.83)	
6-month rate, % (95% CI)	91 (84, 95)	78 (69, 85)	90 (85, 94)	87 (81, 92)
12-month rate, % (95% CI)	78 (69, 85)	58 (48, 67)	81 (74, 86)	71 (63, 77)
24-month rate, % (95% CI)	51 (40, 61)	35 (25, 44)	61 (52, 69)	45 (37, 53)
OS events, n (%)	48 (45)	57 (53)	52 (30)	69 (41)
mOS, months (95% CI)	37.7 (34.5, NC)	32.4 (28.0, 37.6)	NR (NC, NC)	NR (35.2, NC)
HR (95% CI)†	0.72 (0.49, 1.06)		0.74 (0.52, 1.06)	
12-month rate, % (95% CI)	89 (81, 93)	87 (79, 92)	89 (83, 93)	95 (91, 98)
24-month rate, % (95% CI)	78 (69, 85)	64 (54, 72)	81 (74, 86)	77 (70, 83)
36-month rate, % (95% CI)	55 (43, 65)	41 (30, 51)	69 (61, 76)	56 (47, 64)

*Patients with both mutations were included in the Ex19del subgroup. Three patients in the study had unknown mutation status and were not included in either subgroup. †Subgroup analysis was performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by-subgroup interaction term.
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NC, not calculable; NR, not reached; osi, osimertinib.

Keywords: Osimertinib, EGFR-mutated NSCLC, EGFR-TKI

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.66 Overcoming Osimertinib Resistance in EGFR<+ NSCLC: PI3K Inhibitor Combined With Osimertinib Restores Drug Sensitivity

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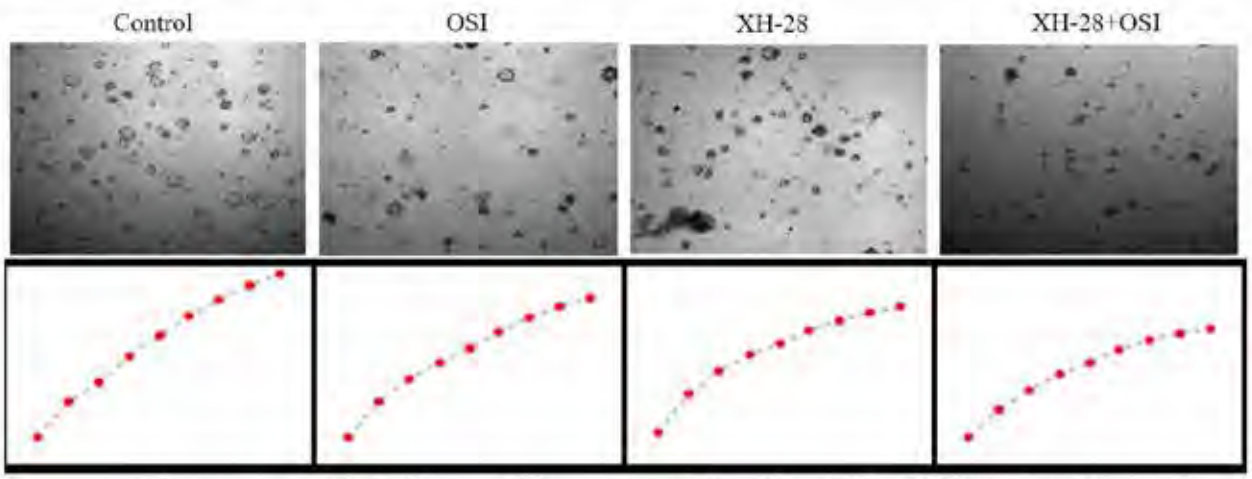
Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with EGFR mutation-positive non-small cell lung cancer (EGFRm+ NSCLC) patients often developing resistance to EGFR tyrosine kinase inhibitors (TKIs) such as Osimertinib. Currently, effective strategies to overcome this resistance are limited. PI3K activation has emerged as a key mechanism contributing to Osimertinib resistance. In this study, we investigated the potential of a novel PI3K inhibitor, XH-28, combined with Osimertinib to suppress the EGFR-PI3K-AKT signaling pathway, induce apoptosis, and inhibit proliferation and metastasis in Osimertinib-resistant NSCLC cells.

Methods: A novel PI3K inhibitor, XH-28, was synthesized. Osimertinib-resistant NSCLC cell lines (PC9-OR and H1975-OR) were established from Osimertinib-sensitive EGFRm+ NSCLC cell lines (PC-9 and NCI-H1975). The combined effects of XH-28 and Osimertinib on cell proliferation, apoptosis, cell cycle progression, migration, and protein expression of EGFR, PI3K and AKT were evaluated. Three-dimensional (3D) tumor organoid models were generated from clinical NSCLC patient specimens using the hanging drop method to assess the synergistic effects of PI3K inhibition on Osimertinib cytotoxicity. Additionally, a xenograft mouse model of H1975-OR NSCLC was used to evaluate the antitumor activity of the combination therapy in vivo.

Results: The novel PI3K inhibitor XH-28 was successfully synthesized and validated. Osimertinib-resistant models (PC9-OR, H1975-OR, 3D organoids, and xenografts) exhibited significantly reduced sensitivity to Osimertinib. The combination of XH-28 and Osimertinib suppressed the EGFR-PI3K-AKT pathway, induced apoptosis, and arrested the cell cycle at the G1 phase. Migration capacity decreased by 60% ($p<0.001$). In 3D organoids, combination therapy reduced growth by 45% ($p<0.05$). In vivo, XH-28/Osimertinib dual therapy inhibited tumor growth by 70% ($p<0.001$) and suppressed EGFR phosphorylation in xenografts.

Conclusions: Our findings demonstrate that PI3K inhibition restores Osimertinib sensitivity in resistant NSCLC cells. The combination of XH-28 and Osimertinib offers a promising therapeutic strategy for overcoming Osimertinib resistance in EGFRm+ NSCLC, with significant clinical and economic implications.



The upper panel illustrates the morphological changes of 3D tumor organoids derived from EGFRm+ NSCLC patients following 48-hour treatment with XH-28 and/or Osimertinib. The lower panel displays the corresponding cell viability profiles, as determined by the Alamar Blue assay, at 0h, 6h, 12h, 18h, 24h, 30h, 36h, 42h, and 48h post-treatment.
Treatment groups:
- **Control**: Untreated organoids.
- **OSI**: Osimertinib monotherapy (200 nmol/L).
- **XH-28**: XH-28 monotherapy (20 nmol/L).
- **XH-28+OSI**: Combination therapy with Osimertinib (200 nmol/L) and XH-28 (20 nmol/L).

Keywords: Osimertinib resistance, PI3K pathway, Combination therapy

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.67 Redefining Tolerability: A Head-To-Head IPD Toxicity Comparison of Amivantamab+Lazertinib vs Osimertinib+Chemotherapy in EGFR-Mutant NSCLC

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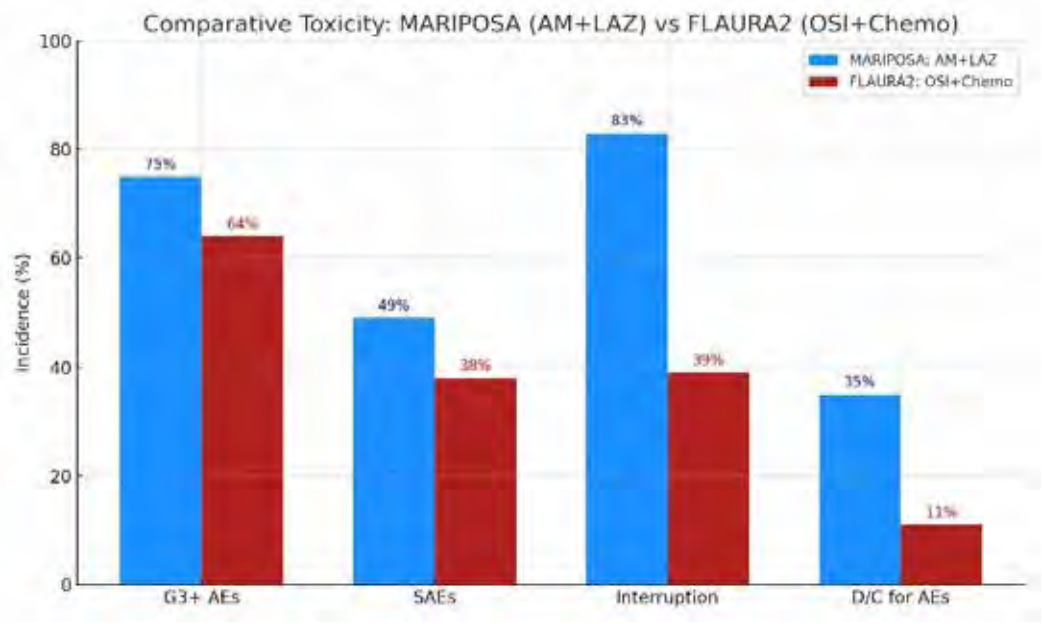
Introduction: Background: First-line treatment paradigms for EGFR-mutant non-small cell lung cancer (NSCLC) are rapidly evolving with the introduction of novel combination regimens. Amivantamab plus lazertinib (AMI+LAZ) and osimertinib combined with platinum-based chemotherapy (OSI+CT) have each demonstrated clinical efficacy as first-line treatments for EGFR-mutant NSCLC in phase III trials (MARIPOSA and FLAURA2, respectively); however, direct comparative data on their safety profiles remain unavailable.

Methods: Individual patient data (IPD) meta-analysis from the MARIPOSA (n=429; AM+LAZ) and FLAURA2 (n=276; OSI+CT) trials was conducted. Adverse events (AEs), grade ≥3 AEs, serious AEs (SAEs), and treatment discontinuation due to AEs were assessed. Odds Ratios (Ors) and p-values were calculated using Fisher's exact test. Subgroup analyses were performed based on age, sex and ECOG performance status.

Results: Baseline characteristics were balanced between groups (median age 64, 56% female, 60% ECOG PS1). In terms of high-grade toxicity, grade ≥3 AEs were reported in 75% of patients in the AMI+LAZ arm, compared to 64% in the OSI+CT arm. This translated to a significantly higher likehood of experiencing severe treatment-related toxicity with AMI+LAZ, with an OR of 1.68 (95% confidence interval [CI], 1.21-2.34 p=0.0022). Similarly, SAEs occurred in 49% of the patients treated with AMI+LAZ, compared to 38% of those who received OSI+CT. This differenced also reached statistical significance, with an OR of 1.56 (95% CI, 1.15-2.13, p=0.0052), suggesting a higher burden of serious toxicity with the dual EGFR-MET inhibition regimen. Treatment discontinuations due to AEs occurred in 10% of the AMI+LAZ combination and 11% of the OSI+CT. Despite the higher frequency of high-grade toxicity in the Amivantamab-based regimen, this did not translate into a significantly higher discontinuation rate. The OR for treatment discontinuation was 0.91 (95% CI, 0.56-1.50, p=0.7064), indicating no statistically significant difference between the two treatment strategies in terms of treatment cessation due to toxicity.

Conclusions: This IPD meta-analysis reveals a striking disconnect: AMI+LAZ carries a significantly higher burden of severe and serious AEs, yet discontinuation rates mirror those of OSI+CT. These findings challenge traditional definitions of "tolerability" and highlight the need to weigh toxicity trade-offs as critically as efficacy. In the absence of head-to-head trials, safety may emerge as the decisive factor in frontline treatment selection for EGFR-mutant NSCLC.



Keywords: EGFR-mutant NSCLC, individua patient data, safety

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.68 Regulating Autophagy Will Be a Potential Key Point in Overcoming EGFR TKI Resistance in Non-Small Cell Lung Cancer

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Introduction: Patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations demonstrate high initial response rates to first- and second-generation EGFR tyrosine kinase inhibitors (TKIs). However, most patients develop drug resistance within one year of treatment, leading to cancer recurrence. Autophagy is an essential mechanism that regulates intracellular metabolism, and plays a dual role in promoting cell death by anticancer treatment while playing an important role in the survival of cancer cells. Therefore, it is possible that inhibiting autophagy can improve the efficacy of anticancer drugs. This study aims to investigate whether inhibiting autophagy can overcome EGFR TKI resistance in lung cancer.

Methods: We asssembled the TMA composed 579 surgically resected tumor tissues from lung adenocarcinoma patients and evaluated protein expreession of autophagy flux-related signal molecues. To identify autophagy-related processes affected in resistant cell lines, Gene Ontology (GO) analysis was conducted (http://www.geneontology.org), focusing on biological processes (BP) and molecular functions (MF).

Results: Immunohistochemical analysis was performed to assess the expression of autophagy-related markers (P-AMPK, p-Beclin1, ULK1, GABARAPL1) in FFPE tissues from patients with advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutations. Among the 29 patients included in the study, 11 were male (53.9%), and the median age was 65.5 years (range, 41-83 years) When comparing tissue samples before EGFR TKI treatment and at the time of treatment failure, autophagy markers generally showed an increased expression after treatment. In particular, p-Beclin1 expression significantly increased after treatment failure (13.0 ± 10.9 vs. 59 ± 7.2, $P < 0.018$). These findings suggest that autophagy markers, especially p-Beclin1, may serve as potential predictive biomarkers for EGFR TKI resistance.

Conclusions: In this study, we demonstrated that ULK1 and GABARAPL1 partially contribute to resistance development in NSCLC cells through Osimertinib-induced autophagy. While these genes may not be ideal direct therapeutic targets, they show potential as biomarkers, warranting further investigation. Additionally, our findings suggest that combination therapy with the autophagy inhibitor HCQ may be an effective strategy for overcoming Osimertinib resistance.

Keywords: autophagy, EGFR TKI, drug resistance

P3.12.69 Updated Efficacy and Safety of Taletrectinib in Chinese Patients With ROS1+ Non-Small Cell Lung Cancer: Phase 2 TRUST-I Study

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Introduction: Taletrectinib, an oral, potent, central nervous system-active, selective next-generation ROS1 inhibitor, demonstrated high overall and intracranial response rates, prolonged progression-free survival (PFS), and activity against the G2032R acquired resistance mutation with a favorable safety profile in patients with ROS1+ non-small cell lung cancer (NSCLC) in the TRUST-I trial (NCT04395677; Li W, et al. J Clin Oncol. 2024;42(22):2660-2670). With an additional 11 months of follow-up, we report updated efficacy and safety in tyrosine kinase inhibitor (TKI)-naive and crizotinib-pretreated patients treated with taletrectinib in the regional pivotal TRUST-I trial.

Methods: The TRUST-I trial is a multicenter, single-arm, open-label, pivotal phase 2 study of taletrectinib conducted in China that enrolled TKI-naive and crizotinib-pretreated patients. All patients in the registrational cohorts received taletrectinib 600 mg once daily. The primary endpoint was objective response rate (ORR) by independent review committee per RECIST 1.1. Secondary endpoints included duration of response (DOR), PFS, overall survival (OS), and safety. The efficacy-evaluable population included patients who started treatment at the 600-mg dose of taletrectinib.

Results: As of October 28, 2024, 173 patients were enrolled in TRUST-I. Demographics and baseline patient characteristics were consistent with those previously reported in Li W, et al. J Clin Oncol. 2024;42(22):2660-2670 (median age: 55 years; 58% female; 74% never smoked). In 103 efficacy-evaluable TKI-naive patients, ORR was 90% (95% CI: 83, 95) and median DOR was not reached (NR). In 66 efficacy-evaluable TKI-pretreated patients, ORR was 52% (95% CI: 39, 64) and median DOR was 13.2 months (95% CI: 7.7, 24.9). Median PFS was 44.6 months in TKI-naive and 7.6 months in crizotinib-pretreated patients (Table). OS was NR for TKI-naive patients and 25.6 months for crizotinib-pretreated patients. With longer follow-up, there were no new or unexpected safety findings, and the reported frequency, types, and severity of adverse events were similar to previously reported safety profiles.

Conclusions: With longer follow-up in TRUST-I, taletrectinib continues to demonstrate high and durable ORRs and prolonged PFS with a favorable safety profile in both TKI-naive and TKI-pretreated patients. These results were also consistent with prior reports from the taletrectinib clinical program (Pérol M, et al. J Clin Oncol. 2025;epub April 3, 2025). The efficacy and safety of taletrectinib will be directly compared with crizotinib in an ongoing randomized head-to-head phase 3 trial in TKI-naive patients with locally advanced or metastatic ROS1+ NSCLC (NCT06564324).

Table: Responses in Evaluable Patients With *ROS1*+ NSCLC[a]

	TKI naive (n=103)	TKI pretreated (n=66)
ORR, % (95% CI)	90 (83, 95)	52 (39, 64)
Complete response, n (%)	5 (5)	0
Partial response, n (%)	88 (85)	34 (52)
Median DOR[b], months (95% CI)	NR (30.4, NR)	13.2 (7.7, 24.9)
Median PFS, months (95% CI)	44.6 (30.7, NR)	7.6 (5.5, 12.0)
Median OS, months (95% CI)	NR (41.6, NR)	25.6 (19.2, 31.9)

[a]Response-evaluable patients started treatment at taletrectinib 600 mg and had ≥1 measurable lesion at baseline.
[b]DOR was calculated for patients with confirmed responses.
DOR, duration of response; ORR, objective response rate; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Keywords: ROS1+, Non-small cell lung cancer (NSCLC), Taletrectinib

P3.12.70 Development of a Bispecific Antibody That Safely and Effectively Targets EGFR and B7H3 in NSCLC

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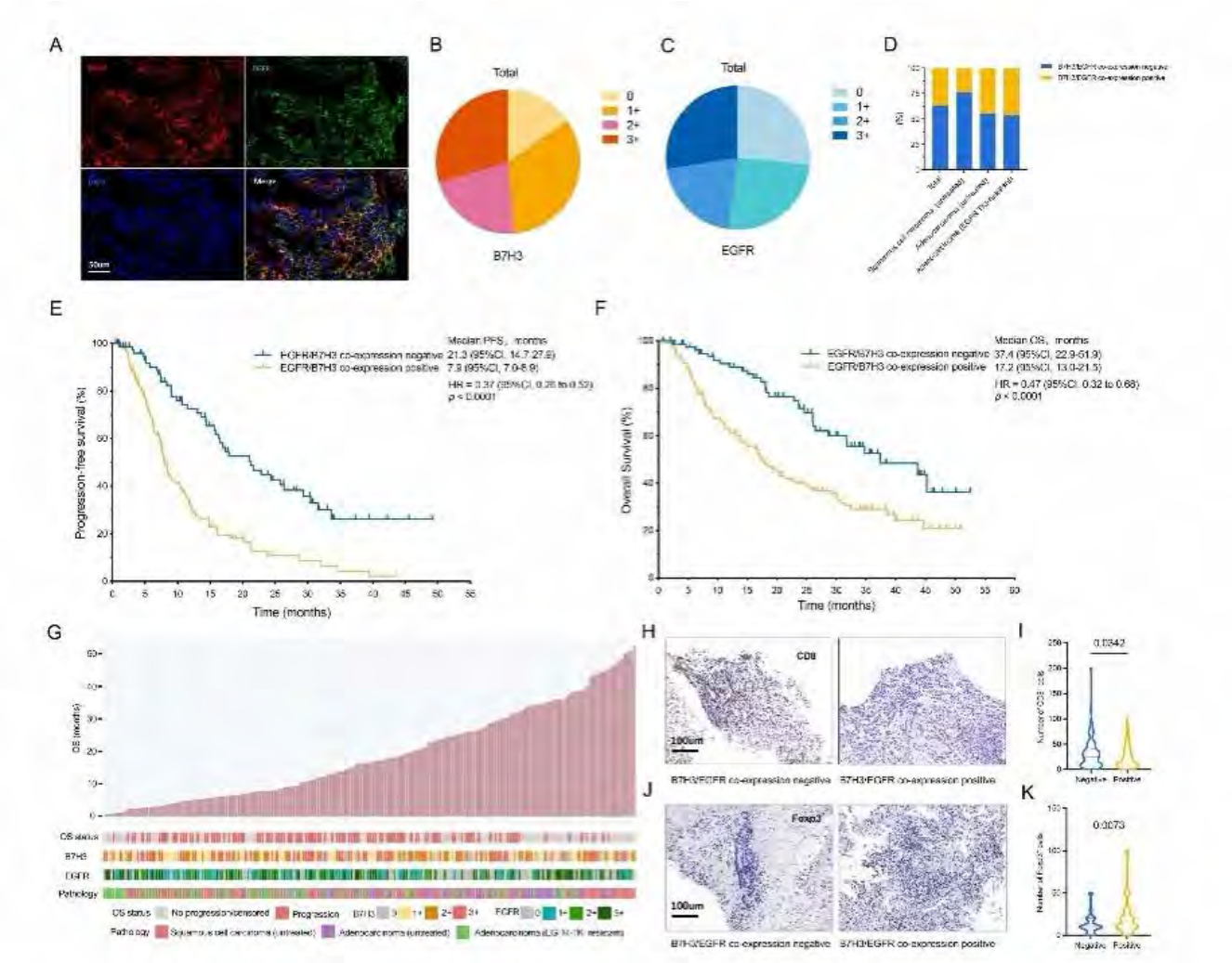
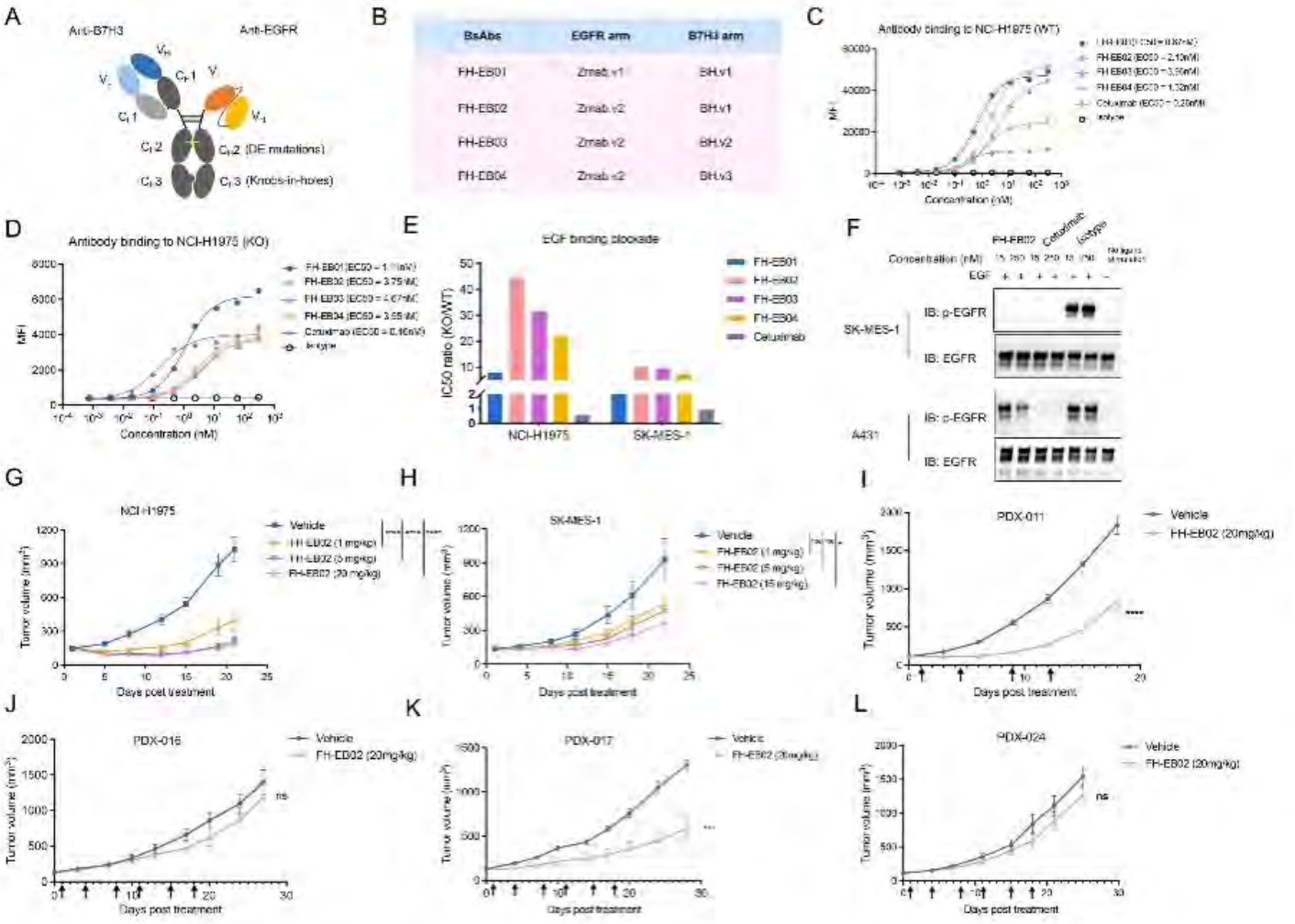
Introduction: The advent of bispecific antibodies has introduced a transformative shift in the treatment of non-small cell lung cancer (NSCLC). The overexpression of epidermal growth factor receptor (EGFR) and B7 homolog 3 protein (B7-H3) is known to drive the growth of NSCLC, thereby positioning them as promising therapeutic targets. This study aimed to develop a bispecific antibody (bsAb) targeting B7H3 and EGFR and validate its efficacy in preclinical NSCLC models.

Methods: We analyzed the co-expression of B7-H3 and EGFR in 222 advanced NSCLC tissues by immunohistochemistry and examined their correlation with immune cells, including CD3, CD8, CD68, and Foxp3. Four bispecific antibodies were designed with varying affinities to B7H3 and EGFR, and their pharmacological activities including EGFR signaling blockade were evaluated. We selected FH-EB02 to assess the tumor growth inhibition in two cell line-derived xenograft (CDX) mouse models and four patient-derived xenograft (PDX) models bearing subcutaneous human NSCLC.

Results: B7H3 and EGFR were co-expressed in 62.6% of advanced NSCLC tissues, and this co-expression was correlated with the shorter PFS and OS. In vitro, the bsAbs demonstrated a stronger binding capacity to tumor cells compared to cetuximab in B7H3 and EGFR double-positive cells. However, the affinity of the bsAbs decreased in B7H3-knockout isogenic cells. FH-EB02, which has a weaker EGFR binding arm and a stronger B7H3 binding arm, showed limited EGFR binding in the absence of B7H3 and exhibited the largest therapeutic window. In vivo, treatment with FH-EB02 resulted in tumor growth inhibition in H1975 and SK-MES-1 xenograft tumor models. FH-EB02 significantly delayed tumor growth in B7H3/EGFR co-expression positive patient-derived xenograft (PDX) models, with tumor growth inhibition (TGI) values of 64.5% (PDX-011) and 54.7% (PDX-017). In contrast, no tumor growth inhibition was observed in two B7H3-negative PDX models.

Conclusions: FH-EB02 demonstrates promising preclinical efficacy in NSCLC models, warranting further investigation.





Keywords: Bispecific antibody, NSCLC, B7H3

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.71 Efficacy and Safety of Pralsetinib in Patients With Advanced Ret Fusion-Positive NSCLC: Phase 1/2 ARROW Study Final Data

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Introduction: RET fusions are targetable oncogenic drivers in 1-2% of non-small cell lung cancers (NSCLC). ARROW (NCT03037385) study results (final data lock May 20, 2024) supported the US FDA approval of pralsetinib, a highly potent, oral, selective RET inhibitor for metastatic RET-altered NSCLC. Here, we present final study results

Methods: ARROW was a phase 1/2 open-label study conducted at 84 sites in 13 countries. In phase 2, patients with RET fusion-positive NSCLC (confirmed by central analysis) received 400 mg pralsetinib once daily (QD). Initially, only treatment-naïve patients not candidates for platinum-based therapy were eligible and presented with unfavorable prognostic factors, a requirement removed by protocol amendment in 2019. Primary objectives were overall response rate (ORR, per RECIST v1.1) and safety. Progression-free survival (PFS) and overall survival (OS) are reported in the full efficacy population; the measurable disease population (MDP) was the primary analysis population for ORR and duration of response (DOR).

Results: 281 patients with RET fusion-positive NSCLC received pralsetinib 400 mg QD, with a median treatment duration of 14.95 months. Median age was 60 years; 46% of patients were male; 36% were current/former smokers; 70% had an Eastern Cooperative Oncology Group performance status score ≥1. In the MDP (n=259), ORR was 70.3% (95% confidence interval [CI]: 64.3, 75.8) and median DOR was 19.1 months (95% CI: 14.5, 27.9; Table). In the efficacy population (N=281), median OS was 44.3 months (95% CI: 30.9, 53.1) with median follow up of 47.6 months (95% CI: 44.8, 49.2), and median PFS was 13.1 months (95% CI: 11.4, 16.8). In the overall population, ORR, median DOR, and median PFS (Table) were higher in the US vs. Asia or Europe. Among patients <65 years (n=174; median age 54 years), ORR was 70% (95% CI: 62.7, 76.8) with a median DOR of 22.6 months (95% CI: 14.5, 38.3). In the safety population, 95% of patients experienced treatment-related adverse events (TRAEs); 66% experienced ≥grade 3. Common TRAEs included increased AST (n=128 [46%]), anemia (n=121 [43%]), increased ALT (n=98 [35%]), and hypertension (n=77 [27%]). 3 patients died due to TRAEs (pneumonia, n=2; interstitial lung disease and rhabdomyolysis, n=1 each). No new safety signals were identified with this update.

Conclusions: Pralsetinib produced clinically meaningful and durable responses in patients with RET fusion-positive NSCLC (regardless of prior therapies) with a manageable safety profile, confirming with this longer follow-up previously published results.

Table

	Overall	Prior Platinum	Treatment-naive
Measurable Disease Population			
ORR, % (95% CI)	(n=259) 70.3 (64.3, 75.8)	(n=130) 63.1 (54.2, 71.4)	(n=106) 78.3 (69.2, 85.7)
US	(n=58) 77.6 (64.7, 87.5)	(n=31) 64.5 (45.4, 80.8)	(n=19) 100 (82.4, 100)
Europe	(n=89) 65.2 (54.3, 75)	(n=36) 63.9 (46.2, 79.2)	(n=43) 65.1 (49.1, 79)
Asia	(n=112) 70.5 (61.2, 78.8)	(n=63) 61.9 (48.8, 73.9)	(n=44) 81.8 (67.3, 91.8)
Median DOR, months (95% CI)[a]	(n=182) 19.1 (14.5, 27.9)	(n=82) 31.8 (15.1, 40.4)	(n=83) 13.4 (9.4, 21.7)
US	(n=45) 33.0 (14.5, 47.9)	(n=20) 22.3 (12.9, –)	(n=19) 24.2 (9.0, –)
Europe	(n=58) 19.1 (14.5, 31.4)	(n=23) 31.4 (14.8, 45.1)	(n=28) 19.1 (10.3, 29.3)
Asia	(n=79) 13.4 (9.4, 27.9)	(n=39) 33.7 (9.2, 46.7)	(n=36) 9.9 (7.4, 18.4)
Median DOR follow-up, months (95% CI)	46.8 (42.3, 50.2)	50.3 (46.9, 56.8)	42.3 (37.4, 44.2)
Efficacy Population			
Median PFS, mo (95% CI)[a]	(n=281) 13.1 (11.4, 16.8)	(n=141) 16.4 (11.4, 23.5)	(n=116) 12.1 (9.2, 16.6)
US	(n=64) 25.9 (14.7, 43.3)	(n=34) 22.14 (7.7, 42.4)	(n=22) 42.5 (10.9, NR)
Europe	(n=95) 12.8 (8.8, 16.6)	(n=38) 16.4 (7.4, 33.1)	(n=46) 11.6 (7.3, 21.1)
Asia	(n=122) 12.6 (9.2, 15.2)	(n=69) 12.8 (8.7, 28.6)	(n=48) 9.2 (7.4, 13.5)

[a]Per FDA censoring rule.
CI, confidence interval; DOR, duration of response; ORR, overall response rate, defined as the proportion of patients with best overall response of confirmed complete response or partial response.

Keywords: NSCLC, RET inhibitor

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.72 FIN-EGFR/CNS: Real World Survival and Patient Characteristics of EGFR Mutated NSCLC Patients With Cns Metastases in Finland

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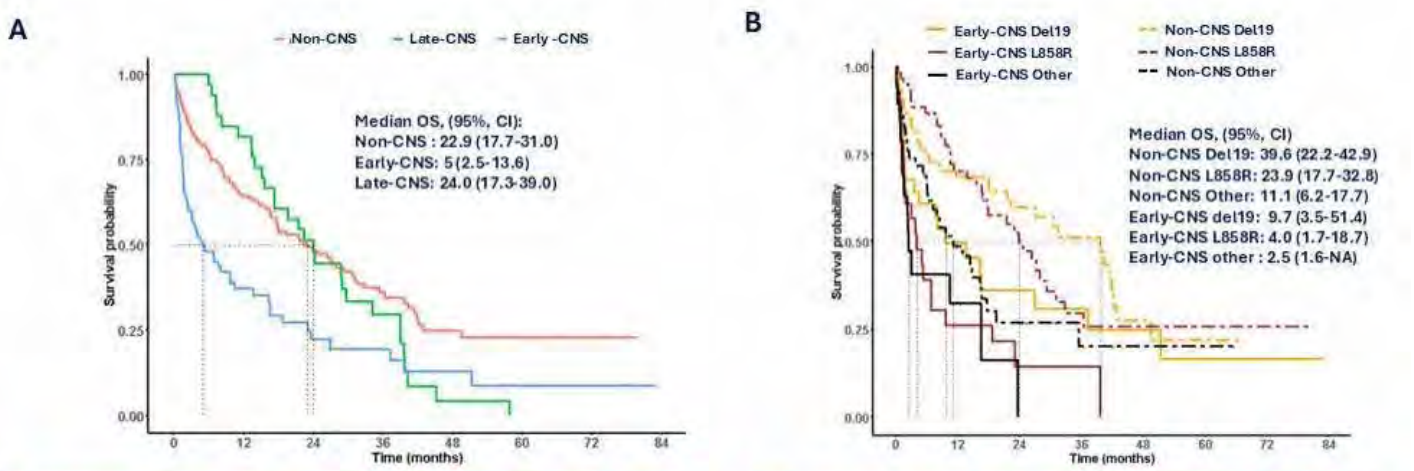
Introduction: The incidence of central nervous system (CNS) metastases is higher in Epidermal Growth Factor Receptor (EGFR)-mutation positive Non-Small Cell Lung Cancer (NSCLC) patients compared to those without EGFR-mutations. Approximately 30%-50% of the EGFR-mutation positive patients develop CNS metastases within 5 years of diagnosis. However, real-world studies on these patients, their characteristics, and treatment outcomes remain scarce.

Methods: This retrospective observational study analysed hospital data lakes and national registry data, for EGFR-positive NSCLC patients with CNS metastases from two Finnish university hospitals (2017-2023), representing ~55% of NSCLC diagnosed cases in Finland. The study assessed incidence, patient characteristics, treatment patterns and survival of EGFR-positive NSCLC patients with brain metastasis using Kaplan-Meier analysis.

Results: A total of 544 EGFR mutation positive NSCLC patients were included in the study. 286 (53%) were diagnosed with advanced stage disease (aNSCLC) of which 242 patients (85%) had stage IV disease at first diagnosis. During the study, 21% (n=115) of the whole study population and 40% of the patients with advanced disease developed CNS metastases. 24% (n=70) of the advanced stage patients had CNS metastases at first diagnosis +/- 3 months (Early-CNS group). 12% (n=33) developed CNS metastases later in the advanced stage treatment path (Late-CNS group) and ~5% of the early-stage patients were later diagnosed with CNS metastases (Recurrent-CNS group not included in analysis here). The Early-CNS group had a lower median age (69.2 years) compared to the aNSCLC without CNS-metastasis (Non-CNS group) (73.2 years). 56% of the Early-CNS patients were in first line treated with tyrosine kinase inhibitors, 25% received palliative radiotherapy only and 9% got no active lung cancer treatment. Median OS for the Non-CNS patients was 22.9 months (95% CI: 17.7-31.0 months), while it was 24 months (95% CI: 17.3-39.0 months) in the Late-CNS group and only 5 months (95% CI: 2.5-13.6 months) for the Early-CNS patients (Figure 1A). OS for the Early-CNS patients varied by mutation: Del19 (9.7 months), L858R (4.0 months), and all other EGFR-mutations combined (2.5 months). Corresponding OS-results for the Non-CNS-patients was 39.6, 23.9, and 11.1 months, respectively (Figure 1B).

Conclusions: EGFR mutation positive NSCLC patients with CNS metastases exhibit poor OS regardless of the EGFR mutation present. This highlights the need for early diagnosis and better treatments to prevent and manage CNS metastases in EGFR-mutant NSCLC.



Time (months)	0	12	24	36	48	60	72	84
Non-CNS	183	98	50	25	13	8	2	0
Late-CNS	33	27	14	7	1	0	0	0
Early CNS	70	20	9	6	3	2	1	0

Time (months)	0	12	24	36	48	60	72	84
Early-CNS del19	28	11	7	5	3	2	1	0
Early-CNS L858R	23	6	2	1	0	0	0	0
Early-CNS other	19	3	0	0	0	0	0	0
Non-CNS del19	76	44	23	14	6	3	0	0
Non-CNS L858R	61	37	19	8	6	4	2	0
Non-CNS other	46	17	8	3	1	1	0	0

Figure 1: OS for patients in the A) Non-CNS, Early-CNS and Late-CNS groups and B) Non-CNS and Early-CNS stratified by del19, L858R and all other EGFR mutations combined.

Keywords: Epidermal Growth Factor Receptor mutation, Central nervous system metastasis, Real-word evidence

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.73 Phase I/II Study on WSD0922-FU in EGFR C797S+ NSCLC

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Introduction: Although 3rd-generation EGFR TKIs are highly effective in front-line treatment of metastatic EGFR-mutated (EGFRm) NSCLC, acquired resistance ultimately occurs, including the emergence of the on-target C797S mutation. WSD0922-FU is an oral, central nervous system (CNS)-penetration, wildtype-sparing, ATP non-competitive, reversible EGFR inhibitor targeting EGFR aberrations in NSCLC. It has shown promising preclinical and clinical activity. WSD0922-102 (NCT06631989) is an ongoing phase 1/2, open-label, multicenter trial evaluating the efficacy and safety of WSD0922-FU as a monotherapy in patients with EGFR C797Sm+ advanced NSCLC in China.

Methods: Adult patients with EGFR C797Sm+ NSCLC were given with WSD0922-FU orally, with five doses based on PK coverage and selected from phase I dose escalation (NCT04197934) as a bridging PK study in China. After DLT evaluation, expansion was initiated for each dose and then phase 2 study started using the dose of RP2D. Key inclusion criteria included patients ≥18 years of age with metastatic EGFR C797Sm+ NSCLC; ECOG PS 0-1; and previously treated with 3rd G EGFR TKI. EGFR C797S mutation was detected via tissue/liquid samples. Key exclusion criteria were tumors harboring EGFR T790M mutations, EGFR exon 20 insertions, or MET aberrations. Phase 1 dose escalation primary endpoints were maximum tolerated dose, RP2D and safety. The expansion and extension primary endpoint was overall response rate by RECIST 1.1. Secondary endpoints included duration of response, disease control rate, progression-free survival, overall survival, CNS activity (iORR) by RANO-BM, and safety. Patients were enrolled into 3 treatment cohorts: dose escalation (n≈12-15), dose expansion (n≈20), and dose extension (n≈70). The treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Clinical trial information: NCT06631989.

Results: All 42 patients received treatment at the time of data cutoff (Jul 31, 2025). For all evaluable patients in efficacy set (n = 33), ORR assessed by investigator is 60.6% (20/33), and the disease control rate was 100%. Median PFS is not reached. In the 120mg BID cohort, Overall ORR is 63.2% (12/19). Among the 4 subjects in 120mg BID cohort with baseline brain metastases eligible for RANO BM assessment, 3 subjects achieved objective response in the central nervous system, with an objective response rate of 75% (3/4), and another case had the central nervous system disease controlled, with DCR of 100% (4/4). In safety set (n=42), the most common possibly causally related adverse events were rash (59.5%), diarrhea (33.3%), anemia (33.3%), headache (33.3%), vomiting (26.2%), dry skin (26.2%), hypertriglyceridemia (23.8%), loss of appetite (21.4%), hair loss (21.4%), dizziness (21.4%), and weakness (21.4%). ≥grade 3 treatment-related adverse events (TRAE) associated with the study drug were rash (2.4%), decreased lymphocyte count (2.4%), diarrhea (2.4%), and vomiting (2.4%). Conclusion: In patients with EGFRm+ C797S advanced NSCLC who progress after 3rd generation EGFR-TKI treatment, WSD0922-FU provides a good efficacy and tolerability with an ORR of 63.2% at RP2D. This study supports further investigation of WSD0922 in extension cohort to potentially establish standard 2nd/3rd line for NSCLC patients progression after 1st line 3rd generation EGFR TKI treatment with C797S mutation.

Keywords: 4th Generation EGFR TKI, WSD0922-FU, EGFR C797S

P3.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.12.74 IMM2510, an Anti-PD-L1/VEGF Bispecific Antibody Fusion Protein for Advanced IO-treated SQ-NSCLC: A Phase I Study

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Introduction: IMM2510 is a novel bispecific antibody fusion protein targeting PD-L1 and VEGF. The data of dose-escalation phase were previously reported in ASCO2024.Here we present preliminary data on efficacy and safety of IMM2510 in advanced immunotherapy-treated squamous non-small-cell-lung-cancer (NSCLC) patients from escalation and expansion stages.

Methods: The study IMM2510-01 was designed as a phase I, multicenter, open-label study to evaluate the safety, efficacy, recommended phase II dose (RP2D), and pharmacokinetics (PK) of IMM2510 monotherapy (NCT05972460).

Results: As of 13 June 2025, 23 squamous-NSCLC patients were treated with IMM2510, including 2 subjects at 3mg/kg, 1 subject at 6mg/kg, 4 subjects at 10mg/kg, 16 subjects at 20mg/kg. The median age of enrolled subjects was 61. Seventeen patients (73.9%) had an ECOG PS of 1. The median prior lines of systemic treatments were 2 (1-5 lines). The numbers of patients with TPS scores < 1%, 1-49% and ≥ 50% were 7 (30.4%), 8 (34.8%) and 3 (13.0%), respectively. Twenty-three patients (100%) previously received PD-(L)1 and chemotherapy, 6 patients (26.1%) previously received anti-VEGF treatments. All patients (100.0%) experienced treatment-related adverse events (TEAEs). 13 subjects experienced ≥G3 TEAE(56.5%), and 1 subject experienced TEAE(4.3%) leading to dose discontinuation. The most common TRAEs of any grade were infusion related reaction (IRR) (65.2%), anemia (52.2%), and platelet count decreased (43.5%). The most common TRAEs ≥ Grade 3 were platelet count decreased (8.7%), lymphocyte count decreased (8.7%) and IRR (8.7%). The occurrence rate of VEGF-related TRAEs is low, no≥G3 hypertension, ≥G3 proteinuria (n=1, 4.3%),≥G3 hemoptysis (n=1, 4.3%). No patient experienced TRAE that led to death. Of 17 efficacy-evaluable squamous-NSCLC patients, the ORR was 29.4% (5/17), and DCR was 76.5 % (5 PR and 8 SD). The median DoR was 7.59 months, and median PFS was 9.4 months. Notably, in 16 EGFR/ALK wild-type squamous-NSCLC patients, the ORR was 31.3% (5/16). The enrollment of squamous-NSCLC and further PD, PK analyses are ongoing.

Conclusion: IMM2510monotherapy demonstrated potent anti-tumor activity in advanced immunotherapy-treated squamous-NSCLC patients with tolerable and manageable safety profiles. Based on these findings, phase II studies of IMM2510 combined with chemotherapy in advanced NSCLC are in progress, to further explore its therapeutic potential.

Keywords: IMM2510, Advanced Immunotherapy-treated Squamous-NSCLC, Phase I Clinical Trial

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.01 Effect of Patient Management System and Medical Resources on Outcomes of SCLC Treated With Chemo-ICI

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Introduction: Although chemotherapy with immune checkpoint inhibitors (chemo-ICI) is the standard of care for the first-line treatment of extensive-stage small cell lung cancer (SCLC), some patients are compelled to discontinue treatment due to its toxicities. Effective patient management systems and sufficient medical resources may play a crucial role in managing the toxicities associated with chemo-ICI, potentially improving treatment continuity.In this study, we focused on evaluating treatment outcomes in terms of treatment continuity to assess the impact of hospital resources and patient management systems on patients with SCLC receiving chemo-ICI.

Methods: The study endpoints were the time to treatment failure (TTF) of ICI and the incidence of grade 3 or higher hematologic toxicities and other adverse events.Patients with SCLC who received first-line treatment with cisplatin/carboplatin + etoposide + ICI (atezolizumab/durvalumab) were extracted from the DATuM IDEA® database. This database integrates electronic medical records from multiple National Hospital Organization institutions in Japan based on the Next Generation Medical Infrastructure Act. The dataset provided for analysis was fully de-identified prior to access by researchers, ensuring patient confidentiality.Patients were categorized into two groups based on the number of hospital beds: hospitals with fewer than 500 beds (<500 group) and those with 500 or more beds (≥500 group). The number of beds was used as a surrogate marker for hospital resources and patient management systems, as larger hospitals generally have more comprehensive infrastructure and established management protocols. Baseline characteristics were adjusted between groups using propensity score matching (PSM), including regimen, gender, age, Charlson Comorbidity Index, interstitial pneumonia (IP), and the prescription of proton pump inhibitors, anti-infectives, and corticosteroids.

Results: After PSM, 80 patients were extracted from each of the <500 group and ≥500 group.The median TTF was 4.6 months in the <500 group and 4.8 months in the ≥500 group, with a difference of only 0.2 months. There was no statistically significant difference (P = 0.459, log-rank test), indicating that treatment outcomes in terms of efficacy were comparable between the groups.Among grade 3 or higher hematologic toxicities, the incidence of leukopenia was 66.3% versus 46.3%, and the incidence of neutropenia was 75.0% versus 57.5%, with both being significantly lower in the ≥500 group (P < 0.05, Fisher's exact test). This suggests that treatment outcomes in terms of safety were better in the ≥500 group.

Conclusions: Treatment efficacy was comparable between the <500 group and the ≥500 group.However, patients in the ≥500 group experienced fewer grade 3 or higher hematologic toxicities, indicating better treatment safety.These findings suggest that larger hospitals, with more established patient management systems and greater medical resources, may provide more appropriate patient care, leading to improved safety outcomes.

Keywords: Small cell lung cancer, Immune checkpoint inhibitor, Healthcare resource availability

P3.13.02 The Effectiveness of Anatomical Versus Non-Anatomical Resection for Treatment of Small Cell Lung Carcinoma

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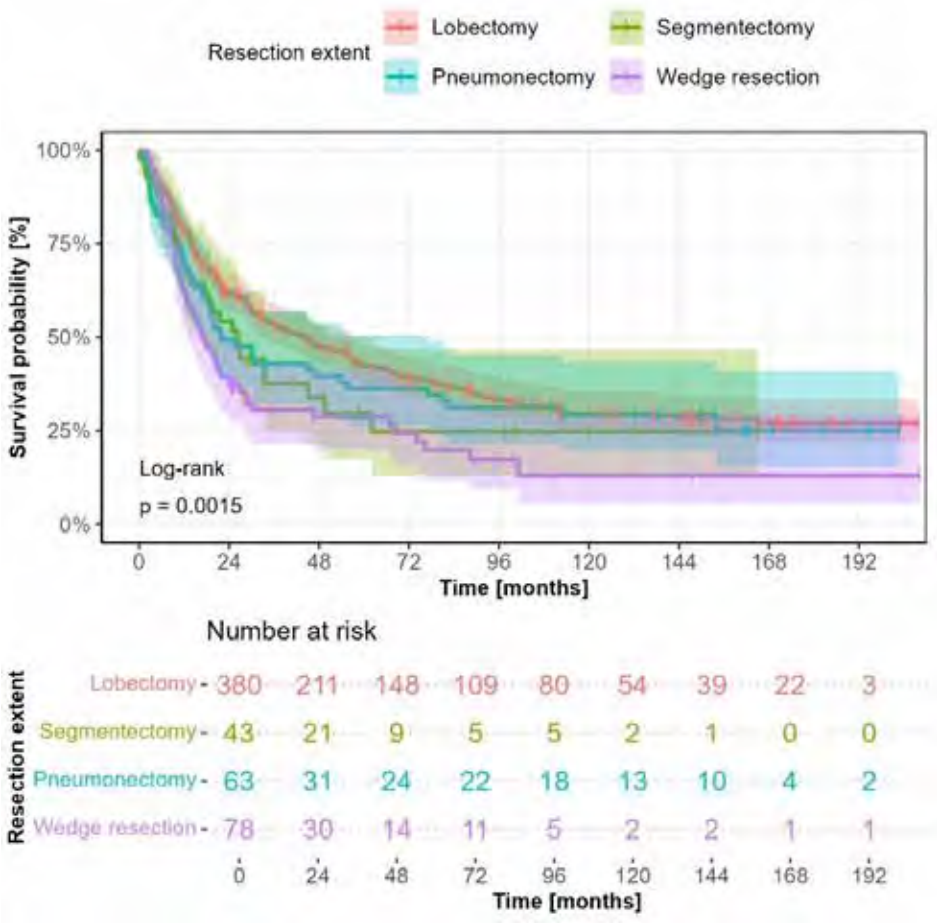
Introduction: Small Cell Lung Carcinoma (SCLC) is a highly aggressive type of tumor with a significant potential for early metastases. Currently, chemotherapy serves as a gold standard for first-line treatment, with a significant number of studies conducted. However, the role of surgical management, especially the effectiveness of anatomical versus non-anatomical resections, remains a subject of debate and is often underestimated in clinical practice. The aim of the study was to assess the impact of resection extent on overall survival

Methods: The patient data was collected retrospectively from the Polish Lung Cancer Study Group database (PLCSG), which incorporates records of surgically treated patients from nearly 30 thoracic centers across Poland. The study included patients with confirmed SCLC in histopathology who underwent radical surgical resection between the years 2007-2023 and had complete data.

Results: A total of 564 patients were included in the analysis. Most of them were men (54.8% vs 45.2%), and the median age was 64 years. Smokers comprised a larger proportion of the cohort compared to non-smokers (72.0% vs. 28.0%). All of the patients were staged according to the 9th edition of tumor-nodes-metastases (TNM) classification, and the most common stages were IA3 (14.4%), IB (14.6%), and IIB (22.4%). Lymph node involvement was identified in 30.1% of cases, with pN1 (16.5%) and pN2B (11.3%) being the most frequently observed stages. Based on the size of the tumor, the most common stages were I and II, which were 50.5% and 30.5%, respectively. Surgical treatment included pneumonectomy (11.2%), lobectomy (67.4%), segmentectomy (7.6%), and wedge resection (13.8%). The overall survival rate (OSR) was assessed at the 5-year mark, and anatomical resections were favored over non-anatomical. Among the surgical procedures, lobectomy and pneumonectomy had the highest 5-year survival rates at 42.3 (95% CL; 47.90 - 37.32) and 36.3% (95% CL; 50.39 - 26.10), respectively. These were followed by segmentectomy at 29.6% (95% CL; 50.28 - 17.48) and wedge resection at 28.6% (95% CL; 41.37 - 19.82).

Conclusions: This multicenter retrospective analysis highlights the potential benefit of surgical intervention in selected patients with SCLC. The results demonstrate that anatomical compared to non-anatomical resections are associated with superior 5-year overall survival rates, with lobectomy correlated with the most favorable outcomes.



Keywords: Small Cell Lung Carcinoma, Anatomical Resection, Non-anatomical Resection

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.03 Proteomic Profiling of Small Cell Lung Cancer Patients Reveals Blood-Based Prognostic Proteins

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Introduction: Small cell lung cancer (SCLC) remains an aggressive thoracic malignancy with poor overall survival (OS) rates (5-year OS<7%). Additionally, since personalized therapeutic approaches are not yet available in routine clinical practice, there is a need to investigate the heterogeneous molecular profile for potential biomarkers. Our group is among the first to utilize mass spectrometry-based proteomics, which enables the detection of even low abundant proteins in a sample, to elucidate differences in the SCLC proteome for biomarker discovery. Here, we aimed to explore proteomic signatures in the blood plasma of SCLC patients, focusing specifically on prognostic proteins.

Methods: In this prospective study, we analyzed clinical data and pre-treatment blood plasma samples of 144 SCLC patients from two Central-European thoracic institutions. Proteomic profiling was performed via mass spectrometry-based proteomics at Lund University, Sweden, and 1,338±209.23 proteins were quantified per sample. Consecutive bioinformatic analysis for prognostic protein detection included multivariate Cox regression analyses, a custom-built machine-learning algorithm, weighted gene co-expression network analysis (WGCNA), or pathway enrichment analysis. Additionally, we analyzed patient progression-free survival data and examined predictive proteins in relation to SCLC standard-of-care therapy. Lastly, the appearance of treatment-related side effects was also investigated.

Results: The SCLC cohort was reflective of patients with extensive disease stage (69.44% stage 4). 47.92% of patients were female and the median age was 68.73 years. Multivariate Cox regression analysis including clinical data known at the time of sample collection yielded 60 proteins prognostic for OS (adjusted (adj.) p<0.05). Notably, CHGA (multivariate hazard ratio, HR=1.44, adj. p<0.001) was significantly associated with worse survival, whereas FETUB (multivariate HR=0.4, adj. p<0.001) demonstrated better prognosis, among others. Our machine-learning model strengthened the selected protein list. Subsequent data exploration through WGCNA yielded six distinct modules (=groups of co-expressed proteins). Of these, the MEpink module was associated with worse prognosis (multivariate HR=2.41, p=0.034), while the MEdarkred module was linked to better OS (multivariate HR=0.05, p=0.030 at sampling), respectively. We detected significant associations with clinical parameters for specific modules (e.g. liver metastasis presence at the time of sample collection for MEpink, female gender for MEdarkred, or associations with non-smokers for MEgreenyellow). Finally, proteins of the MEdarkred and MEpink modules showed enrichment of biologically relevant pathways such as ‘complement cascade’ or ‘coagulation’.

Conclusions: Coupling proteomic profiling with bioinformatic analyses of blood plasma samples yielded independent prognostic proteins concerning OS. SCLC is a disease reflective of short survival time. Therefore, it is necessary to investigate clinical samples to support patient surveillance and the selection of optimal treatment strategies for SCLC patients.

Keywords: Small cell lung cancer, Proteomics, Prognostic biomarkers

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.04 Consolidation Thoracic Radiotherapy After Chemoimmunotherapy in ES-SCLC: A Multicentric Retrospective Analysis

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Introduction: The role of consolidative thoracic radiotherapy (TRT) following first-line (1L) chemotherapy in extensive-stage small cell lung cancer (ES-SCLC) was established by the CREST trial, which demonstrated an improvement in 2-year overall survival (OS). An exploratory analysis revealed that patients with residual intrathoracic disease treated with TRT had a significantly longer OS compared to those who did not receive TRT. However, registration 1L chemoimmunotherapy (ChIO) trials did not allow TRT, leaving its role in the immunotherapy era uncertain.

Methods: We retrospectively analysed consecutive patients (pts) with ES-SCLC who received 1L ChIO between January 2020 and January 2024 at The Christie (Manchester, UK) and Istituto Tumori Giovanni Paolo II (Bari, Italy). TRT was delivered at a total dose of 30 Gray over 10 fractions. Patients without radiological disease progression at the first post-treatment assessment were considered eligible. We compared local recurrence rates, progression-free survival (PFS), and OS between those who received TRT and those who did not.

Results: A total of 183 pts were identified, of whom 71 (38.8%) received TRT. Clinical characteristics are summarised in Table 1 and are well balanced. Patients who received TRT had a lower rate of intra-thoracic progressive disease (PD) compared to those who did not (42.3% vs 65.2%, $p < 0.001$). Among the 54 pts who developed PD despite TRT, only 15 (27.8%) experienced progression within the radiotherapy field. With a median follow-up of 29.0 months (95% CI, 23.5-34.4), there were no significant differences in median PFS (6.9 vs 5.9 months, $p = 0.128$) and OS (13.0 vs 12.9 months ,$p = 0.183$) between the TRT and non-TRT group.

Table 1. Clinical characteristics of patients who received TRT vs those who did not receive TRT.div>

Conclusions: TRT after 1L ChIO improved local control but did not result in a significant difference in survival outcomes. Prospective trials are needed to further evaluate the potential benefit of RT to the thorax and metastases on quality of life as well as survival in this patient population within the IO era.

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.05 First-In-Human Study of 225Ac-ABD147 for SCLC and LCNEC Post-Chemotherapy: Pharmacokinetics, Biodistribution and Safety Insights

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Introduction: 225Ac-ABD147, a targeted radioligand therapy, uses actinium-225 (225Ac, an alpha emitting radionuclide) coordinated to the VHH-Fc -chelator conjugate ABD147. It specifically binds the delta-like ligand 3 (DLL3) receptor, over expressed in Small Cell Lung Cancer (SCLC) and Large Cell Neuroendocrine Carcinoma of the Lung (LCNEC) but not on normal tissue. 111In-ABD147 serves as a single-photon emission computerized tomography (SPECT) imaging surrogate to evaluate pharmacokinetics (PK), biodistribution and normal organ dosimetry. Preclinical data, previously presented at AACR [1], provide the foundation for this Phase 1a/b study, which evaluates the tolerability, biodistribution, PK, and preliminary tolerability of 225Ac-ABD147 in patients with locally advanced or metastatic SCLC and LCNEC post platinum-based chemotherapy.

Methods: Phase 1a involves escalating doses to determine the safety, tolerability, dosimetry, PK, and to establish the Phase 1b expansion dose. Phase 1b will assess safety and preliminary efficacy to recommend the Phase 2 dose (RP2D). Using centralized core lab services, organ-level SPECT-based dosimetry assessments will be made on up to 10 patients for 111In-ABD147 and 3 to 6 patients for 225Ac-ABD147. Radiation pharmacokinetic assessments will be performed using a two-compartment model. Eligible patients must have confirmed locally advanced or metastatic SCLC or LCNEC, completion of platinum-based chemotherapy. Subjects must have measurable disease by RECIST v1.1. Exclusion criteria include hypersensitivity to 225Ac or 111In, active infection, uncontrolled bleeding, or non-healing wound and prior EBRT to >25% of the bone marrow. Phase 1a dose escalation is ongoing in the US (NCT06736418).

Results: As of April 2025, PK, biodistribution, and dosimetry assessments with 111In-ABD147 are ongoing for Cohort 1. Patients who received 225Ac-ABD147 are being followed for safety. The presentation will summarize key PK findings, biodistribution patterns, dosimetry assessments, and early safety data from Cohort 1, with additional insights from Cohort 2 as data become available.

Conclusions: This marks the first clinical data presentation for ABD147. The findings will provide a foundational evaluation of the investigational agent's safety, PK profile, and potential clinical implications.

Reference: [1] Iva Kulic, Etienne S. Melese, Emma Cummins, Alex Mandel, Raja Viswas, Michael Abrams, Adam Judge. Preferential tumor-to-normal tissue biodistribution and single-dose efficacy with ABD147, a DLL3-targeted engineered antibody-based radiotherapeutic, in preclinical small cell lung cancer models [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2024; Part 1 (Regular Abstracts); 2024 Apr 5-10; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2024;84(6_Suppl): Abstract nr 6028.

Keywords: Targeted Radiopharmaceutical, DLL3, Small Cell Lung Cancer

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.06 Comprehensive Assessment of the Tumor Microenvironment of Resected Small Cell Lung Cancer

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Introduction: Small cell lung carcinoma (SCLC) accounts for approximately 15% of all lung cancer cases and remains one of the most aggressive subtypes, with a dismal five-year survival rate of less than 5%. Unlike non-small cell lung carcinoma (NSCLC), the development of targeted therapies for SCLC has been hindered by the lack of targetable alterations and treatment options remain limited. While immunotherapy has shown some benefit in selected patients, reliable predictive biomarkers are still lacking. The proposed classification system, based on transcriptomic data, categorizes SCLC into four subtypes, characterized by the expression of the transcription factors ASCL1, NeuroD1, POU2F3, and an "inflamed" phenotype (SCLC-A, N, P, and I, respectively). This classification has shown promise in predicting responses to immunotherapy. However, little is known about their relationship with the tumor microenvironment (TME) as well as how subclassifying diagnostic samples may provide insight into TME characteristics. In this study, we aim to investigate the TME in relation to SCLC molecular subtypes.

Methods: We retrospectively selected a cohort of 56 patients who underwent lung resection for primary SCLC between 2004 and 2021. Clinical and pathological data were retrieved from our institutional biobank. Tissue microarrays (TMAs) were constructed using three cores per tumor from different regions, distributed across three TMAs. Subtyping was performed by immunohistochemistry for ASCL1, NeuroD1, and POU2F3. Two readers assessed staining using an H-score, classifying each core based on the highest score. Triple-negative cores were categorized as the "inflamed" subtype. TME profiling was performed using mass cytometry (CyTOF), with single-cell analysis of over 500,000 cells and 36 markers to enable a detailed spatial characterization of 18 stromal and immune cell lineages. Differences in the percentage of cells and cellular neighborhoods across subtypes was assessed using Kruskal-Wallis with Bonferroni correction.

Results: The cohort included 31 females (56.4%) with a mean age of 65.2 years. Most patients had a smoking history (former 36.4%, active 61.8%). A total of 134 TMA cores were analyzed and classified as follows: SCLC-A (n=80, 59.7%), SCLC-N (n=16, 11.9%), SCLC-P (n=24, 17.9%), and SCLC-I (n=14, 10.4%). The TME of SCLC-P was significantly more vascularized than that of SCLC-A and SCLC-I, both at the cellular level ($p = 0.016$; $p = 0.023$, respectively) and within the cellular niche (CN) ($p = 0.012$; $p = 0.030$, respectively). Additionally, the TME of SCLC-N exhibited a significant enrichment in classical monocytes compared to SCLC-P, at both the cellular level ($p = 0.039$) and the CN level ($p = 0.043$). Clustering analysis based on TME composition identified cores enriched in cytotoxic and helper T cells and others enriched in M1 macrophages, though these patterns showed no significant association with molecular subtypes.

Conclusions: SCLC exhibits TME variability, with few consistent associations between molecular subtypes and immune composition. This variability may limit the utility of molecular subtyping in predicting TME characteristics from diagnostic samples.

Keywords: Small cell carcinoma, Immune microenvironment, Mass cytometry

P3.13.07 Real-World Implementation of Immunotherapy for Stage III-IV Small Cell Lung Cancer: Insights From the National Cancer Database (2016-2021)

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Introduction: Immune checkpoint inhibitors (ICIs) have redefined the treatment landscape for extensive-stage small cell lung cancer (SCLC), with landmark approvals following the IMpower133 (2018) and CASPIAN (2019) trials. However, real-world adoption and equitable delivery remain uncertain. We examined temporal trends and access patterns in immunotherapy utilization using the National Cancer Database (NCDB)—a hospital-based oncology registry that captures over 70% of newly diagnosed cancer cases in the United States.

Methods: We conducted a retrospective analysis of over 55,000 patients diagnosed with Stage III-IV SCLC between 2016 and 2021 in the NCDB. The primary outcome was receipt of immunotherapy. Multivariable logistic regression was used to assess associations with demographic, socioeconomic, and treatment center variables. Odds ratios (OR), 95% confidence intervals (CI), and p-values were reported.

Results: Immunotherapy utilization rose from 1.7% in 2016 to 42% in 2021, with the sharpest increase following 2018, coinciding with IMpower133 and CASPIAN trial publications. However, fewer than half of patients received immunotherapy in 2021, despite national guideline recommendations, raising concerns about barriers to adoption that extend beyond clinical contraindications. Patients treated at academic centers were more likely to receive immunotherapy [OR: 1.23 (1.19-1.27), p<0.001]. Insurance type was strongly associated with treatment: private insurance was linked to increased odds of receipt [OR: 1.19 (1.12-1.26)], while Medicare [OR: 0.79 (0.75-0.83)], no insurance [OR: 0.75 (0.67-0.85)], and other government coverage [OR: 0.78 (0.69-0.88)] were associated with lower odds (all p<0.001). Patients from areas with high school non-completion ≥15.3% had reduced odds [OR: 0.80 (0.74-0.86), p<0.001]. Residence in rural areas was associated with increased use [OR: 1.21 (1.09-1.34), p<0.001], while urban vs. metro location showed no difference. Female patients had slightly lower odds than males [OR: 0.94 (0.91-0.97), p<0.001]. No statistically significant differences were observed across race/ethnicity groups.

Conclusions: This large national cohort demonstrates a substantial increase in immunotherapy use for Stage III-IV SCLC following pivotal trial publications. However, real-world delivery continues to lag behind clinical potential, with fewer than half of patients receiving immunotherapy even in 2021. Treatment variation persists across insurance type, education level, residential setting, and sex. These findings highlight the need for targeted strategies to close access gaps and better understand barriers beyond contraindications, ensuring that advances in SCLC therapy are implemented equitably.

Year	SCLC Immunotherapy (N, %)	OR (95% CI), p	Disparity Category	Comparison	OR (95% CI), p
2016	310 (1.7%)	Reference	Facility Type	Academic vs. Non-Academic (ref.)	1.23 (1.19–1.27), p<0.001
2017	483 (2.7%)	1.58 (1.37–1.83), p<0.001	Race/Ethnicity	Black vs. White (ref.)	0.96 (0.90–1.02), p=0.20
				Hispanic vs. White (ref.)	0.91 (0.82–1.01), p=0.071
				Asian/Pacific Islander vs. White (ref.)	0.99 (0.88–1.11), p=0.80
2018	2,006 (11%)	7.05 (6.26–7.98), p<0.001	Insurance Type	Private vs. Medicaid (ref.)	1.19 (1.12–1.26), p<0.001
				Medicare vs. Medicaid	0.79 (0.75–0.83), p<0.001
				Not Insured vs. Medicaid	0.75 (0.67–0.85), p<0.001
				Other Gov. vs. Medicaid	0.78 (0.69–0.88), p<0.001
2019	6,650 (36%)	33.9 (30.3–38.2), p<0.001	Socioeconomic Status	$74,063+ vs. ≤$46,277 (ref.)	1.06 (0.99–1.13), p=0.076
2020	6,862 (40%)	40.4 (36.0–45.5), p<0.001	Education	15.3%+ vs. <5% HS Non-Completion (ref.)	0.80 (0.74–0.86), p<0.001
2021	7,110 (42%)	42.6 (38.0–48.0), p<0.001	Location	Rural vs. Metro (ref.)	1.21 (1.09–1.34), p<0.001
				Urban vs. Metro	1.00 (0.96–1.05), p>0.9
			Sex	Female vs. Male (ref.)	0.94 (0.91–0.97), p<0.001

Keywords: Immunotherapy, SCLC, Real-world outcomes

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.08 Autologous Vax-NK/HCC Consolidation Therapy in ES-SCLC

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Introduction: While first-line treatment of extensive-stage small-cell lung cancer (ES-SCLC) with platinum-based chemotherapy combined with atezolizumab (ACE regimen) has demonstrated improved progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone, disease progression during atezolizumab maintenance remains a clinical challenge. This study aims to evaluate the feasibility and safety of autologous natural killer cell (Vax-NK/HCC) consolidation following the four cycles of ACE.

Methods: This is a single-center, open-label, prospective, single-arm clinical trial (Figure 1). Vax-NK/HCC, a natural killer cell product amplified from patient-derived peripheral blood mononuclear cells (PBMCs) via leukapheresis and co-cultured with 100 Gy gamma-irradiated K562 cells at a 1:6 ratio in the presence of proliferation-inducing cytokines, was administered. After completing the ACE, patients received two cycles of Vax-NK/HCC (1 x 109 cells/injection) over five consecutive days. Atezolizumab (1200 mg) was administered on the second day following each Vax-NK/HCC cycle and repeated every three weeks until disease progression or unacceptable toxicity. The primary endpoint was PFS. Secondary endpoints included OS and safety profile. Pre- and post-therapy PBMCs were collected from patients for immunophenotypic analysis of NK cells and various other immune cells.

Results: This ongoing trial has completed Vax-NK/HCC administration in eight patients with a median age of 62 (range, 50-70) years. The mean viability of the Vax-NK/HCC product was 95.0%, and the mean cytotoxicity was 78.0%. The median PFS was 4.79 months (95% CI, 4.59-4.98), and the median OS was 9.64 months (95% CI, 5.23-14.06). Grade 3 treatment-related adverse events (TRAEs) were observed in two patients, specifically ileus and immune-related myositis. Grade 2 TRAEs included nausea, constipation, myalgia, herpes zoster, and hypoglossal nerve palsy. Notably, patients with a relatively longer PFS showed high CXC chemokine receptor expression profiles in pre-therapy PBMCs.

Conclusions: This interim analysis indicates that autologous natural killer cell consolidation therapy following the ACE regimen is feasible and exhibits a manageable toxicity profile in patients with ES-SCLC. However, the antitumor activity and survival data are currently preliminary, and long-term outcomes may be improved with the aid of predictive blood biomarkers.

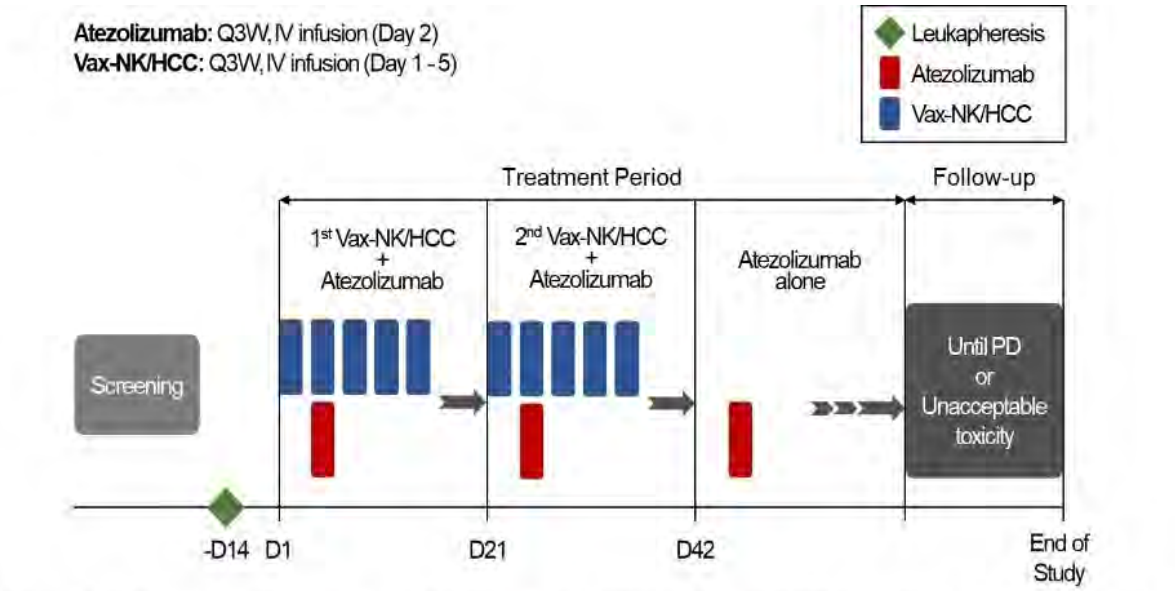

Figure 1. The schematic scheme for the treatment schedule of Vax-NK/HCC combined with atezolizumab.

Keywords: Atezolizumab, Natural killer cell, Small cell lung cancer

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.09 Surface Targeting Strategies to Overcome Heterogeneity Associated With Treatment Resistance in Small Cell Lung Cancer (SCLC)

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Introduction: Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy characterized by rapid onset of chemoresistance and poor clinical outcomes. The recent FDA approval of tarlatamab, a DLL3 targeting bispecific T-cell engager (BiTE), alongside unprecedented response rates observed with multiple antibody-drug conjugates (ADCs), have ushered in a paradigm shift towards surface targeting strategies in relapsed SCLC patients. While providing much-needed optimism for SCLC patients, resistance, both intrinsic and acquired, is common and must be better characterized to maximize the potential of these new therapeutic classes. We hypothesize that combinatorial targeting of multiple surface proteins using distinct strategies (i.e., BiTEs, ADCs, etc.) represents a novel way to overcome intratumoral heterogeneity common to relapsed SCLC and enhance antitumor immunity engendered by ADC payloads (i.e., topoisomerase 1 [TOP1] inhibitor).

Methods: To better define the surfaceome of relapsed SCLC, we performed surfaceome mass spectrometry analysis of SCLC cell lines, naïve and relapsed patient derived xenografts (PDXs), and PDXs treated with frontline chemotherapy until relapse occurred, and identified a number of known (i.e., TROP2, HER2, B7H3) and novel surface proteins. These same surface targets were transcriptionally profiled at the single cell level in relapsed SCLC patient biopsies. To determine efficacy of combination surface targeting strategies, SCLC cell lines and PDX organoids, including those that are from neuroendocrine-low subtypes with poor response to platinum chemotherapy, were treated with DLL3-targeted therapies and TROP2- or HER-ADCs and proliferation was measured.

Results: Results: Single-agent surface targeting strategies are effective in preclinical models, including those resistant to other common SCLC therapies (i.e., platinum chemotherapy). Notably, single-cell transcriptional profiling of relapsed SCLC patient biopsies revealed mutually exclusive expression of surface genes in distinct cell populations (i.e., DLL3/SEZ6 vs. TROP2/HER2/B7-H3), including senescent, drug tolerant persister cells (DTPCs), representing a unique opportunity to target heterogeneous populations. Furthermore, combination targeting of different surface proteins (e.g., DLL3, TROP2, HER2) using both immune (i.e., chimeric antigen receptor T-cells, BiTEs) and payload-based modalities (i.e., ADCs) was more effective than single-agent targeting in resistant, neuroendocrine-low models.

Conclusions: Intratumoral heterogeneity associated with relapsed SCLC, which limits efficacy of single-agent surface targeting strategies, may be exploited with combinatorial therapies to target resistant cell populations, including DTPCs, using payload and immune-based methods.

Keywords: SCLC, heterogeneity, surface targets

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.10 Real-World Outcomes of Prophylactic Cranial Irradiation (PCI) in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) in the US

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Introduction: The role of PCI in ES-SCLC remains controversial due to uncertain overall survival benefits and concerns about long-term neurocognitive toxicity. The integration of immunotherapy (IO) into ES-SCLC management further challenges the need for PCI, as IO can cross the blood-brain barrier and potentially reduce brain metastasis (BM) risk. This real-world study evaluated PCI utility in patients with ES-SCLC without BM who achieved a real-world response (rwR) to first-line (1L) platinum-based chemoimmunotherapy by evaluating real-world overall survival (rwOS), real-world progression-free survival (rwPFS), and cumulative incidence of BM and brain radiation treatment (RT) based on PCI exposure.

Methods: This retrospective observational cohort study used the US-based Flatiron Health Research Database, an electronic health record-derived deidentified database, to select 20,000 patients diagnosed with SCLC after January 1, 2018. Patients with ES-SCLC without BM who received 1L platinum-based chemotherapy with immunotherapy (atezolizumab or durvalumab), had an rwR during the baseline window, had no real-world progression (rwP) before index, survived through the baseline window, and who had five months of potential follow up from index date were included. Index date was the last order/administration of cisplatin/carboplatin in 1L, and patients were evaluated for PCI receipt during a baseline window from 1L start to 90 days post-index. Kaplan-Meier methods and log-rank tests evaluated rwOS and rwPFS. Cox proportional hazards regression was adjusted for covariates including Eastern Cooperative Oncology Group performance status, age, sex, race, ethnicity, number of metastases, receipt of upfront chest RT, and type of rwR (partial vs complete) to 1L. Cumulative Incidence Function estimated BM and therapeutic brain RT, accounting for death as a competing risk.

Results: Of 2,502 patients, 144 (6%) received PCI and were more likely to be younger (median age, 65 vs 68 years; P<.001) and diagnosed before 2022 (80% vs 56%; P<.001), achieve a real-world complete response (8.3% vs 4.1% P=.031), and receive upfront chest RT (44% vs 20%; P<.001). Median rwOS (95% CI) was 11.4 months (10.0-13.7) in the PCI group and 9.4 months (9.0-9.9) in the unexposed group (P=.053). The unadjusted rwOS hazard ratio (HR; unexposed vs PCI) was 0.83 (0.69-1.00; P=.05) and 0.85 after adjustment (0.70-1.03; P=.10). Median rwPFS (95% CI) was 4.8 months (4.3-5.8) in the PCI group and 3.7 months (3.7-3.9) in the unexposed group (P<.001). Unadjusted and adjusted rwPFS HR (unexposed vs PCI) were 0.70 (0.59-0.84; P<.001) and 0.72 (0.60-0.86; P<.001). The 1-year cumulative incidence of BM (95% CI) was 17% (11%-23%) in the PCI group and 44% (42%-46%) in the unexposed group (P<.001). The 1-year cumulative incidence of therapeutic brain RT was 5.2% (2.3%-9.8%) in the PCI group and 35% (33%-37%) in the unexposed group.

Conclusions: The use of PCI has declined in the chemoimmunotherapy era. Although PCI was associated with reduced incidence of BM and therapeutic brain RT at 1 year, it did not confer an rwOS benefit and provided a limited rwPFS advantage of 1 month. Risk-benefit assessment is needed when considering PCI in the modern treatment landscape.

Keywords: Extensive-Stage Small Cell Lung Cancer (ES-SCLC), Prophylactic Cranial Irradiation (PCI), Real-World Data

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.11 HER2- and TROP2-Directed Antibody Drug Conjugates Show Potent Antitumor Activities in Small Cell Lung Cancer

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Introduction: Small cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma of the lung, characterized by poor prognoses, limited treatment options and rapid emergence of resistance. Recently, surface targeting strategies have shown considerable promise in SCLC. A DLL3-targeting T-cell engager (tarlatamab) has been FDA-approved for relapsed SCLC, with a 40% overall response rate. However, a majority of patients fail to derive benefit, likely due to heterogenous DLL3 expression. Antibody-drug conjugates (ADCs) targeting SEZ6, TROP2, and B7H3 have also demonstrated encouraging outcomes in clinical trials in relapsed SCLC. ADCs against HER2 and TROP2 are also approved for treatment of other solid cancers. We hypothesize that targeting cell surface HER2 or TROP2 using ADCs could provide an effective therapeutic strategy in biomarker-defined SCLC patient populations.

Methods: We analyzed ERBB2 (HER2) and TACSTD2 (TROP2) expression and regulation in treatment-naïve and relapsed SCLC patient tumors, LCNEC patient tumors, and other extrapulmonary hgNEC tumors using bulk and single-cell RNA sequencing, and methylation profiles. Efficacy of trastuzumab deruxtecan (HER2-ADC), trastuzumab, sacituzumab govitecan (TROP2-ADC), sacituzumab and the TOP1 inhibitor payloads (deruxtecan and SN-38) were evaluated in SCLC preclinical models.

Results: Both limited and extensive stage treatment-naïve SCLC tumors as well as relapsed tumors expressed a range of ERBB2 (HER2) and TACSTD2 (TROP2) expression, with enrichment in the non-neuroendocrine SCLC-P tumors. Expression of both targets (ERBB2 and TACSTD2) was negatively correlated with methylation levels in SCLC cell lines and patient tumors. Notably, SCLC tumors lacking DLL3 expression, the target of the newly approved drug tarlatamab, expressed abundant levels of both ERBB2 and TACSTD2. In preclinical models, both HER2- and TROP2-ADCs demonstrated potent in vitro activity with significant induction of apoptosis. While target expression was not predictive of ADC sensitivity, SLFN11 and TOP1 levels were identified as potential biomarkers of response. Compared to trastuzumab alone, HER2-ADC showed sustained tumor growth inhibition with prolonged tumor regression and survival in HER2-positive xenograft models. TROP2-ADC similarly demonstrated significant antitumor activity.

Conclusions: These findings demonstrate that targeting cell surface HER2 and TROP2 using ADCs is effective in SCLC, including the SCLC-P subtype, which typically is resistant to standard of care therapies and likely to tarlatamab, due to low DLL3 expression.

Keywords: Antibody drug conjugates, SCLC, SCLC-P

P3.13.12 Multi-Institution Analysis Evaluating Safety, Efficacy and ctDNA Dynamics Following Tarlatamab in ES-SCLC and LCNEC Patients

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Introduction: Tarlatamab, a bispecific T-cell engager (BiTE) targeting delta-like ligand 3 (DLL3) and CD3 on T cells, recently received FDA approval for the treatment of relapsed extensive-stage small cell lung cancer (ES-SCLC), with additional evidence suggesting effectiveness in patients with large cell neuroendocrine carcinoma (LCNEC). This novel therapy has demonstrated promising antitumor activity and durable objective responses in phase I/II clinical trials, however, is also associated with a unique side effect profile which includes cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) requiring close monitoring. How these safety and efficacy outcomes translate into real-world practice is an ongoing question.

Methods: We performed a retrospective, multi-institutional analysis of patients who received tarlatamab for ES-SCLC or LCNEC from July 2024-March 2025 at two tertiary care centers. Side effects of special interest (SESI) including CRS, ICANS and dysgeusia were reported using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Treatment response was determined using clinical interpretation of radiological disease assessment from those patients with available post-treatment imaging. Median progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods. A subcohort of patients had ctDNA collection using standard of care Guardant360 assay at pre- and post-treatment timepoints (drawn prior to C1D1 and on C3D1) and were included for molecular response assessment by measuring trends in tumor fraction.

Results: 32 patients received at least 1 dose of tarlatamab. The majority had SCLC histology (94%). Median age at C1D1 was 68 years, with 59% females and 88% being current/former smokers. Median number of prior therapies were two and ECOG PS ranged from 0-3 (9%/62%/26%/3%). SESI were observed in 26/32 patients (81%). CRS was observed in 56% of patients, all grade 1/2 in severity, with median onset within 24 hours following C1D1 and 44% requiring tocilizumab. ICANS was observed in 31% of patients, with one grade 3 event reported. Dysgeusia was noted in 57% of patients, with an average onset within 25 days from C1D1. 20 patients were included in our treatment response analysis. Best overall response rate was 60% and disease control rate (DCR) was 80% (1 CR, 11 PR, 4 SD, 4 PD). With median follow up of 4 months, median PFS was 4.5 months (95%CI: 3.1-NR) and median OS was 5.0 months (95%CI: 3.5-NR). 6 patients had ctDNA data available for molecular response analysis, with ctDNA trends corresponding with radiographic response. DCR was 100% for those patients with decreasing ctDNA fraction of ≥50% (n=4), while patients with increasing ctDNA had progressive disease at first interval imaging (n=2).

Conclusions: In our multicenter cohort of patients with SCLC/LCNEC, tarlatamab continued to show encouraging efficacy in terms of response and PFS, mirroring results from the DeLLphi-301 trial. However, in this non-trial setting, rates and timing of CRS/ICANS differed from previous reports, highlighting the need for careful observation and care coordination as this therapy is utilized in real-world practice. Novel biomarkers of response and resistance are needed in this setting, with longitudinal ctDNA dynamics showing potential promise, though larger, prospective studies are needed.

Keywords: small cell lung cancer, bi-specific T cell engagers, immunotherapy

P3.13.13 A Phase II Study of Vobramitamab Duocarmazine in Patients With Relapsed or Refractory Extensive-Stage Small-Cell Lung Cancer

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Introduction: Relapsed/refractory extensive-stage small-cell lung cancer (ES-SCLC) carries a poor prognosis, with suboptimal treatments. B7 homolog 3 protein (B7-H3), a member of the B7 family of immune checkpoint molecules, is highly expressed in SCLC and has emerged as a promising therapeutic target. Several B7-H3-targeting antibody-drug conjugates (ADCs) in development utilize topoisomerase I inhibitors as their cytotoxic payloads. Vobramitamab duocarmazine (MGC018) is an ADC targeting B7-H3, utilizing DNA alkylating agent duocarmycin as its cytotoxic payload. We present a phase II study of vobramitamab duocarmazine for relapsed/refractory ES-SCLC.

Methods: We conducted an investigator-initiated, single arm, open-label, phase 2 trial to evaluate vobramitamab duocarmazine in patients with relapsed/refractory ES-SCLC. Patients with progression on platinum-based chemotherapy were enrolled (NCT06227546). The trial employed Simon's two-stage design. The initial dose was 2.7 mg/kg administered every 28 days, but mid-trial was reduced to 2.0 mg/kg with a maximum of 8 cycles, based on treatment-related adverse events (TRAEs) from other clinical trials using vobramitamab duocarmazine. Primary endpoint was overall response rate (ORR) assessed by RECIST v1.1. Secondary endpoints were AEs assessed using CTCAE v5.0, duration of response (DOR), progression free survival (PFS), and overall survival (OS). An exploratory objective was assessed to evaluate treatment efficacy based on tumor tissue and plasma extracellular vesicles (EVs) B7-H3 expression.

Results: A total of 9 patients were enrolled. The median age was 64 (range: 49-77) with 5 men and 4 women. Patients received a median of 1 prior line of therapy (range 1-2); all patients received frontline platinum-etoposide chemotherapy with anti-PD-L1 immunotherapy. The starting dose was 2.7 mg/kg for 6 patients (66.7%) and 2.0 mg/kg for 3 patients (33.3%). No objective responses were observed. Stable disease (SD) was observed in 4 patients (44.4%) with 1 patient having SD through 8 cycles of treatment. Median number of cycles of treatment was 2 (range: 2-8). The most common any-grade TRAEs were anorexia, fatigue, and anemia (each in 4 patients, 44.4%), followed by neutropenia, conjunctivitis, rash, and thrombocytopenia (each in 3 patients, 33.3%), and pleural effusions (in 2 patients, 22.2%). Grade 3 TRAEs were pneumonia, oral mucositis, lymphopenia (each in 1 patient, 11.1%). Grade 4 neutropenia occurred in one patient (11.1%). Dose reductions were required for two patients per sponsor guidance and for one patient due to AEs. Median PFS was 2.0 months (95% CI: 1.8, NA) and median OS was 4.3 months (95% CI: 3.4, NA). The trial did not proceed to the second stage due to no objective responses. B7-H3 expression in tumor tissue and EVs and its correlation with treatment efficacy will be presented at the conference.

Conclusions: In this phase II study of vobramitamab duocarmazine in patients with relapsed/refractory ES-SCLC, limited efficacy was observed, with no objective responses leading to early termination of trial. For optimization of B7-H3 ADCs for SCLC, further work is needed to understand the ideal cytotoxic payload, dosing strategy, and biomarkers of response and resistance.

Keywords: ES-SCLC, antibody-drug conjugate, B7-H3

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.14 Lab Data-Based Prediction for Clinical Efficacy of Immunochemotherapy in ES-SCLC Using Statistical and Machine Learning Models

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Introduction: The combination therapy of programmed death-ligand 1 (PD-L1) inhibitors with chemotherapy has been established as the standard therapy for extensive-stage small cell lung cancer (ES-SCLC). It is widely recognized that neither PD-L1 expression nor tumor mutational burden can accurately predict the clinical efficacy of immunochemotherapy in patients with ES-SCLC. Although several studies have indicated a relationship between gene expression signatures from RNA-seq data and the clinical efficacy of immunochemotherapy, it is currently not practical to apply RNA-seq to clinical practice. Hence, we developed a statistical and machine learning model to predict the clinical efficacy of immunochemotherapy using lab data.

Methods: We defined patients with "prolonged progression-free survival (PFS)" as those with a PFS of 5 months or more. Of 213 patients with ES-SCLC who had progressed within 5 months after first-line immunochemotherapy or had a follow-up period of 5 months or more, 150 patients were randomly assigned to the training set and 63 patients to the test set to construct a prediction model for PFS. To calculate the probability of achieving a prolonged PFS, a non-linear logistic regression model was employed, using lab data collected just before the start of treatment as explanatory variables. In this model, an estimated probability of 0.58 or higher was interpreted as a marker for prolonged PFS. Furthermore, we defined "prolonged overall survival (OS)" patients as those with an OS of 12 months or more and constructed an OS prediction model in a similar manner. The predictive accuracy of the obtained models was verified on an independent validation set of 46 patients with ES-SCLC.

Results: We found a weak correlation between PFS/OS and lab data including NLR (Neutrophil-to-lymphocyte ratio), LDH, albumin and CRP levels. In the training set (n = 150), a non-linear logistic regression model was constructed to predict "prolonged PFS/OS" patients using the four lab data as explanatory variables. When the performance of the prediction model was evaluated on the test set (n = 63), a significant PFS/OS benefit was observed in patients predicted to have prolonged PFS/OS (PFS - 5.7 vs 4.3 months, HR 0.53 [95% CI, 0.31 to 0.92]; OS - 24.9 vs 10.3 months, HR 0.45 [95% CI, 0.22 to 0.95]). Further evaluation on the validation set (n = 46) also showed a clear PFS/OS benefit in patients predicted to have prolonged PFS/OS (PFS - 5.7 vs 4.3 months, HR 0.46 [95% CI, 0.21 to 1.00]; OS - 26.0 vs 10.6 months, HR 0.29 [95% CI, 0.10 to 0.86].

Conclusions: We developed a prediction model for PFS/OS in immunochemotherapy for ES-SCLC using lab data that can be measured in daily clinical practice.

Keywords: ES-SCLC, Immunochemotherapy, PFS/OS prediction model

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.15 First-Line Immunochemotherapy in ES-SCLC Patients With ECOG PS =2: Real-World Evidence From the ASTRUM-005R Trial

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Introduction: First-line immunochemotherapy regimens have been widely adopted for extensive-stage small cell lung cancer (ES-SCLC) based on multiple randomized controlled trials (RCTs). However, patients with poor performance status (PS) are often excluded from RCTs, leaving the efficacy of immunochemotherapy in patients with an Eastern Cooperative Oncology Group (ECOG) PS ≥2 uncertain. This subgroup analysis, based on the real-world ASTRUM-005R study, aimed to evaluate the effectiveness of first-line serplulimab-based immunochemotherapy in this underrepresented population.

Methods: ASTRUM-005R (NCT06748495) is a nationwide, real-world, observational study conducted in China to assess the safety and effectiveness of first-line serplulimab-based immunochemotherapy in patients with ES-SCLC. This subgroup analysis focused on patients with ECOG PS ≥2 to explore the feasibility and clinical outcomes in this population. Key endpoints included overall survival (OS), real-world progression-free survival (rwPFS), and overall response rate (ORR).

Results: A total of 75 patients with ECOG PS ≥2 were included in this analysis, accounting for 11.8% of the overall ASTRUM-005R cohort. Among them, 71 patients had PS 2 and 4 had PS 3. The median follow-up duration was 16.37 months (range, 1.90-23.60). Compared to patients with PS <2, poor performance status did not significantly affect rwPFS (HR = 1.15, P = 0.366). The median rwPFS for patients with PS ≥2 was 6.97 months (95% CI, 6.23-10.43), with a 1-year rwPFS rate of 26.62% (95% CI, 17.22-41.14). Similar to the overall cohort, baseline brain metastases had no significant impact on rwPFS (HR = 0.98, P = 0.953). However, patients with liver metastases had significantly shorter rwPFS than those without (4.93 vs. 10.30 months; HR = 1.95, P = 0.018). OS was poorer in patients with PS ≥2 compared to those with PS <2 (HR = 1.89, P < 0.001), with a median OS of 12.33 months (95% CI, 10.43-15.57). Again, brain metastases had no significant effect on OS (HR = 0.86, P = 0.640), while liver metastases were associated with inferior OS (9.67 vs. 14.03 months; HR = 3.01, P = 0.001). Among 74 patients with measurable disease and at least one post-treatment radiological evaluation, the ORR was 66.22% (95% CI, 54.28-76.81). Safety profiles in patients with ECOG PS ≥2 were generally consistent with those observed in the overall population. Adverse events (AEs) were reported in 20 patients (26.67%), and 15 patients experienced immune-related adverse events (irAEs), with 5 reporting grade ≥3 irAEs.

Conclusions: This subgroup analysis of the ASTRUM-005R study demonstrates that first-line serplulimab-based immunochemotherapy remains clinically effective and feasible in ES-SCLC patients with ECOG PS ≥2. Liver metastases, but not brain metastases, were associated with inferior outcomes. These findings support the potential benefit of immunochemotherapy even in patients traditionally excluded from clinical trials, warranting further investigation and validation in prospective studies.

Keywords: immunochemotherapy, serplulimab, ECOG PS

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.16 Survival Outcomes With Carboplatin Versus Cisplatin and the Impact of COVID-19 on Platinum Choice in SCLC in the Netherlands

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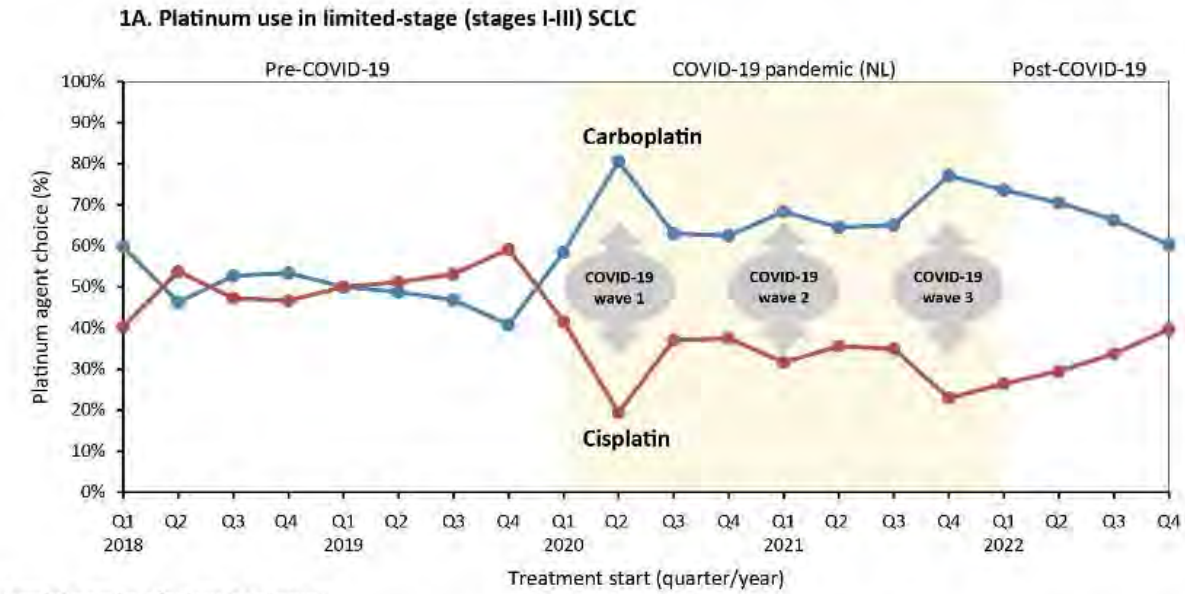
Introduction: Current guidelines recommend cisplatin as chemotherapy backbone in the first-line treatment for small cell lung cancer (SCLC), especially in limited-stage disease (LS-SCLC). However, during the COVID-19 pandemic, carboplatin use likely increased due to logistical advantages. We evaluated the pandemic's impact on platinum agent utilization in the Netherlands and compared overall survival (OS) and safety between cisplatin and carboplatin.

Methods: Netherlands Cancer Registry (NCR) data were analyzed for patients who received first-line platinum-based treatment for both LS-SCLC and extensive-stage SCLC (ES-SCLC) between January 2018 and March 2023. The COVID-19 epidemic period in the Netherlands extended from February 2020 to April 2022. Overall survival (OS) was evaluated using univariable and multivariable analyses. Additionally, patient records at three teaching hospitals were assessed to study grades 3-5 treatment-related adverse events.

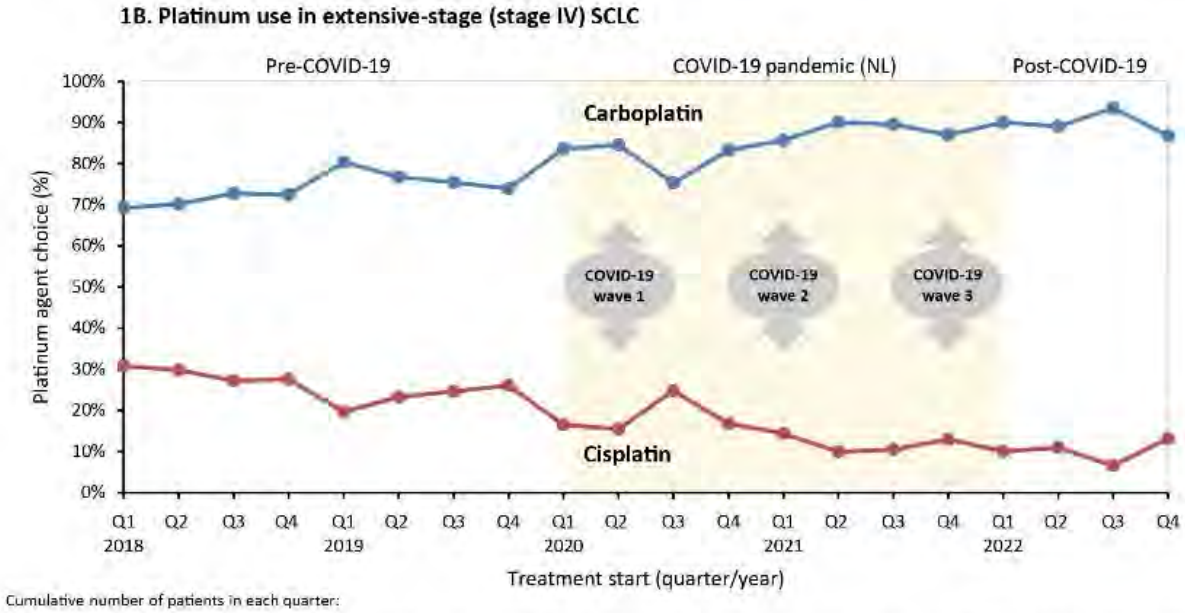
Results: We identified a total of 1683 (32%) patients with LS-SCLC (median [IQR] age 68 [62-74] years; 985 [58.5%] females; carboplatin, N=1011 [60%]; cisplatin, N=672 [40%]) and 3668 (68%) ES-SCLC patients (median [IQR] age 68 [62-73] years; 1866 [50.9%] females; carboplatin, N=3002 [82%]; cisplatin, N=666 [18%]). During the pandemic, quarterly usage rates of carboplatin increased, reaching as high as 81% in LS-SCLC (Figure 1A) and 90% in ES-SCLC (Figure 1B). Post-pandemic use of carboplatin in ES-SCLC remained elevated (up to 94%). In LS-SCLC, univariable analysis showed the median OS to be significantly shorter with carboplatin compared to cisplatin (17.9 vs. 26.3 months; HR, 1.48; 95%CI, 1.31-1.68; P<0.001). Similar findings were observed in ES-SCLC (8.0 vs. 9.3 months; HR, 1.19; 95%CI, 1.09-1.30; P<0.001). However, multivariable analyses, after adjusting for confounders, showed no difference in OS between carboplatin and cisplatin in either LS-SCLC (HR, 1.06; 95%CI, 0.90-1.25; P=0.463) or ES-SCLC (HR, 1.01; 95%CI, 0.92-1.12; P=0.785). Confounders were performance status (PS), age, sex, and chemoradiotherapy type for LS-SCLC, and PS, age, sex, stage, and liver metastases for ES-SCLC. Individual patient data revealed more hematologic toxicity with carboplatin, while more nonhematologic toxicity was seen with cisplatin.

Conclusions: Population registry data revealed significant increases in carboplatin use during the COVID-19 pandemic. Comparable OS was seen in both LS-SCLC and ES-SCLC treated with carboplatin or cisplatin. These findings challenge the long-standing belief of the superiority of cisplatin-containing chemotherapy doublets in SCLC and support the adoption of carboplatin in SCLC.



Cumulative number of patients in each quarter:

	Q1 2018	Q2	Q3	Q4	Q1 2019	Q2	Q3	Q4	Q1 2020	Q2	Q3	Q4	Q1 2021	Q2	Q3	Q4	Q1 2022	Q2	Q3	Q4
Carboplatin	43	37	39	55	41	41	45	40	45	54	51	55	54	49	54	64	64	55	57	44
Cisplatin	29	43	35	48	41	43	51	58	32	13	30	33	25	27	29	19	23	23	29	29



Cumulative number of patients in each quarter:

	Q1 2018	Q2	Q3	Q4	Q1 2019	Q2	Q3	Q4	Q1 2020	Q2	Q3	Q4	Q1 2021	Q2	Q3	Q4	Q1 2022	Q2	Q3	Q4
Carboplatin	108	113	139	126	151	129	144	139	152	142	149	144	155	154	188	154	180	146	186	138
Cisplatin	48	48	52	48	37	39	47	49	30	26	49	29	26	17	22	23	20	18	13	21

Figure 1. Platinum use in the first-line treatment of limited-stage (A) and extensive-stage (B) SCLC in the Netherlands prior to, during, and after the COVID-19 pandemic

The first case of COVID-19 caused by Sars-Cov-2 in the Netherlands was reported on February 27, 2020. The second and third surge in COVID-19 cases ("waves") started in October 2020 and October 2021, respectively. Data from Q1 2023 were not complete and are therefore not shown. *Abbreviations*: SCLC, small cell lung cancer; COVID-19, coronavirus disease; NL, Netherlands; Q, quarter.

Keywords: Small Cell Lung Cancer, Carboplatin, Cisplatin

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.17 A Comparative Analysis of TNM 8 and TNM 9 Classification Systems in Small Cell Lung Cancer

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Introduction: The Tumor-Node-Metastasis (TNM) classification system is the international accepted standard for staging lung cancer, facilitating prognosis and treatment decision. It has been primarily developed and validated for non-small cell lung cancer (NSCLC), with limited applicability to small-cell lung cancer (SCLC), due to the latter's distinct biology and fast progression. The previous TNM classification did not capture key prognostic factors, namely the extent of mediastinal nodal involvement and the number and distribution of distant metastases. The 9th edition of the TNM classification, released in 2024, addresses these limitations, subdividing N2 into N2a (single-zone) and N2b (multi-zone), and M1c into M1c1 (single-organ) and M1c2 (multi-organ). This study evaluates the impact of the 9th versus the 8th TNM classification in staging SCLC and survival prediction.

Methods: We analyzed a single-center cohort of SCLC patients diagnosed between 2016-2022. Available diagnostic imaging investigations (i.e. whole body CECT or FDG-PET) were retrospectively reviewed. Each case was thereafter reclassified according to both 8th and 9th edition. Overall survival (OS) was assessed based on the T, N, and M descriptors, with comparisons made between staging groups. Multivariate Cox regression models were used to evaluate the independent prognostic significance of TNM staging, adjusted for key clinical variables (Sex, age and WHO performance status).

Results: A total of 421 patients from the Karolinska University Hospital in Sweden were included. Stage migration between editions occurred in 5.5% of all cases (n = 23), primarily affecting Stage II and III patients. Specifically, one patient migrated from IIB to IIA; eight from IIIA to IIB; and 14 from IIIB to IIIA. Subclassification changes affected 328 cases (78%). The introduction of N2a and N2b reclassified 134 cases (45% N2a, 55% N2b), while M1c1 and M1c2 subdivided 212 cases (44% M1c1, 56% M1c2).Median OS improved for Stage IIA according to the 9th edition (57 vs. 37 months), while IIIA survival decreased (13 vs. 16 months), likely due to migration effects.Kaplan-Meier survival analysis demonstrated significantly worse survival for N2b (median OS 5 Months) vs N2a (Median OS 9 months; log-rank p = 0.008, regardless of M status) and M1c2 (median OS 4 months) versus M1c1 (Median OS 7 months, log-rank p = 0.02, regardless of N status).Univariate Cox regression identified N2b (HR = 1.6, 95% CI: 1.1-2.3) and M1c2 (HR = 1.4, 95% CI: 1.1-1.8) as negative prognostic factors. These findings were confirmed by multivariate analysis.

Conclusions: This study represents the first real-world evaluation of the 9th TNM edition in a SCLC cohort. While overall stage migration was limited (5.5%), making it difficult to determine whether the updated staging system improves survival stratification at the full stage level, the new N2a/N2b and M1c1/M1c2 subclassifications demonstrated prognostic relevance. Survival analysis confirmed a worse outcome for patients with N2b and M1c2 disease supporting the clinical utility of these reclassifications within the 9th TNM edition.

Keywords: Small-cell lung cancer, TNM classification, Real-world data

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.18 Immunotherapy Pooled Analysis in 1L Extensive-Stage Small Cell Lung Cancer

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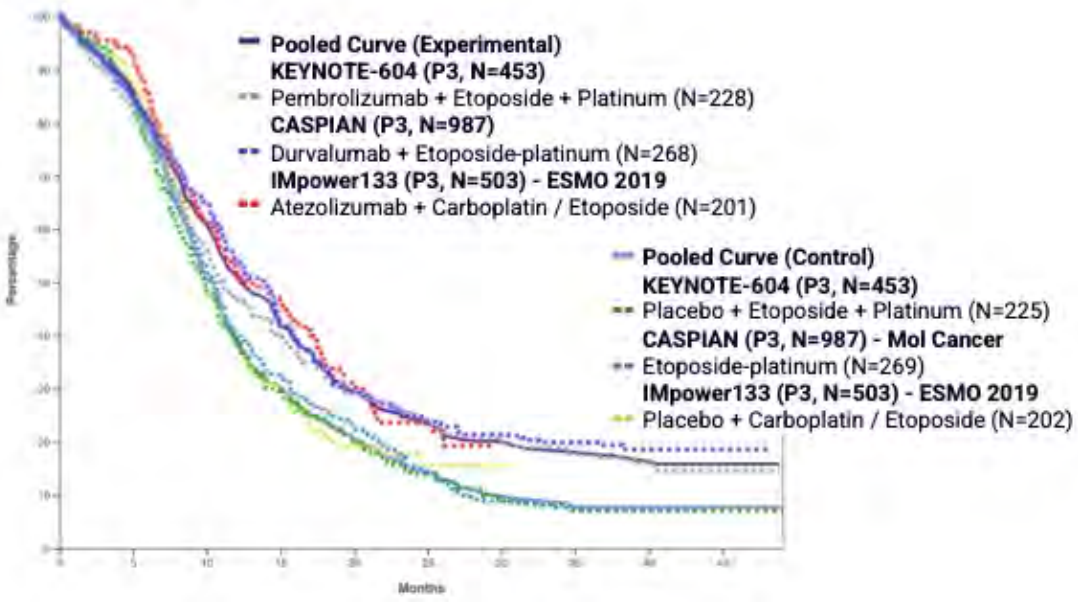
Introduction: Extensive-stage small cell lung cancer (ES-SCLC) remains a challenging disease with limited treatment success. Survival benefits have been observed with the addition of immunotherapy (IO) to chemotherapy. To provide a unified and survival estimate with IO-based regimens in 1L ES-SCLC, we conducted a pooled analysis across landmark clinical trials.

Methods: We leveraged LARVOL CLIN, an oncology outcomes database with 130k+ Trials, 100k+ digitized Kaplan-Meier (KM) curves. We implemented the validated algorithm developed by Guyot et al. (2012) to obtain pseudo-individual patient data (pseudo-IPD) from published KM curves and at-risk data. We pooled the reconstructed datasets by treatment arm and performed a synthetic KM survival analysis to estimate the median OS.

Results: Three phase III clinical trials were selected based on the availability of published overall survival (OS) KM curves for 1L ES-SCLC. CASPIAN (durvalumab, HR=0.71*), KEYNOTE-604 (pembrolizumab, HR=0.76) and Impower133 (atezolizumab, HR=0.7*) evaluate the addition of their respective IO to chemotherapy (experimental arm N= 644 and control arm N= 643). The median OS in the IO + chemotherapy arm was 11.9 months, compared to 10.0 months in the chemotherapy-alone control arm. Estimated one-year survival probabilities were 49.9% in the IO + chemotherapy arm and 38.6% in the control arm. Two-year survival probabilities were 22.5% and 14%, respectively. Synthetic KM curves from the pooled pseudo-IPD analysis (Image 1) illustrated a separation in survival between arms beginning at approximately 5.8 months, which was maintained through follow-up. Cox proportional hazards modeling showed a hazard ratio (HR) of 0.76 (95% CI: 0.68-0.85, p-value <0.001), indicating statistically significant survival benefit with IO-based regimens compared to chemotherapy alone.

Conclusions: IO combined with chemotherapy has become the standard of care for 1L ES-SCLC. Pseudo-IPD-derived pooled KM curves affirm the statistically significant OS benefit of adding IO to chemotherapy. The analysis establishes a framework to benchmark IO-based regimens in this setting. Collectively, survival benefits diverge around 6 months and are maintained through follow-up, reflecting the delayed onset of immunotherapy's clinical effect. Pooled analysis findings of course should be interpreted with caution, as there might be heterogeneity in trial design, treatment exposure, or follow-up schedules. Nevertheless, this analysis provides a practical benchmark for evaluating emerging therapies in ES-SCLC, particularly in settings where delayed survival benefits are expected.

Image 1. Pseudo-IPD-generated KM curve for OS



Keywords: ES-SCLC, Pooled Analysis, Immunotherapy

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.19 High Throughput Drug Screening for Small Cell Lung Cancer Based on Machine Learning and Organoid Platforms

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Introduction: Small cell lung cancer (SCLC) remains a therapeutic challenge with limited treatment options. We developed a high - throughput drug screening platform combining machine learning (ML) prediction models with patient-derived organoids (PDOs) to identify novel therapeutic agents and targets for SCLC.

Methods: The candidate drug library was screened from three sources. First, The R 'oncoPredict' package was applied to predict drug responses. Utilizing drug response data from CTRP v2, GDSC v1&v2, and PRISM databases, we trained ML models to predict drug sensitivity. SCLC datasets (GSE30219, GSE43346, GSE149507) from GEO were used as the prediction set, identifying 68 SCLC-specific drugs with selective efficacy. Second, by mining the phase I/II clinical trials for SCLC (excluding immunotherapy) on Clinical Trials. gov, 31 drugs were selected. Finally, for the other drug selection part, two points were considered: a. Select corresponding compounds according to the drug pathways or targets involved in SCLC clinical trials; b. the intersection of drugs from the cancer stem cell compound library and the anti-tumor metabolism compound library was selected. A total of 171 drugs were screened in this part. Ultimately, 270 compounds were subjected to high throughput primary screening on SCLC-LCOs. Drugs that could inhibit the viability of organoids below 30% were selected for the subsequent re-screening stage. Finally, the candidate drugs were screened out and further clarified the relevant mechanisms.

Results: Primary screening using 2 chemo-sensitive and 2 resistant SCLC-LCOs identified 25 compounds with potent activity. Subsequently, these 25 drugs were re-screened on sensitive/resistant cell lines and organoids, and several drugs with good inhibitory effects were finally screened out, including PI3K inhibitors, CDK7 inhibitors, etc. In particular, the natural product acriflavine showed good inhibitory effects on both sensitive and drug - resistant organoids (IC50 in sensitive PDOs was 0.1-0.2μM, and IC50 in drug-resistant PDOs was 0.4 μM). RNA-seq results showed that differential genes such as ATF3, CDKN1A, and GADD45B were significantly upregulated after acriflavine treatment. Over-expression analysis(ORA) indicated that acriflavine could upregulate the stress response of EIF2AK4 to amino acid deficiency. Verified by the GEO database, compared with normal lung tissues, the EIF2AK4 and ATF3 genes were significantly downregulated in SCLC. Western blot showed that acriflavine could induce the phosphorylation of EIF2AK4, resulting in the phosphorylation of EIF2A and the over-expression of ATF3. Quantitative PCR (qPCR) showed that after acriflavine treatment, the mRNA levels of EIF2AK4 and ATF3 were upregulated in a dose - dependent manner, confirming the transcriptional activation of the stress response pathway. In addition, apoptosis detection by flow cytometry presented an obvious acriflavine dose - dependent apoptosis. These findings further confirm the role of acriflavine in activating EIF2AK4 - mediated endoplasmic reticulum stress and mediating apoptosis in SCLC.

Conclusions: Acriflavine activates EIF2AK4-mediated endoplasmic reticulum stress and apoptosis in SCLC, highlighting its therapeutic potential. The ML-PDOs platform effectively identifies agents suppressing SCLC growth while revealing actionable targets and pathways, accelerating translational research in precision oncology.

Keywords: small cell lung cancer, patient-derived organoid, drug screening

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.20 Integrative Spatial Analysis Reveals Ferroptosis Heterogeneity and Novel Therapeutic Vulnerabilities in Small Cell Lung Cancer

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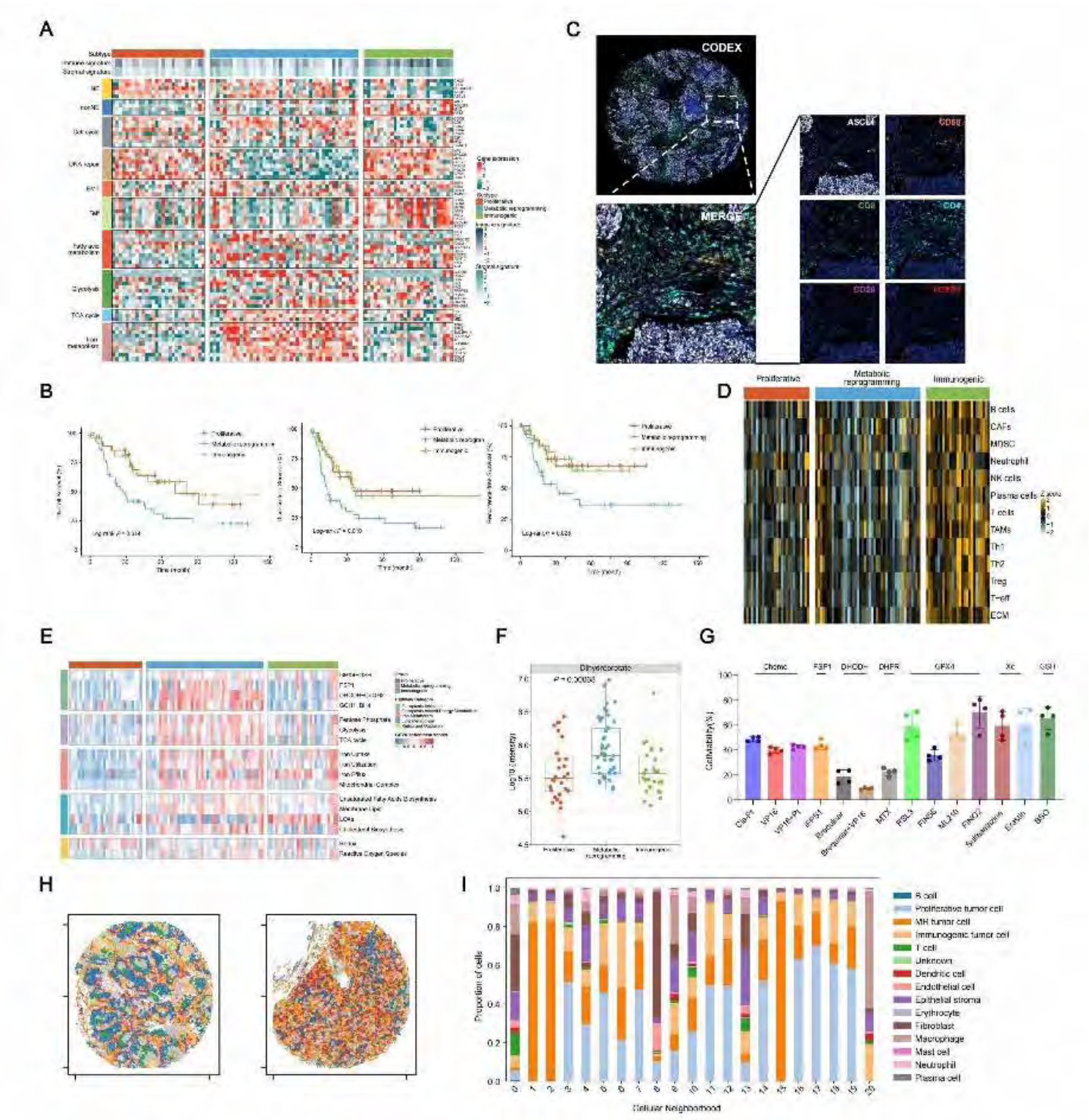
Introduction: Treatment of small cell lung cancer (SCLC) remains challenging. Deciphering the orchestration of molecular heterogeneity especially from the spatial dimension will provide new insights into SCLC therapeutic strategies.

Methods: We performed genomic, transcriptomic, metabolomic, lipidomics and spatial single-cell resolved transcriptomic (CosMx) and proteomic (CODEX) analyses on 100 patients from the Fudan University SCLC (FU-SCLC) cohort. A robust molecular classification was established with each subtype characterized by clinical, multi-omics and spatial signatures.

Results: Through comprehensive integrative analysis, we identified three subtypes of SCLC: proliferative, immunogenic, and metabolic reprogramming (MR) subtypes, which significantly stratified patient outcomes for recurrence-free survival, disease-free survival, and overall survival. The proliferative subtype was characterized by neuroendocrine lineage commitment (ASCL1+ tumor cell enriched), elevated proliferative activity, and an immune-deserted tumor microenvironment. The immunogenic subtype exhibited non-neuroendocrine differentiation, extensive immune cell infiltration, and extracellular matrix remodeling. The MR subtype represented a special transitional phase of SCLC neuroendocrine dedifferentiation, demonstrating enhanced glycolytic flux, tricarboxylic acid (TCA) cycle activity, and ferroptosis resistance, leading to poorest prognosis. Notably, non-canonical ferroptosis defense axis DHODH-COQH2 was aberrantly activated in the MR subtype, accompanied by elevated corresponding metabolites. Pharmacological inhibition of DHODH using Brequinar selectively suppressed proliferation and induced ferroptosis in MR SCLC cell lines. Spatial transcriptomic and proteomic profiling further revealed that ferroptosis-resistant tumor cells orchestrated a pro-tumorigenic ecotype marked by defective DNA damage repair and immune exclusion in their microenvironment, suggesting a potential immunotherapy target.

Conclusions: The ferroptosis heterogeneity across SCLC emphasizes the need to map individual patient landscapes to develop personalized treatment strategies. Our findings provide critical insights into SCLC biology and serve as a valuable resource for future molecular investigations and therapeutic exploration.



Keywords: Small cell lung cancer, Molecular heterogeneity, Ferroptosis defense

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.21 Refining Patient Selection for Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer: A Multicenter Cohort Study

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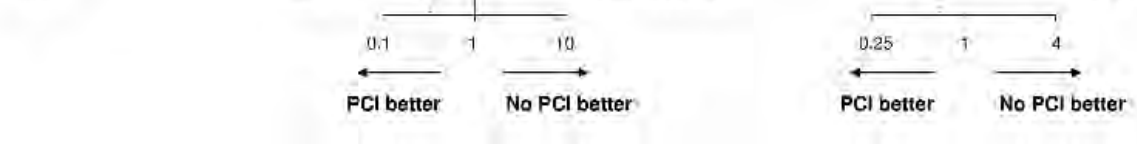
Introduction: We aimed to evaluate the efficacy of prophylactic cranial irradiation (PCI) in the contemporary management of limited-stage small-cell lung cancer (LS-SCLC) and to identify optimal strategies for patient selection.

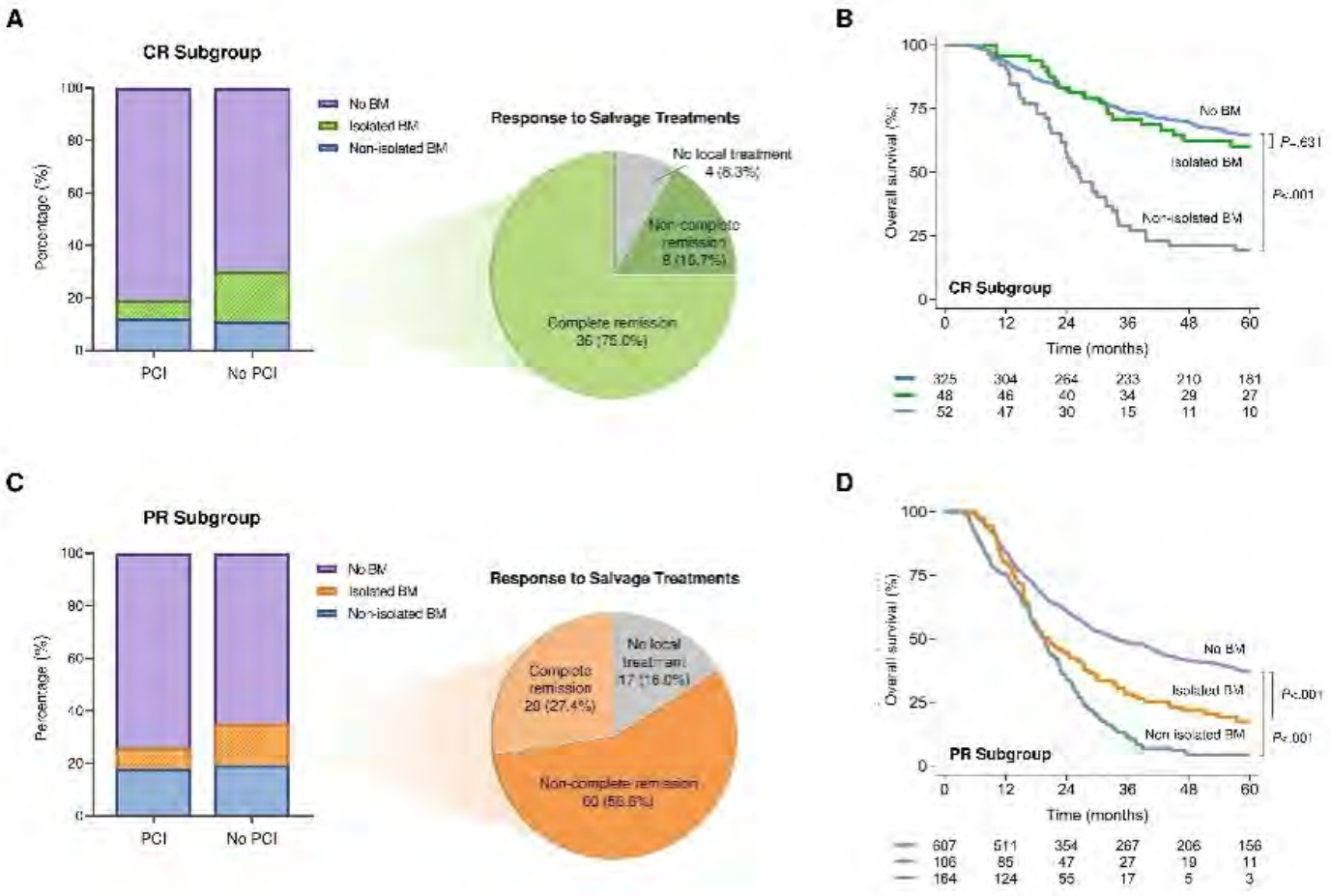
Methods: This multi-institutional cohort study included LS-SCLC patients who underwent definitive chemoradiation between 2006 and 2022, all staged using brain magnetic resonance imaging (MRI) and positron emission tomography. We compared the incidence of brain metastases (BM) and overall survival (OS) between patients who received PCI and those who did not. Additionally, we analyzed the differential effect of PCI across 22 subgroups. BM was classified as either isolated or non-isolated, with cumulative incidence calculated using a competing risk model. Outcomes of salvage treatments for isolated BM were also assessed.

Results: Among the 1302 study patients, 672 (51.6%) received PCI and 630 (48.4%) did not. During a median follow-up of 30.5 months (range, 4.2-227.2), PCI significantly reduced the cumulative incidence of BM (17.4% vs. 27.6% at 2 years; P<.001), primarily by decreasing isolated BM (6.5% vs. 16.1% at 2 years; P<.001), but had no significant effect on non-isolated BM. PCI consistently reduced the incidence of isolated BM across all subgroups, which led to improved OS except for patients who achieved complete response (CR) to primary treatment (hazard ratio [HR] 1.03; P=.865). CR patients who developed isolated BM, and received local salvage treatment achieved an 81.8% remission rate, resulting in OS comparable to those without BM development (HR 1.10; P=.631). Stereotactic radiosurgery for BM salvage treatment showed superior OS compared to whole-brain radiotherapy or systemic treatment alone.

Conclusions: PCI did not improve OS in patients achieving CR, who demonstrated excellent outcomes with BM salvage treatment. Our findings suggest that MRI surveillance, combined with effective salvage treatment, may serve as a viable alternative for selected LS-SCLC patients.

Subgroup	n	Isolated brain metastasis: SHR (95% CI)	Isolated brain metastasis: *P* value for interaction	Overall survival: HR (95% CI)	Overall survival: *P* value for interaction
Age			0.749		0.971
< 70 years	1047	0.33 (0.22–0.49)		0.71 (0.61–0.83)	
≥ 70 years	255	0.27 (0.12–0.60)		0.72 (0.52–0.99)	
Sex			0.893		0.663
Male	1129	0.32 (0.22–0.47)		0.70 (0.60–0.81)	
Female	173	0.34 (0.14–0.84)		0.75 (0.51–1.10)	
ECOG performance status			0.875		0.890
0–1	1217	0.32 (0.22–0.46)		0.70 (0.61–0.81)	
≥ 2	85	0.30 (0.12–0.76)		0.73 (0.53–1.00)	
Smoking history			0.497		0.694
No	153	0.36 (0.15–0.85)		0.75 (0.53–1.06)	
Yes	1149	0.31 (0.21–0.45)		0.70 (0.61–0.81)	
T stage			0.394		0.633
T1–T2	751	0.28 (0.17–0.47)		0.68 (0.57–0.82)	
T3–T4	551	0.37 (0.24–0.58)		0.73 (0.60–0.90)	
N stage			0.330		0.308
N0	112	0.26 (0.13–0.53)		0.51 (0.33–0.79)	
N1–N3	1190	0.36 (0.24–0.53)		0.71 (0.62–0.82)	
Overall stage			0.560		0.210
I–II	220	0.26 (0.10–0.68)		0.53 (0.36–0.78)	
III	1082	0.34 (0.23–0.50)		0.73 (0.63–0.84)	
Chemoradiation sequence			0.869		0.688
Concurrent	1178	0.32 (0.22–0.46)		0.75 (0.65–0.86)	
Sequential	124	0.27 (0.11–0.68)		0.72 (0.56–0.92)	
Chemotherapy regimen			0.632		0.693
Etoposide + cisplatin	1080	0.28 (0.13–0.61)		0.70 (0.60–0.82)	
Others	222	0.35 (0.23–0.52)		0.77 (0.57–1.03)	
Thoracic radiation dose			0.731		0.306
≥ 60 Gy	203	0.37 (0.16–0.86)		0.76 (0.56–1.04)	
< 60 Gy	1099	0.32 (0.22–0.48)		0.63 (0.54–0.74)	
Treatment response			0.767		0.006
Complete response	425	0.35 (0.20–0.63)		1.03 (0.78–1.36)	
Partial response	877	0.33 (0.21–0.50)		0.67 (0.56–0.80)	
Total	1302	0.33 (0.23–0.46)		0.70 (0.61–0.80)	





Keywords: Small-cell lung cancer, Prophylactic cranial irradiation, Complete response

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.22 Efficacy and Safety of Surufatinib, Durvalumab in Combined With Chemotherapy as First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer

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Introduction: The combination of platinum-based chemotherapy plus etoposide with immunotherapy has become the new standard of care for the first-line treatment of extensive-stage(ES) small-cell lung cancer(SCLC). Surufatinib, a multi-kinase inhibitor on VEGFR, FGFR and CSF1R in combined with immunotherapy has shown synergistic effect in many solid tumors, including SCLC. To further improve the prognosis of ES-SCLC, we performed this study to explore the efficacy and safety of surufatinib in combination with standard durvalumab, etoposide and platinum chemotherapy regimen in ES-SCLC as first-line treatment. The trial is still ongoing, and we are now reporting the preliminary results.

Methods: This is an ongoing single-arm, multi-center, open-label study conducted in China. The study would enroll 20 patients with ES-SCLC. Patients would receive surufatinib at a dose of 250 mg once per day, with durvalumab 1500 mg intravenously on day 1, etoposide 100 mg/m2 intravenously on day 1-3, and cisplatin 75 mg/m^2, once daily, continuous IV infusion for over 3 hours, on day 1-3, or carboplatin, AUC 5-6, intravenous infusion, day 1 of each treatment cycle, in every 21-day cycle. If available, tumor assessments were performed every 2 cycles ± 7 days according to RECIST version 1.1.

Results: By March 10, 2025, 13 eligible patients had been enrolled, of whom 12 (92.3%) were female. The median age was 64 (range: 46-72). 12 (92.3%) patients presented with ECOG performance score of 1. 10 (76.9%) patients had smoking history. With a median follow-up time of 13.40 months, 11 patients received at least one post baseline tumor assessment, of whom all the patients achieved partial response(PR). The median overall survival(OS) was 15.80 (95% CI: 8.61-NA) months, and the median progress-free survival(PFS) was 7.95 (95% CI: 4.70-9.03) months. The median time-to-response was 1.58 (95% CI: 1.41-3.02) months and median duration of response was 5.22 (1.71-7.79) months. The most common adverse events(AEs) of all grades were white blood cells decreasing (61.54%), anemia (46.15%), and platelet decreasing (38.46%), and those of grade 3 or higher were white blood cells decreasing (46.15%), platelet decreasing (15.38%), fatigue (7.69%), and immune-related pneumonia (7.69%).

Conclusions: Surufatinib in combination with the current recommended durvalumab, etoposide, and EP/EC chemotherapy regimen exhibited promising efficacy and manageable toxicity as first-line treatment for patients with ES-SCLC. The trial is still ongoing.

Keywords: Small-cell Lung Cancer, Immunotherapy, anti-angiogenesis

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.23 Copy Number Gain of MYC-Paralogs Represents Proliferative Phenotype and Poor Prognosis in Resected Small Cell Lung Cancer

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Introduction: Emerging evidence highlighted the critical role of amplified MYC-paralogs (MYC, MYCL and MYCN) genes in driving chemoresistance and disease recurrence in small cell lung cancer (SCLC). However, the existing immunohistochemistry (IHC) and single-probe of fluorescence in situ hybridization (FISH) tend to miss copy number variations of MYC-paralogs at lower levels. This study developed a novel triple-probes of FISH (triple-FISH) to investigate the prevalence of MYC-paralogs copy number gain (CNG) and their clinical and biological implications in surgically resected SCLC specimens.

Methods: A novel triple-FISH (MYC, MYCL and MYCN) and IHC were employed to characterize the expression and copy number variation of MYC-paralogs in surgical resected SCLC samples (n = 56). The copy number gain was defined when any of the MYC-paralogs exhibited ≥ 3.0 signals per cell as detected by triple-FISH. Conversely, the neutral group was defined as the condition where all MYC-paralogs showed < 3.0 signals. Whole genome sequencing (WGS) was conducted to validate the copy number of MYC-paralogs. Multiplex immunohistochemical (mIHC) profiling with a 6-plex antibody panel (Pan-CK, Ki67, CD3, CD31, CD11b and CD68) characterized the cellular composition of the samples.

Results: A total of 30 MYC-paralogs CNG were identified using the triple-FISH, including 10 MYC, 18 MYCL and 2 MYCN. Kaplan-Meier survival curves revealed that SCLC patients with MYC-paralogs CNG had significantly poorer overall survival (OS) than those in the neutral group (p = 0.042). Furthermore, in multivariate analyses, apart from lymph node metastasis (HR = 7.05, 95%CI: 1.92-25.90, p = 0.003), the MYC-paralogs CNG also emerged as an independent prognostic risk factor for OS (HR = 5.72, 95%CI: 1.20-27.27, p = 0.028). Next, we identified 6 distinct cell populations with a resolution of more than 2 million cells, namely tumors cells, Ki67+ tumors, macrophages, T cells, endothelial cells and undefined cells. We found that the proportion of Ki67+ tumor was significantly higher in samples with MYC-paralogs CNG (p = 0.031) compared to the neutral group, suggesting that MYC-paralogs CNG promotes proliferative phenotype in SCLC, which may result in poor prognosis.

Conclusions: We established a novel triple-probes of FISH to identify copy number gain of MYC, MYCL and MYCN, which indicates the elevated Ki67+ tumor infiltration with poor prognosis in SCLC.

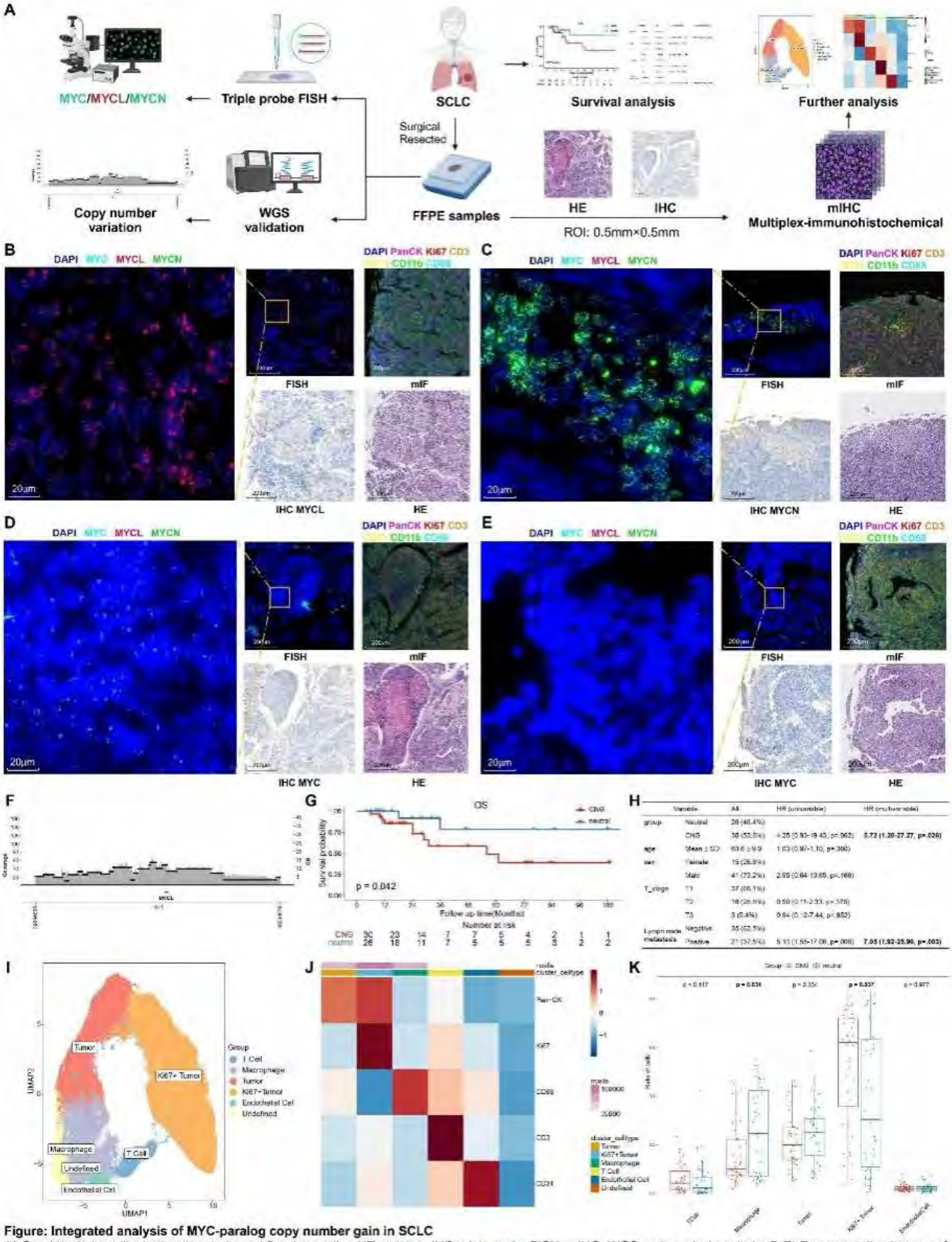

Figure: Integrated analysis of MYC-paralog copy number gain in SCLC

A) Graphic abstract illustrating the study workflow integrating HE staining, IHC, triple probe FISH, mIHC, WGS and survival analysis. B-E) Representative images of SCLC samples showing the copy number status of: (B) MYCL, (C) MYCN, (D) MYC, (E) neutral. Triple probe FISH for MYC/MYCL/MYCN (cyan/red/green signals), mIHC for DAPI/Pan-CK/Ki67/CD3/CD31/CD11b/CD68 (blue/pink/red/orange/yellow/green/cyan signals). F) WGS analysis quantitated the copy number variations of amplified MYC-paralogs. G) Kaplan-Meier curves demonstrating OS differences between CNG (n = 30) and neutral (n = 26) groups. H) Multivariate Cox proportional hazards model showing CNG and lymph node mestasis as independent prognostic factors for OS. I-K) mIHC analysis revealing: (I) UMAP plot of 222,796 cells clustered into 6 distinct cell populations, (J) averaged expression levels of markers across the 6 identified cell populations, (K) cellular composition between CNG and neutral groups.

Keywords: small cell lung cancer, copy number gain, MYC-paralogs genes

P3.13.24 Longitudinal Plasma Proteomics Identifies Predictive Biomarkers for Anti-PD-L1 Therapy in SCLC

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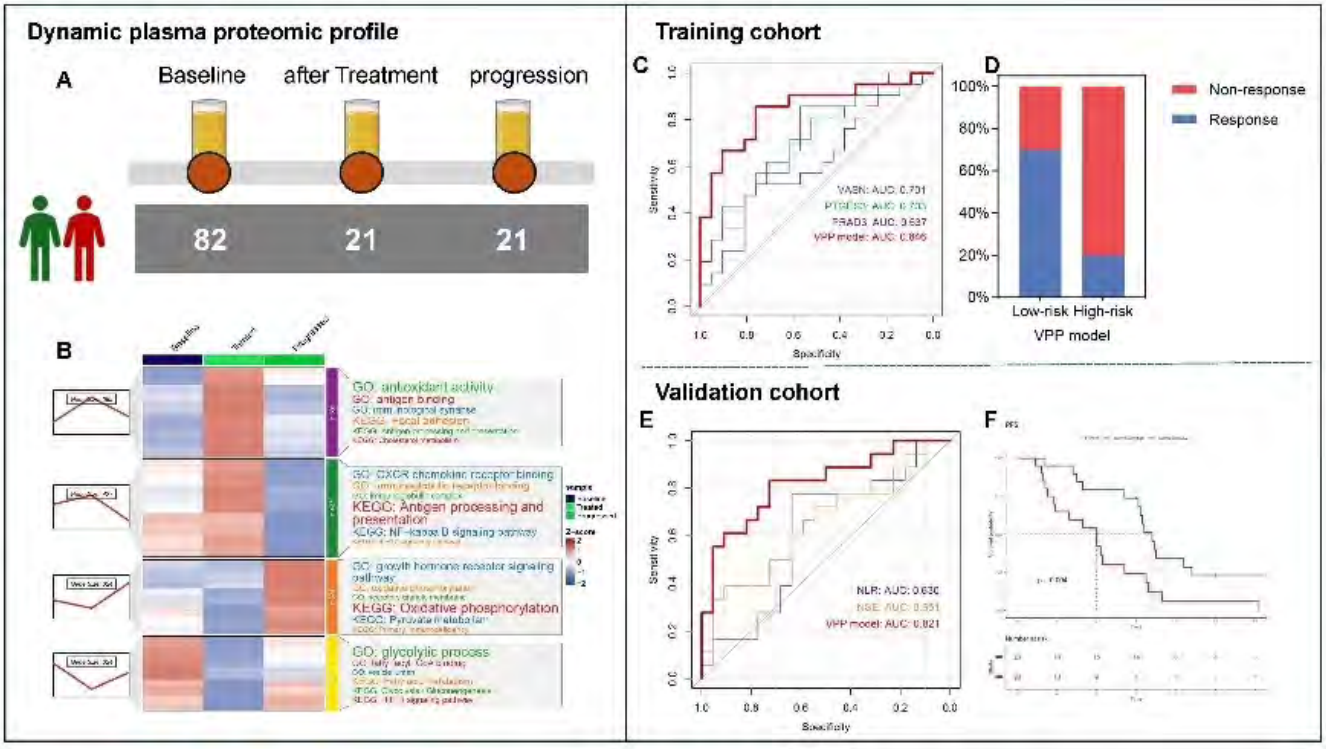
Introduction: Immune checkpoint inhibitors have revolutionized the treatment of small cell lung cancer (SCLC). However, patient responses vary significantly, and reliable predictive biomarkers for treatment selection remain unavailable. This study characterizes dynamic plasma proteomic changes and identifies predictive biomarkers for SCLC patients undergoing immunotherapy.

Methods: Longitudinal plasma samples were collected from SCLC patients before and during chemo-immunotherapy. Protein quantification was performed using 4D-DIA mass spectrometry (MS). Patients with a median progression-free survival (PFS) of less than six months were classified as non-responders (NR), while others were categorized as responders (R). Bioinformatic analyses were conducted to delineate the dynamic plasma proteomic landscape. Machine learning models were applied to identify biomarkers predictive of immunotherapy response, and candidate biomarkers were validated using ELISA in an external cohort.

Results: A total of 82 SCLC patients treated with anti-PD-L1 plus chemotherapy were included, and plasma samples were analyzed using DIA-MS. Differential expression analysis identified 651 differentially expressed proteins (DEPs; 485 upregulated, 166 downregulated) in the R group compared to the NR group. Enrichment analysis revealed that upregulated proteins in responders were associated with TRC complex function and NF-kappaB-inducing kinase activity, while downregulated proteins were linked to negative regulation of interleukin-1 beta production and protease inhibitor complex activity. Longitudinal proteomic analysis at baseline, post-anti-PD-1 therapy, and at disease progression identified 648 proteins associated with immunotherapy benefits. A LASSO model was applied to identify predictive biomarkers, resulting in the selection of three key proteins: VASN, PTGES3, and PRAD3. In the training cohort (n = 42), these biomarkers achieved AUC values of 0.701, 0.703, and 0.637, respectively. The combined VPP-Model, integrating all three biomarkers, demonstrated superior predictive performance with an AUC of 0.846. External validation in a cohort of 40 patients confirmed its robustness, yielding an AUC of 0.832. The VPP-model was significantly superior to previously reported biomarkers, such as neuron-specific enolase (NSE, AUC=0.651, P = 0.03) and neutrophil-to-lymphocyte ratio (NLR, AUC=0.630, P = 0.02). Based on the VPP-model, response rates were significantly higher in the low-risk group (70%) compared to the high-risk group (20%; P = 0.004). Median PFS was 6.87 months in the low-risk group and 3.97 months in the high-risk group (HR = 0.39; 95% CI: 0.19-0.812; P = 0.005).

Conclusions: This study provides a comprehensive analysis of the dynamic plasma proteomic landscape in SCLC patients receiving chemo-immunotherapy. The identified plasma-derived biomarkers exhibit superior predictive performance compared to previously reported biomarkers.



Keywords: SCLC, immunotherapy, biomarker

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.25 Comprehensive Immune Microenvironment Profile of EGFR-Mutant Non-Small Cell Lung Cancer Transformation Towards Small Cell Lung Cancer

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Introduction: Neuroendocrine transformation of epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) represents a significant mechanism underlying acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). This histological transformation lacks effective treatments. We investigated the immune microenvironment of primary EGFR-mutant NSCLC and paired transformed small cell lung cancer (T-SCLC) with the aim of understanding the immune landscape of this subtype of T-SCLC.

Methods: Nine patients harbouring EGFR mutations who developed T-SCLC and were treated with programmed cell death-1 (PD-1) axis blockade were enrolled. RNA transcriptome sequencing and multiplex immunohistochemistry were conducted to investigate the tumor immune microenvironment. We additionally used gene expression data of primary small cell lung cancer (P-SCLC) from GEO dataset to analyze the differences between T-SCLC and P-SCLC.

Results: Nine patients received EGFR-TKI before rebiopsy to confirm T-SCLC. The median progression-free survival (mPFS) and overall survival (mOS) of T-SCLC with ICIs were 5.1 and 11.7 months, respectively. T-SCLC harboring EGFR L858R tended to have inferior survival to EGFR 19del (mPFS:3.8 vs 5.7 months, P = 0.11; mOS:6.9 vs 11.7 months, P = 0.09). Our data revealed that paired T-SCLC exhibited an immune-suppressive microenvironment compared with EGFR-mutant NSCLC, which included the downregulation of multiple immune regulatory pathways, reduced immune cell infiltration, decreased scores of immune-related signatures. Additionally, we found a more immunosuppressive tumor microenvironment in P-SCLC compared with T-SCLC. In P-SCLC, the degree of almost all immune signatures was significantly lower than that in T-SCLC, such as MHC signature, T cell-inflamed GEP signature and IFN-gamma signature. Notably, clinically relevant immune checkpoints LAG3 and TIGIT were downregulated in T-SCLC compared with P-SCLC.

Conclusions: Our findings provide novel insights into the immune microenvironment profile of T-SCLC. Specifically, a significantly suppressed immune microenvironment is observed in T-SCLC that develops from EGFR-mutant NSCLC following TKI resistance; however, it remains more favorable compared to P-SCLC.

Keywords: EGFR-mutant, Neuroendocrine transformation, Small Cell Lung Cancer

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.26 Sequencing of Stereotactic Body Radiation Therapy and Chemotherapy in Stage I Small Cell Lung Cancer: Practice Patterns and Outcomes

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Introduction: The current standard-of-care for limited-stage small cell lung cancer (LS-SCLC) includes definitive thoracic radiotherapy (TRT) with concurrent chemotherapy. For patients with stage I disease who do not undergo surgical resection, stereotactic body radiation therapy (SBRT) has emerged in recent years as an alternative to conventionally fractionated radiation therapy. However, the optimal sequencing of SBRT with regards to chemotherapy remains unknown. We sought to identify practice patterns of SBRT timing relative to chemotherapy and assess survival outcomes for patients with stage I SCLC in the United States.

Methods: We identified patients in a large national database with clinical stage I SCLC who underwent SBRT and chemotherapy between 2004 and 2020. Patients were categorized into two cohorts: SBRT before chemotherapy initiation (Group 1) and SBRT concurrent with or after chemotherapy initiation (Group 2). Chi-squared tests were used to compare patient characteristics between the groups. Univariable and multivariable logistic regressions were used to determine patient characteristics associated with treatment cohorts, while Cox proportional hazard models evaluated their impact on survival outcomes. The Kaplan-Meier method and the log-rank test were used to compare survival outcomes between cohorts.

Results: Among 631 patients with clinical stage I SCLC who were treated with SBRT and chemotherapy, 416 patients were categorized in Group 1 and 215 patients in Group 2. Patients diagnosed between 2019-2020 were less likely to receive SBRT concurrent with or after chemotherapy (OR=0.46, 95% CI=0.31-0.65, p<0.001). Patients diagnosed with clinical T2 stage were more likely to receive RT concurrent with or after chemo (OR=1.76, 95% CI=1.05-2.95, p=0.03). No statistically significant difference in survival was observed between the two treatment sequencing cohorts (Group 1: median 40.5 months vs. Group 2: 35.6 months, log-rank p=0.30). On multivariable analysis, SBRT sequencing was not associated with overall survival (HR=1.11, p=0.35, 95% CI=0.89-1.37).

Conclusions: Our findings suggest there is no statistically significant difference in survival outcomes for patients who receive SBRT before chemotherapy compared to those who receive SBRT concurrent with or after chemotherapy.

Keywords: SBRT, SCLC, Stage I

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.27 Toripalimab Consolidation After Chemoradiotherapy in Limited-Stage Small Cell Lung Cancer: A Phase II, Randomized Controlled Study

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Introduction: Immune checkpoint inhibitors plus chemotherapy has demonstrated survival benefits in the management of extensive-stage small cell lung cancer (SCLC). The integration of immunotherapy with chemoradiotherapy may improve survival outcomes in limited-stage SCLC. This phase II, randomized controlled study was designed to evaluate the efficacy and safety of toripalimab consolidation versus observation in patients with limited-stage small cell lung cancer (LS-SCLC) after concurrent chemoradiotherapy (CCRT).

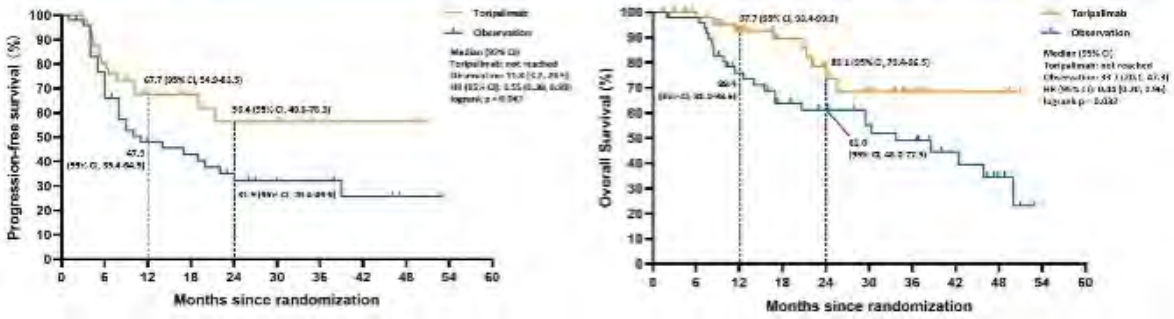
Methods: We enrolled patients with LS-SCLC who had an ECOG performance status of 0-1 and demonstrated no disease progression following CCRT. Eligible patients were randomized 1:1 to either toripalimab consolidation (240mg every 3 weeks for up to 6 months) or observation. Randomization was stratified according to disease stage (I or II vs. III) and receipt of prophylactic cranial irradiation (yes vs. no). The primary end point was progression-free survival (PFS). The secondary endpoints included overall survival (OS), duration of response (DOR) and toxicities. Toxicities were graded according to CTCAE v.5.0. Post hoc power analyses included conditional power (CP) and post hoc predictive power of success.

Results: Between June 30, 2020, and May 31, 2024, 96 patients were randomized to receive either toripalimab (n=48) or undergo observation (n=48) following CCRT. The median follow-up duration was 27.8 months. The baseline characteristics are well balanced between toripalimab and observation groups. The median PFS was not reached in the toripalimab group, compared with 11.8 months (95% CI, 3.2-20.5 months) in the observation group(HR= 0.55, 95% CI, 0.30-0.98). The median OS was not reached in the toripalimab group, compared with 33.7 months (95% CI, 20.1-47.3 months) in the observation group (HR= 0.44, 95% CI, 0.20-0.96). The incidence of grade 3 or 4 adverse events was 22.9% among patients receiving toripalimab and 27.1% among patients with observation. Adverse events led to toripalimab discontinuation in 8.3% (4/48) of the patients. Grade 3 or 4 pneumonitis or radiation pneumonitis occurred in 4.2% of the patients in toripalimab group and 2.1% of those in observation group. No grade 5 events occurred in both groups.

Conclusions: In patients with LS-SCLC, toripalimab consolidation significantly improved OS and PFS with an acceptable safety profile.

Baseline Characteristics of Patients

Variables	Toripalimab (N=48)	Observation (N=48)
Age, y		
median (range)	60 (29-79)	60 (39-71)
Sex, n (%)		
Male	42 (85.7%)	42 (85.7%)
Female	7 (14.3%)	7 (14.3%)
ECOG performance status, n(%)		
0	11 (22.4%)	10 (20.4%)
1	38 (77.6%)	39 (79.6%)
Smoking status, n(%)		
Current or former	44 (89.8%)	46 (93.9%)
Never	5 (10.2%)	3 (6.1%)
TNM stage, n(%)		
I or II	4 (8.2%)	4 (8.2%)
III	45 (91.8%)	45 (91.8%)
Receipt of prophylactic cranial irradiation before randomization, n(%)	32(65.3%)	32(65.3%)



Keywords: Limited stage small cell lung cancer, Toripalimab consolidation

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.28 Survival Outcomes in Advanced Large Cell Neuroendocrine Carcinoma of the Lung in Immunotherapy Era: An NCDB Analysis

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Introduction: Large cell neuroendocrine carcinoma of the lung (LCNEC) is a relatively rare and aggressive malignancy with a high recurrence rate. The impact of immunotherapy on survival in advanced LCNEC remains unclear, with existing data limited to case reports and small retrospective studies. Utilizing the National Cancer Database (NCDB), which captures over 70% of newly diagnosed lung cancers in the United States, we evaluated survival outcomes in advanced LCNEC based on treatment type and compared these outcomes with those of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Methods: Demographics, treatment, and survival data for histologically confirmed stage IV LCNEC cases diagnosed between 2015 and 2020 were extracted from NCDB. Stage IV NSCLC (adenocarcinoma and squamous cell carcinoma) and SCLC diagnosed during the same period were used as comparisons. Survival analyses were conducted using the log-rank test, and Cox multivariate regression adjusted for confounders, including age, sex, race, comorbidities, insurance, treatment facility type (academic vs. community), and brain metastases.

Results: A total of 238,920 patients were identified, including 2,945 LCNEC, 191,237 NSCLC, and 44,738 SCLC. Of the 2,014 LCNEC that received systemic therapy as the first course of treatment, 1,397 (69%) received chemotherapy alone, 46 (2%) received immunotherapy alone and 571 (29%) received chemoimmunotherapy. LCNEC patients treated with chemoimmunotherapy had improved survival compared to chemotherapy alone (median overall survival [OS] 10 vs. 8.5 months; HR 0.82, 95% CI 0.72-0.95, p = 0.007). LCNEC had significantly shorter survival compared to NSCLC when treated with chemotherapy alone (median OS 8.5 vs 11.4 months, HR 0.74, 95% CI 0.71 - 0.79, p<0.001) as well as when treated with chemoimmunotherapy (median OS 10 vs 12.9 months, HR 0.75, 95% CI 0.66-0.84, p<0.001). LCNEC had marginally longer median overall survival compared to SCLC when treated with chemotherapy alone (median OS 8.5 vs 8.4 months, HR 1.13, 95% CI 1.07 - 1.21, p<0.001). No difference in survival was observed between LCNEC and SCLC when treated with chemoimmunotherapy (median OS 10 months vs 9.6 months, HR 0.08, 95% CI 0.96 - 1.22, p = 0.2).

Conclusions: To our knowledge, this study represents the largest analysis of survival outcomes in advanced LCNEC in the immunotherapy era. Stage IV LCNEC patients demonstrated modestly improved survival with chemoimmunotherapy compared to chemotherapy alone; however, overall survival remained inferior to NSCLC regardless of treatment. LCNEC showed no clear survival advantage over SCLC, with only a marginal difference observed with chemotherapy alone and no significant difference with chemoimmunotherapy. These findings highlight the aggressive nature of LCNEC and the limited benefit of current systemic therapies. Future studies should integrate biomarkers such as PD-L1 expression and genomic alterations, as well as evaluate optimal chemotherapy partners in chemoimmunotherapy regimens to improve outcomes for this rare lung cancer subtype.

Keywords: LARGE CELL NEUROENDOCRINE CARCINOMA, IMMUNOTHERAPY, NCDB

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.29 Somatostatin Receptor Expression and First-Line Somatostatin Analog Therapy: A Comparative Analysis in Thoracic Neuroendocrine Neoplasms

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Introduction: Thoracic neuroendocrine neoplasms (NENs) are rare group of neoplasms. Thoracic NENs are divided into well-differentiated typical carcinoid (TC, G1), atypical carcinoid (AC, G2), AC with higher mitotic index (MI) and Ki-67 (considered G3), and poorly differentiated neuroendocrine carcinomas (NECs), including large-cell (LCNEC) and small-cell (SCLC) types. AC G2 and G3 are not officially separated, however, for analysis, we identified a distinct subgroup - AC G3 - by analogy with gastrointestinal NETs, based on morphology, MI, Ki-67. Data on therapy efficacy in G3 subgroup are limited. The assessment of SSTR expression allows for the consideration of somatostatin analog (SSA) therapy.

Methods: We analyzed 155 patients with thoracic NENs (1997-2025), including lung (n=137/88%) and thymic neoplasms (n=18/12%). NENs were classified as G1 (n=34/22%), G2 (n=81/52%), G3 (n=20/13%), LCNEC (n=20/13%). SCLC was excluded from the analysis. SSA therapy was administered to 96 patients (62%); LCNEC patients received SSA plus platinum-based chemotherapy.

Results: SSTR expression was determined in 126 cases (81%): IHC in 61.9% (78/126), Ga68 DOTA-TATE PET/CT in 66,7% (84/126), and both in 30.2% (38/126). SSTR positivity was observed in 51.3% by IHC (40/78), 84.5% by PET/CT (71/84). Among 38 patients assessed by both methods, discordant results were seen in 52.6%. PET/CT identified 39.5% as IHC-negative but PET-positive, while 13.2% - PET-negative but IHC-positive. By IHC, SSTR positivity rates: G1 - 60% (n=9/15), G2 - 48.8% (n=20/41), G3 - 66.7% (n=6/9), LCNEC - 38.5% (n=5/13). SSTR2A expression: G1 - 46.7% (n = 7/15), G2 - 46.3% (n = 19/41), G3 - 55.6% (n = 5/9), LCNEC - 30.8% (n = 4/13). SSTR5 expression: G1 - 13.3% (n = 2/15), G2 - 9.8% (n = 4/41), G3 - 11.1% (n = 1/9), LCNEC - 7.7% (n = 1/13). 4 patients with G3 received monotherapy in first-line with SSA (4/16). These patients had favorable course (median of Ki-67 = 37%, low tumor burden). While the rest patients received SSA with chemotherapy (12/16). Median progression-free survival (mPFS) on first-line SSA: G1 - not reached, G2 - 22 mo ± 4,3 (13,6-30,4). The whole mPFS in G3 subgroup - 11 mo ± 4,5 (2,2-19,8) (SSA - 9 mo, combination - 11 mo, p=0,4), p=0.001. Disease Control Rate (DCR) in G1 - 94.1% (n = 16/17), objective response rate (ORR) - 5.9% (n = 1/17), no progressive disease (PD) cases. G2: DCR - 77.2% (n = 46/57), ORR - 3.5% (n = 2/57), PD - 14% (n = 8/57). G3 whole subgroup: DCR - 81.3% (n = 13/16), PD - 18.8% (n = 3/16). LCNEC: DCR - 83.3% (n = 5/6), PD - 16.7% (n = 1/6).

Conclusions: Ga-68 DOTA-TATE PET/CT showed higher sensitivity for SSTR detection, though IHC revealed 13% of additional SSTR-positive cases. SSA therapy was most effective in G1-G2 (DCR up to 94%) and showed meaningful activity in selected G3 and LCNEC patients. Dual-method SSTR assessment improves treatment selection in thoracic NENs.

Keywords: Thoracic NENs, SSTR, SSA

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.30 Whole Exome Sequencing Analysis of Somatic Mutations in Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

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Introduction: Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is a disease characterized by widespread foci of nodular proliferations of neuroendocrine cells in the small airways that can progress to aggressive carcinoid tumors or cause respiratory failure secondary to airway obstruction. The cause of DIPNECH is unknown. We hypothesize that a set of acquired somatic mutations in pulmonary neuroendocrine cells may lead to NECH development and their subsequent spread throughout the airways in affected individuals.

Methods: A cohort of 47 patients with clinical and pathologic features of DIPNECH was identified. All the patients showed more than three NECH lesions on histological review. Lesions classified histologically as NECH, carcinoid tumorlets and carcinoid tumors were collected using micro-dissection from the archived formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Genomic DNA from the micro dissected lesions and the germline DNA from lymph nodes or matched normal lung tissue were extracted and whole exome sequencing (WES) was performed to identify common somatic mutations in DIPNECH patients.

Results: DNA was extracted from a total of 122 lesions from 47 patients collected by micro-dissection, including 87 NECH lesions, 12 tumorlets and 23 carcinoid tumors. After stringent filtering of polymorphisms and assessment of potential oncogenic impact, an average gene variant impact score (AGVIS) for each gene affected was calculated providing a score ranging from 0 to 4. A high number represents potential high impact of the gene in disease development and progression. We then identified 69 genes with a high frequency of somatic mutations (variants ≥ 10) and a high AGVIS >2 in the DIPNECH cohort (Table 1). With further confirmation of the potential tumorigenicity of these gene mutations using the cBioPortal database, we identified the PABPC family, NOTCH1 and MTOR as harboring potential critical gene mutations in the pathogenesis and the progression of DIPNECH. PABPC proteins have global effects on gene expression and mutations in NOTCH1 and MTOR effect cellular proliferation and other cellular activities that are associated with tumorigenesis. Thirty-one patients of the DIPNECH cohort carry potentially oncogenic somatic variants in at least one of these three genes (or gene family).

Conclusions: Somatic mutations with high tumorigenic impact are common in DIPNECH patients. A set of potential driver mutations were identified in WES results. These gene variants are present within and across patients with high frequency. Further investigations are planned to validate the function of these gene variants in the pathogenesis and progression of DIPNECH.

Table 1. Top 25 high AGVIS genes mutation frequency. AGVIS, average gene variant impact score.

Gene	AGVIS	mutation frequence	patients (47) with gene variants	lesions (122) with gene variants
ATM	3.27	26	34% (16)	17% (21)
FAM8A1	3.18	11	17% (8)	8% (10)
RBM33	2.92	12	11% (5)	9% (11)
GXYLT1	2.67	21	23% (11)	11% (14)
DNAH7	2.6	15	23% (11)	11% (13)
TBCD	2.6	10	9% (4)	7% (8)
PABPC family	2.58	50	40% (19)	21% (26)
SKOR2	2.58	19	13% (6)	10% (12)
KMT2D	2.57	23	36% (17)	16% (20)
MICAL3	2.5	10	19% (9)	8% (10)
SDK1	2.5	10	19% (9)	7% (9)
MTOR	2.45	11	21% (10)	9% (11)
MUC17	2.45	11	17% (8)	8% (10)
AKAP13	2.4	10	19% (9)	7% (9)
NBEAL1	2.4	10	21% (10)	8% (10)
TRIO	2.36	11	21% (10)	9% (11)
DYNC2H1	2.32	19	36% (17)	15% (18)
NOTCH1	2.31	13	26% (12)	10% (12)
ARID1A	2.3	10	15% (7)	7% (8)
SBF1	2.3	10	15% (7)	7% (8)
WDR89	2.3	10	13% (6)	5% (6)
CACNA1I	2.27	11	19% (9)	8% (10)
GRIN2A	2.27	11	19% (9)	8% (10)
NEB	2.27	22	40% (19)	15% (18)
CREBBP	2.27	15	26% (12)	11% (14)

Keywords: DIPNECH, somatic mutations, whole exome sequencing

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.31 Real-World Effectiveness and Safety of Lurbinectedin for Small Cell Lung Cancer (SCLC): Updates From Jazz EMERGE 402

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Introduction: Lurbinectedin is approved for adults with metastatic (US and Switzerland) or stage III/metastatic (Canada) SCLC who progressed on/after platinum-based chemotherapy based on results from a phase 2 basket trial (NCT02454972).

Methods: EMERGE 402 is a prospective, observational, phase 4 trial (NCT04894591), evaluating lurbinectedin in extensive stage (ES)-SCLC in real-world practice in North America initiated in 2021. The primary endpoint is overall response rate (ORR). Secondary endpoints include progression-free survival (PFS) and overall survival (OS). Tumor responses are assessed in patients with baseline measurable disease per RECIST v1.1.

Results: As of February 4, 2025, 265 patients had received ≥1 cycle of lurbinectedin; 14 (5%) had ongoing treatment. Among 250 (94%) discontinuations, disease progression was the most common reason (n=169 [68%]). At baseline, median patient age was 67 years, 51 (19%) had an ECOG score ≥2, and 66 (25%) had CNS metastases. 137 (52%) patients had platinum-sensitive disease (chemotherapy-free interval [CTFI] ≥90 days). All except one patient received lurbinectedin as monotherapy: 168 (63%) as second-line (2L) and 77 (29%) as third-line. Overall median (interquartile range [IQR]) number of lurbinectedin treatment cycles was 4 (2-7), with a median (IQR) duration of 91 (60-168) days. Among all patients with measurable disease at baseline, ORR (95% CI) was 26.6% (20.5-33.4) overall (n=192), 28.9% (20.1-39.0) with CTFI ≥90 days (n=97), and 29.3% (22.2-37.3) without CNS metastases (n=150). Overall median (95% CI) PFS and OS were 3.3 (2.6-4.1) and 7.6 (6.6-9.2) months, respectively; 3.1 (2.5-4.2) and 9.4 (7.6-11.9) months with CTFI ≥90 days; and 3.8 (2.7-4.9) and 8.5 (6.5-10.0) months without CNS metastases. Overall 6- and 12-month OS rates were 61% and 34%, respectively. Table shows effectiveness by line of therapy. With lurbinectedin in 2L, ORR was 29.3% overall, 36.7% with CTFI ≥90 days, and 32.3% without CNS metastases. Also with 2L, median PFS and OS were 3.3 and 7.6 months, respectively, overall; 3.8 and 11.9 months with CTFI ≥90 days; and 4.0 and 8.6 months without CNS metastases. Among all patients (N=265), 86 (32.5%) patients experienced treatment-related adverse events (AEs), including 28 (10.6%) with serious AEs. The most common AEs of special interest included increased hepatic enzyme (10.6%), anemia (9.4%), neutropenia (7.9%), and thrombocytopenia (7.5%).

Conclusions: The study enrolled an SCLC population with worse prognostic factors than those in the phase 2 basket trial. Lurbinectedin demonstrated clinically meaningful effectiveness and an acceptable safety profile in this real-world patient population, including poor prognosis subgroups.

Table 1. Effectiveness outcomes by line of therapy

	Overall (n=192[a])		CTFI ≥90 days (n=97[b])		CTFI <90 days (n=64[b])		CNS metastases (n=42[b])		No CNS metastases (n=150[b])	
Tumor Responses in Patients per RECIST Version 1.1[a]										
	2L (n=123)	3L (n=57)	2L (n=60)	3L (n=29)	2L (n=42)	3L (n=18)	2L (n=30)	3L (n=11)	2L (n=93)	3L (n=46)
ORR,[a] % (95% CI)	29.3 (21.4-38.2)	22.8 (12.7-35.8)	36.7 (24.5-50.1)	17.2 (5.8-35.8)	23.8 (12.0-39.4)	16.7 (3.6-41.4)	20.0 (7.7-38.6)	9.1 (0.2-41.3)	32.3 (22.9-42.8)	26.1 (14.3-41.1)
Median PFS, months (95% CI)	3.3 (2.4-4.1)	3.8 (2.5-4.9)	3.8 (2.3-4.3)	2.9 (2.4-4.7)	3.1 (2.0-4.2)	3.8 (1.4-6.3)	2.7 (1.6-3.4)	2.1 (0.6-4.4)	4.0 (2.4-4.9)	4.5 (2.6-5.3)
Median DoR, months (95% CI)	3.7 (2.7-4.8)	4.7 (2.7-6.3)	3.2 (2.3-8.5)	3.5 (2.6-6.2)	3.6 (1.4-4.8)	4.7 (1.5-6.3)	2.7 (0.7-4.2)	4.9 (NR-NR)	4.2 (2.7-6.9)	3.5 (2.6-6.3)
DCR,[a] % (95% CI)	46.3 (37.3-55.6)	47.4 (34.0-61.0)	53.3 (40.0-66.3)	41.4 (23.5-61.1)	42.9 (27.7-59.0)	38.9 (17.3-64.2)	36.7 (19.9-56.1)	27.3 (6.0-61.0)	49.5 (38.9-60.0)	52.2 (37.0-67.1)
Survival Outcomes										
	Overall (n=265[a])		CTFI ≥90 days (n=137[b])		CTFI <90 days (n=87[b])		CNS metastases (n=66[b])		No CNS metastases (n=199[b])	
	2L (n=168)	3L (n=77)	2L (n=84)	3L (n=41)	2L (n=59)	3L (n=21)	2L (n=44)	3L (n=17)	2L (n=124)	3L (n=60)
Median OS, months (95% CI)	7.6 (6.4-9.4)	7.6 (5.8-10.8)	11.9 (7.8-14.6)	8.7 (5.4-12.2)	5.8 (4.6-7.2)	5.5 (3.8-6.8)	7.6 (5.6-8.7)	5.5 (2.1-10.6)	8.6 (6.4-11.9)	8.7 (5.8-12.2)

Data cutoff date: February 4, 2025.
[a]Patients with measurable disease at baseline per RECIST version 1.1.
[b]Additional patients received lurbinectedin monotherapy after 3 lines of therapy.
2L, second line; 3L, third line; CI, confidence interval; CNS, central nervous system; CTFI, chemotherapy-free interval; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Keywords: lurbinectedin, effectiveness, safety

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.32 Real-World Outcomes of Patients With Bronchopulmonary Neuroendocrine Tumors Treated With Lutetium Lu 177 DOTATATE (Lutathera)

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Introduction: Bronchopulmonary neuroendocrine tumors (BPNETs) comprise an estimated 20-30% of all neuroendocrine tumors (NETs). Management of metastatic BPNETs remains largely individualized, with lutetium-177 (177Lu) DOTATATE (Lutathera), a peptide receptor radionuclide therapy (PRRT), emerging as a promising treatment in NETs with selective targeting of somatostatin receptor expressing cells. Here, we present real-world utilization and outcome data of PRRT in BPNETs.

Methods: We conducted a retrospective analysis of patients with metastatic BPNETs treated at Mayo Clinic sites (AZ/FL/MN) with PRRT between 2014 and 2025. Patients were identified via institutional records and confirmed using the Mayo Data Explorer platform. Tumor grade and histology were defined by Ki-67 and per WHO 2017 criteria, respectively. Treatment response was assessed by 3-month post-treatment interval restaging imaging and clinician document assessment. Progression free survival (PFS) defined as time from PRRT initiation to any disease progression, death or last follow up at conclusion of data review (3/15/25). Overall survival (OS) was defined as time from PRRT initiation to death or last known follow up. Statistical analyses were performed with Stata 18.0.

Results: Twenty-three patients [median age 66] were included [14 (61%) males]. Eleven patients had active or former tobacco use with 33 average pack-years. Grade 1, 2, and 3 tumors were seen in 26% (n=6), 39% (n=9) and 26% (n=6) patients, respectively. Histologically, 10 patients had typical carcinoid while 13 had atypical carcinoid. Seven patients (30%) reported functional carcinoid syndrome. Most frequent sites of metastasis were liver (78%, n=18), bone (61%, n=14), pancreas (9%, n=2) and contralateral lung (4%, n=1). Majority of patients had Krenning score-4 (57%), followed by score-3 (30%), and score-2 (13%). PRRT was most commonly administered as third-line systemic therapy (52%), followed by fourth-line (22%), second-line (17%), and later-lines (9%). Preceding cancer-directed therapies included somatostatin analogs (100%), systemic chemotherapy (65%; 10/15 single-line, 5/15 multiple-lines; 8/15 platinum/etoposide, 4/15 capecitabine-temozolomide), everolimus (43%), and tyrosine kinase inhibitor (9%). 17/23 (74%) patients received 4 doses PRRT (median 4, range 2-6). No patient had complete response; partial response was observed in 17% (4/23), stable disease in 30% (8/23), progressive disease in 43% (9/23). Most common adverse events included fatigue (35%), nausea (26%), abdominal pain (22%), and decreased appetite (13%); no events ≥ grade 3 were reported. Median PFS was 10.8 months (IQR: 7.3-18.6; 95% CI: 6.5-15.2). In subgroup analysis, median PFS by Krenning score 4 vs. ≤3 was 14.7 vs. 7.5 months (p=0.036). By histology, median PFS for typical vs. atypical tumors was 13.5 vs. 8.4 months (p=0.172). Median OS was 21.2 months (IQR:12.2-34.0; 95% CI:13.9-28.5) with 9/23 (39%) patients alive at time of data collection. Following PRRT, 10/23 (43%) patients received no further treatment, with 4/23 (17%) receiving 1 additional line and 7/23 (30%) receiving ≥2 lines.

Conclusions: In this retrospective analysis of patients with metastatic BPNETS, lutetium (177Lu) DOTATATE demonstrated a response rate of 17%, disease control rate of 48%, and a median PFS of 10.8 months. In clinical practice, decision of when to utilize PRRT varies widely, found here most commonly as a 3rd line systemic agent.

Keywords: lutetium-177 DOTATATE, Peptide Receptor Radionuclide Therapy, Neuroendocrine Tumor

P3.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.13.33 Clinical Outcomes and Single-Cell Map of Neoadjuvant Immunochemotherapy for Stage II-IIIb LS-SCLC : A Real-World Study

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Introduction: Approximately one-third of small cell lung cancer (SCLC) cases are diagnosed at the limited stage. For those with N1-N2 nodal metastasis, the standard concurrent chemoradiotherapy (CCRT) based regimen yields suboptimal outcomes. While immunotherapy has revolutionized SCLC treatment, the neoadjuvant immunochemotherapy has shown curative potential in NSCLC. This study investigates the efficacy of neoadjuvant immunochemotherapy in stage II-IIIB SCLC, with parallel exploration of underlying mechanisms through translational research.

Methods: Based on the objective performance criterion of single-arm rate, we estimated that 16 patients would be required. In this study, we retrospectively enrolled 9 patients and prospectively included 16 patients in potentially resectable stage II-IIIB(N2) LS-SCLC. Patients underwent Multidisciplinary team (MDT) evaluation for local treatment after at least 3 cycles of neoadjuvant immunochemotherapy, non-surgical candidates converted to radiotherapy. All candidates received neoadjuvant immunochemoterapy as Full Analysis Set (FAS), while surgical patients completing protocol as Treatment-Completed Cohort (TCC). Additionally, we retrospectively collected 87 patients treated with concurrent CCRT and 10 patients who received neoadjuvant chemotherapy as control groups. Propensity score matching (PSM) was applied to the CCRT group based on stage, age, sex, and smoking-status. The primary endpoints were 18-month Event-free survival (EFS) rate and pathological complete response (pCR) rate. Secondary endpoints included 18-month overall survival (OS) rate and objective response rate (ORR) to neoadjuvant therapy.We also collected single-cell RNA sequencing (scRNA-seq) on fresh surgery tumor tissue and tumor-draining lymph nodes(tdLN) at post-IO treatment.

Results: Among 25 enrolled patients, 16 underwent surgery, other 9 received consolidative radiotherapy after neoadjuvant therapy. In the FAS, the 18-month EFS and OS rates were 58.8% and 89.2%, respectively, with an ORR of 84%. TCC analysis revealed a pCR rate of 50% and an MPR rate of 56.3%, with 18-month EFS and OS rates of 76.6% and 80.8%, respectively. Notably, no tumor progression was observed in pCR patients.The TCC demonstrated significantly superior 18-month EFS rates compared to the IC+Radiotherapy group (33.3%) (HR=4.066, P=0.032), though 18-month OS (100%) did not reach statistical significance. PSM yielded 15 paired controls, confirming the TCC survival advantage 18-month EFS rates: 83.9% vs. 33.3%, P=0.011; OS rates: 90% vs. 66.7%, P=0.031). The chemotherapy-only neoadjuvant group showed comparable outcomes (18-month EFS/OS rates: 70%/90%) to the TCC.TCC with 87.5% R0 resection and minimally invasive surgery rates. No SAEs occurred in the FAS. 22 specimens of scRNA-seq (8 patients) were divided into pCR(5/8) and non-pCR(3/8). We found that the pCR group has expanded marcophage and naïve CD4+ T cells with upregulated migration-related genes expressed in both tumor and tdLNs. While the non-pCR group has expanded CD14+ monocytes and exhausted T cells with enhanced immune activation pathway, but suppressed migratory signatures in tdLNs.

Conclusions: Our study demonstrates the efficacy of neoadjuvant chemoimmunotherapy followed by surgery in potentially resectable stage II-IIIB LS-SCLC, showing significant EFS benefits compared to current regimens, though OS advantages require longer follow-up. Mechanistically, scRNA-seq analysis revealed that expanded naïve CD4+ and proliferating T cells, coupled with enhanced immune migration-related gene expression in tdLN, underlie the superior treatment response.

Keywords: LS-SCLC, Neoajuvant, Immunochemotherapy

P3.13.34 Tarlatamab Efficacy and Safety in Chinese Patients with Advanced Small Cell Lung Cancer: Phase 2 DeLLphi-307

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Introduction: Small cell lung cancer (SCLC) is an aggressive disease with poor survival rates. Despite response to initial therapy for extensive-stage disease, relapses are common and treatment options remain limited. Tarlatamab, a bispecific T-cell engager (BiTE®) immunotherapy that harnesses cytotoxic T cells to kill SCLC cells by targeting delta-like ligand 3 (DLL3), has demonstrated durable responses and significant survival benefit with long-term tolerability in patients with previously treated SCLC (Ahn, NEJM 2023; Sands, WCLC 2024; Mountzios, NEJM 2025). We report results from the DeLLphi-307 phase 2a trial, evaluating tarlatamab in the third-line and beyond (3L+) SCLC setting in China.

Methods: Eligible patients were Chinese adults with extensive-stage SCLC who progressed following a platinum-based first-line regimen (including anti-PD-[L]1) and at least one other prior line of therapy. The primary endpoint was objective response rate (ORR) based on blinded independent central review per RECIST 1.1. Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results A total of 31 patients (84% male, median age 57 years) received tarlatamab. The median follow-up for this analysis was 3.8 months for efficacy outcomes (Table). ORR was 39% and median DOR was not reached, with responses ongoing in 11 of 12 (92%) responders at data cutoff. Median PFS was 2.9 months, and median OS was not reached. The most common treatment-emergent adverse event (TEAE) was cytokine release syndrome (CRS, 87%), which primarily occurred after the first and/or second tarlatamab dose. CRS events were low grade (Table) per ASTCT 2019 Consensus grading, with grade 1 reported for 19 patients (61%), of which about half (10 of 19 patients; 53%) had fever as the only recorded CRS symptom, and grade 2 reported in 8 patients (26%). There were no Grade 3 or above CRS events and no report of any immune effector cell-associated neurotoxicity syndrome (ICANS) event. The most common grade 3 or higher TEAEs were lymphopenia (16%), neutropenia (13%), and hyponatremia (13%). No treatment discontinuations occurred due to an adverse event.

Conclusions Tarlatamab demonstrated anticancer efficacy with promising durable responses and survival outcomes in Chinese patients. There were no new or unexpected safety concerns. This encouraging region-specific clinical evidence supports tarlatamab's potential as a new treatment option for Chinese patients with previously treated extensive-stage SCLC.

	Tarlatamab 10 mg Q2W (N = 31)
Efficacy measures	
ORR, confirmed, % (95% CI)	39 (22, 58)
Complete response, n (%)	1 (3.2)
Partial response, n (%)	11 (35.5)
Stable disease, n (%)	7 (22.6)
Progressive disease, n (%)	12 (38.7)
Median DOR, months (95% CI)	NE (2.9, NE)
Disease control rate % (95% CI)	61.3 (42.2, 78.2)
Median PFS, months (95% CI)	2.9 (1.4, NE)
Median OS, months (95% CI)	NE (NE, NE)
Safety measures	
CRS, n (%)	27 (87)
Grade 1, n (%)	19 (61)
Grade 2, n (%)	8 (26)
Grade ≥ 3, n (%)	0 (0)
TEAE Grade ≥ 3, n (%)	13 (42)
TEAE leading to treatment discontinuation, n (%)	0 (0)

NE = not estimable

Keywords: Tarlatamab, DeLLphi-307, Small Cell Lung Cancer

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.01 Global Trends in Asbestos Related Mesothelioma Mortality From 1990 to 2021

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Introduction: Mesothelioma, a rare but aggressive cancer primarily caused by asbestos exposure, remains a significant global health concern. Despite regulatory efforts to limit asbestos use, the burden of mesothelioma continues to rise, with notable variations across age groups, sexes, and socio-demographic regions. This study examines trends in asbestos-related mesothelioma deaths from 1990 to 2021, highlighting shifts in incidence, mortality, and exposure patterns worldwide.

Methods: We utilized data from the Global Burden of Disease database to analyze global mesothelioma deaths attributable to occupational asbestos exposure from 1990 to 2021. Results were reported per 100,000 population and stratified by gender, age groups (20-54, 55+), and global sociodemographic index (SDI; high, high-middle, middle, low-middle, low).

Results: Between 1990 and 2021, the global incidence of mesothelioma nearly doubled, rising from 16,493 cases in 1990 to 31,908 in 2021. In 2021, mesothelioma caused 29,619 deaths worldwide, with 27,136 (92%) linked to occupational asbestos exposure—almost twice the 13,763 asbestos-related deaths reported in 1990. Most deaths occurred in men aged 55 and older (n=18,257), representing a 101% increase from 1990 (n=9,070). Deaths among older women also rose substantially, reaching 6,293 in 2021, a 99% increase from 31 years prior. Younger individuals experienced smaller but notable increases: mesothelioma deaths among younger men rose 62.5% (1,137 to 1,848), while younger women saw an 86.3% increase (396 to 738).Despite the overall rise in deaths, age-adjusted mortality rates per 100,000 people declined slightly among older adults, decreasing by 10% for both men (2.91 to 2.61) and women (0.88 to 0.80). However, rates increased among younger adults, rising by 11% for men (0.09 to 0.10) and 33% for women (0.03 to 0.04). Occupational asbestos exposure was the leading cause of mesothelioma deaths in 2021, accounting for 97% of cases in older men and 94% in older women. Among younger adults, asbestos-related cases were lower, at 66% in men and 53% in women. Mesothelioma deaths increased across nearly all SDI levels, ages, and sexes. In 2021, most deaths occurred in older men (n=11,062) and women (n=2,790) in high-SDI countries, consistent with 1990 patterns. The largest increases occurred in middle- and low-middle-SDI countries, where asbestos-related deaths rose by 145%-312% in older adults and 149%-237% in younger adults.

Conclusions: These findings highlight the shifting burden of asbestos-related mesothelioma. The persistence of occupational asbestos exposure as a primary cause underscores the need for stronger global policies on asbestos regulation, early detection, and workplace safety.

Keywords: Mesothelioma, Global burden of disease, Global disparities

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.02 Clinical Implications of BAP1 Status in Pleural Mesothelioma (PM)

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Introduction: PM is a rare and locally advanced cancer with poor prognosis. BAP1 mutations are the most common molecular alteration in PM. The prognostic value of somatic BAP1 has been analyzed in several studies with controversial results. BAP1 is a predictive biomarker for survival after chemotherapy with platinum, but the predictive role of somatic BAP1 mutations with immunotherapy (IO) has not been evaluated in clinical trials. Preclinical data suggest that BAP1 loss may sensitize to IO. The objective of this study is to describe the prognosis and predictive value of BAP1 in a series of patients (pts) with PM.

Methods: Retrospective real-world cohort of pts visited at our institution. Associations between clinical variables and outcome were assessed with multivariate time-dependent Cox regression models. Survival data were calculated by the Kaplan-Meier method.

Results: 257 pts with PM attended at our institution from 2005 to 2024. Clinical characteristics: median age 68 years (range 29-88 years), mostly males (72%), PS1 (66%), asbestos exposure (80%), epithelioid (81%), first line therapy in 87%. Median overall survival (OS) of the entire cohort was 21.3 months [m](18.3- 23.9). Significant prognostic factors for survival in the series were performance status, clinical stage, histology, and treatment with cisplatin. Median OS of pts with PS0,1 and 2 was 28.4 m, 18.5 m and 1.7 m (p<0.001). Median OS of pts with epithelioid histology was 23.8 vs 10.3 m no-epithelioid (p<0.001). Median OS for pts with stage I-II was 27.8 m and for III-IV 18.2 m (p=0.002). Patients treated with cisplatin in first line had OS of 23.3 m vs 18.3 m p treated with carboplatin (p=0.009). In total, 50 patients were evaluated for BAP1 through immunohistochemistry and 28 pts (56%) had BAP1 loss. In our series BAP1was not prognosis nor predictive factor for therapy. Median OS of patients with BAP1 loss was 21.8 m vs 21.0 m BAP1 retained (p= 0.7). Considering platinum treatment in first line (cisplatin or carboplatin) we did not detect any differences in OS according to BAP1 status: median OS for BAP1 positive pts treated with platinum was 20.9 m versus 22.5 m in those with BAP1 loss (p=0.9). In our series, 14 pts with BAP1 status received IO in first line, and median OS for BAP1 loss was 19.5 m vs 37.6 m for those with BAP1 positive (P=0.3). In second line, 11 pts with BAP1 status received IO and OS was 11.3 m for BAP1 vs 8.5 m for BAP retained (p=0.6). In a time dependent Cox analysis, there was no association of BAP1 status with OS according to IO exposure (p=0.13).

Conclusions: In our series BAP1 status is not a reliable marker for selecting treatment with platinum or immunotherapy. Confirmatory studies with larger numbers of patients are needed to establish the predictive value of BAP1 in PM.

Keywords: pleural mesothelioma, BAP1, immunotherapy

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.03 Loss of MHC Class I and II Defines an Immune Excluded Subtype in Pleural Mesothelioma

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Introduction: First-line immune checkpoint blockade (ICB) has shown clinical benefits in a subset of pleural mesothelioma (PM) patients, but not all patients respond, and reliable predictive biomarkers remain lacking. The antigen presentation machinery (APM), including MHC class I and II complexes, is essential for T-cell activation and has been implicated in immune evasion in several cancers. Its role in PM and its influence on ICB response remain underexplored.

Methods: We analyzed MHC class I and II gene expression in two independent ICB-naïve PM cohorts (n = 211 and n = 150) using unsupervised hierarchical clustering. Associations between MHC expression and T-cell infiltration were assessed, and patients were stratified into subgroups based on APM status and immune infiltration. These subgroups were evaluated for differential copy-number alterations, predicted neoantigen expression, and overall survival using Kaplan-Meier analysis.

Results: We identified four reproducible PM subtypes based on differential MHC class I and II expression and T-cell infiltration. Approximately 25% of tumors showed loss of either MHC class I or II, while ~45% lacked both. Dual expression of both MHC class I and II was associated with higher T-cell infiltration, while absence of MHC class II, and to a lesser extent MHC class I, was linked to reduced T-cell infiltration. Loss of chromosome 22q12.2, which contains the NF2 tumor suppressor gene, was more frequent in APM-deficient tumors. No associations were observed between APM status and predicted neoantigen load, protein coding mutation burden, or overall survival in ICB-naïve patients.

Conclusions: This study provides the first comprehensive transcriptomic characterization of APM in PM. We show that ~70% of tumors exhibit loss of MHC class I, II, or both, which may underlie immune evasion and resistance to immunotherapy. Ongoing work will evaluate how APM loss affects ICB response and the interplay between APM expression and cytokine signaling in the tumor microenvironment.

Keywords: Mesothelioma, Immune Checkpoint Blockade, Antigen Presentation

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.04 High-Volume Surgical Centers for Pleural Mesothelioma Are Associated With Lower Perioperative Mortality

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Introduction: Volume-outcome relationships have been defined for various operations, often demonstrating improved outcomes in high-volume centers for complex procedures requiring nuanced management. Prior work in the era of extrapleural pneumonectomy suggested improved outcomes following surgery for pleural mesothelioma at centers performing > 5 cases per year. We evaluate factors associated with 90-day survival across a broad range of centers performing mesothelioma surgery in the contemporary era.

Methods: A retrospective cohort analysis was completed using the National Cancer Database, the largest clinical cancer registry in the world. The NCDB includes Commission on Cancer accredited programs, which account for nearly 80% of new cancer diagnoses in the United States. Patients undergoing definitive resection from 2012-2019 were included in the analysis. High-volume surgical centers were defined as facilities performing more than 5 operations per year. Pearson's Chi-square and Student's t-tests were utilized to compare groups. Multivariable logistic regression was completed to analyze factors associated with 90-day survival from definitive resection.

Results: A total of 3,101 patients underwent operations at 664 centers. Epithelioid histology was most common (61.2%), as was pathologic stage III disease (30.2%). Ten facilities (1.5%) met the definition of "high-volume;" they performed 31% of the operations with a median of 13 cases per year. Low-volume centers performed, on average, at least one operation in only 4 of the 8 eligible years. High-volume centers were more likely to be academic (100% vs. 42%, p<0.001) and have patients treated at multiple centers for multidisciplinary care (51.3% vs. 34.2%, p<0.01). High-volume centers were less likely to operate on patients with sarcomatoid disease (4.4% vs. 8.7%) and more likely to on epithelioid or biphasic histology (89.1% vs. 73.6%, p<0.01). There were no statistically significant differences in patient age, sex, or race between groups. Patients in high-volume centers were more likely to receive nodal resection (84.9% vs. 49.5%, p<0.01), and less likely to undergo resections classified as "partial/debulking" (38.6% vs. 54.3%, p<0.01). Thirty-day readmission rates were greater at high-volume centers (11.1% vs 5.6%, p<0.01). 30- and 90-day mortality was lower in high-volume centers (2.4% and 7.5% vs. 5.4% and 12.6%, p<0.001). On multivariable analysis controlling for several patient, surgical and tumor characteristics, high-volume centers were associated with improved 90-day survival (odds ratio for death: 0.47, 95% confidence interval [0.32-0.69]).

Conclusions: A small number of centers perform most resections for pleural mesothelioma. High-volume surgical centers are associated with improved survival in the perioperative period following resection.

	Odds ratio	95% Confidence Interval		P-Value
Volume				
Low-Volume	1			
High-Volume	0.47	0.32	0.69	<0.01
Age	1.02	1.00	1.04	0.03
Charlson-Deyo Comorbidity Index				
0	1			
1	0.88	0.59	1.32	0.54
2	0.91	0.45	1.82	0.79
3	0.79	0.30	2.07	0.64
Histology				
Mesothelioma, NOS	1			
Fibrous	2.12	1.22	3.68	0.01
Epithelioid	0.60	0.38	0.94	0.03
Biphasic	1.40	0.84	2.35	0.20
Clinical Stage				
1	1			
2	0.75	0.44	1.29	0.30
3	1.37	0.91	2.04	0.12
4	1.84	1.22	2.79	<0.01
Surgical Approach				
Open	1			
Video-assisted thoracoscopic	1.22	0.85	1.75	0.28
Robot	1.32	0.58	2.99	0.51
Surgery				
Partial removal	1			
Total removal	0.94	0.60	1.48	0.79
Debulking	1.42	0.72	2.78	0.31
Radical surgery	1.06	0.71	1.57	0.78
Systemic Therapy				
None	1			
Neoadjuvant	0.51	0.33	0.80	<0.01
Adjuvant	0.15	0.10	0.24	<0.01
Neoadjuvant and adjuvant	0.14	0.03	0.59	0.01

Table: Multivariable regression analysis for factors associated with 90-day mortality.

Keywords: Mesothelioma, Volume, Surgery

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.05 Survival Outcomes of Sequential Therapies in Malignant Pleural Mesothelioma: A Real-World Analysis of Second-Line Treatments

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Introduction: Dual immunotherapy with ipilimumab and nivolumab (IPI-NIVO) has recently become the standard first-line option for malignant pleural mesothelioma (MPM), though platinum-based chemotherapy remains a viable alternative. However, the real-world effectiveness of second-line treatments following immunotherapy or chemotherapy remains unclear. This study aimed to assess survival outcomes in patients with MPM receiving second-line carboplatin-pemetrexed (CARBO-PEM) or nivolumab (NIVO) after progression on first-line treatment.

Methods: We performed a multicentre retrospective study involving patients with MPM who received second-line treatment with CARBO-PEM or NIVO. Primary endpoints were progression-free survival (PFS) and overall survival (OS) from second-line therapy initiation (PFS2 and OS2). Survival curves were estimated using Kaplan-Meier analysis, and differences between groups evaluated using the log-rank test, with statistical significance set at $p<0.05$.

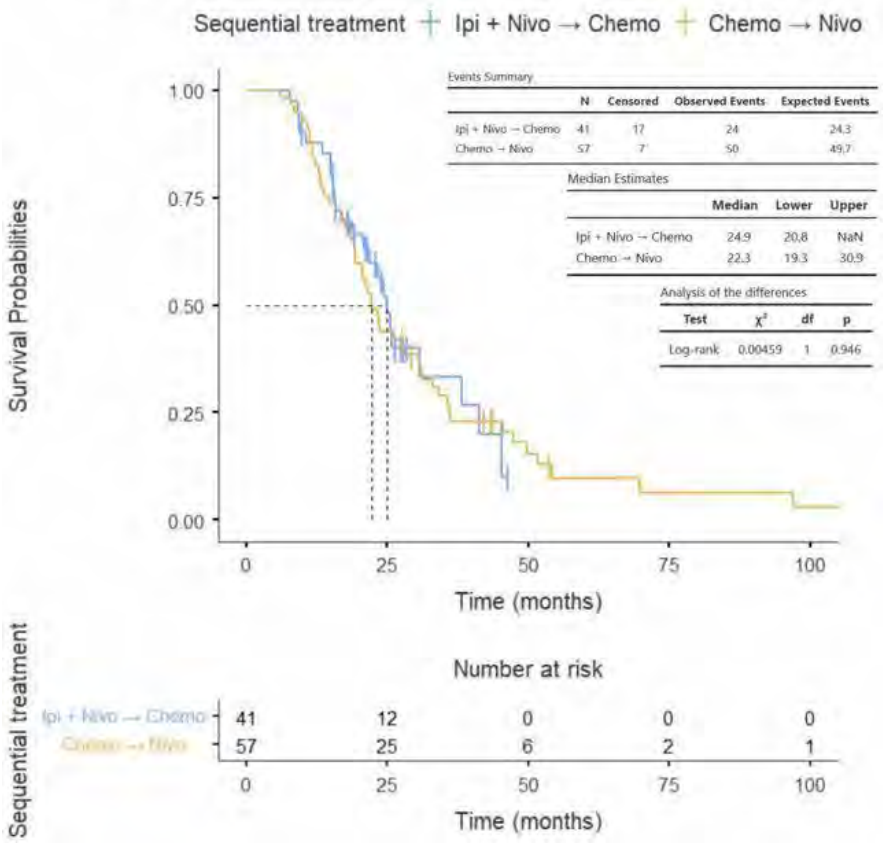
Results: A total of 98 patients were included, of whom 81 (82.7%) had epithelioid histology. 41 patients (41.8%) received second-line CARBO-PEM, while 57 patients (58.2%) had second-line NIVO. Baseline characteristics, including age, sex, ECOG performance status, and histology, were well-balanced between the two groups. The median follow-up was 45.2 months. The median PFS2 and OS2 for second-line CARBO-PEM were 6.15 and 11.6 months, respectively, compared to 2.73 and 11.6 months for second-line NIVO (Table 1). Log-rank tests revealed no significant differences in PFS2 ($p=0.437$) or OS2 ($p=0.554$) between the two cohorts. From first-line treatment initiation, the median PFS1 was 8.26 months with IPI-NIVO and 8.13 months with CARBO-PEM. Sequential treatment strategies showed no significant differences in OS: IPI-NIVO followed by CARBO-PEM achieved a median OS of 24.9 months, compared to 22.3 months for CARBO-PEM followed by NIVO ($p=0.946$), Figure 1.

Conclusions: Second-line CARBO-PEM following first-line IPI-NIVO showed numerically superior PFS2 versus NIVO post-chemotherapy, though without statistical significance. Sequential treatment sequences demonstrated comparable OS outcomes. Further investigations are warranted to identify predictive biomarkers and optimize therapeutic sequencing in real-world practice.

Table 1. Summary of survival outcomes for each treatment cohort and comparison with available data. *NR: not reached; N/A: not applicable; CI: confidence interval.*

OUTCOME	IPI-NIVO ↓ CARBO-PEM median (95%CI)	CARBO-PEM ↓ NIVO median (95%CI)	CHECKMATE 743 median (95%CI)	CONFIRM median (95%CI)	FLORA median (95%CI)
PFS1	8.26 months (5.49–10.23)	8.13 months (6.74–9.44)	IPI-NIVO: 6.8 months (5.6–7.4) CARBO-PEM: 7.2 months (6.9–8.0)	N/A	IPI-NIVO: 5.5 months (4.8–6.3)
PFS2	6.15 months (3.32–8.06)	2.73 months (2.34–4.80)	N/A	NIVO: 3.0 months (2.8–4.1)	CARBO-PEM: 5.6 months (4.9–6.3)
OS2	11.6 months (7.76–NR)	11.6 months (8.72–15.6)	N/A	NIVO: 10.2 months (8.5–12.1)	CARBO-PEM: 8.2 months (7.4–9.1)
OS sequential treatment	24.9 months (20.8–NR)	22.3 months (19.3–30.9)	N/A	N/A	N/A

Figure 1. Overall survival analysis for different sequential treatment strategies.



Keywords: Mesothelioma, Second-line, Real-World

P3.14.06 Attitude of Italian Physicians Towards Germline and Somatic Genetic Testing in Pleural Mesothelioma: Preliminary Results of a Nationwide Survey

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Introduction: Up to 10% of patients (PTS) with pleural mesothelioma (PM) harbor a pathogenic germline mutation in cancer predisposing genes, a condition generally associated with better overall survival at diagnosis. Conversely, less than 1% of PTS with PM present potentially actionable somatic mutations. The 2025 ASCO guidelines on PM recommend germline genetic testing for all PM PTS, while discouraging routine somatic testing. This survey aims to assess the attitude and current clinical practice of Italian physicians treating PM regarding genetic testing.

Methods: From March 1st, 2025 to March 31th, 2025, a nationwide survey was distributed to an expert network of Italian physicians treating PM (MEsothelioma Team Italy- MET-I). The questionnaire investigated clinical practice in genetic testing, barriers to its implementation and educational needs.

Results: Thirty-seven responders (RS) completed the survey. Most RS were female (23, 62%), aged 30-45 years (24, 65%), medical oncologists (26, 70%), working in academic hospitals (32, 87%) based in the North of Italy (31, 83%), and managing at least 20 PM cases per year (16, 43%).Most RS don't recommend germline testing (22, 60%) or do it occasionally (12, 34%), and only three (8%) routinely recommend it in PM PTS. The main criteria for requesting germline testing include: a family history (FH) of PM (87%), FH of genetic mutations predisposing to PM (78%) and FH of tumors associated with PM (70%). In most cases, germline testing is available through genetic counselling (23, 62%), witheither monogenic BAP1 testing (11, 30%) or multigenic panelsincluding BAP1 (18, 49%).The main barriers to routine germline testing in PM include: cost (65%), limited access to dedicated genetic counselling (54%), and lack of physician awareness (51%). Proposed solutions involved increasing education on the topic (24, 65%), improving access to genetic counselling (21, 57%), and implementing dedicated institutional policies (54%).Somatic testing is routinely performed by four RS (11%), occasionally performed by 13 RS (35%), and never performed by 20 RS (54%). The main criteria for somatic testing in mesothelioma are the availability of a clinical trials with targeted agents (62%) and a young age (<50 years) at diagnosis (51%). Somatic test results influenced treatment decisions often or never in six RS (16%) and sometimes in nine RS (24%).Finally, 68% of RS were aware of the 2025 ASCO guidelines on PM, and 54% stated they would modify their clinical practice accordingly.

Conclusions: The survey highlights the underuse of germline testing among Italian physicians managing PM. High costs, limited access to genetic counselling, and lack of physician awareness are the primary barriers to germline testing. Implementing medical education programs on PM genetics, establishing dedicated genetic counselling services, and introducing institutional policies for germline testing could enhance the management of PM PTS in Italy.

Keywords: Mesothelioma, Germline genetic testing, Somatic genetic testing

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.07 Recent Studies on Mesothelioma as a Model to Understand the Interaction of Gene and Environment (G X E)

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Introduction: Mesothelioma arises from transformed mesothelial cells (HM) and is associated with asbestos exposure. HM exposed to crocidolite, chrysotile, and erionite experience programmed cell necrosis, releasing HMGB1, which initiates and sustains chronic inflammation, and it plays critical role in mesothelioma development and progression. Mesothelioma development involves complex gene-environment interactions. Germline mutations of BAP1, a multifunctional deubiquitylase, are linked to mesothelioma incidence, by affecting transcription, metabolism, and DNA repair. BAP1's role in mesothelial transformation also involves HMGB1, as BAP1 forms a trimeric complex with HMGB1 and HDAC1. BAP1 mutations lead to hyper-acetylated HMGB1 release, promoting inflammation and cell transformation. The Gene-Environment (GxE) interactions approach, integrating genetic features and environmental factors, significantly advanced the knowledge of asbestos-related carcinogenesis. Northern Nevada's terrain is rich in minerals, including asbestos, erionite, arsenic (As), and other carcinogens. Inhalation of long, thin, mineral fibers may cause mesothelioma and other respiratory diseases, while ingestion of arsenic from groundwater is associated with various skin, pulmonary, and cardiovascular diseases, including cancer. Recent data show higher mortality rates among young individuals residing in Northern Nevada. However, despite the higher presence of carcinogens in the environment and the higher mortality rates for associated diseases, the amount and extent of human exposure remain unknown. This multidisciplinary study aimed to evaluate the carcinogenic potential of mineral fibers and arsenic naturally found in the Northern Nevada environment causing mesothelioma.

Methods: We identified and collected mineral fibers present in the natural environment of three different areas in Northern Nevada nearby the Reese River, the Eastgate communities, and the Segerstrom-Heizer Min. In the first two locations, we identified mainly erionite, while tremolite asbestos was found at Segerstrom-Heizer Mine. These mineral fibers were tested comprehensively by using both in vitro and in vivo assays to evaluate the toxicity and carcinogenesis.

Results: In tissue culture, all the mineral fibers significantly reduced the cell viability of primary human mesothelial (HM) cells in a dose-dependent manner, shorter fibers displayed less cytotoxic effects. The amount of arsenite present in wells was not cytotoxic and did not increase fiber cytotoxicity in vivo, although cells co-esposed to both fibers and arsenite showed a reduction in mitochondrial respiration. In mice, the erionite fibers longer than 10 µm present in the natural environment of the Eastgate communities caused mesothelioma in wild type mice. Moreover, these fibers caused a higher frequency of mesothelioma in mice carrying germline BAP1 mutations (gene x environment interaction) suggesting individuals carrying these mutations may be at higher risk of mesothelioma if living in this environment.

Conclusions: Our studies suggest that preventive strategies should be implemented among Nevadans to reduce exposure to the erionite present in the natural environment, and that that the ongoing Healthy Nevada Project to genotype the Northern NV population will be very helpful to identify families at higher risk.

Keywords: mesothelioma, erionite, BAP1

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.08 Genetically Defined Mouse Models of Malignant Pleural Mesothelioma Recapitulate Human MPM Phenotypes and Response to Therapy

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Introduction: Introduction: Malignant Pleural Mesothelioma (MPM) is a devastating cancer that lacks a clear pre-malignant precursor, is difficult to distinguish from chronically inflamed hyperplastic mesothelium, and is largely refractory to treatment. To use genetically defined mouse models of mesothelioma to advance the understanding of autochthonous disease biology and, in particular, to garner insight into the biological differences between benign and malignant disease and the transition between the two.

Methods: Adult mice carrying multiple conditional alleles for CRE-mediated deletion of Bap1, Cdkn2a, Nf2 and/or Tp53 in various combinations were induced by intrapleural injection with Lentiviral vectors carrying Mesothelin promoter-driven CRE recombinase, followed by Amosite Asbestos. Mice were harvested at different time points, with tissue and pleural lavage (or effusion, when present) subject to analysis by transcriptomics, proteomics, metabolomics, histology, flow cytometry and immunohistochemistry.

Results:

• Combined deletion of Cdkn2a, Nf2 and Tp53 yields predominantly epithelioid MPM whereas loss of Bap1, Cdkn2a and Nf2 yields sarcomatoid MPM, spanning the histological subtypes of human disease. • Disease progression is dramatically accelerated by asbestos injection, indicating a critical role for chronic inflammation beyond acquisition of causative mutations. • Transcriptional profiling showed differential expression of signalling and metabolomic pathways. • Comparative analysis of pleural fluid proteomics data indicates differences across various genotypes and disease stages. • Flow cytometry data suggest a dynamic relationship of nascent mesothelioma tumours with the immune cells of the pleural cavity. • PD1 blockade resulted in a profound survival benefit in the sarcomatoid model but had no impact on epithelioid MPM, similar to the results of the Checkmate 743 trial of canonical immune checkpoint inhibition in human MPM.

Conclusions: Our models provide an unparalleled opportunity for mechanistic investigation of MPM aetiology and differential responses to therapy.

Keywords: Mesothelioma, GM Mouse model, Asbestos

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.09 Sex-Based Differences in Mesothelioma: Insights From the ICO Cancer Registry

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Introduction: Several European countries, including France and Italy, established national mesothelioma registries to monitor and determine the incidence and causes of this asbestos-related cancer. These registries provide data on both occupational and non-occupational exposure sources.

Methods: We conducted a retrospective analysis of incident mesothelioma cases recorded in the ICO registry. Patient data, including demographics, clinical characteristics, histological subtypes, and treatment modalities, were extracted. Survival outcomes were assessed using relative survival analysis, comparing observed survival with expected survival in a matched general population. The primary endpoint was to determine the 3-year relative survival (RS).

Results: From 2013 to 2023, a total of 420 incident mesothelioma cases were recorded, distributed across different anatomical locations: pleural (91%), peritoneal (8%), and pericardial and testicular (0.5% each). The median age at diagnosis was 73 years (IQR, 67-78), with a predominance of male patients (70%). Occupational exposure to asbestos was more frequently reported in males (52%) than in females (10%), while ambiental exposure was more commonly reported in females (24%) than in males (5%) p<0.001). Exposure to asbestos could not be captured in 18% of patients. The 3-year RS was higher in women (33%, CI95%: 24.7-43.6) than in men (20%, CI 95%: 15.4-26.5). Additionally, a progressive improvement in 3-year RS was observed, increasing from 20% (CI 95%: 13.7-28.6) in the 2013-2016 period to 28% (CI 95%: 18.2-43.7) in 2021-2022.

Conclusions: Women with mesothelioma have better survival outcomes and distinct pattern of asbestos exposure compared to men. Collection of asbestos exposure is challenging in retrospective studies. Mesothelioma surveillance and prospective data collection on asbestos exposure is warranted to assess the health impact of asbestos and promote policies aimed at preventing exposure risks.

Keywords: mesothelioma, asbestos

P3.14.10 Ultrasound Detection of Effusion and Neoplasia in Genetically Defined Mouse Models of Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM), driven by asbestos exposure and genetic susceptibility, lacks reliable early detection methods and effective therapies. To model MPM pathogenesis, we developed genetically engineered mouse models with combined CRE-mediated Bap1, Cdkn2a, Nf2, and Tp53 deletions alongside asbestos exposure (BCN and CNP models). Using longitudinal ultrasound imaging, we characterised pleural effusion dynamics and tumour onset patterns to establish biomarkers of disease progression.

Methods: Tumours were initiated in adult BCN and CNP mice by intrapleural injection of Lenti-Msln-CRE, followed by 25ug asbestos. Mice underwent serial ultrasound scans, commencing at 30 days post induction until the study endpoint. Effusion volume and tumour localisation were monitored and correlated with survival outcomes. Negative and blank controls were included for baseline comparison. Histopathological analysis validated ultrasound findings, with targeted examination of tumour sites: pericardial fat pad, diaphragm, ribcage, and mediastinal lymph nodes.

Results: 1) Survival. The BCN model demonstrated a longer median survival (121 days) compared to the CNP model (112 days). Sex-based differences were observed in both models: BCN: Males = 121 days, Females = 130.5 days; CNP: Males = 97 days, Females = 116 days.2) Effusion. Pre-tumour effusion was minimal (<200 µL). An effusion surge (>400 µL) predicted endpoint within 30 days (observed in 60% of BCN mice vs. 100% of CNP mice). All CNP and BCN males developed significant effusion; only 1/3 of BCN females did. Controls maintained low effusion, consistent with injected volumes (<200 µL).3) Tumour Onset: Ultrasound imaging revealed the pericardial fat pad as the earliest and most frequent site of tumour development, with detection rates of 40% at 30 days, 80% at 60 days, and 100% by 90 days post-injection. This site consistently showed tumour formation ≥30 days earlier than diaphragm or ribcage involvement. The second most common site was the diaphragm, followed by the ribcage. Histopathological analysis confirmed these findings and further demonstrated frequent oesophageal involvement (>90% of cases), while cardiac involvement was the least observed.

Conclusions: Pleural effusion volume is a critical prognostic marker for late-stage MPM in GDMMs, with rapid escalation preceding death. Ultrasound enabled early detection of pericardial fat pad tumours—the primary site of onset—suggesting utility for preclinical intervention studies. These findings underscore the potential of imaging-driven biomarkers to refine MPM modelling and therapeutic testing.

Keywords: Mesothelioma, Effusion, Tumour onset

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.11 Real-World Outcomes and Toxicity of First-Line Dual Immunotherapy in Unresectable Pleural Mesothelioma

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Introduction: Nivolumab/Ipilimumab (N/I) is a standard of care first line treatment for patients with inoperable pleural mesothelioma (PM). Checkmate 743 reported 30% of patients (pts) experienced grade ≥3 treatment-related adverse events (AEs). We undertook a real-world analysis to determine the incidence and management of AEs in patients with PM treated with N/I.

Methods: This retrospective single institution study included patients treated with first line N/I at the Princess Margaret Cancer Centre, Toronto, CA between 2020-2023. Primary endpoints were incidence and management of AEs related to N/I. Clinical data were abstracted from electronic medical records following REB approval. Toxicity was assessed retrospectively using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Immune-related adverse-events (irAE) were categorised based on whether they were simply asymptomatic laboratory abnormalities or associated with symptoms. Steroid usage for managing irAE was reported descriptively. Kaplan-Meier survival analysis was performed, with subgroup comparisons using the log-rank test.

Results: Of 41 pts, the median age at start of treatment was 69 years (65.7-73.3), 28 male (68%); 15 (36%) had previous occupational asbestos exposure, 59% (24/41) never-smokers, 88% (36/41) had an ECOG ≤1 at baseline, 10% (4/41) had a pre-existing autoimmune disease, and 70% had an epithelioid histology.Twenty seven pts experienced ≥1 irAE (66%); 29% grade ≥3 (12/41); 22% (9/41) required hospitalization of which 2 required ICU and 1 dialysis; 26% (7/27) of irAE were laboratory abnormalities only. Systemic steroids were administered in 59% (16/27); 75% (12/16) oral. 37.5% (6/16) required >1 course of steroid; 6 pts required an increase in the steroid dose during initial treatment. Excluding infusion related reactions, the median duration on steroids was 65 days (7-380). Eighteen percent (5/27) required additional immunosuppressive agents. Steroid-related complications occurred in 38% (6/16), mainly hyperglycemia. Treatment-related AE that led to permanent discontinuation to either component of the regimen was observed in 10 pts (24%). The median OS for the entire cohort was 20.1 months (m) (95% CI 11.7-NR). Patients with irAEs had significantly longer survival (27.2 months) compared to those without irAEs (11.7 months, HR=0.29, p=0.005).

Conclusions: In this real-world cohort, real world N/I had a similar toxicity profile compared to the clinical trial population. Steroid use and hospitalization were commonly required However, patients who experienced irAEs had longer survival outcomes compared to those who did not.

Keywords: Mesothelioma, Toxicity, Immunotherapy

P3.14.12 Pseudo-Senescence Induced by Palbociclib Does Not Sensitize Pleural Mesothelioma Cells to Combinations With Classical Senolytics

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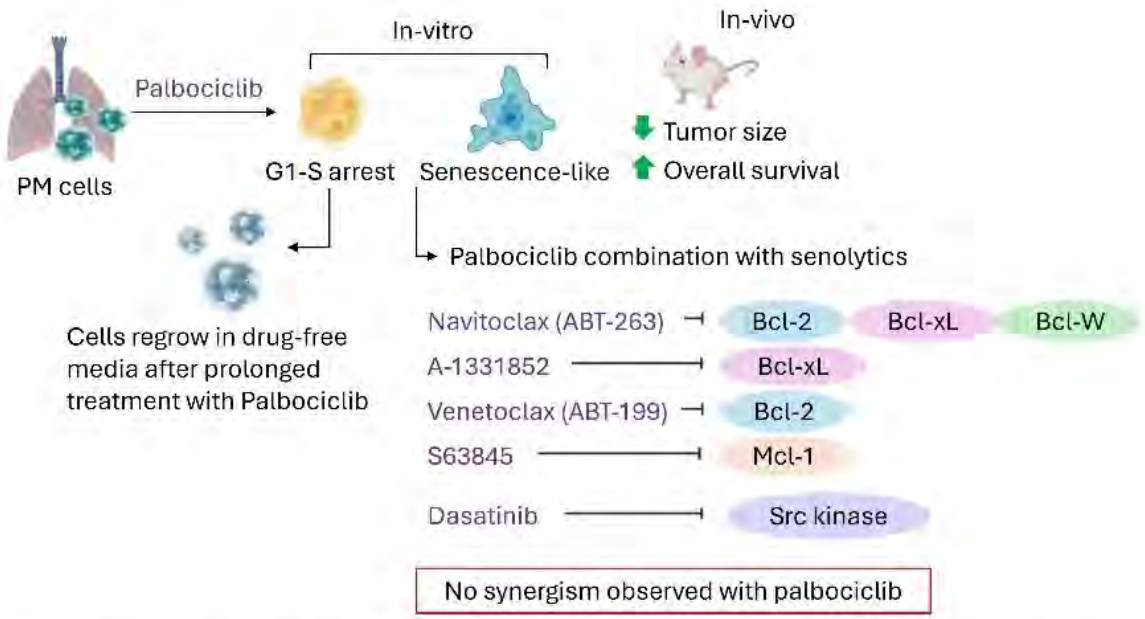
Introduction: Pleural Mesothelioma (PM) is an aggressive neoplasm of the lung pleura with a dismal prognosis, necessitating the exploration of novel therapeutic options. CDK4/6 inhibitors have shown therapeutic efficiency in various tumour models, especially in treating metastatic breast cancer. In mice models of MPM, abemaciclib and palbociclib reduced tumour growth and prolonged overall survival.

Methods: We have studied the nature of senescence induced by the CDK4/6 inhibitor palbociclib and the chemotherapeutic drug cisplatin in commercial and patient-derived PM cell line models. We observed markers for senescence (Cell size, β-galactosidase activity, ability to re-enter the cell cycle) both during palbociclib treatment and after drug removal. We attempted to eradicate palbociclib pre-treated PM cells with conventional senolytics like Navitoclax and Dasatinib.

Results: Palbociclib-induced cell cycle arrest leads to senescence-like cell size increase and increased β-galactosidase activity but no apoptosis. However, the effects of palbociclib were reversed upon drug removal as cells regrew and lost their senescent-like features. Combining BH3 mimetics like venetoclax (Bcl-2 inhibitor), navitoclax, the specific Bcl-xL inhibitor A-1331852, or the Mcl-1 inhibitor S63845 with palbociclib did not enhance cell death. Other drugs previously described as senolytics, like dasatinib, do not synergize with palbociclib and failed to kill the cells. In contrast, we found that the chemotherapeutic drug cisplatin induces permanent cell cycle arrest and complete senescence in PM.

Conclusions: Our observations challenge the notion that Palbociclib induces classical senescence in PM, as it did not sensitize the cells to combinations with senolytics. If palbociclib induces "pseudo-senescence" in mesothelioma, the clinical use of CDK4/6 inhibitors is challenged by the risk of tumour regrowth. Our findings underscore the complexity of therapy-induced senescence and the importance of understanding its nature when assessing the effectiveness of senolytics in specific tumour models.



Palbociclib-induced cell cycle arrest leads to senescence-like cell size increase and increased β-galactosidase activity but no apoptosis in PM. However, the effects of palbociclib were reversed upon drug removal as cells regrew and lost their senescent-like features. Combining BH3 mimetics like venetoclax (Bcl-2 inhibitor), navitoclax, the specific Bcl-xL inhibitor A-1331852, or the Mcl-1 inhibitor S63845 with palbociclib did not enhance cell death. Other drugs previously described as senolytics, like dasatinib, do not synergize with palbociclib and failed to kill the cells.

Keywords: Cyclin-Dependent Kinase inhibitors, Senescence, Senolytics

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.13 Sex and Histology Related Profile of Gut Microbiota (GM) in Pleural Mesothelioma (PM): Preliminary Results of a Prospective Observational Study

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Introduction: There is scarce evidence regarding the prognostic and predictive role of GM in PM patients. A single prospective experience highlights the positive prognostic value of Prevotella and Eubacterium ventriosum and the negative prognostic value of Erysipelatoclostridium in a small cohort of patients treated with atezolizumab and bevacizumab as salvage therapy. Nevertheless, the differences in GM composition according to demography and pathology are undisclosed yet. In this preliminary report we highlight the differences in GM composition in naïve PM patients according to sex and histology.

Methods: Since February 2022, a prospective translational study (Micromeso) of GM assessed at baseline and at subsequent relevant time points has been performed at AOUAL. All enrolled patients signed an informed consent and were treated according to national guidelines. For each patient enrolled, rectal swabs were collected and sequenced with 16s RNA sequencing. Baseline demographic, body composition, pathology and treatment related data have been collected, as well as treatment related adverse events and survival data. In this preliminary report we focus on differences in the baseline gut microbiota related to sex and histology features.

Results: Fifty pts have been enrolled in the study. Pts were mostly male (41/50), median age was 72 years (IQR 65-76), were treated with pemetrexed and platinum derivatives chemotherapy (34/50), had an epithelioid histology (34/50). Alpha diversity did not significantly differ according to sex and histology when assessed with the Shannon (p 0.33) and Simpson index (p=0.24), respectively. Conversely, beta diversity was significatively different between the epithelioid and non-epithelioid patients and between male and female patients (p 0.019). Non-epithelioid histology was enriched with Anaerococcus sp. (p 0.04) and Dialister propionifaciens (p 0.04). Epithelioid histology was enriched with Phocaeicola vulgatus (p=0.03) and unclassified Lachnospiracee (p=0.02). Finally, Fusicatenibacter sp., unclassified Prevotellaceae were more abundant in epithelioid histology male and non-epithelioid female patients (p 0.02 and 0.04), respectively.

Conclusions: These preliminary results highlight a significant difference in beta diversity as well as species specific GM composition in PM patients, related to histology and sex. Further correlative analyses on the impact of GM composition, its modification during treatment and its association with response and survival are planned.

Keywords: Mesothelioma, Gut microbiota, translational research

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.14 Ten-Year Longitudinal Analysis of Mesothelioma Incidence: A Nationwide Cohort Study Based on the 2012 Korean Health Screening Registry

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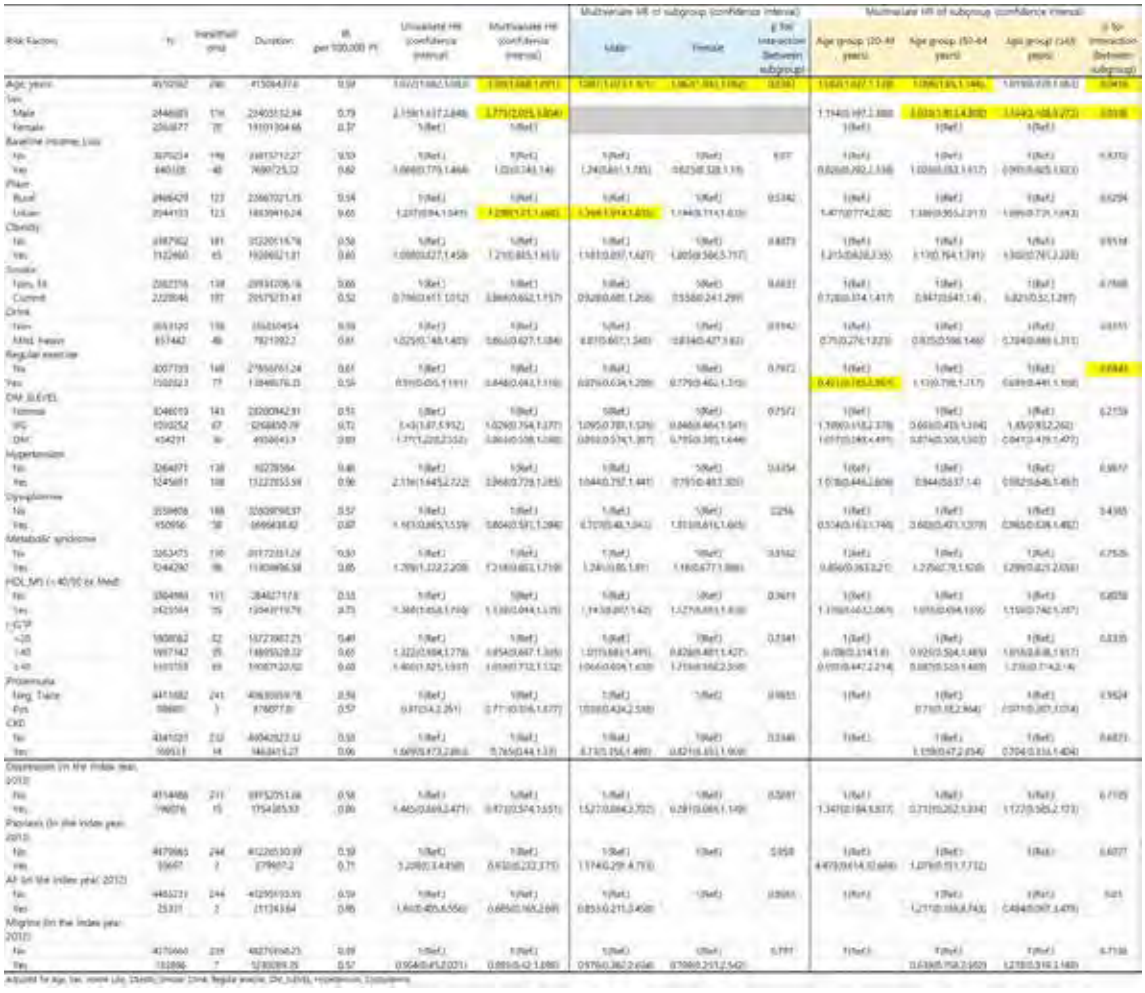
Introduction: Mesothelioma is a rare but aggressive malignancy primarily associated with asbestos exposure. Its long latency period poses challenges for early detection and population-level surveillance. Despite its clinical importance, large-scale, long-term epidemiological data on mesothelioma incidence remain limited, particularly in East Asian populations.

Methods: We conducted a nationwide, population-based cohort study using data from the Korean National Health Insurance Service (NHIS). A total of 4.51 million adults who underwent health screening between January 1 and December 31, 2012, were enrolled and prospectively followed for up to 10 years (median follow-up: 9.33 years). Incident mesothelioma cases were identified through linked claims data. Cox proportional hazards models were used to estimate hazard ratios (HRs) for potential risk factors.

Results: A total of 246 mesothelioma cases were identified during the 10-year follow-up period, corresponding to an average annual incidence of 5.45 cases per 1,000,000 population. Older age, male sex, urban residence, and lack of regular exercise were significantly associated with increased mesothelioma incidence. The risk was nearly threefold higher in men compared to women (HR 2.78, 95% CI: 2.03-3.80), and urban residents had a higher risk than those in rural areas (HR 1.30, 95% CI: 1.01-1.67). Regular physical activity was associated with reduced risk, particularly among younger adults (HR 0.42, 95% CI: 0.18-0.96 in the 20-49 age group). In contrast, metabolic and biochemical factors—including smoking, alcohol consumption, diabetes, obesity, metabolic syndrome, elevated γ-GTP, chronic kidney disease, and proteinuria—were not significantly associated with mesothelioma incidence.Among the 246 mesothelioma cases, pleural mesothelioma was the most common subtype (76.8%), followed by peritoneal (17.1%), pericardial (2.0%), and other forms (4.1%). A total of 155 patients (63.0%) died during the follow-up period. The mean survival time was 1.34 ± 1.8 years, with a median survival of 0.68 years (interquartile range: 0.26-1.57 years).

Conclusions: In this large-scale nationwide cohort, mesothelioma incidence was primarily associated with demographic and environmental factors rather than metabolic or systemic health conditions. These findings underscore the importance of targeted surveillance strategies in high-risk populations, particularly older men and urban residents.



Keywords: Mesothelioma, Cohort Study, Environmental Exposure

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.15 Thymic Cancer in France: A Comprehensive Analysis of Incidence Based on French National Healthcare Data

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Introduction: Thymic epithelial tumors (TETs) are rare malignancies with an estimated incidence in the European Union of 0.18 cases per 100,000 person-years. Comprehensive national data are limited. This study aimed to evaluate the epidemiology, clinical characteristics and associated conditions of TETs in France.

Methods: A retrospective cohort was extracted from the French National Health Data System (SNDS), which covers >99% of the French population and integrates data from health insurance reimbursements and hospital records. We identified patients hospitalized with a primary diagnosis of malignant thymic neoplasm (ICD-10 code C37). Demographic and clinical data were collected. Incidence rates were calculated based on the first hospitalization for a malignant thymic neoplasm and were expressed as the mean number of new cases per year divided by the mean total French population during the study period.

Results: Between 2015 and 2019, 2,205 patients (pts) were identified, of whom 42.06% (927) were female. The median age was 64 years. The mean annual incidence of TETs was 0.71 cases per 100,000 persons. Among the patients, 349 pts (15.83%) had autoimmune conditions, including myasthenia gravis (12.97%), aplasia (1%), and systemic lupus erythematosus (1.18%). Autoimmune conditions preceded TET diagnosis in 22 pts (1%), with a mean lead time of -17.66 months (median: -25 months). Autoimmune conditions coincided with or followed the TET diagnosis within two years in 221 pts (10%), with a mean delay of 15.44 months (median: 2.03 months). A total of 326 pts (14.8%) received immunoglobulin therapy. We evaluated the occurrence of second primary malignancies. To reduce misclassification and diagnostic overlap, thoracic tumors (C33, C34, C38, and C39) and unspecified secondary malignancies (C76-C80) were excluded. Overall, 719 pts (32.6%) had other malignancies, with the most common second primary tumors being male genital malignancies (C60-C63, 118 cases), and hematologic malignancies (C81-C96, 110 cases). An estimated 430 hospitalization episodes for another cancer were recorded in the two years preceding thymic cancer diagnosis, with a gradual increase from 8 cases/month at -24 months to 42 estimated cases in the month immediately prior. In the two years following diagnosis, an estimated 850 hospitalization episodes occurred, with 210 cases (24.7%) within the first three months and 75 (8.8%) in the second month alone.

Conclusions: This study indicates a much higher incidence of TETs compared to previous reports. The rate of autoimmune diseases was consistent with existing literature, while the incidence of secondary malignancies was remarkably high despite a relatively short follow-up period. These findings raise critical questions about the underlying causes of increased cancer risk in this population.

Keywords: Thymic epithelial tumors, Incidence, National health data

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.16 Prospects of Applyingconvolutional Neural Network Models for of Surgical Videos in Clinical Practice

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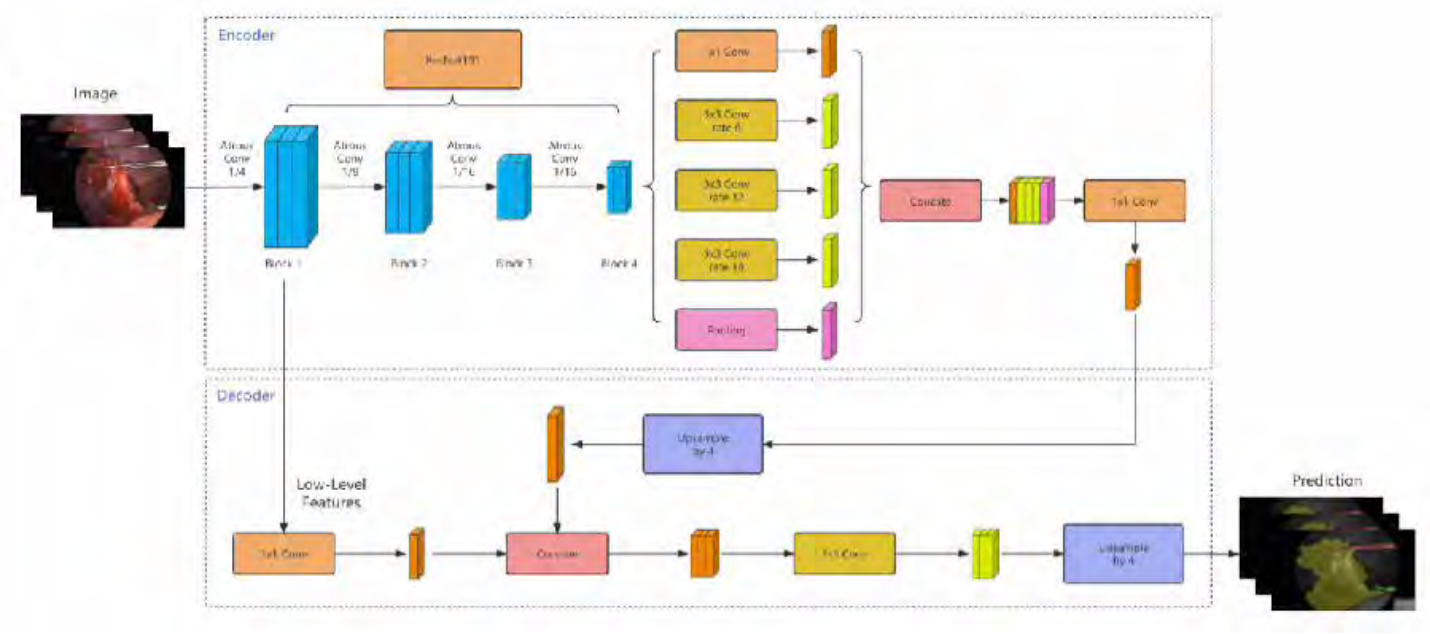
Introduction: With the widespread adoption of AI and artificial intelligence technologies, high-tech innovations have permeated various fields, including da Vinci Surgical System,robotic bronchoscopy for precise positioning, and 3D reconstruction for visualization. However, applications in medical image processing remain limited. Currently, semantic segmentation models have been used in radiology to identify tumors and inflammatory regions. By leveraging annotations from clinical experts, convolutional neural network (CNN) models can be trained to autonomously recognize tumor locations.Our goal is to apply semantic segmentation to surgical videos, identifying anatomical structures, tumors, and surgical instruments. By training a model to recognize these elements in real-time, we aim to enable automated identification of instruments, organs, and tumor regions during surgeries. This advancement could greatly assist surgeons in anatomical localization and deep tumor detection, enhancing surgical precision and efficiency.

Methods: We collected surgical videos from 90 cases of simple thymic epithelial tumors and 36 cases of complex thymic epithelial tumors. Using the LabelMe software, we manually annotated the videos. These annotations were then used to train a convolutional neural network model. The model achieved an accuracy of 80%-95% in recognizing surgical instruments and 85% in identifying anatomical structures. Further refinement of the model will be conducted using EI VIDEO software for video fitting.

Results: The model demonstrated an 80%-95% accuracy in recognizing surgical instruments and 85% accuracy in identifying anatomical structures. These results validate the feasibility of semantic segmentation in surgical imaging, offering significant benefits in preserving critical anatomical structures during surgery and improving tumor localization.

Conclusions: By employing a convolutional neural network model based on machine learning, we processed and annotated key frames from 126 surgical videos for semantic segmentation of anatomical structures and tumor regions. This approach enables accurate prediction of these critical areas, paving the way for improved surgical outcomes and decision-making.It's much more easy to apply in Lung cancer surgery because the shape of lung is more well-defined than thymus.



Keywords: Deep learning, Machine learning, Thymic epithelial tumors

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.17 Oncological Outcomes of Complete Versus Limited Thymectomy in Stage I Thymic Epithelial Tumours

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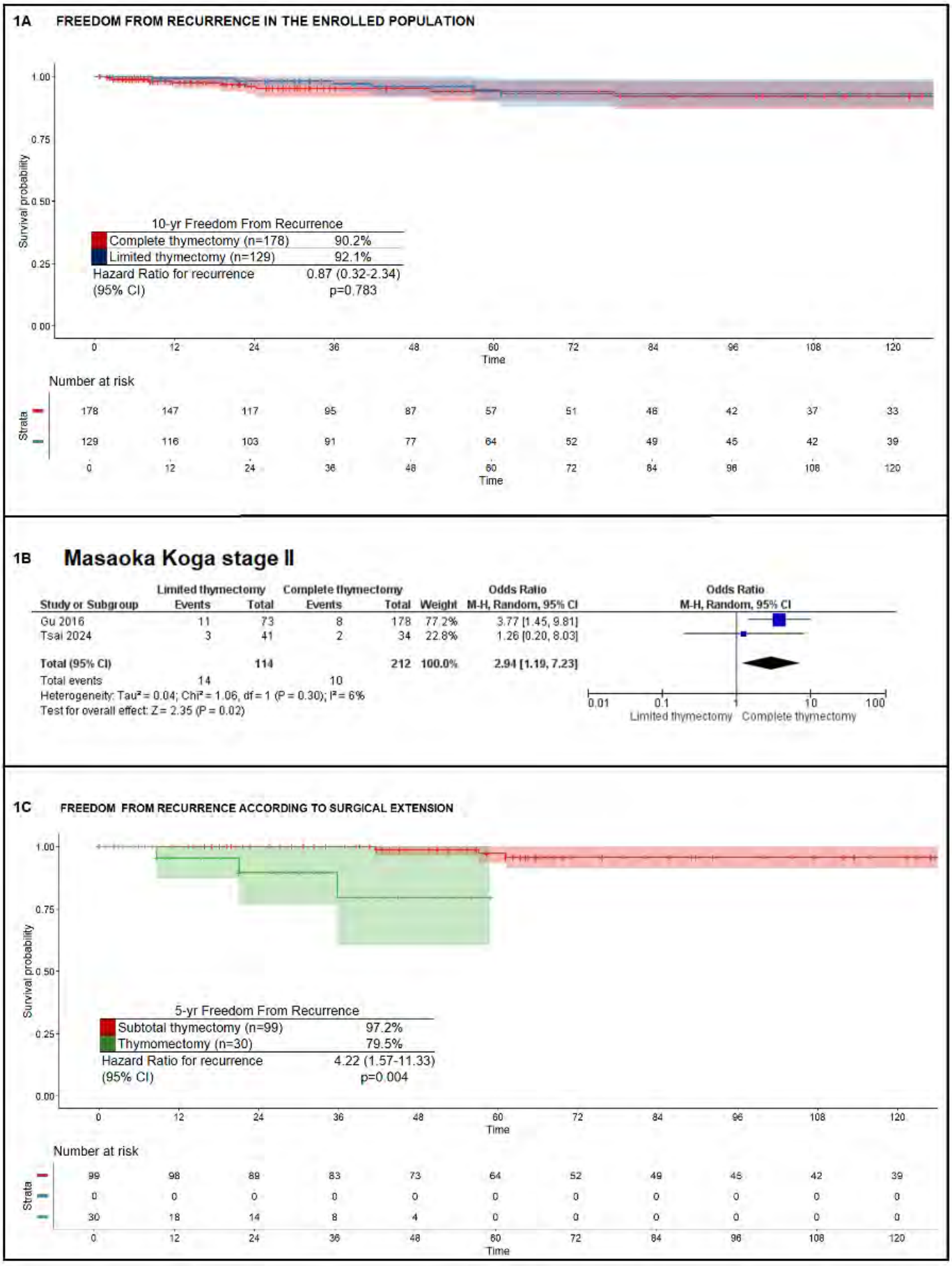
Introduction: Limited thymectomy, resecting the tumour alone or en-bloc with a part of thymic gland, has been proposed as a tissue-sparing alternative to complete thymectomy in early-stage thymic epithelial tumours (TETs). However, previous analyses are heterogeneous in both used survival measures and in the extent of thymus removed during limited thymectomy hindering generalizability and comparability of findings across studies.

To clarify the role of limited versus complete thymectomy in stage I TETs we performed a systematic-review and an individual patient data (IPD) meta-analysis using standardised survival measures and predefined oncological outcomes.

Methods: An IPD meta-analysis of studies investigating complete versus limited thymectomy for stage I TETs was conducted. IPD was extracted from published Kaplan Meier curves using the IPDfromKM method. When possible, we extracted IPD from propensity-score matched curves. Survival measures were defined as: freedom from recurrence (FFR) from surgery to recurrence in studies without R+ patients; time to progression (TTP) from surgery to recurrence in studies with R+ patients. Primary endpoint of the study was FFR in complete versus limited thymectomy. Secondary endpoints were: TTP; overall survival; recurrence rate in the overall population and stratified per Masaoka-Koga stage; survival measures according to resection extension (thymomectomy-alone vs hemi-thymectomy vs subtotal thymectomy). Hazard-ratios (HR) and relative 95% confidence intervals (95%CI) were estimated with Cox regression analyses. Odds-ratio (OR) with 95%CI were used to derive categorical variables.

Results: Of the 7 eligible retrospective studies, four were based on nationwide databases. Three studies used propensity-score matching. Overall, IPD from 2314 patients (1434 complete thymectomy and 880 limited thymectomy) were retrieved. For FFR, IPD were extracted from three studies including 307 patients receiving complete thymectomy (n=178) and limited thymectomy (n=129). Median follow up was 51.2 months 95%CI 37.5-64.8 in complete thymectomy and 63.4 months 95%CI 53.2-73.6 in limited thymectomy. The 10-year FFR for complete versus limited thymectomy were 90.2% vs 92.1%, respectively (Fig1A). No differences were found in TTP, overall survival and recurrence rate in the two groups. In those patients presenting a Masaoka-Koga stage II disease, OR for recurrence favoured complete over limited thymectomy (p=0.02). Finally, according to limited thymectomy extension, FFR favoured subtotal thymectomy compared to thymomectomy-alone (fig1C).

Conclusions: In conclusion, no evidence favoured limited over complete thymectomy in early-stage TETs treatment according to standardise survival measures. However, in Masaoka Koga stage II disease, complete thymectomy showed lower recurrence rate. Finally, among patients receiving limited thymectomy, thymomectomy-alone may lead to worse prognosis.



Keywords: Thymic Epithelial Tumours, Thymectomy, Limited Thymectomy

P3.14.18 The Role of Induction Therapy Followed by Surgery in Advanced Thymic Epithelial Tumors: A Systematic Review and Meta-Analysis

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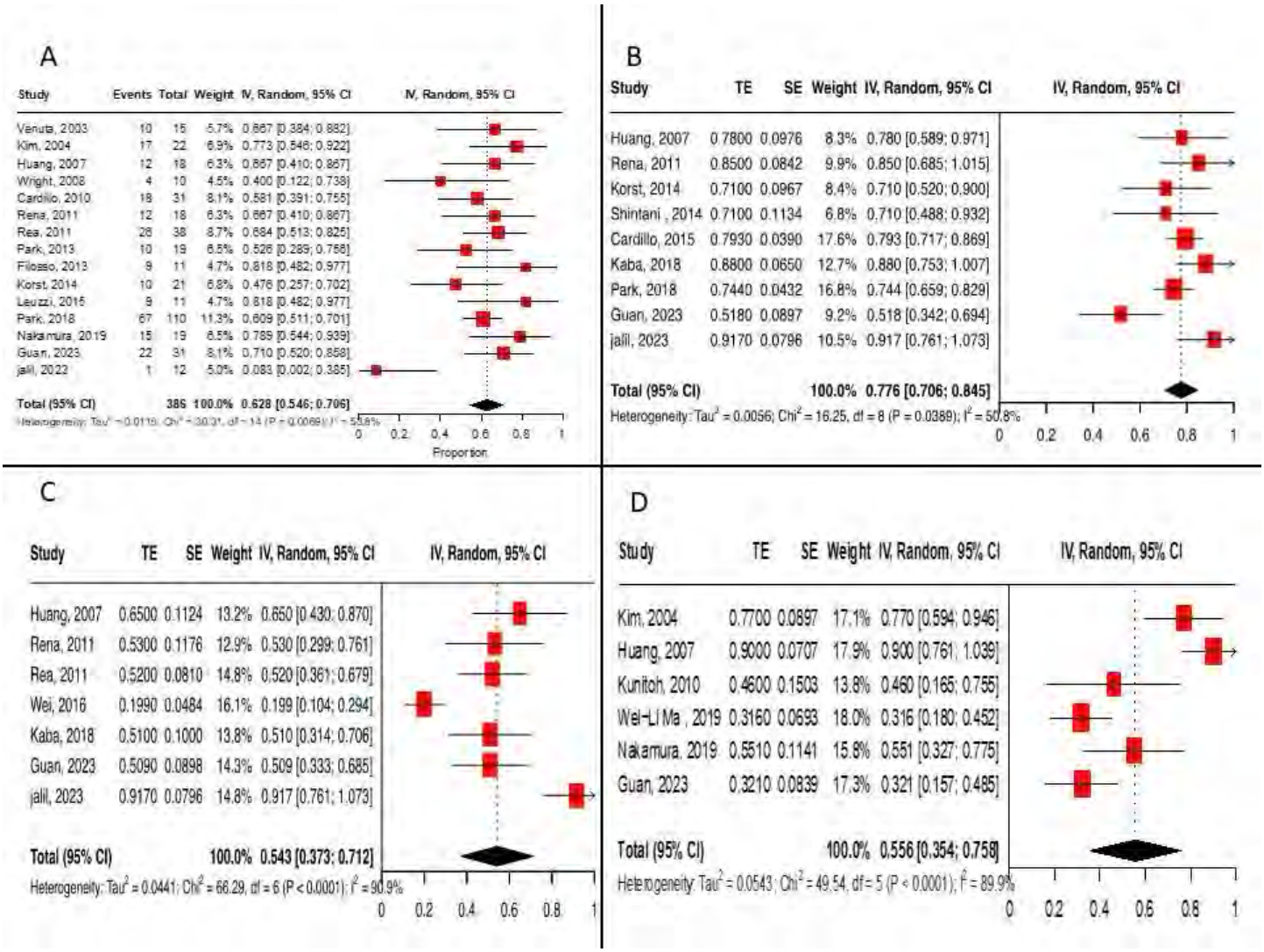
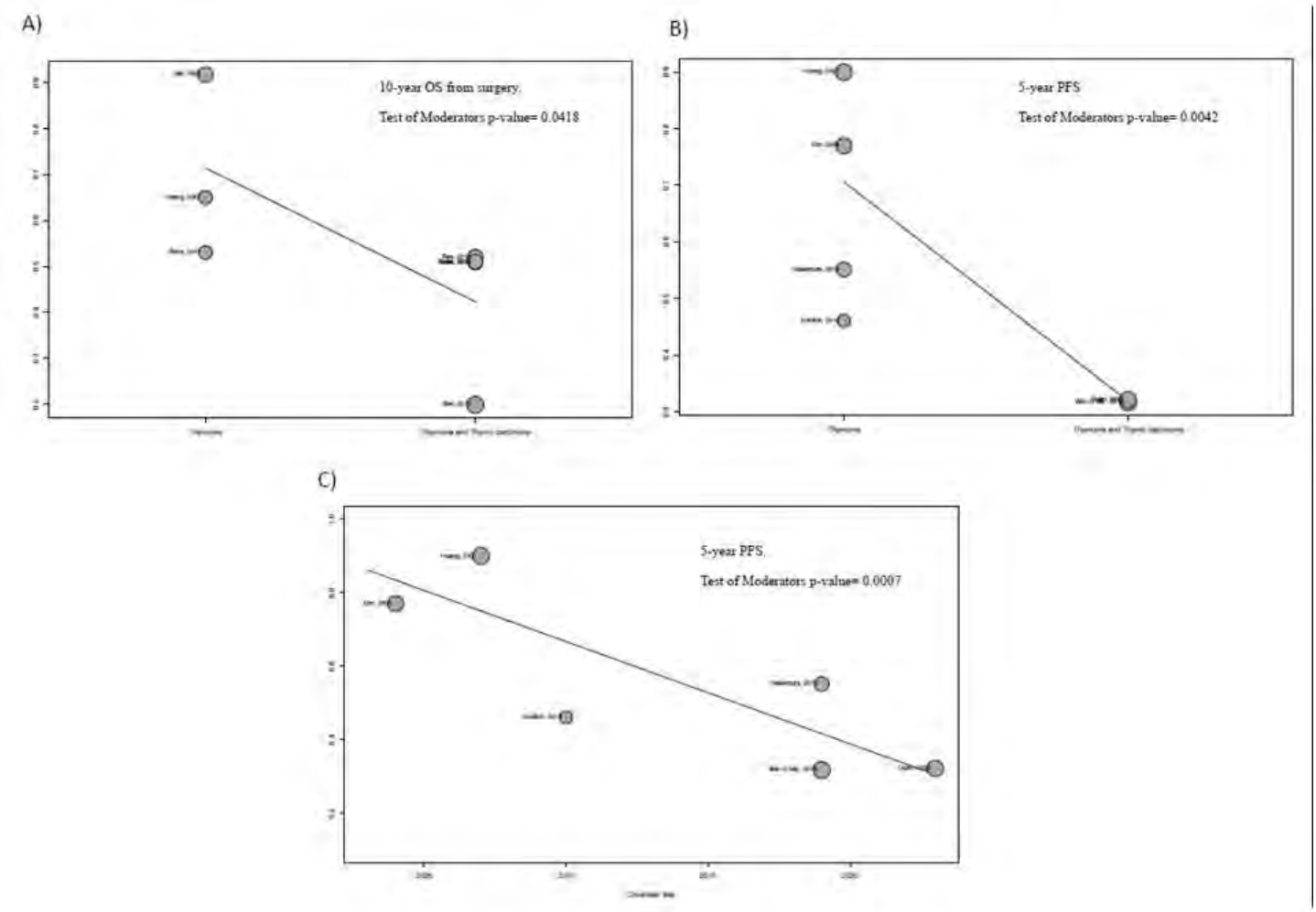
Introduction: Despite the availability of multimodal treatment strategies, there is currently no universally accepted guidelines for management of advanced Thymic Epithelial Tumors (TETs). To address this issue, we conducted a systematic review and meta-analysis to evaluate surgico-pathological and oncological outcomes in patients with Masaoka-Koga stage III-IVA TETs who underwent induction therapy (IT) followed by surgical resection.

Methods: According to the MOOSE guidelines, 24 studies on TETs undergoing IT were included in the meta-analysis. We performed a random-effects meta-analysis and assessed heterogeneity and publication bias. Meta-regression was used to examine moderators of the effect, including year of publication, histology and stage.

Results: Included studies were published from 2003 to 2023, 6 were prospective and 18 retrospective, with a total of 749 patients. Nine studies included thymomas only, while 15 included both thymoma and thymic carcinoma. Four, 11 and 3 studies included, respectively, only stage III tumors, stage III and stage IV TETs and stage IV only; 2 papers analyzed stage I and stage II tumors as well. The response was evaluated by RECIST and WHO criteria in 11 and 4 studies, respectively. The pooled rate of radiological response to IT, completeness of resection, 5-year OS, 10-year OS and 5-year PFS were, respectively, 62.8%, 71.6%, 77.6%, 54.3% and 55.6% (Fig. 1). Meta-regression analyses revealed no significant effects, except for histology on 10-year OS from surgery (p-value 0.0418) as well as on PFS (p-value 0.0042) and treatment period on PFS (p-value 0.0007) (Fig. 2).

Conclusions: Our meta-analysis demonstrates that IT followed by surgical resection is associated with acceptable long-term outcomes in patients with advanced TETs. However, while histology remained a significant prognosticator for the outcome, 10-yr OS has not changed yet in the last 20-year, underling the need for novel therapeutic approaches to enhance long-term survival, according to different histologies as well.





Keywords: thymic tumors, induction therapy, meta-analysis

P3.14.19 The Role of Tumors Size in Different Thymic Tumors Histology: Results Form the ESTS Thymic Database

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Introduction: Tumor size is recently proposed as prognosticator in thymic tumors and introduced as descriptor in the 9th TNM edition. The aim of this study is to investigate the prognostic role of different tumor size cut-offs in the different thymic tumor histology

Methods: Clinical and pathological data of patients from ESTS thymic database underwent surgery for TETs from 1/2000to12/2022 were reviewed and analysed.Patients clinical data, tumour characteristics, size at 5cm and 3 cm cut-off, WHO histology and organs infiltration were collected and correlated to overall survival(OS), Disease free Survival (DFS) And Cancer Specific Survival(CSS) using Kaplan-Meier curves. The log-rank test was used to assess differences between subgroups.

Results: The final analysis was conducted on 2556patients. Histology resulted thymoma in 2231 (87.3%), thymic carcinoma in 271 (10.6%) and neuroendocrine tumors (NET) in 54(2.1%) cases. In 1518(59.4%) size resulted >5cm.During a FUP, a recurrence occurred in 390(15.2%) patients, 255(9.9%)died,95 due to tumor progression.A significant difference was present considering the 5 cm size cut-off: 5-10YDFS of 82.4% and 76% vs 73.8% and 60.0%(p<0.001) in TETs ≤5cm vs >5cm, 5-10YOS of 91.2% and 82.8% vs 86.1% and 73%(p<0.001) in TETs ≤5cm vs >5cm, 5-10Y CSS 96.9% and 92.3% vs 94.1 and 88.8%(p=0.012) in TETs ≤5cm vs >5cm..The survival difference was significant also considering thymoma and thymic carcinoma/NET, with a 5-10Y DFS of 85.4% and 78.1% vs 77.6% and 62.4% in ≤5cm vs >5cm thymomas (p<0.001) and a 5-10YOS of 92.4%and79.4% vs 88% and 74.5% in ≤5cm vs >5cm thymomas (p=0.002). In thymic carcinoma/NET, 5-10Y DFS resulted of 61.3% vs 53.3% and 46.9% in ≤5cm vs >5cm carcinomas/NET (p=0.042), while 5-10YOS resulted 84.9%and 79.4% vs 74.9% and 64.9% in ≤5cm vs >5cm (p=0.002)(table). The survival difference resulted statistically significant for CSS also thymic carcinoma/NET(p=0.014) but not in thymomas(p=0.225). No significant differences were present considering a 3cm cut-off.Patients with B3 histology presented a significant worse survival outcome compared to other histology in all size subgroups but not in case of tumors ≤3cm. Considering size ≤5cm or >5cm, B3 tumors presented a significant worse CSS (p= 0.042 and p=0.003) and DFS (p=0.027 and p<0.001) compared to A-B2. Same results were presents in CSS and DFS terms considering tumors >3cm while the difference in OS was not statistically significant(figure table).

Conclusions: Tumor size resulted a significant prognosticator in TET, in thymoma and thymic carcinoma/NET, confirming its validity in prognosis prediction in these tumors independently by the histotype.

Survival outcome according to tumor size and histology.
DFS: disease free survival; OS: overall survival, CSS cancer specific survival. TET: Thymic Epithelial Tumor

TET SIZE	HISTOLOGY	5y OS%	10y OS%	p-value	5y DFS%	10y DFS%	p-value	5YCSS %	10YCSS %	p-value
≤5cm	THYMOMA	92,4	83,4	**0,002**	85,4	78,1	**<0,001**	97,5	92,9	0,225
>5cm		88	74,5		77,6	62,4		96,6	91,5	
≤3cm		95,3	82,2	0,92	87,5	76,5	0,060	99,2	91,7	0,473
>3cm		89	77,2		79,8	67		96,6	91,9	
≤5cm	THYMIC CARCINOMA/ NET	84,9	79,4	**0,042**	61,3	61,3	**0,042**	95,4	89,2	**0,014**
>5cm		74,9	64,9		53,3	46,9		79,9	73,2	
≤3cm		84,3	84,3	0,387	69,5	69,5	0,01	100	100	0,067
>3cm		77,8	68,2		53,9	49,9		82,8	76,6	
≤5cm	A	90,7	77	0,771	82,9	66,6	0,351	98,9	98,9	0,371
	AB	87,2	77,8		86	81,9		94,6	88,3	
	B1	97	94,2		92,6	89,8		100	97,1	
	B2	94	85,1		85,8	84,2		98,1	90,4	
	B3	93,7	88,7		79,8	75,4		95,1	95,1	
>5cm	A	85,9	68,3	0,156	79,1	58,3	<0,001	98,4	98,4	**0,010**
	AB	90,7	77,9		86,3	73,8		99,5	95,9	
	B1	84,9	76,5		75,3	64,9		93,1	93,1	
	B2	88,7	77,5		77,4	64,8		95,7	88,7	
	B3	92,4	55,3		63,6	40,1		92	76,2	
≤3cm	A	94,8	94,8	0,654	75,4	50,2	0,556	100	100	0,302
	AB	92,6	92,6		95,9	87,2		96,6	64,4	
	B1	96,9	96,9		86	86		100	100	
	B2	96,2	85,2		90,1	85,1		100	93,8	
	B3	100	75		87,1	65,3		100	100	
>3cm	A	86,9	70,5	0,239	82,2	63,5	**<0,001**	98,3	96,8	**0,003**
	AB	89,4	78,7		85,4	74,7		98,1	95,2	
	B1	88,3	80,7		81	71,8		95,1	93,9	
	B2	90,2	80,7		79,7	71,4		96,2	89,2	
	B3	84,8	65,2		66,8	49,8		92,4	81,8	
≤5cm	A-B2	91,8	82,8	0,986	86,5	80,3	**0,027**	98,1	92,9	**0,042**
	B3	93,7	88,7		79,8	75,4		95,1	95,1	
>5cm	A-B2	88,3	75,9	0,060	80,7	67	**<0,001**	97,1	93,6	**0,003**
	B3	83,8	55,3		63,6	40,1		92	76,2	
≤3cm	A-B2	94,9	83,2	0,811	87,5	79,8	0,634	99,2	90,3	0,587
	B3	100	75		87,1	65,3		100	100	
>3cm	A-B2	89,1	77,9	0,067	82,4	70,8	**<0,001**	97,1	93,6	**<0,001**
	B3	84,9	65,2		66,8	49,8		92,4	81,8	

Keywords: thymic tumors, staging, size

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.20 MTAP Deficiency in Thymic Epithelial Tumors

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Introduction: Thymic epithelial tumors (TETs), including thymoma and thymic carcinoma, represent rare malignancies with challenging outcomes and limited therapeutic options, especially in the advanced setting. Standard treatment typically involves platinum-based chemotherapy; however, the proportion of responders is minimal, with an urgent need for alternative treatments. MTAP (methylthioadenosine phosphorylase) deficiency, often co-occurring with deletions in CDKN2A and CDKN2B, has emerged as a promising target in other malignancies due to sensitivity to PRMT5 inhibitors. We aimed to characterize the prevalence of MTAP deficiency and related genomic alterations in patients with TETs.

Methods: We conducted a retrospective genomic analysis of 85 thymic tumor samples from the Dana-Farber Cancer Institute (DFCI) cBioPortal database that underwent molecular testing with next-generation sequencing (NGS). Tumors were categorized by histology into thymic carcinoma, thymoma, thymic neuroendocrine tumors, and thymic epithelial tumors not otherwise specified (TET, NOS). Copy number alterations (CNAs) in MTAP, CDKN2A, and CDKN2B were analyzed. An additional validation cohort was obtained using genomic data from DFCI's OncDRS, a comprehensive data retrieval tool that provides clinical, genomic, and specimen oncology data for research. Data analysis included the identification of homozygous (dual copy) deletions and co-deletion patterns.

Results: A total of 85 TET samples were identified in DFCI cBioPortal (cohort 1), with 47.1% (n = 40) classified as thymic carcinoma, 42.4% (n = 36) as thymoma, 5.9% (n = 5) as TET, NOS, and 4.7% (n = 4) as thymic neuroendocrine tumors. The cohort was evenly distributed by sex (41 males, 42 females, and 2 others). CNA analysis revealed deletions in CDKN2A and CDKN2B in 11.8% of cases (n = 10/85 each), and MTAP deletions in 9.1% (n = 4/44) of cases. A similar analysis of 548 TETs from DFCI OncDRS (cohort 2) identified 350 thymic carcinomas, 163 thymomas, 24 TET-NOS, and 11 thymic neuroendocrine tumors. Somatic mutation data were available for only 11/548 tumors, among which 10 (91%) harbored CDKN2A and 1 (9%) had a CDKN2B mutation, corresponding to 1.8% (10/548) of the overall TET cohort. Copy number variation (CNV) data were available for 48 TETs, representing 1.25% (48/3833) of all TET tumors profiled, demonstrating the low proportion of these patients that get next-generation sequencing. Of these, 9 tumors (18.75%) harbored MTAP CNVs, including 8 thymic carcinomas and 1 thymoma. CNVs in CDKN2A and CDKN2B were found in 41.7% (n = 20/48) and 39.6% (n = 19/48), respectively, with homozygous loss observed in 11 cases for each gene. These alterations were primarily observed in thymic carcinoma.

Conclusions: MTAP deficiency is prevalent in thymic epithelial tumors, particularly thymic carcinoma, and frequently co-occurs with CDKN2A/B deletions. However, the majority of the patients in our cohort did not have full NGS testing, emphasizing the importance of genomic testing in this population that harbors poor prognosis with new potential targeted therapeutic options.

Keywords: MTAP deficiency, Thymic Epithelial Tumors, Thymic Carcinoma

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.21 Single-Nucleus RNA Sequencing Reveals Key Pathways and Prognostic Markers in Thymic Carcinoma

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Introduction: Thymic carcinoma (TC), a rare and aggressive malignancy of the anterior mediastinum, is associated with limited therapeutic options and poor prognosis. The identification of novel biomarkers and therapeutic targets remains critical.

Methods: Comprehensive analysis of single-nucleus RNA sequencing (snRNA-seq) and bulk RNA-seq was performed to characterize transcriptional dynamics in the tumor immune microenvironment of TC and establish a prognostic model.

Results: A total of 1,244 differentially expressed genes (DEGs) were identified across TC, thymoma, and normal thymic tissue. Weighted gene co-expression network analysis (WGCNA) revealed two key gene modules, enriched in immune and membrane-related processes. Functional enrichment analysis highlighted pathways linked to cell adhesion molecules (CAMs) and immune response. A LASSO machine learning model prioritized five hub genes (JAM-A, VCAN, NECTIN1, CD8B, and NEGR1), with JAM-A demonstrating the highest diagnostic accuracy (AUC = 1.0 in PUMCH_TC and 0.94 in GEO cohort). Combining the snRNA-seq data of 2 normal and 3 TC samples, a total of 45,673 cells were divided into eight clusters, including epithelial cells (KRT5, KRT19), fibroblasts (CFD, ACACB, COL1A1), macrophages (CD163), B cells (CD79A, MS4A1, IGHM), plasma cells (MZB1, IGKC), T_NK cells (CD3D, IL7R, TRAC), endothelial cells (PECAM1), and smooth muscle cells (ACTA2, MYL9). SnRNA-seq analysis highlighted cellular heterogeneity in TC, revealing ectopic JAM-A expression in epithelial subtypes. The elevated expression of JAM-A in TC was validated by qPCR and Western. Immunohistochemistry-based survival analysis confirmed that high JAM-A expression was associated with poor overall survival (OS, $P < 0.001$, 95%CI 1.68 - 100.53) and progression-free survival (PFS, $P < 0.001$, 95%CI 1.96 - 109.86) in TC patients.

Conclusions: This study identifies JAM-A as a novel prognostic biomarker in TC, implicating its role in tumorigenesis through CAMs-related pathways. Elevated JAM-A expression independently predicts adverse clinical outcomes, underscoring its potential as a therapeutic target.

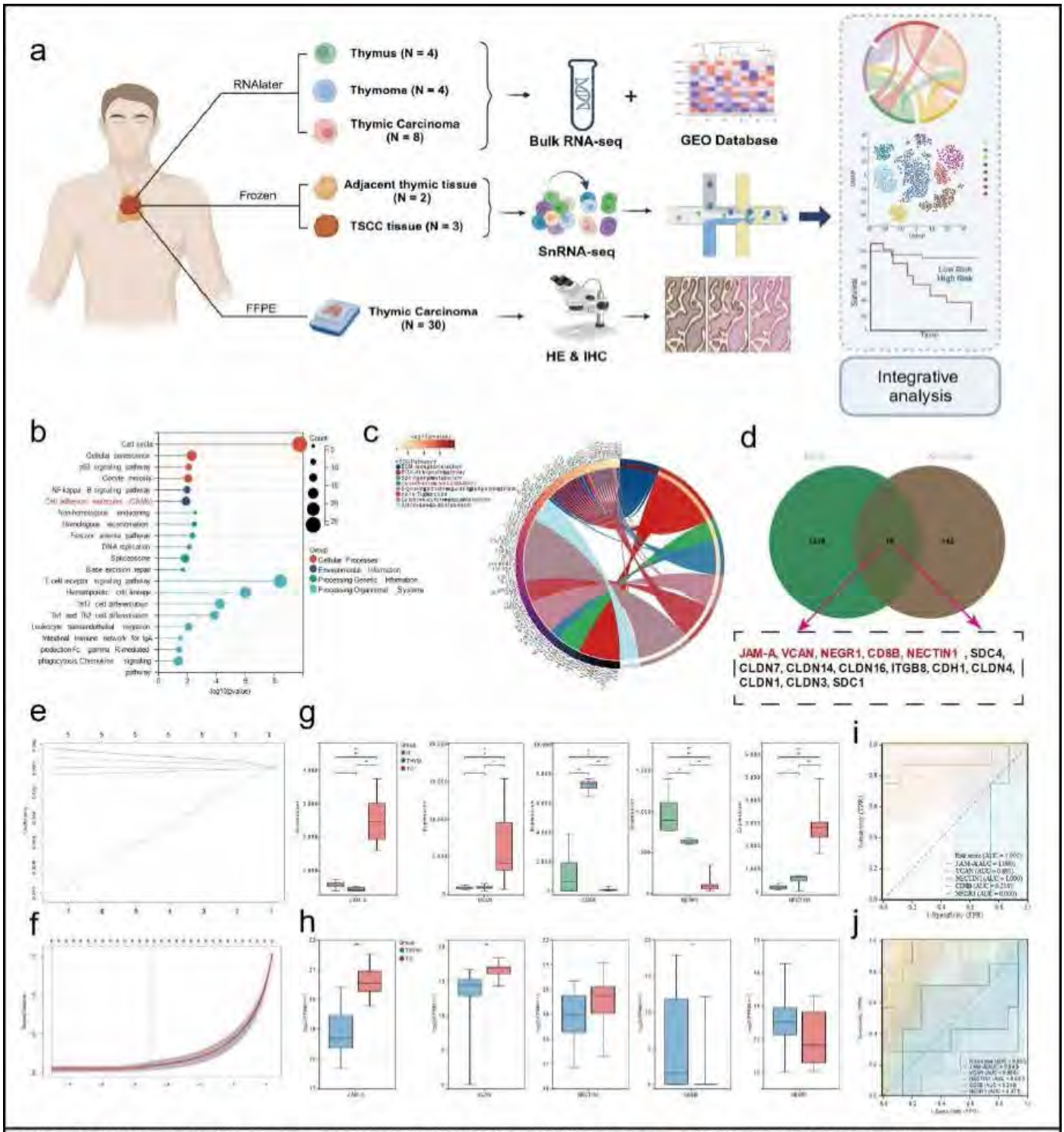

Fig. 1: Differential gene expression analysis and key gene analysis. (a) Study flow diagram. (b) KEGG enrichment analyses for WGCNA key module. (c) Chord diagram showing relationships between enriched KEGG pathways and DEGs. (d) Venn diagram identifying overlapping genes between DEGs and CAMs pathways. Highlighted genes are potential key biomarkers. (e-f) LASSO regression analysis identifying the aforementioned key genes. (g-h) Boxplots of key gene expression in TC, thymoma, and thymus groups. (i-j) ROC curves for selected key genes in *PUMCH_TC* cohort (i) and *GSE57892* cohort (j), showing their diagnostic performances.

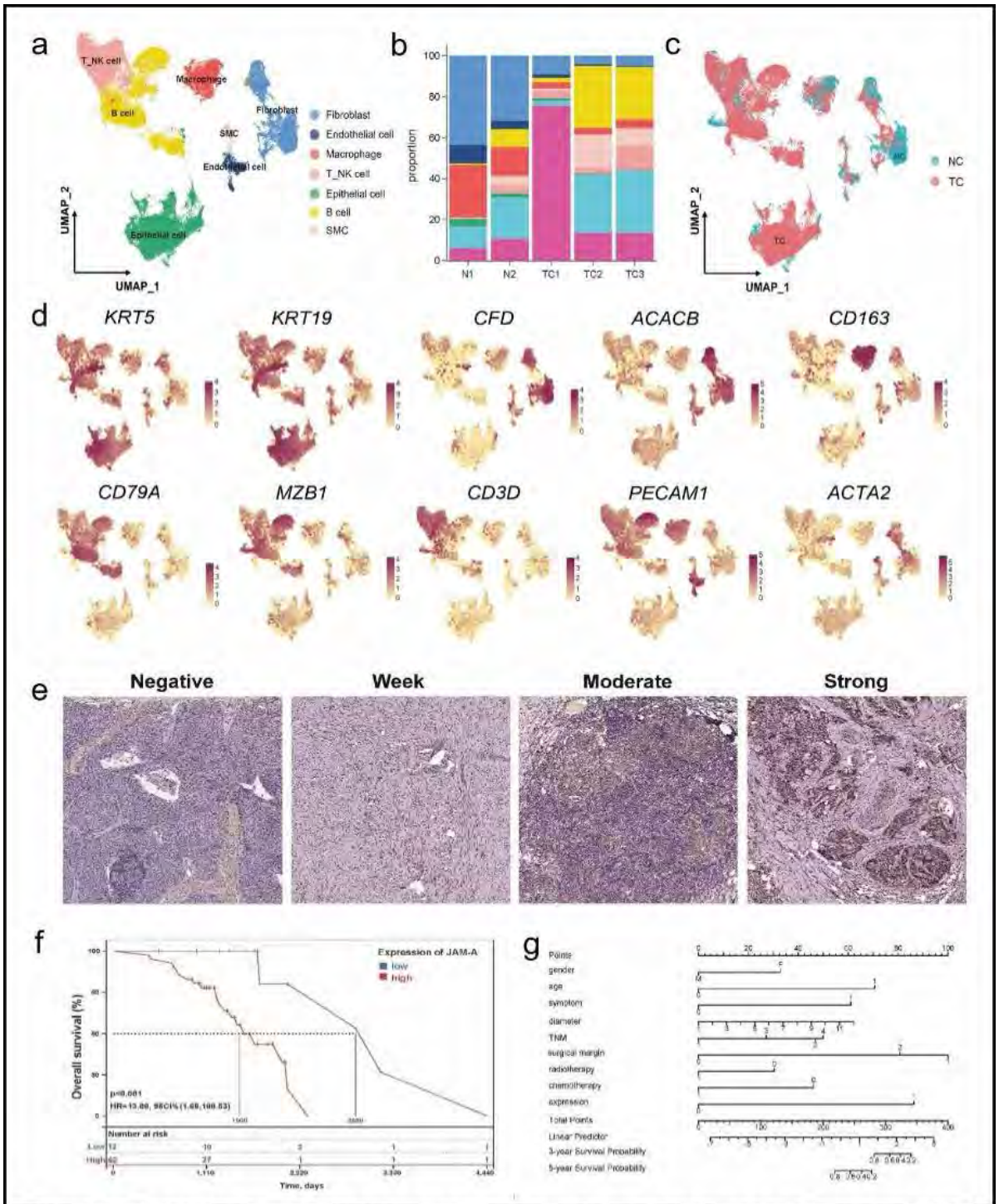

Fig. 2: SnRNA-seq analysis and prognostic analysis of TC. (a) UMAP plot showing the clustering of single cells into distinct cell types. (b) Proportion of each cell type in normal and tumor samples. (c) UMAP plot of tumor and normal cells. (d) UMAP plot of expression distribution of marker genes. (e) Representative IHC staining images (×10) of JAM-A in tissue samples with varying expression levels: negative, weak, moderate, and strong. (f-g) KM survival curves (f) and nomogram (g) of OS in TC patients.

Keywords: Thymic carcinoma, single-nuclei RNA sequencing, JAM-A

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.22 Outcomes to Systemic Standard-Of-Care Therapies in Patients With MTAP-Deleted Advanced Non-Small Cell Lung Cancer

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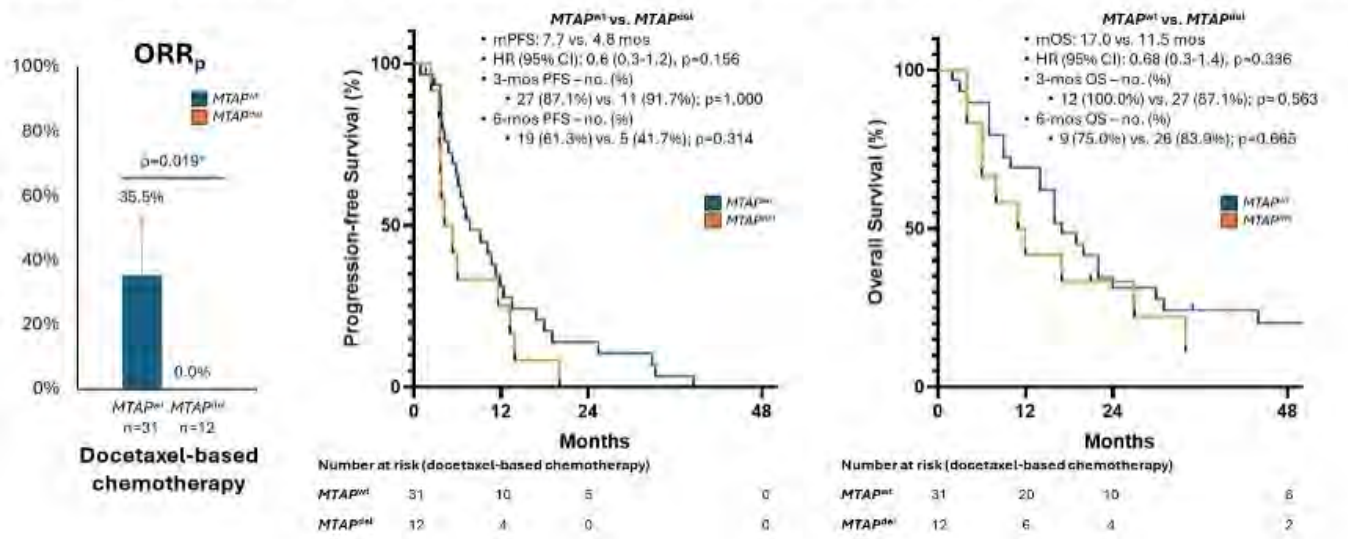
Introduction: Methylthioadenosine phosphorylase two-copy deleted (MTAPdel) cancer cells are vulnerable to protein arginine methyltransferase 5 (PRMT5) or methionine adenosyltransferase 2 (MAT2A) inhibition, making them promising therapeutic targets. There are limited outcomes data, however, for MTAPdel metastatic advanced non-small cell lung cancer (mNSCLC) within current treatment paradigms.

Methods: Patients with mNSCLC who had large panel, tissue-based, DNA NGS at a single center from 7/2013-3/2024 and known MTAP status (MTAP two-copy deletion [MTAPdel] vs MTAP-intact [MTAPwt]) were included. All patients received platinum doublet + anti-PD-(L)1, anti-PD-(L)1 monotherapy, and/or docetaxel-based chemotherapy and were followed through 11/2024. Patients included in the MTAPwt cohort were randomly selected without matching. Measured outcomes included PFS and OS. Response rate (ORRp) was determined using a validated natural language processing model trained on imaging radiology reports annotated with the Pathology, Radiology/Imaging, Signs/Symptoms, Medical oncologist assessment, and bioMarkers (PRISSMM) framework. Kaplan Meier curves were used to estimate survival and corresponding logrank tests were used to compare endpoints.

Results: Overall, 105 MTAPdel and 120 MTAPwt patients were included; 64.0% were women, 83.1% had adenocarcinomas, and 68.4% had stage IV disease at diagnosis. MTAPdel patients had less of a smoking history (median 15.0 vs. 30.0 pack-years, p=0.039) and lower PD-L1 TPS (median 3.5% vs. 10.0%, p=0.040), but were more likely to have stage IV disease at diagnosis (78.1% vs. 60.0%, p=0.004). CDKN2Adel (88.6% vs 7.5%), CDKN2Bdel (87.6% vs. 5.6%), and 9p21.3del (77.1% vs 6.7%) were enriched in MTAPdel vs MTAPwt patients (p<0.001). On univariate analysis, among targetable co-mutations, MTAPdel patients were more likely to have EGFR mutations (24.8% vs. 13.3%, p=0.039), and among the top 30 frequently co-mutated genes not limited to targetable mutations, MTAPdel was associated with EGFR and FANCM mutations (44.8% vs. 25.8%, p=0.003; 9.5% vs. 2.5%, p=0.041). ORRp, PFS, and OS after platinum doublet + anti-PD-(L)1 or anti-PD-(L)1 monotherapy did not differ between the two cohorts. MTAPdel patients had lower ORRp after docetaxel-based chemotherapy (0.0% vs. 35.5%, p=0.019), and numerically worse PFS/OS (mPFS 4.8 vs. 7.7 months, HR 0.6, 95% CI 0.3-1.2, p=0.156; 6-month PFS 41.7% vs. 61.3%, p=0.314; mOS 11.5 vs. 17.0 months, HR 0.7, 95% CI 0.3-1.4, p=0.336; 6-month OS 75.0% vs. 83.9%, p=0.665) (Figure).

Conclusions: Compared to patients with MTAPwt mNSCLC, those with MTAPdel mNSCLC have no significant difference in PFS or OS after standard therapy, but may have worse response rates to docetaxel. Effective agents targeting MTAPdel mNSCLC are needed, particularly in those with previously-treated disease.

Figure. Comparisons of ORR_p and Kaplan-Meier curves of PFS and OS after docetaxel-based chemotherapy



Keywords: MTAP, Metastatic Non-Small Cell Lung Cancer

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.23 The Mechanism of Immunotherapeutic Resistance in Pulmonary Sarcomatoid Carcinoma

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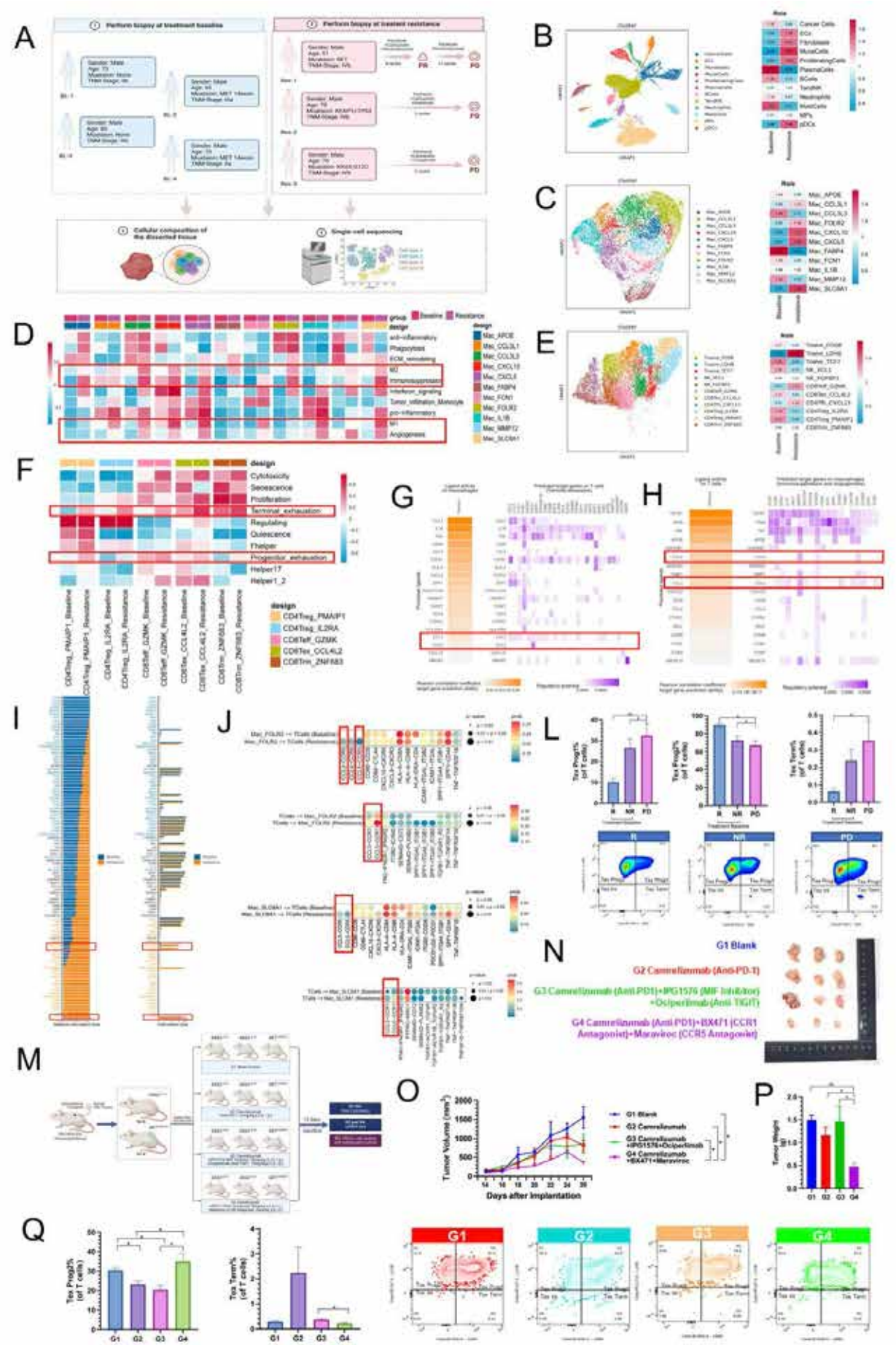
Introduction: Pulmonary sarcomatoid carcinoma (PSC) represents a rare subset (0.4%) of highly aggressive and poorly differentiated NSCLC, characterized by sarcoma-like or sarcoma (spindle- or giant-cell) elements. Currently, there is no research specifically investigating the mechanisms of immunotherapy resistance in PSC. To address this gap, we conducted scRNA-seq on baseline treatment samples and immunotherapy-resistant specimens of PSC. We also performed relevant experimental validations and implemented targeted interventions in animal models. This comprehensive approach aims to develop novel therapeutic strategies for enhancing sensitivity to immunotherapy or reversing resistance in PSC.

Methods: The scRNA-seq protocol used here was following the manual instructions of Singleron Biotechnologies. PDX models were established by subcutaneously implanting small tissue fragments from PSC patients into HuHSC-NOG-EXL mice (Charles River Laboratories). Experimental mice were divided into four groups, with the exposure of following drugs: IPG1576 (MIF inhibitor; 10 mg/kg, i.p., q2d), BX471 (CCR1 antagonist; 50 mg/kg, s.c., q2d), Camrelizumab, Ociperlimab and Maraviroc [CCR5 antagonist] (all 10 mg/kg, i.p., q3d).

Results: We analyzed 4 baseline and 3 immunotherapy-resistant PSC specimens using scRNA-seq (Fig.1A). Resistant samples exhibited increased stromal cells (Fig.1B), SLC8A1+/CXCL10+/CXCL5+ macrophages (Fig.1C), and GZMK+ CD8 Teff, LDHB+ T naïve (Fig.1E) with enhanced macrophage immunosuppressive/angiogenic functions (Fig.1D) and T cell terminal exhaustion (Fig.1F). Cell communication analysis revealed CCL3/CCL5-mediated crosstalk driving macrophage polarization and T cell exhaustion (Figs.1G-H, J), alongside upregulated MIF and TIGIT-Nectin2 signaling (Fig.1I). Flow cytometry of PSC patient PBMCs confirmed elevated precursor-exhausted CD8+ T cells in responders (n=5) versus terminal-exhausted subsets in non-responders (n=9) and progressive disease (n=5) (Fig.1L). In humanized PDX models (Fig.1M), the CCR1/CCR5 inhibitor combination (G4) outperformed MIF inhibitor/ anti-TIGIT (G3) (Figs.1O-P), reversing resistance by increasing precursor-exhausted and reducing terminal-exhausted CD8+ T cells (Fig.1Q). These findings identify CCR1/CCR5 blockade as a novel strategy to reverse immunotherapeutic resistance in PSC

Conclusions: The additional combination of CCR1/CCR5 blockade with anti-PD-1 demonstrated a synergistic efficacy to immunotherapy-resistant tumors via reshaping the microenvironment, potentially offering a novel approach to combat immunotherapy resistance in PSC.



Keywords: pulmonary sarcomatoid carcinoma, immunotherapy, therapy resistance

P3.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.14.24 Tracheal Resection Surgery: Comparison of Continuous Vs. Interrupted Suture of the Membranous Wall in a Series of 162 Cases

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Introduction: Tracheal tumors are a rare entity, and their surgical treatment generally requires segmental resection with reconstruction through tracheoplasty. This technique is also used in the management of benign tracheal stenosis, where tracheal anastomosis is traditionally performed using interrupted sutures. At our center, we have implemented continuous suturing of the posterior wall of the anastomosis and seek to compare its outcomes with the conventional interrupted suture technique in terms of safety and postoperative complications.

Methods: A retrospective study was conducted using prospectively collected data from a referral thoracic surgery center. A total of 162 patients who underwent tracheoplasty for benign tracheal stenosis associated with mechanical ventilation (MV) between 2010 and 2023 were included. Patients were divided into two groups based on the suturing technique: Group A (interrupted sutures, n=85) and Group B (continuous sutures, n=77). Demographic variables such as age at surgery, sex, comorbidities, associated injuries, underlying condition leading to MV, duration of MV, time to symptom onset after extubation, lesion extent, and prior treatments were analyzed. Postoperative outcomes, including short- and long-term complications, were compared. Follow-up was at least 12 months. Statistical analysis was performed using R software version 4.3.1, applying Chi-square, Fisher's exact, and Mann-Whitney tests, with a significance level of $p<0.05$.

Results: No significant differences were found between groups in terms of age, sex, or associated risk factors. However, two differences were noted: Group B had a higher rate of previous endoscopic dilations (84.4% vs. 63.5%; p=0.004), whereas Group A had a higher rate of stent placement (14.1% vs. 2.6%; p=0.011). Additionally, protective muscle flap reinforcement of the anastomosis was more frequently used in Group B (50.6% vs. 14.1%; $p<0.001$). Immediate postoperative complications showed no significant differences between groups (29.4% in A vs. 32.5% in B; p=0.735). However, complications at one month were more frequent in Group A (11.8% vs. 1.3%; p=0.010), as was dysphonia at one month (8.2% in A vs. 0% in B; p=0.014). No significant differences were observed in the restenosis rate at 3 months or 1 year.

Conclusions: Continuous suturing of the membranous portion of the tracheal anastomosis is a safe technique, with an incidence of immediate complications comparable to that of interrupted suturing. However, it is associated with a lower rate of complications at one month and a reduced incidence of early dysphonia. Although this study focused on cases of benign pathology, these findings may be extrapolated to tracheal resection and reconstruction for tracheal tumors. Prospective studies are needed to evaluate its impact on the oncologic treatment of this rare condition.

Keywords: tracheal tumor, Tracheal Resection, Anastomotic Techniques

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.01 Lung Cancer Patients' Understanding of and Involvement in Their Treatment and Care: Insights From a Global Patient Experience Survey

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Introduction: The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 31 nations, reaffirms in its charter the right of all lung cancer patients to be treated with dignity and respect and to have access to quality health care, including informed self-determination and physical and mental integrity.

Essential to these rights is how patients engage with their treatment and support teams. To better understand patient experiences, GLCC sought to explore patients' involvement in decision-making, whether they receive and understand information about their condition, and their preferences on how this information is delivered.

Methods: For its sixth annual survey, GLCC commissioned Censuswide to conduct a global survey of lung cancer patients. The survey is currently in the field across 18 countries (Australia, Argentina, Brazil, Canada, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Portugal, South Africa, Spain, Taiwan, UK, USA). As part of this survey, GLCC included questions to understand respondents' involvement in decision-making, what information they received and if they understand it, and their preferred format for receiving information.

Results: Results will be available for presentation. The survey assesses the levels of involvement patients have in decision-making and patients' satisfaction with the quality, timing, comprehensibility, and relevance of the information provided by their treatment and support teams. The results will also include findings on patients' preferred formats for receiving information.

Conclusions: It is anticipated that these findings can help healthcare providers better understand and meet the needs of lung cancer patients, ensuring they appropriately involve patients in decisions about their care, and tailor their current approaches to providing patients with information about their condition.

Questions	Answer options										
When talking to your treatment and support team, did you feel involved in the decisions about your treatment and care? Please choose the option that best describes you.	Yes, I've been fully involved	Yes, I've been involved mostly, but wanted to be more involved	Yes, I've been involved mostly, and didn't want to be more involved	Yes, I've been involved sometimes, but wanted to be more involved	Yes, I've been involved sometimes and didn't want to be more involved	Yes, other please specify	No, but I would like to be involved	No, but I didn't want to be involved	No, but my caregiver was involved	No, other please specify	
The GLCC believes that lung cancer patients should receive high quality information, which tells you what you want to know, at the right time for you. What best describes how you feel about the information you received from your treatment and support team about your lung cancer? Please choose the option that best describes you. Matrix: Answers are provided across a row of the following options: •At diagnosis •When starting treatment •When changing treatment •When ending treatment / follow-up •When accessing palliative care	I got the information I needed at the right time	The information wasn't helpful	The information came too late	The information wasn't helpful and it was also given too late	I had to look for other information on my own	I didn't understand the information provided	I didn't get any information	I didn't want to know any information	Other way	No way in particular	Not applicable
To accompany the discussions with your treatment and support team, what is your preferred format for receiving information about your condition: Select one	Audio materials	Apps	Cancer support hotline	Infographic	Print material	Videos	Website	Education programme (for example chemo education)	Other (please use the text box below)	No preference/ no preferred way	

Keywords: Patient involvement, Health information, Treatment

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.02 Cancer Patients' Advocacy and Policy Impact in Japan, How 3,623 Voices Halted a National Cost-Sharing Reform

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Introduction: Japan's High-Cost Medical Expense Benefit system is a national policy designed to limit monthly out-of-pocket payments for medical care, thereby ensuring that all citizens—including those with serious illnesses—can access necessary treatment without incurring catastrophic health expenditures. As part of Japan's universal health coverage framework, this system has long served as a critical safety net, especially for patients requiring ongoing and high-cost treatments, such as cancer care.

In 2025, a government proposal to raise this cap sparked concern among patients and healthcare professionals. Fears centered on treatment discontinuation and increased financial hardship.

This abstract describes a unique patient advocacy movement that arose in response: a coalition of cancer patient organizations, including our group One Step, rapidly gathered 3,623 voices through a national survey. The initiative drew public and political attention, ultimately leading the government to suspend the proposed reform. This report aims to present how a collective patient response can influence national health policy, with relevance to global discussions on equitable access and financial protection in cancer care.

Methods: We reviewed open-ended responses from the January 2025 survey and documented the advocacy process. This included coordinated communication, media engagement, and petition delivery to the Prime Minister. One Step supported outreach to include lung cancer patient perspectives.

Results: Many feared the policy would force them to stop treatment or compromise daily life. Younger patients noted current costs were already burdensome. The petition's public handover to the Prime Minister amplified patient voices and contributed to halting the reform.

Conclusions: This case highlights rare direct policy impact by patient voices in Japan. The campaign encouraged civic participation and cross-cancer solidarity. Statements from academic societies, including the Japan Lung Cancer Society, further influenced the decision. This may offer a model for advocacy in other nations facing similar healthcare challenges.

Keywords: Patient Advocacy, Health Policy, inancial Toxicity

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.04 Lung Cancer Treatment in Brazil: The Gap Between Incorporation and Real-World Access

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Introduction: Lung cancer is the most commonly diagnosed cancer worldwide (excluding nonmelanoma skin cancer) and remains the leading cause of cancer-related deaths globally. In Brazil, it is the fourth most common cancer, with an estimated 32,560 new cases annually. Brazil has a universal healthcare system (SUS), which serves approximately 160 million people, or 75% of the population. Ensuring equitable access to lung cancer treatment within such a complex system is a significant challenge. The incorporation of new technologies in SUS is determined by the National Commission for Technology Incorporation in the Public Health System (Conitec), which conducts Health Technology Assessments (HTA) to decide on their adoption. Theoretically, once incorporated by Conitec, the technologies should be available to all patients cared for by SUS.However, Patient Advocacy Organizations frequently support patients who face barriers to accessing approved treatments. To strengthen advocacy efforts and generate evidence regarding the real-world availability of incorporated treatments, a Brazilian Cancer Advocacy Group conducted a study to assess the accessibility of lung cancer drugs incorporated by Conitec.

Methods: The study focused on all medications incorporated by Conitec for lung cancer until September 2023, namely: Erlotinib and Gefitinib, for treatment of patients with advanced or metastatic non-small cell lung cancer with EGFR mutation (incorporated in 2013), and Crizotinib for advanced ALK-positive non-small cell lung cancer (incorporated in 2022).To investigate the availability of these treatments, the Brazilian Freedom of Information Law was used, which allows citizens to request data from public institutions. Between September 2023 and January 2024, requests were submitted to 268 accredited public cancer centers, asking for their treatment protocols for five types of cancer (breast, prostate, colorectal, lung, and melanoma). This publication focuses on the responses related to lung cancer.

Results: A total of 43 cancer centers submitted their lung cancer treatment protocols specifying the medications available. Each protocol was analyzed to determine the inclusion of the most recently incorporated Conitec-approved lung cancer treatments. Of the protocols received, 12 (27.9%) included Erlotinib in their treatment protocols, 18 (41.9%) included Gefitinib and only 2 (4.7%) included Crizotinib. Notably, only 2 hospitals (4.65%) had full adherence to Conitec incorporations, offering targeted treatments for both ALK and EGFR mutations. Most glaringly, 22 (51,2%) of respondent hospitals offer none of the incorporated drugs.

Conclusions: This study highlights significant disparities in the availability of lung cancer treatments within Brazil's public healthcare system. Despite their official incorporation, access to these medications remains inconsistent across hospitals. Furthermore, the inclusion of a drug in a hospital's protocol does not guarantee its consistent availability or usage, as factors such as stock shortages and implementation barriers may impact actual patient access.The findings underscore the need for improved mechanisms to ensure that the incorporation of new treatments translates into real-world access for patients. Strengthening monitoring and enforcement strategies is essential to bridging the gap between policy decisions and patient care.

Keywords: Inequality, Access, Patient Advocacy

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.05 Exploring Quality of Life in Oncogene Addicted NSCLC Patients and Their Caregivers

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Introduction: The introduction of targeted therapies has radically changed the therapeutic landscape of oncogene-addicted non-small cell lung cancer (NSCLC). Despite this progress, data on quality of life (QoL) remain heterogeneous, and those concerning self-efficacy for caregiving are particularly limited. Here we present the results of a QoL-focused survey conducted in collaboration with the patient advocacy group Women Against Lung Cancer in Europe (WALCE), during two events entirely dedicated to patients and their caregivers (BeMutual Days, Rome, November 2023 and November 2024).

Methods: Patients with oncogene-addicted advanced NSCLC receiving targeted therapies were included. Self-efficacy for caregiving was assessed through the Caregiver Inventory (CGI). Patients completed the Functional Assessment of Cancer Therapy-Lung (FACT-L) and the Brief Pain Inventory (BPI) to evaluate QoL and pain impact, respectively. Data were collected anonymously and analysed in aggregate form.

Results: A total of 87 patients and 72 caregivers from 12 Italian oncology centres participated. FACT-L results showed higher scores in the physical well-being domain compared to emotional and functional well-being ($p<0.001$). Notably, satisfaction with sexual activity was significantly lower than other aspects within the social/family well-being domain ($p<0.001$). Pain, as assessed by the BPI, was generally mild and well-controlled. Interestingly, 17.2% (n=15) patients reported using their TKI as the main treatment for pain control, likely reflecting the effective symptom management achieved over time. When present, pain was most disruptive in terms of work ability, sleep, and enjoyment of life. Caregivers (CGI) reported greater confidence and competence in maintaining a close relationship with the patient over time. Conversely, they expressed lower self-efficacy when addressing the patient's potential death, the inability to control events (e.g., disease progression), or when managing negative emotions related to illness ($p<0.001$). Additionally, caregivers tended to neglect self-care while prioritizing coping strategies for both themselves and the patient ($p<0.001$).

Conclusions: These findings highlight the presence of unmet needs among both patients (emotional/functional well-being and sexuality) and caregivers, particularly in the area of self-care. Joint initiatives with patient organizations (e.g., WALCE) may help address these gaps and enhance the overall oncological care.

Keywords: Oncogene addicted NSCLC, Quality of life, Patients advocacy

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.06 The Saving Lungs Behind the Chair Model Is Increasing Lung Cancer Awareness in US Black Communities

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Introduction: Despite advances in lung cancer treatment, awareness and early detection remain significant challenges in underserved communities. Lung cancer is the #1 cause of cancer-related death in Black men in the US, and Black Americans have the highest lung cancer mortality rate of all racial and ethnic groups in the US. In 2021, only 5.8% of eligible Americans were screened. Lung Cancer Foundation of America (LCFA) developed the Saving Lungs Behind The Chair campaign to address these health inequities by leveraging trusted relationships in the Black community via licensed beauty hair professionals in Metro Atlanta.

Methods: This pilot program recruited and trained 59 hair professionals (33 stylists, 26 barbers) to serve as community health ambassadors, providing lung cancer education to clients. Critical messaging conveyed included screening and biomarker testing. The campaign operated across seven counties with high Black populations (26.1% to 68.1%). Implementation included hair professional training, community event participation, and direct client education, with data collected through participant surveys and tracked client interactions. LCFA collaborated with a local community organization, Community Spark Solutions, which was recommended to enhance the reach and impact of health initiatives.

Results: In less than 90 days, the campaign reached 2,404 community members: 700 through direct client conversations of which 22% registered for more information, 153 hair professionals approached in which 59 were recruited as ambassadors, and 1,551 individuals via social media. Following education, among clients eligible for screening, 90% expressed intent to schedule screening within 3-6 months, which was higher than the 77% expressed in a similar study regarding Barbers and prostate cancer education. The pilot demonstrated remarkable sustainability potential, with 98% of hair professionals willing to participate in future events.

The campaign fostered a space for survivors to share their experiences, and fight stigma by highlighting that lung cancer affects anyone with lungs. This peer-led approach effectively reached communities with healthcare mistrust and may improve survival outcomes.Community Impact and Innovation: Through the trusted hair professional-client relationship, the campaign established natural health conversations in non-clinical settings that might otherwise never occur. The remarkable 90% intent-to-screen rate signals a potential breakthrough in community-based lung cancer advocacy. With 22% of conversations converting to registrations, this model effectively overcomes engagement barriers in underserved communities. By transforming hair professionals and clients into lung cancer awareness advocates, the program created a ripple effect of information through established community networks.

Conclusions: The Saving Lungs Behind The Chair campaign demonstrates the effectiveness of community-based approaches to lung cancer education. This model effectively addresses specific barriers to lung cancer screening in Black communities—medical mistrust, lack of awareness, and limited access - in ways that many healthcare-centered initiatives cannot. The model shows promise for expansion to other metropolitan areas with large Black populations, which LCFA is currently exploring. By meeting people within their trusted community spaces, this innovative approach has potential to significantly impact lung cancer outcomes and reduce health disparities in underserved communities.

Abstract developed with assistance from CauseWriter.AI, powered by Anthropic's Claude AI assistant (2023).

Keywords: Health Equity, Awareness, Education

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.07 Canadian Action Plan for Lung Cancer - Patient Perspective

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Introduction: Lung cancer remains the leading cause of cancer-related deaths in Canada, underscoring the urgent need for a unified approach to improve outcomes. The Canadian Action Plan for Lung Cancer represents a groundbreaking effort to incorporate patient perspectives into national cancer strategy development. This initiative, co-designed by patient advocates, researchers, clinicians, and policymakers, emphasizes the value of lived experience in shaping evidence-based solutions.

Methods: The development process began with a nationwide survey using open-ended questions. Patients, caregivers, clinicians, and policymakers shared their priorities, challenges, and unmet needs. Key themes emerged: reducing stigma, enhancing early detection, improving access to treatment, and investing in research for innovative therapies. These insights informed a second survey, in which a select group of constituents were asked to prioritize these themes.

The plan culminated in a one-day summit, during which Patient advocates worked alongside scientific and medical experts to co-create actionable goals. The day included a mix of panels and workshops presenting specific issues and viewpoints.

Results: To ensure inclusivity, special focus was given to engaging underrepresented groups, such as Indigenous communities and rural populations, whose experiences with lung cancer often differ. The resulting Action Plan integrates patient-centered recommendations with measurable objectives, such as increasing lung cancer screening participation rates, funding research on targeted therapies, and implementing supportive care programs.

Conclusions: This initiative exemplifies the transformative potential of patient-researcher partnerships in addressing complex health challenges. The Canadian Action Plan for Lung Cancer sets a precedent for future cancer strategies globally by amplifying patient voices and prioritizing equitable access.

Keywords: Priorities, Advocacy, Planning

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.08 Feasibility of Engaging Latino Individuals in a Lung Cancer Screening Study Through Mychart

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Introduction: To assess the feasibility of engaging Latino individuals in a lung cancer screening study using MyChart.

Methods: The electronic health record (EHR) at the University of Rochester Medical Center was used to identify individuals who: (1) self-identified as Hispanic/Latino, (2) were between 50 and 80 years old, and (3) currently smoked. Identified individuals with a MyChart account received an invitation to participate in a lung cancer screening study tailored for Latino individuals. Those who expressed interest were contacted by the study team for eligibility assessment and potential enrollment. Eligibility criteria, aligned with U.S. Preventive Services Task Force recommendations, included: (1) a history of 20 pack-years of smoking, (2) current smoking or having quit within the past 15 years, and (3) no recent lung cancer screening. The interest rate was calculated as the proportion of individuals who expressed interest relative to those invited. The enrollment rate was calculated as the proportion of eligible individuals who enrolled.

Results: A total of 1,745 individuals were identified in the EHR. Among them, 668 had a MyChart account and were invited to participate. Forty-six individuals expressed interest (6.8% interest rate, 46/668), and 33 were contacted by the study team. Fifteen individuals were ineligible, with the most common reason for ineligibility being a smoking history of less than 20 pack-years (40%, 6/15). Among those eligible, nine individuals qualified for the study, and seven enrolled (77.7% enrollment rate, 7/9).

Conclusions: Findings suggest that engaging Latino individuals in a lung cancer screening study through MyChart is feasible. This approach may enhance outreach efforts and promote early detection within this population.

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.09 A Study of Testing Knowledge Regarding Lung Cancer Screening Among General Population and Caregivers

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Introduction: Over 70000 yearly cases of Lung-Cancer are reported in India. Smoking is a leading cause of Lung-Cancer beside sources like second-hand smoke, hazardous substances at work, etc. Awareness about sources and screening methods play major in battling Lung-Cancer. Early detection is key. Objectives of the study were to identify difference in awareness about sources and screening of Lung-Cancer between general-population and caregivers of Lung-Cancer patients and assess attitude towards Lung-Cancer screening procedures and prevention.

Methods: Caregivers of Lung-Cancer patients were approached for one-on-one interview both in-person and online.

A section of general-population was interviewed both online and in-person. Candidates were selected based on prerequisites and eligibility criteria such as age (over 50y), smoking history, exposure to hazardous factors at work, etc.

Questionnaire was provided to individuals enquiring about respective demographics, knowledge, experience, and opinions about Lung-Cancer.

Results: The survey reports most of the general-population to be employed males whereas most caregivers to be female homemakers. Most respondents from either group have received formal education. In general-population candidates, over 65% had a history of regular smoking, nearly 20% smoked occasionally and around 15% had never smoked. Nearly 30% had tried to quit. No respondents from either group had undergone Lung-Cancer screening. More than 70% of the caregiver-population and only 35% from the general-population reported engaging in activities and behaviours for reducing Lung-Cancer risk that included diet, exercise, quitting smoking etc. Most caregivers reported that their respective patients were receiving palliative care. The average time of experience in caregiving was 1 year. Most caregivers reported undertaking medical and lifestyle management of the patient, however only few reported spiritual, emotional and psychological support. Around 95% of caregivers agreed that Lung-Cancer is preventable. Most of them agreed that death by Lung-Cancer was preventable with early detection. Whereas only 30% of general-population thought that Lung-Cancer is preventable. All caregivers responded to have known or learnt about Lung-Cancer screening processes such as CT-Scans, PET-Scans, X-Ray, MRI, and USG. Whereas over half of the general-population had no knowledge of such screening methods. Almost everyone from either group agreed that smoking causes Lung-Cancer. However, most of them, primarily respondents from the general-population, did not report any awareness about second-hand smoke and exposure to harmful substances such as asbestos as reasons, many of whom were exposed to hazardous substances at work or second-hand smoke in their daily lives. Most respondents denied wearing a mask outside or at work-place. Majority from both groups agreed to be part of Lung-Cancer Awareness programs and webinars and workshops if offered a chance.

Conclusions: The study shows that Caregivers of Lung-Cancer patients are significantly more aware about the sources of the disease and its screening methods compared to general-population. Many are unaware that second-hand smoke or other sources like asbestos can cause cancer. Most agree that smoking causes cancer. Early detection and prevention of Lung-Cancer is possible with more awareness among general-population. Caregivers could play an active role in spreading awareness among general population.

Keywords: Lung Cancer Awareness, Lung Cancer Advocacy, Knowledge

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.10 Co-Designing a Resource to Reduce Stigma in Lung Cancer Screening

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Introduction: Stigma in lung cancer is widespread and worse than for other cancer types. It not only has psychosocial consequences for patients (e.g., shame, distress), but also negatively impacts healthcare engagement. Currently, little is known about stigma prior to diagnosis, particularly during lung cancer screening (LCS). With many jurisdictions now designing or implementing LCS programs, understanding and managing stigma for people during LCS is paramount. For the Australian National LCS Program commencing July 2025, the strength and success of tobacco control policies suggest stigma will be a critical issue.

Methods: This project involved two studies in the context of the Australian National LCS Program. First, qualitative investigation using semi-structured interviews to explore potential experiences and impacts of stigma in LCS with consumers, i.e., people eligible for LCS. Second, co-design of a communication-based strategy to reduce stigma in LCS with consumers and experts, i.e., health professionals including general practitioners, medical and nursing specialists (respiratory medicine and other), radiographers, behavioural scientists and health managers. Participants were purposively sampled to achieve representation across key variables (for consumers, smoking characteristics, cultural and linguistic diversity, and education levels; for experts, job role). Interviews and workshops were analysed using abductive thematic analysis. We collaborated with a consumer advisor for the project's duration, including co-facilitation of consumer workshops in Study 2.

Results: In Study 1, 24 consumers were interviewed. One quarter identified as from culturally and linguistically diverse backgrounds; most reported education after high school (71%), high levels of health literacy (96%), and resided in major cities (75%). Four themes were identified: (1) Harmful narratives of personal responsibility and self-infliction; (2) Smoking stigma is a "necessary evil"; (3) Self-perception as part of the LCS group; (4) Previous interpersonal interactions with health professionals shape expectations of stigma in LCS. The co-design process in Study 2 consisted of design and iterative revision of a solution through consultation with consumers (2 workshops, n=5) and experts (interviews and focus groups, n=44). Similar characteristics to Study 1 were reported for consumers. Half of experts were from primary care (as the national program is primary care-led). The final designed solution was a 4-page A4 document targeted at health professionals to support communication during LCS for use in the Australian National LCS Program. Key thematic content included: (1) Taking the onus off the individual; (2) Fostering understanding and empathy; (3) Positive framing. A lexicon guide for person-first and empowerment language was also included based on existing literature.

Conclusions: People eligible for LCS have likely perceived previous stigma in healthcare, and this is a key barrier to LCS. This project developed a practical, scalable resource to reduce stigma for LCS participants, for implementation in a national screening program. This is expected to support health professionals in delivering LCS, and (1) reduce psychological harm to participants, and (2) improve screening engagement. Measurement of these outcomes, and feasibility and acceptability of the resource in practice, are future research priorities. Intersectional stigma for LCS-eligible populations additionally needs further investigation, along with targeted stigma-reduction strategies for marginalised communities.

Keywords: stigma, lung cancer screening, intervention

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.11 A Pulmón - Lunging It: Climbing Mountains and Breaking Barriers in Lung Cancer Advocacy

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Introduction: Lung cancer remains one of the most stigmatized cancers, often associated with guilt, blame, and fatalism. This stigma negatively impacts diagnosis, patient well-being, and public perception. A pulmón-Lunging It is a Spanish patient advocacy initiative that seeks to transform this narrative through a bold symbolic act: multidisciplinary teams of lung cancer patients, healthcare professionals, and professional mountaineers ascend the highest peaks across Spain, demonstrating resilience, solidarity, and life beyond the disease.

Methods: Since 2023, A pulmón has organized mountain expeditions combining physical challenge with education, reflection, and community-building. Over 50 individuals affected by lung cancer—with clinical stages ranging from I to IV—have participated in climbs alongside oncologists, thoracic surgeons, nurses, psychologists, and researchers. All patients undergo a thorough medical evaluation prior to participation to ensure their physical condition is suitable for the effort. Each climb is dedicated to a specific theme related to lung cancer—such as early diagnosis, immunotherapy, small cell lung cancer, clinical trials, communication, biomarkers, sexuality, or rural health—addressing both the medical and psychosocial dimensions of the disease. Beyond the climb itself, the project includes the creation and dissemination of audiovisual content, outreach campaigns, media appearances, and open dialogues with communities. These activities aim to normalize the presence of people living with lung cancer, increase public awareness, and promote more empathetic and informed narratives around the disease.

Results: In its first two years, A pulmón has completed 12 mountain ascents across Spain, including Mulhacén (3,482 m), Pic de Sotllo (3,073 m), Peña Vieja (2,614 m), and Mesa Tres Reyes (2,434 m). Participants consistently report improved communication between patients and healthcare teams, a stronger sense of agency, and the emotional benefit of achieving shared goals. The presence of researchers on expeditions has fostered deeper insight into the lived experience of lung cancer, strengthening patient-researcher bonds. In 2025, the project plans three additional climbs—including Mount Teide, Spain's highest peak—and will culminate with an international expedition to Mount Ararat, a mountain of profound historical and symbolic significance. This ambitious next phase seeks to further amplify the voice of lung cancer patients and expand the project's impact across borders.

Conclusions: A pulmón represents an innovative model of patient advocacy through symbolic physical action, storytelling, and shared experience. By climbing mountains—literally and metaphorically—lung cancer patients and healthcare teams are reshaping public perception, challenging stigma, and building new narratives rooted in strength, dignity, and connection. The ongoing growth of the project reflects a deep need for initiatives that humanize the disease and create space for visibility, solidarity, and hope.

Keywords: Lung cancer stigma, Patient advocacy, Symbolic mountain expeditions

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.12 Analysis of the Nationwide Database on the Penetration Rate of Lung Cancer Biomarker Tests in Japan

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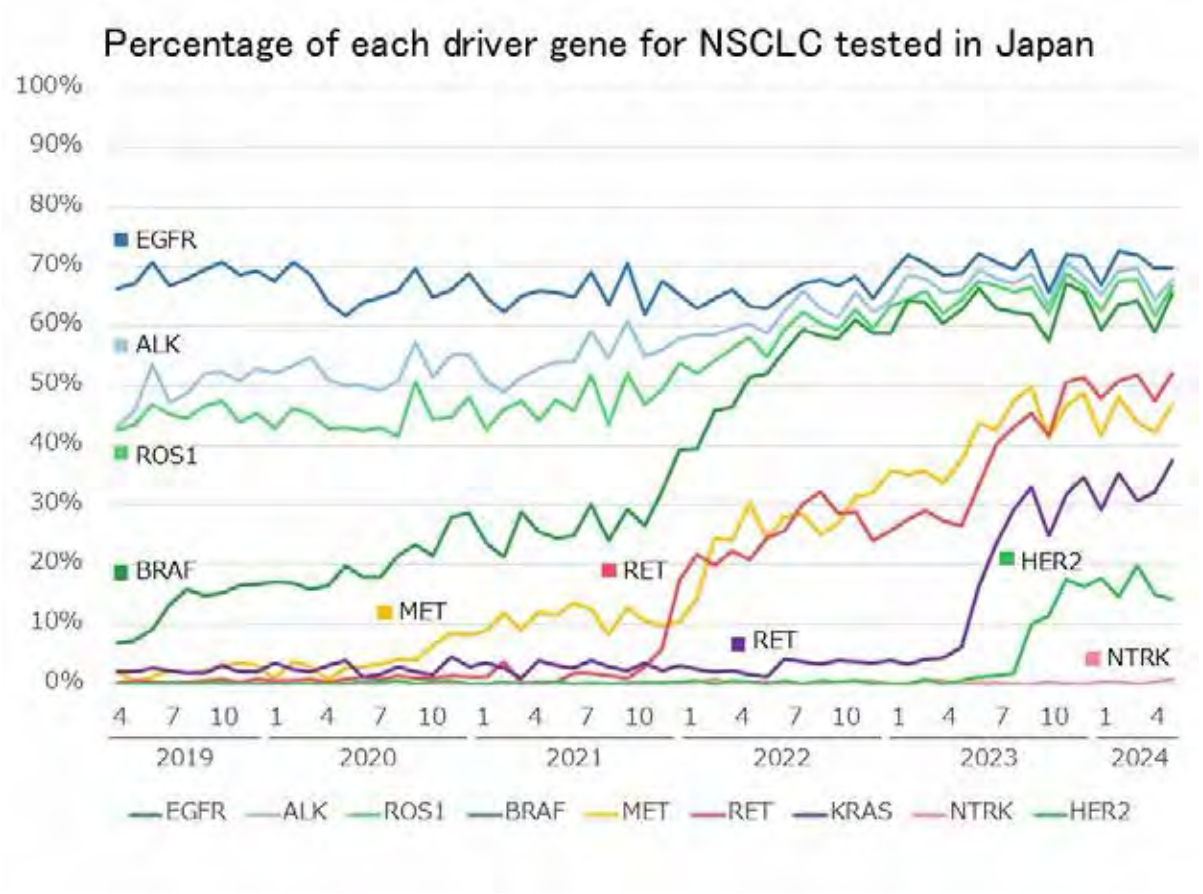
Introduction: Since 2000, many molecularly targeted therapies have been developed for non-small cell lung cancer (NSCLC) with driver gene mutations. In Japan, 21 agents targeting 11 distinct driver genes have been approved; however, companion diagnostics (CDx) are essential for their use. Japan's universal health insurance system covers all citizens, with out-of-pocket medical expenses ranging from 10% to 30%. Monthly medical expense caps are also approximately $300 to USD 1,000. However, the complex coverage status of CDx tests for individual drugs under the national health insurance system raises concerns about the widespread adoption of CDx testing.Patient advocacy activities have revealed that many patients are unaware of CDx information for drugs launched since 2020. Therefore, we investigated this situation using Diagnosis Procedure Combination (DPC) data.

Methods: We analyzed DPC data provided by Global Health Consulting Japan, Inc., from April 2019 to May 2024. Data were extracted for each month, focusing on cases that met the following criteria: "underwent lung biopsy," "diagnosed with non-small cell lung cancer," and "diagnosed with stage IV disease according to the TNM classification." The implementation status of CDx testing was then evaluated.

Results: Data from 302 hospitals, encompassing 25,015 patients (male/female ratio: 68.7%/31.3%; age distribution: <50 years, 3.3%; 50-60 years, 33.9%; 70s, 47.4%; ≥80 years, 15.1%) were extracted. The average number of lung biopsies performed per month was recorded as 388, and the average monthly CDx testing rate was found to be 70.1%. A comparison of CDx rates for specific gene mutations between April 2019 and April 2024 revealed the following changes: EGFR (66.3% to 69.7%), ALK (43.2% to 67.8%), ROS1 (42.6% to 66.7%), BRAF (6.8% to 65.5%), METex14sk (2.1% to 46.8%), RET (0.2% to 52.1%), KRAS G12C (2.1% to 37.5%), HER2 (0% to 14.2%), and NTRK (0% to 0.7%). The CDx rates for specific gene mutations were found to be associated with the insurance coverage status of multiplex testing platforms, including the Oncomine Dx Target Test multi-CDx system and the AmoyDx lung cancer multi-gene PCR panel test. For example, although Tepotinib and Capmatinib were launched in June 2020 and August 2020, respectively, the CDx rate for METex14sk remained around 10% until January 2022, when AmoyDx received insurance coverage for CDx testing of Tepotinib. Following this approval, the CDx rate increased to approximately 30%.

Conclusions: Our study shows that driver gene searches using multiple diagnostics are becoming more widespread in Japan in 2019 compared to 2024.



P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.13 Using Group Concept Mapping to Identify Research Priorities by Patient and Caregiver Stakeholders Affected by Lung Cancer

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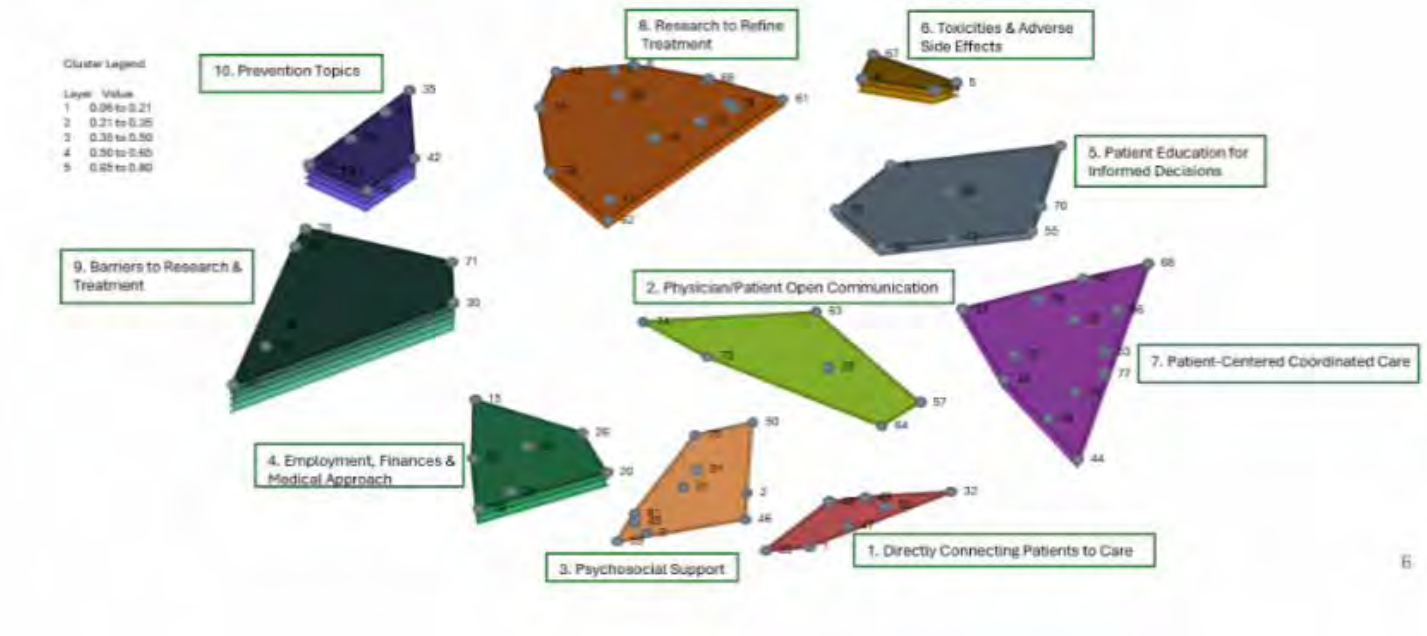
Introduction: To improve the lives of individuals affected by lung cancer, greater investment is needed in patient-centered quality of care and quality of life research. Given constrained funding resources, it is essential to identify research priorities of greatest importance to patients and family caregivers affected by lung cancer.

Methods: This PCORI-funded project convened a broad network of patients and caregivers affected by lung cancer (LCEN) and engaged them in a rigorous multi-phase research prioritization project. Between May and October 2024, LCEN recruitment was conducted using several outreach strategies including personalized email communications, direct mail campaigns, and targeted social media marketing. This work was guided by a scientific advisory board and followed a mixed methods approach to Group Concept Mapping (Kane & Rosas, 2018). In addition to providing information on patient background characteristics (demographics, illness and treatment), participants completed surveys and participated in semi-structured focus group discussions addressing research priorities. During the brainstorming phase, participants were asked to identify one or more specific areas of research that could improve how care is provided and/or the quality of life for people with lung cancer. In the sorting and rating phase, a subset of the brainstorming phase participants sorted the specific research topics into broader research categories and rated on 5-point likert scales the perceived importance and likely impact of these research topics for improving the quality of care delivery and/or quality of life for people affected by lung cancer.

Results: In total, 140 participants (125 patients and 15 caregivers) identified 143 research priority statements that were subsequently consolidated into 81 unique research priority themes. Of the 24 participants who completed the sorting and rating phase, 22 were patients/survivors and 17 had a known mutation with a targeted treatment. As shown in the Figure below, multidimensional scaling/cluster analysis was performed using groupwisdom™, web-based software revealing a final cluster solution of 10 unique research priorities having the highest importance and impact endorsement. Bridging values for clusters were generally low-medium (0.06-0.37) indicating adequate agreement. Focus group discussions cross-validated the cluster solution.

Conclusions: This patient-engaged study identified 10 important and impactful research priorities representing the opinions of patient and caregiver stakeholders affected by lung cancer. The findings represent a patient-centered blueprint for future patient-centered lung cancer research.

Figure: 10-Cluster Solution for Research Priorities



Keywords: quality of life, quality of care, patient-centered research

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.14 The Influence of Deprivation on Lung Cancer Care Experiences in Urban, Rural, and Coastal Areas: A Qualitative IPA Study

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Introduction: Globally, lung cancer remains the leading cause of cancer-related mortality, disproportionately affecting individuals residing in socio-economically deprived areas. Geographic distance and deprivation are well known barriers to timely and effective care, yet few studies qualitatively explore how these factors impact patient experiences. This research aimed to explore how deprivation can influence lung cancer patients' and carers' experiences across urban, rural, and coastal areas in the East of England.

Methods: This study undertook a secondary analysis of semi-structured qualitative interviews with lung cancer patients and informal carers (conducted as part of a wider study) between January-October 2024. Transcripts of participants from urban (n=6), rural (n=4), and coastal (n=6) areas who resided in the most deprived quintiles (i.e. quintile 1 and 2) according to the UK Index of Multiple Deprivation were purposefully selected for analysis. An Interpretative Phenomenological Analysis (IPA) methodology was chosen due its focus on idiographic depth; prioritising individual meaning and its capacity to explore how socio structural contexts (such as deprivation) influence health-related experiences.

Results: Analysis revealed five main themes which highlight unique and shared patient and carer experiences of deprivation: (1) Healthcare access barriers; (2) Lack of structured support and guidance; (3) Delayed diagnosis and fragmented healthcare communication; (4) Psychological, physical, and financial impacts; (5) Role of formal and informal support. Patients from all settings described healthcare access difficulties, including inadequate parking, insufficient proactive guidance, and unclear information about treatment pathways. Distinct geographical disparities were also evident. Coastal and rural participants encountered more pronounced travel barriers compared to those from urban areas, due to the significant distance from specialist cancer services. Coastal participants frequently reported logistical complexities such as overnight hotel stays, unreliable public transport, and exhausting long-distance journeys for treatments (daily for radiotherapy) which caused substantial impact. Rural participants similarly faced extensive travel-related burdens, for example collecting medications required repeated journeys lasting several hours, which significantly exacerbated their physical strain and stress levels. Financial hardship was particularly severe amongst coastal residents, and was compounded by higher travel expenses, fuel costs, and limited local healthcare infrastructure. Psychological distress was universally reported among all settings. Formal support from clinical nurse specialists, cancer charities, and other healthcare professionals, along with informal networks of families and friends, offered critical alleviation of these burdens but was insufficient in fully addressing the extensive inequities faced by lung cancer patients and carers from deprived areas.

Conclusions: This qualitative IPA study provides novel insights into the experiences of lung cancer patients and carers who reside in deprived urban, rural, and coastal areas. Inadequate structured information, fragmented communication, and psychological distress were experienced across all settings. Lung cancer patients and carers who resided in deprived rural and coastal areas were further disadvantaged by long travel distances, poor transport capabilities, financial strain and restrictive employment. Informal networks and formal healthcare support can partially mitigate or reduce the strain of these issues. Addressing these challenges through tailored interventions, as well as policy recommendations, is essential for achieving equitable and patient-centred lung cancer care across diverse geographical contexts.

Keywords: Lung Cancer, Deprivation, Qualitative

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.15 Giving Back - Co-Creation of Data Dashboard to Share Survey Results With Patients and Caregivers

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Introduction: Dissemination of research results relies heavily on conference presentations and peer-reviewed manuscripts. These often are not the optimal method to disseminate research findings to research participants or people living with the conditions being studied. Here we report on a community dissemination model that can be used for observational data that uses an online interface.

Methods: A collaborative team including patients and caregivers, dashboard developers, and researchers used descriptive data analytics from an online survey of people living with EGFR-positive cell lung cancer. The descriptive analytics were storyboarded by the team to guide the development of an interactive and user-friendly dashboard to effectively share the survey results with the EGFR-positive lung cancer community. Post-creation of version 1.0 of the dashboard, a short usability survey was created. The goal of the useability survey was to gather feedback on the dashboard from additional patients/caregivers and use the feedback to create the final version.

Results: The team inspected publicly available health dashboards, reviewed software and created a storyboard of the flow for the dashboard. Tableau software was selected to build the dashboard. All descriptive data visualizations selected are familiar to the public (i.e., bar and pie charts). There were 39 patients and caregivers who evaluated the dashboard, approximately half (54%) were using other digital health programs/devices. Most reported the quality of the dashboard was "Good"/"Very Good", and advice was offered to improve the user experience. For example, one participant reported "The main issue is that the text was not properly contained on the webpage. So the user has to scroll over to see the full text." The interactive filters (i.e., select a subset of the data, see Figure 1, sidebar) were also tested by asking participants to use the filters to report the percentage of a subgroup from a figure. Most (83%) participants who attempted (n=23) were able to correctly answer.

Conclusions: There would be no major advancements in high quality lung cancer treatment and care without the dedicated contribution of patients and caregivers. Yet, patients and caregivers rarely see the results of the studies they participate in. This harms research by discouraging diverse participation. Co-creating a data dashboard honors participants' contributions as well as offers other community members important results from people like them to aid in their healthcare decision-making. It can also encourage continued participation in research by offering tangible outcomes from their involvement.

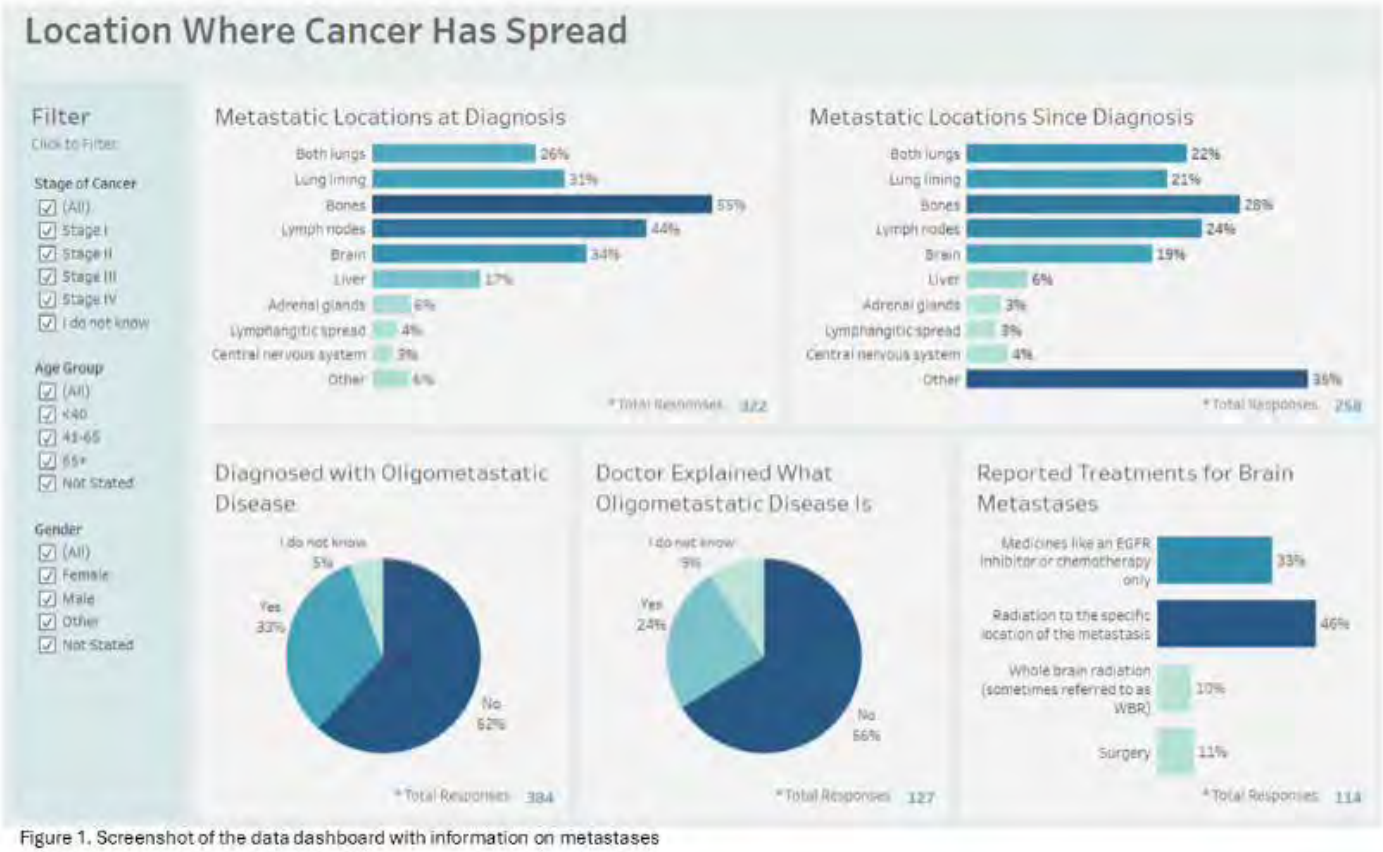

Figure 1. Screenshot of the data dashboard with information on metastases

Keywords: Advocacy, EGFR-positive NSCLC, Dissemination

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.16 The Development of a Patient Education Lung Cancer Nodal Staging Video Toolkit: American Cancer Society National Lung Cancer Roundtable

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Introduction:

Lung cancer staging is an important step in selecting appropriate treatment options for patients. The American Cancer Society National Lung Cancer Roundtable (ACS NLCRT) convened a Staging Summit in March 2023 to develop and prioritize ideas to improve guideline-concordant lung cancer staging. At the summit, clinicians, researchers, patient advocates, and industry partners noted significant variation in lung cancer staging knowledge, particularly nodal staging. A search of publicly accessible online resources revealed a deficiency in patient-centered materials that are approachable and explain the complexities of lung cancer staging in plain language and at a reading level suitable for the general public. The ACS NLCRT developed the Lung Cancer Staging Video Series for Patients to improve their knowledge of staging and prepare for the treatment journey ahead.

Methods: A survey was conducted of all patients previously treated for lung cancer and all multidisciplinary attendees of the ACS NLCRT March 2023 Lung Cancer Staging Summit. The data were analyzed to identify important themes for optimal patient education. The data were analyzed in a numerical ordering system and reported to the group who then individually ranked each item after final presentations and discussions of each concept was discussed in a breakout group. Concepts with the highest number of votes were included as points for focus in the lung cancer nodal staging education platform. Artificial intelligence software was used to develop the narrative component by Kindea Labs. In a collaborative effort of the ACS NLCRT Lung Cancer Staging and Patient Education Taskforce and Triage for Appropriate Treatment Taskforce, we designed and executed 6 succinct patient education videos focused entirely on lung cancer nodal staging to improve patient understanding about this important topic as informed decision makers. Through an iterative process, additional cycles of content development, review, and revision have been completed prior to product launch.

Results: Of the 60 participants surveyed in the ACS NLCRT Patient Education Taskforce, the two most important ranked concepts were: 1) Lack of understanding of lymph node locations and 2) inefficient patient and clinician discussions around lung cancer nodal staging. All participants voted in favor of short segment patient centered lung cancer nodal staging online videos. Six short-segment <3 minute patient education videos were compiled at the 6th grade reading level utilizing Kindea Labs. Each video underwent multiple rounds of editing and revising for both content and patient applicability utilizing feedback from clinician leaders and patient advocates from different age, sex, racial/ethnic, and sociodemographic backgrounds. The final videos were produced and published online and are available in 5 languages including English, Spanish, Mandarin, Hindi and Vietnamese.

Conclusions: To our knowledge, this is the first comprehensive online patient education video series specifically focused on lung cancer nodal staging. This collaborative effort of the ACS NLCRT with lung cancer patient advocates resulted in real-world patient-centered educational content available for individuals and their families facing this disease. Future studies will focus on performance satisfaction surveys of these videos, and the development of a clinician-facing lung cancer nodal staging video series.

Keywords: lung cancer, nodal staging, online patient education video

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.17 Understanding the Awareness of Treatment, Clinical Trails, Biomarkers and Unmet Needs of Chinese NSCLC Patients: A Mixed-Methods Study in China

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Introduction: Recent advances in non-small cell lung cancer (NSCLC) therapies involve novel biomarkers and numerous clinical trials. While diverse treatments improve efficacy yet cause adverse effects, understanding patient perspectives on treatment trade-offs, satisfaction, clinical trial barriers, treatment experiences, and biomarker awareness remains crucial for patient-centered care. In China, unmet needs persist in NSCLC management with no existing studies addressing these aspects from patients' viewpoints. To address this gap and provide guidance for future treatment strategies, we conducted this study.

Methods: This mixed-methods study combined an online survey (Dec 2023-Jan 2024) and qualitative interviews (Jan 2024) to explore experiences of Chinese NSCLC patients. The survey, distributed via IQVIA's platform, included 40 items across six domains (demographics, treatment experiences, future expectations, clinical trial/biomarker perceptions, QoL impacts) and required ≥10 minutes for validity. Interviews involved 10 patients who experienced post-immunotherapy progression and participated in clinical trials, using semi-structured guides aligned with survey themes. Both methods adhered to COREQ and AAPOR guidelines. Participants were recruited nationally through IQVIA and Sun Yat-Sen University Cancer Center, with ethics approval from Fudan University. Data included treatment satisfaction (4-point scale), clinical trial willingness, biopsy preferences, and QoL impacts. Quantitative analysis employed descriptive statistics, Pearson's chi-squared/Fisher's exact tests (SPSS v29), while qualitative data were coded using NVivo 12. Confidentiality was maintained throughout.

Results: This mixed-methods study analyzed 100 NSCLC patient surveys and 15 interviews (patients/caregivers) in China. Participants (mean age 51, 55% female, 95% adenocarcinoma, 67% stage IV) predominantly received targeted therapy (86%), reporting higher satisfaction (3.4/5) versus chemotherapy (2.7) and immunotherapy (3.1). Over 60% changed treatments due to symptom progression or tumor growth. Treatment decisions were predominantly physician/family-driven (55%), with only 22% patient-led. Oral administration was favored (72%) for convenience, while survival extension and tumor shrinkage were key treatment priorities. Cost-effectiveness concerns emerged, with most accepting ≤¥5,000/month. Clinical trial willingness was high (79%), driven by efficacy expectations, though 21% hesitated due to trust in standard care. Trial barriers included safety uncertainties and logistical challenges (e.g., frequent tests). Biomarker awareness was substantial (71%), with EGFR/KRAS being most recognized; 88% supported initial biopsy for biomarker testing, yet 18% resisted re-biopsy fearing tumor spread or costs. Quality-of-life impacts were profound: 58% reported disrupted social/family life, 50% experienced anxiety/depression, and 72% maintained daily activities despite fatigue (37%) and sleep issues (29%) as predominant symptoms. Patients emphasized needs for psychological support and streamlined biomarker communication. Findings highlight NSCLC patients' prioritization of efficacy, cost, and convenience, alongside unmet needs in shared decision-making, biomarker education, and psychosocial care to optimize patient-centered management.

Conclusions: Numerous unmet needs persist in the NSCLC treatment journey, such as poor treatment efficacy and accessibility, significant economic and psychological burdens. Thus, urgent actions are called for highly effective and low-toxicity drugs, optimal clinical trial protocols, enhanced patient awareness of clinical trials and biomarker testing, and robust support system.

Keywords: Biomarkers, Clinical trials, Patient-centered research

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.18 Beyond Clinical Outcomes: A Qualitative Exploration of Wellbeing Among People Living With Onco-Driven Lung Cancer

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Introduction: Lung cancer patients face a unique set of challenges that extend beyond physical health, with significant implications for psychological, emotional, and social wellbeing. Despite advances in treatment, wellbeing remains under-addressed in routine care. This study examines how individuals living with lung cancer in the UK understand and experience wellbeing, identifies sources of support they find beneficial, and explores existing gaps and barriers in wellbeing provision.

Methods: A qualitative thematic analysis was conducted using transcripts from eight semi-structured focus groups with lung cancer patients in the UK. Participants included individuals with varying stages and genetic mutations of lung cancer (including EGFR, ALK and ROS1), the majority of whom were undergoing or had undergone targeted therapies. Discussions were facilitated by trained moderators and focused on the patient's experiences of wellbeing and any helpful supportive resources they had used, as well as identifying unmet needs and any facilitators/barriers to accessing support. Transcripts were systematically reviewed and coded to identify recurring themes.

Results: Five core themes were found. First, 'experiential challenges to wellbeing' where participants described intense emotional distress, particularly at diagnosis, and ongoing "scanxiety" around surveillance imaging. Isolation and a loss of identity, particularly after stopping work or experiencing reduced independence, were also commonly expressed.

Second, 'protective factors' were defined as the ability to maintain emotional resilience, autonomy and normalcy, and connection with others. Peer relationships and a sense of purpose beyond illness were crucial.

Third, 'sources of wellbeing support' included medication, peer support networks (both in-person and online), responsive oncology teams (particularly clinical nurse specialists), active mental health support, and maintaining routine and structure.

Fourth, participants identified 'critical gaps in wellbeing provision', such as a lack of psychological support, poor continuity of care, unmet informational needs, and a scarcity of resources tailored to younger patients or those adjusting post-treatment.

The fifth theme identified multiple 'barriers to accessing wellbeing support', including geographic inequalities, fragmented communication between services, depersonalisation during clinical trials, overwhelmed healthcare services, stigma, and individually internalised pressures to appear "strong". These barriers often left patients feeling isolated or unsupported during periods of vulnerability.

Across the different themes, several participants referenced the benefits of eHealth resources—such as online peer support groups, symptom-tracking apps, and social media communities—as valuable extensions of care.

Conclusions: This study highlights the complex and multifaceted nature of wellbeing in lung cancer patients, which remains under-prioritised despite its critical role in quality of life. Addressing emotional and psychological wellbeing requires more integrated, personalised support, alongside efforts to close systemic gaps and reduce geographical inequalities in care access.

eHealth solutions—such as digital peer networks, self-management tools, and remote psychological support—offer promising avenues to enhance equity, autonomy, and responsiveness in lung cancer care, particularly for those with limited access to in-person services. These findings underscore the need for a holistic, digitally enabled model of care that prioritises lived experiences and wellbeing needs of lung cancer patients.

Keywords: Lung cancer, Wellbeing, Mental Health

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.19 Multilevel Assessment of ChatGPT-4O in Radiation Oncology for Lung Cancer Patient Education

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Introduction: Large language models (LLMs) such as ChatGPT are increasingly discussed as potential tools for patient education in healthcare. In radiation oncology, where patients are often confronted with complex medical terminology and complex treatment plans, LLMs may support patient understanding and promote more active participation in care. However, the readability, accuracy, completeness and overall acceptance of LLM-generated medical content remain underexplored. This study aimed to evaluate the potential of ChatGPT-4o as a supplementary tool for patient education in the context of lung cancer radiotherapy by assessing the readability, content quality, and perceived usefulness of AI-generated responses from both clinician and patient perspectives.

Methods: Eight frequently asked questions about radiotherapy for lung cancer were developed based on clinical experience from a team of clinicians specialized in lung cancer treatment at a university hospital. The questions were submitted individually to ChatGPT-4o (version as of July 2024) using the prompt: “I am a lung cancer patient looking for answers to the following questions.” Responses were evaluated using three approaches: (1) a readability analysis applying the Modified Flesch Reading Ease (FRE) formula for German and the 4th Vienna Formula (WSTF); (2) a multicenter expert evaluation by six multidisciplinary clinicians (radiation oncologists, medical oncologists, and thoracic surgeons) specialized in lung cancer treatment using a 5-point Likert scale to assess relevance, correctness and completeness; and (3) a patient evaluation during the first follow-up appointment after radiotherapy, assessing comprehensibility, accuracy, relevance, trustworthiness and willingness to use ChatGPT for future medical questions.

Results: Readability analysis classified most responses as “very difficult to read” (university level) or “difficult to read” (upper secondary school), likely due to the use of medical language and long sentence structures. Clinician assessments yielded high scores for relevance (mean: 4.5 ± 0.52) and correctness (mean: 4.3 ± 0.65), but completeness received slightly lower ratings (mean: 3.9 ± 0.59). Patients rated the responses positively for clarity (mean: 4.4 ± 0.61) and relevance (mean: 4.3 ± 0.64), but lower for trustworthiness (mean: 3.8 ± 0.68) and usability (mean: 3.7 ± 0.73). No harmful misinformation was identified in the responses.

Conclusions: ChatGPT-4o shows promise as a supplementary tool for patient education in radiation oncology. While patients and clinicians appreciated the clarity and relevance of the information, limitations in completeness, trust and readability highlighted the need for clinician oversight and further optimization of LLM-generated content. Future developments should focus on improving accessibility, integrating real-time readability adaptation and establishing standardized evaluation frameworks to ensure safe and effective clinical use.

Keywords: Artificial intelligence (AI), Large Language Model (LLM), Lung Cancer

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.20 Improving Lung Cancer Screening Uptake in 20 Disadvantaged New York Counties: Early Findings From a Demonstration Project

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Introduction: Lung cancer screening (LCS) has proven effective in early lung cancer detection, yet uptake in disadvantaged communities remains low due to various systemic barriers, including lack of patient and provider awareness and knowledge, and disparities in healthcare access. Led by GO2 for Lung Cancer (a patient advocacy organization) and Roswell Park Cancer Center, this BMSF-funded, 3-year demonstration project aims to reduce the burden of lung cancer by improving LCS rates in 20 disadvantaged New York counties.

Methods: Beginning January 2024, four large-scale interventions were deployed (Table 1.): 1. engagement of community and healthcare partnerships committed to LCS, 2. expansion of high-quality LCS through growth of GO2's designation program, 3. development and activation of a navigator network with shared commitment to impacting lung cancer outcomes. 4. development and uptake of HCP and community informed education. Two approaches to measuring the impact of these interventions in uptake of LCS have been taken: 1. calculation of total number of LDCTs performed over # of individuals currently smoking cigarettes in targeted areas and 2. Using the All Claims Payor Database in targeted areas, analysts calculated a baseline total number of LDCTs performed in 2020. Using 2020 and 2023 data as comparators, 2024 LDCT claims will be calculated to determine the rate of change between 2020, 2023, and 2024 to determine the measurable impact of our interventions.

Results: Measurable progress made (Table 1.) represents successful engagement and activation of a regional community and growing network of equipped leaders and HCPs to provide and promote evidence-based, high-quality LCS. Early efforts have expeditiously reached over 122 PCP offices, 94 CBOs and stakeholders, and 39+ health systems, culminating in newly designated screening programs, HCP educational resources, and a Navigator Network. Finally, the highly anticipated first look at LCS uptake rates in the targeted project counties, measuring the primary aim and success of this project, will be available by June 2025.

Conclusions: Early in its lifecycle, this innovative demonstration project has set itself apart from other state-based initiatives. This initiative has leveraged four novel interventions and galvanized a community to address barriers to LCS, foster community and provider engagement and education, and establish quality initiatives. Ongoing data and lessons learned from this work will inform current efforts, help build a scalable infrastructure for sustainable and local progress. All leading to improved access and uptake of LCS in disadvantaged communities and serving as a template for future regional work.

Table 1. Demonstration Project Interventions, Approaches, and Progress to Date

	Intervention 1 Stakeholder Engagement	**Intervention 2** Quality Screening Initiative	**Intervention 3** Lung Cancer Navigator Network	**Intervention 4** Healthcare Provider Education
Method	Establish a network of engaged stakeholders committed to identifying eligible individuals, enhancing referral pathways, and improving access to LCS.	Improve access and uptake of high-quality lung cancer screening for eligible individuals.	Initiate, grow, and equip a professional cancer navigator network with shared commitment to impacting lung cancer outcomes.	Improve preparedness, competency, and awareness about lung cancer screening and needs of eligible individuals.
Tactical Approach	**Implement Community Outreach:** • Organize and activate the LCS community • Cultivate bidirectional partnerships with healthcare systems, Community Based Organizations (CBOs), public health officials, and local leaders • Identify and partner with organizations that support underserved populations to expand community-driven improvement in equitable access to LCS	**Organizing and Establishing a Mission-Driven Network of Dedicated Collaborators:** • Expand a network of facilities meeting evidence-based, high-quality standards in screening, across NYS under GO2's Centers of Excellence (COEs) lung cancer screening and care designation program.	**Establish NY Lung Cancer Navigator Network:** • Create broad navigator community reach & and collaboration • Prepare navigators through education and development • Build on the collective strengths of the newly established lung cancer navigator community • Improve advocacy and spreading awareness	**Advance Comprehensive Education for Healthcare Professionals:** • Expand education for the delivery of high-quality LCS and care • Provide a communication hub and resource center • Advance LCS screening, program development, and professional growth
Results to Date	**Cultivated a Continuously Expanding Network of Dedicated Leaders Representing:** • 39 Community and Public Health Leaders • 26 County Officials • 29 Community Based Organizations (CBOs) • Regional Commissioner of Health, • Primary Care Providers, • Medical Directors, • Population health, quality improvement initiatives, and practice transformation experts • Cancer navigators, and community health workers (CHWs)	**Newly Established Healthsystem Networks:** • 26 Health Systems • 4 Upstate NY Veteran Health Administration (VHA) Facilities • 4 Newly designated GO2 for Lung Cancer lung cancer screening designated Centers of Excellence • VHA Strategic Screening Summit convened by GO2 for Lung Cancer o 26 Attendees from VHA VISN 2	**Navigator Network Launched March 2025:** • 9 Regional/ Statewide HCP Member Organizations referred cancer navigators to network • 11 Healthcare Systems Represented • 35 navigators joined network • Navigator network comprised of 6 Community Navigators	**Newly Established Contacts and Key Relationships:** • 32 PCP Practices contacted and LCS and project related resource dissemination o Covering Over 98 Offices • VHA-wide Primary Care Practices • 5 FQHCs Practices o 24 Offices represented • 23 Key informant interviews with PCP and other specialties and disciplines • 16 Key topics identified where barriers, current challenges, knowledge gaps and specific needs exist • 13 subject matter experts identified for 16-course content development, launch October 2024 • A micro-education 16-course bundle developed focusing on key topical areas with a target audience of PCPs and community teams. Course bundle available February 2025 • Creation of a regional peer-to-peer forum designed to facilitate the exchange of emerging news and resources.

Keywords: Lung Cancer Screening (LCS), Community Engagement, HCP Education

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.21 The Role of Neighborhood Deprivation in Lung Cancer Diagnosis and Treatment

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Introduction: Lung cancer is the leading cause of cancer-related deaths in the United States, with significant disparities in early detection, treatment access, and clinical trial participation. Social determinants of health (SDOH), including socioeconomic status, healthcare availability, and geographic location, play a critical role in shaping these disparities. Previous research also highlights the disparities that exist between well-resourced populations and those facing systemic barriers to care. While these disparities are well documented, there is a need for a deeper exploration for how SDoH specifically impacts access to care. This study seeks to examine these connections and identify opportunities for more equitable cancer care delivery that have been shown to boost a person's overall length and quality of life.

Methods: Our analysis included participants who had voluntarily enrolled in the GO2 for Lung Cancer's LungMATCH or Lung Cancer Registry programs in 2023. To approximate socioeconomic status, we used the Area Deprivation Index (ADI), which assigns a score from 1 to 10 based on variables such as income, employment, and education. A score of 1 represents the least deprived, highly resourced areas, while a score of 10 indicates the highest level of deprivation and scarcity. We examined several key factors in our analysis, including receipt and stage at diagnosis, timing of biomarker testing, and discussions about or participation in clinical trials. Participants were categorized into either Low ADI (1-5) or High ADI (6-10).

Results: A total of 174 participants were included in the analysis. Individuals residing in Low ADI zip codes were 13% more likely to report having undergone biomarker testing (73% vs. 60%). For this, we calculated a p-value of 0.4274 by using Fisher's Exact Test. While both groups had a majority of metastatic diagnoses (58% Low ADI, 53% High ADI), individuals in High ADI zip codes actually reported higher rates of stage I diagnoses (21% vs. 13%, with a p-value of p=0.3016 by Fishers Exact Test). Additionally, those in Low ADI zip codes were 3% more likely to report participation in a clinical trial (9% vs. 6%). Notably, residing in a Low ADI zip code was correlated with greater odds of discussing clinical trials with a healthcare provider (54% vs 36%, p=0.6658 by Fisher's Exact Test).

Conclusions: This research highlights disparities in the receipt of high-quality lung cancer care based on socioeconomic factors, emphasizing the influence of resource availability on cancer diagnosis, treatment, and clinical trial participation. Understanding these factors will enable providers to better address community needs, improve care delivery, and work to eliminate disparities in cancer outcomes.

Keywords: Lung Cancer, Social Determinants of Health, Access to Care

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.22 Frontline Insights in US Payer Barriers Impacting Patient Access and Participation in Comprehensive Lung Cancer Screening Programs

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Introduction: GO2 for Lung Cancer-designated Centers of Excellence (COE) in Screening implement a structured low-dose CT (LDCT) program utilizing evidence-based, best practice guidelines. Current quality metrics recommended in the US (Mazzone, 2021) and proposed globally (Tammemagi, 2025) anticipate a multi-disciplinary screening process and comprehensive program approach. In contrast, US payers may impose site-of-service restrictions that exclude coverage for lung cancer screening (LCS) in hospital outpatient settings as non-medically necessary, requiring it occur in less expensive free-standing imaging centers independent of a hospital system. This creates patient access barriers to a comprehensive, multi-disciplinary process and undermines screening implementation consistent with recommended quality measures.

Methods: GO2 for Lung Cancer launched an annual Impact Survey among Screening COEs on November 12, 2024. The survey platform Mahalo was used for data collection, and invitations to participate were sent via Mailchimp to the primary point of contact for each COE, followed by individualized phone and email outreach to identify and correct out-of-date contact records. Data was extracted March 10, 2025. 118 programs responded, or 28% of invitees, and represented 37 states plus DC. Community non-teaching hospitals, community teaching/AMC affiliated hospitals, and academic medical centers were evenly reflected in responses (27%, 24% and 22% respectively), with the remainder being VA Medical Centers, independent clinics, and "other" facility types.

Results: One quarter (25%) of COE programs participating in the survey indicated they experienced site-of-service access restrictions for LDCT LCS and/or follow-up LDCT from commercial payers. Optional open-ended responses describe the impact this has on both patients and programs (Table 1).Notably, less than a third (29%) of survey participants indicated that they have awareness, actively track, or attempt to identify when patients receive a bill for their LCS that was expected to be covered as a preventive service by insurance. As such, patients experiencing coverage denial by their commercial payer due to site of service restrictions may occur undetected and at a greater frequency than reported by the comprehensive screening programs completing this survey.

Conclusions: Site-of-service restrictions hinder patient access to screening programs implementing a comprehensive, multidisciplinary screening process. Furthermore, the rate of programs identifying and tracking patients experiencing unexpected screening cost imposition is low even among comprehensive programs. With cost perception being a well-recognized barrier to patient screening adherence, inattention to patient cost experience is an anticipated contributor to low adherence rates and an under-recognized detriment to a patient-centered, high-quality screening process.

Table 1. Impact of Site-of-Service Restrictions for Screening Patients and Programs

Types of Impact	Site-of-Service Denial Frontline Experiences
Screening Participation/Adherence	• "Patient[s] refuse to continue annual screenings…the stress of seeing a huge bill scares people away from ever wanting to screen again." • "We lose track of the patients if they [the payer] wants them to go to an alternate site." • "Unable to ensure patients are getting their follow-up CTs." • "We get a few patients who do not complete screening. It isn't severe, yet." • "Many patients would like to participate in lung screening but are unable to due to cost."
Results Management	• "When patients have had screens done for years at our hospital and all of a sudden…[are required] to go to a free standing facility that has none of their records, is poor patient care. The new facility has nothing to compare their scan to…[and] often calls for a follow up scan because they don't know WE have been watching the nodules they found for years." • "Hav[ing] to go to a stand alone facility…causes a delay in follow up since we…have difficulty obtaining images from various outside facilities."
Program Workflow/Workload	• "We do our best to facilitate getting patients to a program that is covered by insurance or working with their PCP to order the exam for [an] approved facility that does not have a screening program." • "This creates work for navigators who have to send a disk to [an] outside facility to compare to our screening. Also work to get disk from follow up scan for our providers to review if seen in our lung nodule clinic." • "This disrupts the screening process….We are not always the first point of contact when patients are denied, thus delaying the step to coordinate a site of service." • "It takes time to call the patient back to explain that they are able to have the exam performed but may be charged out of pocket."

Keywords: Screening, Barriers, Access

P3.16 PATIENT ADVOCACY
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.16.23 Facilitators to Patient Advocacy Group-Led Engagement of Diverse, Community, Clinical Sites in Multiple Research Types

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Introduction: Only about 8% of US patients with cancer participate in clinical trials. One contributor is that 80% of US patients with cancer are treated in community-based practices, while most clinical trials are conducted in academic practices. We previously demonstrated that a novel trial site recruitment partnership, leveraging an informal, disease-specific, patient-advocacy group (PAG)-led clinical network, successfully engaged diverse, community-based practices in the context of a lung cancer screening implementation-effectiveness study (Ciupek, et.al., 2024). Here, to determine if similar effectiveness could be observed across a diverse array of lung cancer clinical study types, we determined the outcomes of applying this model in several research partnerships.

Methods: Staff at the PAG, GO2 for Lung Cancer (GO2), were actively managing study site recruitment for 5 clinical studies between January 1st, 2022, and March 24th, 2025. Sites were recruited using a "targeted proactive outreach campaign", as previously detailed in Ciupek, et. al., 2024. In brief, sites were identified for outreach using GO2 institutional data from past collaborations alongside self-reported and publicly available data from centers belonging to an informal voluntary network of lung cancer screening and care centers, called the GO2 Centers of Excellence Network. Following study discussion with GO2 staff, sites indicating positive intent to join were connected to the study investigator's team for onboarding. Reasons sites were found ineligible or declined to join were documented. Descriptive statistics were used to report recruitment outcomes and site demographics.

Results: 15 sites were recruited across 5 studies during the tracking period. Study types varied, including 3 non-interventional biospecimen collection studies, 1 clinical implementation feasibility study, and 1 provider skills training evaluation. 80% of recruited sites self-identified or were confirmed by the study team as community hospitals or community teaching hospitals. 6 were in the US Census defined South Region, 4 in the West Region, 3 in the Midwest Region, and 2 in the Northeast Region. 33% of sites were in areas with a "high" area-of-deprivation index score (defined as a score ≥6 out of 10), indicating higher levels of socioeconomic disadvantage locally. 318 active and passive declines to join a study were received. Among 98 active declines to join a study, the top reasons were insufficient staffing numbers or bandwidth (37% of declines) and a lack of interest in or reported poor fit of the research study topic (16%).

Conclusions: Results suggest this model may be broadly applicable for engaging geographically and demographically diverse community-based field sites across a variety of non-therapeutic clinical research types. The model should be explored further as a method for increasing research participant diversity. Additionally, PAGs, who have established relationships with the clinical community through their programmatic work, can be effective partners in diverse study site recruitment. Utility for understanding community sites' study participation barriers was also observed. Reported barriers suggest providing staffing support, decentralizing study activities, and tailoring study design to minimize staff burden, alongside outreach tailored to sites' programmatic priorities and interests may facilitate diverse study site recruitment.

Keywords: clinical trials, field site recruitment, research diversity

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.01 Sex-Based Differences in STAS Positivity and Survival in Stage I Lung Adenocarcinoma: Is Female Prognosis Still Better Despite STAS?

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Introduction: Tumor spread through air spaces (STAS) is an emerging negative prognostic factor, especially in lung adenocarcinomas. While men are more likely to present with aggressive histologic subtypes (micropapillary/solid), women often have lepidic or non-mucinous patterns. Although female sex is generally associated with better survival in non-small cell lung cancer (NSCLC), the impact of STAS on this survival advantage remains unclear. This study aimed to assess STAS prevalence and prognostic implications across sexes, with a specific focus on Stage I lung adenocarcinoma.

Methods: This retrospective cohort study included 296 surgically resected adenocarsinoma patients (2016-2024). STAS positivity status was histo-pathologically identified in 111 cases. Female and male patients were analyzed for differences in STAS positivity, histologic subtypes, and clinical outcomes using Chi-square and Fisher's exact tests. Survivals were analyzed using the Kaplan-Meier method and Cox regression test. Special emphasis was placed on Stage I adenocarcinoma patients.

Results: Among the patients included in the study, 53.7% (n=159) were male, while 46.2% (n=137) were female. There was no difference in the distribution of resection type, T stage, tumor size and visceral pleura invasion between the two genders (p values were 0.33, 0.11, 0.47 and 0.59, respectively). There were statistical differences in the distribution of smoking status, STAS positivity, adenocarcinoma subtype, lympho-vascular invasion and overall survival between genders (p values were 0.00, 0.00, 0.04 and 0.001, respectively). STAS positivity was identified in 44.7% (n= 71/159) of male patients and in 29.2% (n= 40/137) of female patients, demonstrating a statistically significant difference between gender (p = 0.001). When tumor size was analyzed using 2 cm as a cutoff value, tumors smaller than 2 cm and STAS negativity were more frequently observed in both sexes (p = 0.04), particularly in the group without STAS positivity. In subgroup analyses, female patients exhibited more favorable survival outcomes across multiple comparisons: in the overall cohort, in the combined evaluation of STAS and sex, within different histologic subtypes, and among patients without lympho-vascular invasion (p = 0.001, p = 0.000, p = 0.001, p = 0.000, respectively) (Table 1). Although STAS - positive women had better survival compared to STAS-positive men, the survival difference between STAS-positive and STAS-negative women was not statistically significant. However, the difference between STAS-positive women and men was significant (p = 0.001). Amogn histologic subtypes, the best overall survival was observed in women with a lepidic pattern, whereas the worst survival was seen in men with the acinar + papillary subtype.

Conclusions: Women live better than men, even if they are STAS positive. These findings suggest that female sex may serve as a protective modifier of STAS-related risk. This sex-based disparity may be linked to underlying immune-genetic and hormonal factors and highlights the importance of sex-specific approaches in lung cancer screening, prognostication, and personalized treatment planning.$$graphic_{93BFBF7C-B553-4CD6-BB56-B27CA400E327}$$

Keywords: Lung adenocarcinoma, STAS, sex differences

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.02 Sex-Based Differences in Immunotherapy Response via Blood Biomarkers in NSCLC: Interim Results From the ALICE Study

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Introduction: Immune checkpoint inhibitors (ICIs) have significantly enhanced the treatment landscape of non-small cell lung cancer (NSCLC). However, accumulating evidence suggests sex-related disparities in treatment response, with female patients often experiencing inferior outcomes. One potential mechanism may involve alloimmunization—immune activation induced by exposure to non-self human leukocyte antigens (HLA) through pregnancy or blood transfusion—leading to the formation of alloantibodies. The ALICE (Alloimmunization and alloantibodies in male and female NSCLC patients treated with checkpoint inhibitors ICI) study aims to investigate the prevalence of HLA alloantibodies in NSCLC patients and explore their correlation with clinical outcomes on ICI therapy, with a focus on sex-specific patterns.

Methods: The ALICE study is an ongoing, prospective, single-center translational study aiming to recruit 90-100 patients with NSCLC, stages I-IV, all with current or prior treatment with ICIs. At the time of this interim analysis, 59 patients have been enrolled. As part of the study protocol, structured clinical histories are being collected, including prior blood transfusions, pregnancies, menopause status, and previous hormone therapies, to assess potential alloimmunization and hormonal influences. Peripheral blood and tumor samples have been collected for these 59 patients and will continue to be collected in subsequent participants. Analyses include HLA typing, HLA antibodies, immune cell subpopulations, hormone levels. The primary endpoint is to establish a correlation between positive alloimmunization status and objective response rate (ORR) to ICI therapy. Secondary endpoints include the evaluation of clinical parameters, such as progression-free survival (PFS), overall survival (OS) and immune-related adverse events (irAEs), with all outcomes stratified by sex and alloimmunization status.

Results: This first interim analysis of the ongoing prospective ALICE study includes 59 patients with histologically confirmed NSCLC, comprising 27 females and 32 males. The majority of patients had adenocarcinoma (n=47), while 8 had squamous cell carcinoma and 4 had other histologies, including adenosquamous carcinoma. In this interim cohort, antibodies were detected in two cases, one of which may have been due to pregnancy. Participant enrollment and data collection are currently in progress. Final analyses will be initiated once the target sample size has been reached for both the male and female cohorts, ensuring adequate statistical power for sex-specific comparisons and overall study endpoints.

Conclusions: Alloimmunization may represent an underrecognized, sex-linked immunologic factor influencing ICI efficacy in NSCLC. Understanding the role of HLA alloantibodies could pave the way for sex-specific biomarkers and personalized immunotherapy strategies in thoracic oncology.

Keywords: NSCLC, immunotherapy, alloimmunization

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.03 Implementation Study of Lung Cancer Screening Combined With a Smoking Cessation RCT in the Flemish Region: The ZORALCS- and TAMIRO-Stop-Study

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Introduction: Lung cancer (LC) is the leading cause of cancer-related mortality worldwide and in Belgium. Early detection through an annual Low Dose Computed Tomography (LDCT) has been shown to significantly reduce LC mortality in high-risk populations. Despite strong scientific evidence supporting LDCT-based lung cancer screening (LCS), implementation at the population level remains a challenge in Belgium. The ZORALCS-study aims to assess the feasibility of implementing an LCS program in the Flemish region, targeting high-risk adults with a history of heavy smoking.

Methods: The ZORALCS-study is a four-year prospective, non-randomized population based feasibility implementation study designed to evaluate the participation rate and effectiveness of a LCS program combined with a structured smoking cessation program. Every adult aged 55-74 living in the primary care zone South-East Region of Antwerp (ZORA) gets a letter at home (N=26.000). If they smoked more than 100 cigarettes in their life, they are asked to fill in an online questionnaire which contains the two following risk prediction models: PLCOm2012 and HUNT. These models measure the risk of developing a LC in the following six years, respectively >1,51% and >0,64%. When eligible, the respondents have to read and confirm the informed decision making and informed consent. Participants undergo annual LDCT screening for two years. For the recruitment, there is a close collaboration between the study team and all local authorities, digital help services, the primary care zone and all caregivers. They support the participants with (practical) questions and follow-up. Reporting is done by a radiologist, with AI as second reader. Pulmonary nodules are assessed by volumetry and management is according to the new Nodule Management Recommendations from the European Society of Thoracic Imaging (ESTI - accepted for publication European Radiology). If a participant of the ZORALCS-study still smokes or stopped less than one year ago, they are offered smoking cessation support in the TAMIRO-STOP study. This is a randomised controlled trial where participants are randomly assigned to two groups (1:1 - block randomization). After the minimal intervention at the hospital, the intervention group receives eight free sessions of evidence-based smoking cessation counselling by a tobaccologist, including reimbursed pharmacotherapy. The control group gets a referral to a primary health care provider of their own choice.

Objectives: The primary objective is to determine the participation rate of eligible individuals who attend at least one LDCT-scan. Secondary objectives include evaluating all steps of the screening process (e.g. recruitment strategies, assessing the effectiveness of smoking cessation interventions, reporting, compliance rates···).

Expected outcomes: The study will identify barriers and facilitators to participation, assess screening effectiveness, and contribute to the development of regional policies for LC prevention. Additionally, data on incidental findings, radiation exposure, and informed decision-making will inform future screening strategies.

Conclusion: The ZORALCS-study is a Flemish pioneering initiative that bridges the gap between evidence-based LCS recommendations and real-world implementation. The outcomes of this study will be instrumental in guiding national and regional governments in Belgium, providing the necessary insights to support informed decisions on the launch of a nationwide, population-based LCS program.

Keywords: Lung Cancer Screening, Smoking cessation, Implementation research

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.04 MRDSEEKER (JCOG2111A): A Prospective Study to Evaluate MRD and Its Association With Prognosis in Curative-Intent NSCLC

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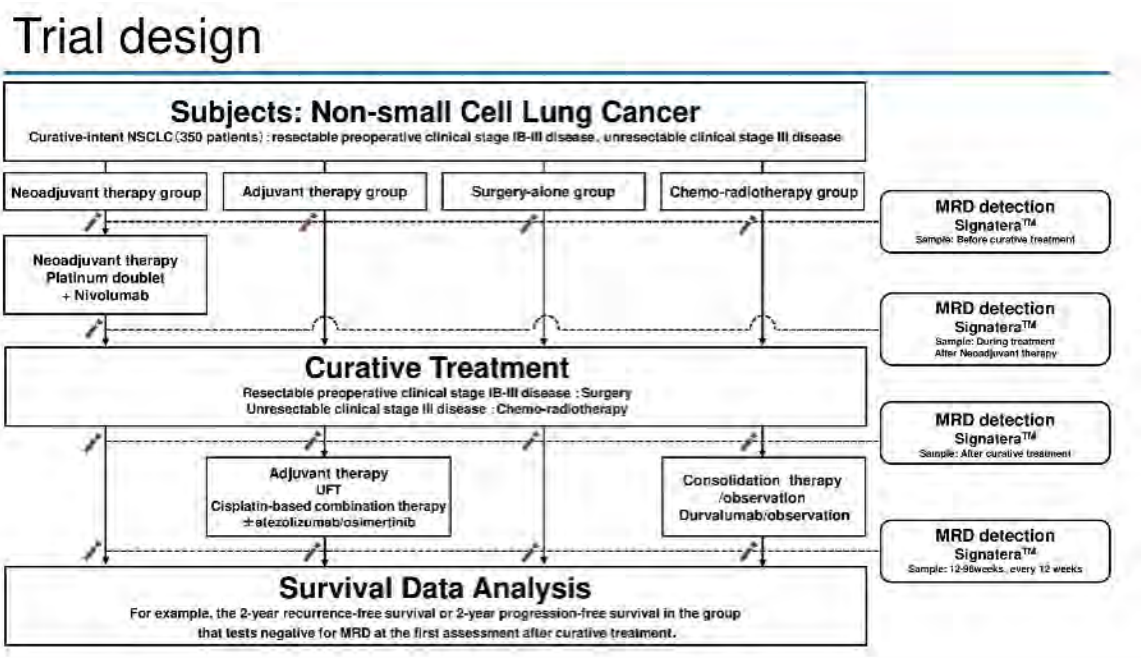
Introduction: There is currently no adequate method to determine which patients will derive survival benefits from immune checkpoint inhibitors or molecularly targeted therapies utilized as perioperative treatment or as consolidation therapy following chemoradiotherapy. It is expected that detecting molecular residual disease (MRD) through the assessment of circulating tumor (ct) DNA may help identify a subgroup of patients with a significantly better prognosis. A concept of de-escalation (or escalation) for MRD-negative (or -positive) subpopulation can be worth evaluating via confirmatory trials. However, there is a significant lack of Japanese data on MRD for predicting prognosis after curative treatment in patients with curative-intent non-small cell lung cancer (NSCLC), and MRD testing is not yet part of routine clinical practice in Japan.

Methods: MRDSEEKER (JCOG2111A) is a prospective cohort study using a personalized, tumor-informed MRD assay (SignateraTM) to evaluate the association between MRD detection and prognosis in patients with NSCLC after curative-intent treatment. Patients aged 18 years or older with histologically confirmed NSCLC are eligible if they meet any of the following criteria: are considered resectable at preoperative clinical stage IB-III with no plan for neoadjuvant therapy; are considered resectable at preoperative clinical stage II-III with a plan for neoadjuvant therapy; or are determined to be suitable for definitive chemoradiotherapy at clinical stage III. The primary aims of this study are to demonstrate that (i) the 2-year progression-free survival (PFS) is sufficiently high in MRD-negative cases, and (ii) the 2-year PFS of MRD-negative cases shows a superior trend compared to that of MRD-positive cases. In this study, we will define multiple patient cohorts and perform survival analyses within each cohort, enabling a more detailed evaluation of therapeutic outcomes. This cohort study will enroll a total of 350 patients: 50 with epidermal growth factor receptor (EGFR) mutation-positive NSCLC, 250 with EGFR mutation-negative NSCLC (including 100 at clinical stage IB, 50 at stage II, 40 at resectable stage III, and 60 at unresectable stage III), and an additional 50 resectable patients at preoperative clinical stage II-III scheduled to receive neoadjuvant therapy including immune checkpoint inhibitors. This study was activated in April 2025. The study is registered with clinicaltrials.gov (NCT06854939).



Keywords: MRD, ctDNA, JCOG

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.05 Enrollment Update for the CSP #2005 Phase III Veterans Affaris Lung Cancer Surgery or Stereotactic Radiotherapy Study [VALOR]

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Introduction: Current evidence-based guidelines recommend upfront lung resection for patients with early-stage non-small cell lung cancer (NSCLC) who have no clinical evidence of lymph node metastasis. Stereotactic body radiation therapy (SBRT) is recommended only for medically inoperable patients, poor surgical candidates, or those who decline surgery after evaluation by a thoracic surgeon. This is despite a growing number of comparative studies suggesting that SBRT offers similar lung cancer-specific and overall survival (OS) outcomes, as well as the absence of randomized clinical trial data demonstrating the superiority of surgical management.

Methods: A multi-site phase III randomized clinical trial was designed to compare OS rates between surgery and SBRT for operable participants with AJCC 7th edition stage I NSCLC. Eligibility requirements include biopsy-confirmed tumors measuring ≤5 cm in maximum diameter, located more than 1 cm from critical structures (e.g. trachea, proximal bronchial tree, esophagus, and spinal cord), and deemed suitable for either an anatomic resection or SBRT. Mandatory staging procedures include fluorodeoxyglucose positron emission tomography (FDG-PET) scans with biopsies of all radiographically suspicious areas for regional or distant metastasis. The study is an event-driven trial designed to randomize 670 patients in a 1:1 ratio to detect a 10% absolute difference in 5-year OS between the treatment groups. The trial will conclude once 339 participants experience a primary event. Two interim analyses will be conducted to assess efficacy or futility. The first interim analysis will occur when one-third (113) of the primary events have occurred, and the second when two-thirds (226) of the primary events have been reached. A sensitivity analysis with OS as the primary outcome is planned to compare only patients who received their randomized treatment. Secondary outcome measures are structured hierarchically to compare: (1) patient-reported quality of life (EORTC QLQ-C30 and LC-13), (2) respiratory function assessed by patient-reported surveys (St George's Respiratory Questionnaire), (3) respiratory function assessed by pulmonary function testing (FEV1, DLCO), (4) health state utilities (EuroQol EQ-5D-5L), (5) lung cancer-specific mortality, and (6) patterns of relapse during post-treatment surveillance.

Results: The trial commenced in April 2017, and as of March 24, 2025, 440 of the planned 670 participants have been randomized. Following randomization, 96% of participants accepted and received their allocated treatment, with only 1% withdrawing consent after refusing both treatment arms. Baseline patient, tumor, and treatment characteristics are summarized in the table. With a median follow-up time of 2.3 years for all surviving participants, no safety concerns have arisen to interrupt the study, nor have there been enough events to trigger the first efficacy or futility analysis. Completion of accrual is estimated for September 2027.

Conclusions: The VALOR study has successfully enrolled 66% of its target accrual within a time frame similar to that required for the CALGB 140503 study, which enrolled a comparable number of participants with early-stage NSCLC (n=697). The final results are expected to clarify the role of SBRT as a potential alternative to surgery for operable clinical stage I NSCLC and facilitate more informed discussions regarding SBRT as a viable option for certain operable patient populations.

Keywords: Non small cell lung cancer, Surgery, Stereotactic body radiation therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.06 Phase 1b Study of a Novel Fluorescent Imaging Agent, LS301, for Lung Cancer Surgery to Localize Tumors and Assess Margins

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Introduction: Surgery for lung cancer has multiple challenges including localizing nodules, ensuring negative margins, and identifying synchronous cancers. One proposed solution is intraoperative molecular imaging (IMI), that is, administering a tumor-targeting fluorescent agent to highlight cancer cells. LS301 is a cyclic peptide that binds phosphorylated Annexin A2 (pANXA2) on malignant cells, conjugated to a near infrared fluorescent molecule, in development for the visualization of cancer. LS301 was evaluated in an open-label Phase 1b clinical trial (NCT06713564), and we present preliminary results of LS301 dose-escalation study from the first 3 of 4 dose cohorts.

Methods: Patients are dosed at least 1 day before surgery across four dose cohorts: 0.025, 0.05, 0.075 mg/kg, and 0.1 mg/kg. LS301 is then imaged during minimally invasive and robotic surgery using multiple NIR devices including the Medtronic VisionSense, Karl Storz IMAGE1 S Rubina, and Intuitive Surgical's Firefly Fluorescence Imaging System for in vivo and ex vivo imaging. The mean fluorescence intensity is calculated to characterize the tumor-to-background ratio. Clinically significant events (CSEs) that altered the surgical procedure were defined as localization of the primary tumor, identification of synchronous tumors and margin assessment, are identified through LS301 imaging alone and confirmed by final histology, which is the gold standard for all outcomes.

Results: A total of 11 patients completed the infusion, surgery and IMI. In vivo and ex vivo fluorescence imaging demonstrated dose-dependent signal enhancement, with stronger fluorescence signals observed at higher dose cohorts. LS301 fluorescence signal was detected and demonstrated reliable signal differentiation from background with all devices including robotic and video assisted thoracoscopic surgery. Preliminary analysis of the imaging data has been completed, and tumor-to-background ratios were calculated for both in vivo and ex vivo imaging that demonstrated high contrast between tumor and background. To date, sensitivity for the primary lung cancer was 100% for ex vivo imaging and there were no false positives by histology. From a surgical outcome perspective, LS301 imaging contributed to four clinically significant events in three patients: (Patient A) aiding primary tumor localization and margin assessment; (Patient B) identifying a synchronous lesion; (Patient C) aiding in primary tumor localization, none of which were found by white light. One patient with a history of hypertension experienced a transient, Grade 2 blood pressure elevation on the day of infusion, which resolved without intervention. The event was considered possibly related to LS301. No other treatment-related adverse events or dose-limiting toxicities were observed.

Conclusions: Findings to date support that LS301 is safe and well-tolerated and provides distinctive intraoperative tumor contrast influenced by dose level, tumor characteristics, and imaging device. These findings also suggest that LS301 aids in localizing the primary tumor, performing margin assessments, and identifying synchronous lesions.

Keywords: Intraoperative Molecular Imaging, Surgery, Margins

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.07 Immunotherapy Combined With Radiotherapy as Neoadjuvant Therapy in Resectable NSCLC: A Single Arm, Phase II Clinical Study

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Introduction: Phase III clinical trials have demonstrated that neoadjuvant immunochemotherapy can elevate the pathological complete response (pCR) rate to approximately 20%-25%. Our center's prior clinical experience has revealed that concurrent radio-immunotherapy can also achieve favorable pathological remission, yet the optimal dosing and timing for combination therapy remain undetermined. This study is designed to evaluate the efficacy and safety of a chemo-free treatment regimen in the neoadjuvant setting.

Methods: This study is a non-randomized, single-arm phase II trial assessing the safety and efficacy of combining the PD-1 inhibitor tislelizumab with chest radiotherapy as neoadjuvant treatment for resectable stage IB-IIIA non-small cell lung cancer (NSCLC) patients aged 18 years or older. Eligible patients will receive intensity-modulated radiotherapy (IMRT) at 40 Gy in 20 fractions (days 1-20) targeting the primary tumor and positive lymph nodes, combined with three to four cycles of tislelizumab (200 mg on day 1, every 3 weeks), followed by curative-intent resection within 3-6 weeks after the last neoadjuvant dose. Adjuvant tislelizumab treatment (200 mg on day 1, every 3 weeks) will commence within 8 weeks post-surgery for up to 1 year. Postoperative minimal residual disease (MRD) detection will be performed at 3-4 weeks, 4 months, and every 6 months thereafter. Patients with detectable MRD will receive additional four cycles of chemotherapy based on their pathological type. The primary endpoints are safety and pCR rate, while secondary endpoints include major pathological response (MPR) and 1-year event-free survival (EFS) rate. Efficacy analyses will follow an intention-to-treat principle, encompassing all patients scheduled for neoadjuvant treatment. Safety assessments will include all patients who have received at least one dose of the study treatment.

Keywords: Neoadjuvant therapy, Radiotherapy, Tislelizumab

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.08 Alectinib as Adjuvant Therapy in Resected ALK-Positive NSCLC: A Prospective Multicenter Cohort Study in China

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Introduction: In China, alectinib was approved for adjuvant treatment of patients with resected anaplastic lymphoma kinase (ALK)-positive early-stage non-small cell lung cancer (NSCLC) in July 2024. The approval was based on the global phase III ALINA study, which demonstrated significantly longer disease-free survival (DFS) in patients treated with alectinib compared with platinum-based chemotherapy. Although alectinib has been the standard of care in this population and was recommended by main guidelines including the National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO), the effectiveness data and the patient journey for Chinese patients in the clinical practice in the real world settings remains scarce.

Methods: This is a multicenter, prospective, cohort study (NCT06862869) enrolled histologically-confirmed, stage II-IIIB (UICC/AJCC v8), ALK-positive, NSCLC adult patients. A decentralized model is employed, representing a contemporary approach where data collection and participant engagement occur remotely. This model capitalizes on digital technologies, including mobile applications and online platforms, to procure data directly from participants within their natural environments and facilitates real-time data collection and analysis. Patients are eligible if they are treated with alectinib monotherapy as adjuvant therapy after complete resection. The planned accrual is 800 patients in about 50 sites from various provinces and cities in China to achieve geographical representation. All evaluations and treatments that the patients receive will be determined by the physicians according to the clinical practice at each study site. Data will be obtained from inpatient and outpatient medical records and patient self-reported information including patient-reported outcomes (PRO) questionnaires. The follow-up visit follows routine visits in real-world practice. Data cut-off for final analysis will occur approximately 2.5 years after the last patient enters the study cohort. The primary effectiveness objective is to evaluate real-world disease-free survival (rwDFS), defined as the time from the first dose of alectinib as adjuvant therapy to cancer recurrence or death from any cause. The secondary effectiveness objectives include the duration of alectinib therapy, patient demographics and disease characteristics, and PROs (emotional and physical function) by SF-36 v2 questionnaires. The safety profile of alectinib as an adjuvant treatment in resected ALK-positive NSCLC in routine clinical practice will be evaluated. The study also explores prognostic factors of recurrence, the healthcare utilization before or after the recurrence, the alterations of ALK or other biomarkers identified between the recurrence and initiation of the next anticancer therapy, and treatment options after recurrence.

Keywords: alectinib, adjuvant, real-world study

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.09 SUNRAY-02: A Phase 3 Study of Olomorasib and Immunotherapy in Stage II-III KRAS G12C-Mutant NSCLC After Definitive Therapy

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Introduction: KRAS mutations are well-characterized oncogenic drivers in multiple solid tumors. KRAS mutations are the most common oncogenic driver in non-small cell lung cancer (NSCLC) and KRAS G12C accounts for 40% of KRAS-mutant lung cancer. Olomorasib is a potent and highly selective second-generation inhibitor of KRAS G12C, which delivers >90% sustained target occupancy at low absolute exposures in preclinical models. The phase 1/2 LOXO-RAS-20001 study (NCT04956640) showed that olomorasib alone and in combination with pembrolizumab demonstrated promising preliminary efficacy and a favorable safety profile in patients with metastatic KRAS G12C-mutant NSCLC. The safety and efficacy of olomorasib in combination with immunotherapy, allows movement into the curative setting, where immunotherapy is the standard perioperative or consolidation therapy with surgery or radiation, respectively.

Methods: SUNRAY-02 (NCT06890598) is a global, multicenter, randomized, double-blind, placebo-controlled phase 3 study that aims to determine the efficacy of olomorasib in combination with standard of care immunotherapy following definitive treatment of stage II-III NSCLC. Eligible participants are at least 18 years old, ECOG PS 0-1, with pathological confirmation of NSCLC (resected stage II-IIIB or unresectable stage III based on AJCC 9th edition) with known KRAS G12C mutation (tissue or blood) and PD-L1 expression (0-100%). Key exclusion criteria include a known EGFR mutation or ALK rearrangement, prior history of NSCLC, pneumonitis/interstitial lung disease requiring steroids, or active autoimmune disease. This study includes two parts: Part A enrolls participants with resected stage II-IIIB NSCLC, who received either neoadjuvant chemoimmunotherapy without achieving a pathological complete response or received adjuvant chemotherapy; Part B enrolls participants with unresectable stage III NSCLC with no evidence of disease progression following concurrent chemoradiation therapy. In Part A, approximately 400 participants will be randomized in a 1:1 ratio to receive either olomorasib or placebo in combination with pembrolizumab. In Part B, approximately 300 participants will be randomized in a 1:1 ratio to receive either olomorasib or placebo in combination with durvalumab. All participants will receive combination treatment for up to approximately 1 year, followed by olomorasib or placebo monotherapy to complete up to 3 years of total treatment. The primary endpoint for Part A is disease-free survival (DFS). Secondary endpoints include overall survival (OS), changes in health-related quality of life (HRQoL), safety, and patient-reported tolerability. The primary endpoint for Part B is progression-free survival (PFS) by blinded independent central review. Secondary endpoints include OS, objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival 2 (PFS2), safety, changes in HRQoL, and patient-reported outcomes.

Keywords: KRAS-G12C, Olomorasib, NSCLC

P3.18.10 Efficacy and Safety of Aumolertinib as Adjuvant Therapy in Resectable Stage IA3 EGFRm NSCLC With High Risk Factors

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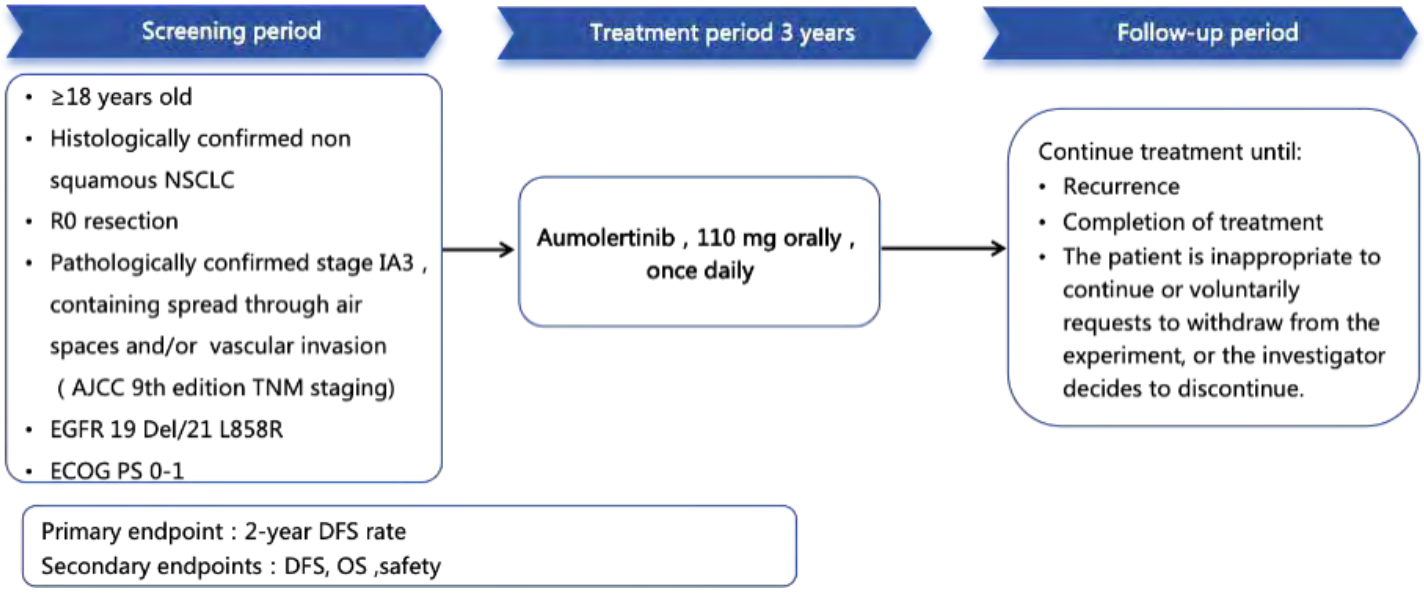
Introduction: With the widespread adoption of low-dose CT screening and the impact of COVID-19, the incidence of stage I NSCLC(especially IA)has risen. While radical surgery remains a key curative approach for stage I NSCLC, historical data indicate that a subset of patients still fail to achieve long-term survival beyond five years.According to the 9th edition of the TNM classification by the International Association for the Study of Lung Cancer (IASLC), stage IA3 is defined as a tumor measuring 2-3 cm without lymph node involvement (N0) or distant metastasis (M0), accounting for approximately 30% of all IA-stage NSCLC. Despite being categorized as "early-stage," IA3 patients with high-risk recurrence factors,such as spread through air spaces (STAS) and vascular invasion(VI),exhibit significantly worse prognoses, with 5-year recurrence-free survival (RFS) rates dropping to 65%-75%. Their postoperative recurrence risk is markedly higher than that of IA1 and IA2 patients, highlighting the urgent need for more precise adjuvant treatment strategies to improve long-term outcomes.Aumolertinib is a novel, promising oral third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), which has demonstrated efficacy in tumors harboring sensitive EGFR mutations . Besides, the results of phase III registration trial with adjuvant aumolertinb versus placebo is about to be released soon and aumolertinb will be the third EGFR-TKI comprising indication concerning adjuvant therapy worldwide. However, no prospective data exist on the adjuvant targeted therapy benefit in IA3 EGFR-mutant NSCLC with high-risk factors. Therefore, this study aims to evaluate the efficacy and safety of aumolertinib as adjuvant therapy in resectable stage IA3 NSCLC patients with high-risk factors.

Methods: This prospective, single-center, single-arm phase II trial enrolls patients with pathologically confirmed stage IA3 (T1cN0M0) NSCLC exhibiting high-risk factors (STAS and/or VI) who underwent complete resection (R0). Key eligibility criteria include EGFR sensitizing mutations (exon 19 deletion or L858R), Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1. This trial is prepared to enroll 30 patients which receiving aumolertinib (110 mg orally once daily) adjuvant treatment for up to 3 years or until disease recurrence/ unacceptable toxicity. Primary endpoint is the 2-year disease-free survival (DFS) rate by investigator assessment, while secondary endpoints include median DFS, overall survival (OS), and safety. Stratification factors include EGFR mutation subtype (exon 19del or L858R) and high-risk factors type (STAS and/or VI). The trial initiated on March, 2025. Now is ongoing.



Keywords: Aumolertinib, Adjuvant Therapy, High risk factors

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.11 Adding Certolizumab to Neoadjuvant Chemoimmunotherapy - Control of Immune-Related Adverse Events and Prevention of Surgical Delays

P.K. Paik, P. Agrawal, M. Bott, I. Preeshagul, B. Park, D. Jones, P. Adusumilli, G. Rocco, J. Isbell, J. Huang, J. Eng, A. Iqbal, F. Santini, R. Rosenblum, W. Travis, R. Daly, J.E. Chaft, M.G. Kris
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Introduction: We have identified a paracrine inflammatory loop (TNF-α, CXCL1/2, S100A8/9) involving both tumor and stromal compartments that engenders chemoresistance and metastatic propagation in lung adenocarcinoma models. Interruption of this loop by TNF blockers leads to chemotherapy re-sensitization and abrogation of metastases. We showed that the addition of certolizumab, a TNF blocker, to platinum doublet chemotherapy in patients with advanced lung cancers increased efficacy with attendant decreases in TNF-α and S100A8 expression compared to controls (Paik et al. Nat Comm 2022). TNF blockers do not increase perioperative morbidity and may lessen immune-related adverse events (irAEs). Based on these data, we designed NEOCERTO (NCT04991025), a phase 2 trial of neoadjuvant certolizumab added to platinum doublet chemotherapy + nivolumab in patients with resectable stage IIA to IIIB squamous and adenocarcinomas, hypothesizing that TNF-α inhibition will increase the efficacy of chemoimmunotherapy, abrogate metastatic propagation, and mitigate irAEs. We report here initial drug delivery, side effect data, and time to resection post neoadjuvant therapy.

Methods: This is a phase 2 study of certolizumab, a TNF blocker, added to histology-specific platinum doublet chemotherapy (paclitaxel, albumin-bound paclitaxel, gemcitabine, or pemetrexed) + nivolumab as neoadjuvant therapy in pts with clinical stage II and III resectable lung cancers. Treatment is given every 3 weeks for 4 cycles. The primary endpoint is pCR rate. Secondary endpoints include safety, ORR, DFS, and metastasis-free survival. Serial blood is being collected for exploratory cytokine analysis and ctDNA dynamics. Transcriptomic analysis of the resection specimens is planned.

Results: Twenty-six patients have completed neoadjuvant treatment and proceeded to surgery; 5 additional patients are currently undergoing neoadjuvant treatment. Among the 26 patients, median age=66 years (range 38-76); 46% female; 92% former/current smoker. Histology: 18 (69%) adenocarcinoma and 8 (31%) squamous cell carcinoma. cStage II 7 (27%), cStage III 19 (73%). Of the total 104 planned cycles of therapy, 102 were completed (98%). No grade 2/3/4 irAEs have been recorded (0%, 95% CI 0 -11%). The only grade 1 possible irAE was rash (N=3). The most common treatment-related AEs were anemia (23%), thrombocytopenia (23%), neutropenia (19%), and nausea (19%). Most were grade 1. Grade ≥ 3 related AEs were hematologic: neutropenia (15%), anemia (8%), and thrombocytopenia (12%). There were 3 treatment-related SAEs (1 febrile neutropenia; 2 creatinine increases) which resolved. All 26 patients underwent surgical exploration. The median time from the end of the last cycle of therapy to surgery was 13 days (range 0-51 days). Surgery was not postponed in any patient due to treatment-related AEs. Among 26 patients who underwent surgical exploration, 25 had an R0 resection (96%). The pCR rate was 31% and MPR rate 62%.

Conclusions: When the TNF blocker certolizumab was added to standard of care neoadjuvant chemotherapy plus nivolumab, 98% of planned neoadjuvant therapy cycles were delivered, no dose-limiting immune related adverse events were observed, surgery was completed within 2 weeks after completion of therapy in most patients, and 96% had complete resections. Accrual is ongoing, with a target goal of 50 patients. Supported by NCI P01CA129243 and UCB Inc.

Keywords: Neoadjuvant, Immune related adverse event, Pathologic complete response

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.12 ARIAN, Adjuvant Treatment With Sacituzumab and ZimberelimAb in Resected Patients: A Phase III Study - Trial in Progress

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Introduction: Surgery continues to be the gold standard treatment with curative intent for patients with resectable early-stage and locally advanced non-small cell lung cancer (NSCLC). Achieving pathological complete response (pCR) following neoadjuvant treatment is considered a potential early predictor of survival in resectable NSCLC whereas the absence of pCR may be associated with poorer outcomes in this patient population. The emerging understanding of the therapeutic synergy between immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs) - such as Sacituzumab Govitecan, a TROP-2-directed ADC - has opened a new chapter in adjuvant NSCLC therapy, offering promising survival benefits in clinical practice.

Methods: ARIAN is an multicenter, open-label, randomized, phase III clinical trial (EUCT Number: 2024-512960-75-00). Patients with stage IB to IIIA-IIIB (T3N2) treated with neoadjuvant chemo-immunotherapy and who do not achieve a pathological complete response (pCR) after complete surgical resection (R0), will be stratified (PDL1- vs PDL1+) and randomized 1:1:1 to: observation for 10 months (Arm 1), Zimberelimab for 13 cycles (Arm 2) or Sacituzumab Govitecan and Zimberelimab for 8 cycles followed by Zimberelimab monotherapy for 5 cycles (Arm 3). 129 patients will be enrolled (43 per arm) in 30 sites and patients must have adequate organic function and do not harbor EGFR, ALK, STK11 or KEAP1 genomic alterations. The primary endpoint is disease-free survival (DFS), defined as time from randomization to first disease recurrence, any new lung cancer or death from any cause. Patients will undergo tumor assessments by body CT scan at baseline (before randomization), during adjuvant treatment or observation every 12 weeks and thereafter, every 3 months for 2 years and every 6 months the 3rd year. Secondary endpoints include overall survival (OS) at 12, 24 and 36 months after the start of adjuvant treatment and safety based on CTCAE v5. Exploratory endpoints include assessing the prognostic value of ctDNA and the antitumor immune response. The study was approved by health authorities on 19 August 2024.

Keywords: ARIAN trial, sacituzumab and zimberelimab, Spanish Lung Cancer Group

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.13 Atezolizumab +/- Tiragolumab Before and After Chemoradiation for Unresectable Stage III Non-Small Cell Lung Cancer (AFT-57)

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Introduction: Some patients with unresectable stage III non-small cell lung cancer (NSCLC) may be cured by chemoradiotherapy (CRT) and adjuvant checkpoint inhibition through PD-L1 blockade. Durvalumab improved survival compared to placebo in the PACIFIC trial (median progression-free survival (mPFS) 16.9 vs 5.6 months (mo), median overall survival (mOS) 47.5 vs 29.1 mo compared to CRT alone) (Spigel D, et al J Clin Oncol 2022). Five-year survival remained below 50% and only patients completing CRT without progression and with good performance status (PS) were eligible to receive adjuvant immunotherapy.

Neoadjuvant checkpoint inhibition allows more patients the potential benefit of immunotherapy and may attenuate tumor-related immunosuppression via depletion of regulatory T cells and clonal expansion of effector T cells, thereby improving tumor immunogenicity. Neoadjuvant atezolizumab appeared promising compared to historic PACIFIC data in the phase II single-arm AFT-16 trial (mPFS 30 mo and mOS not reached; Ross HJ et al JAMA Oncology 2024).

Tiragolumab blocks the immunosuppressive protein TIGIT, and may decrease aspects of the immunosuppressive tumor microenvironment through effects on both lymphoid and myeloid cells. Whether combination immunotherapy with atezolizumab and tiragolumab before and after CRT will further improve outcomes in this setting is the question posed in the AFT-57 trial.

Methods: This phase II randomized Alliance Foundation Trials study (AFT-57) evaluates safety and efficacy of atezolizumab with or without the anti-TIGIT monoclonal antibody tiragolumab before and after definitive CRT. The primary endpoint is PFS in the two experimental arms to select the most promising regimen for further study. AFT-57 will randomly assign 158 patients with unresectable stage III NSCLC (AJCC v8), Eastern Cooperative Oncology Group PS 0-1, no active autoimmune disease and no significant underlying organ dysfunction to 2 cycles of neoadjuvant atezolizumab (intravenous [IV] 1200 mg every 21 days or subcutaneous 1875 mg every 21 days) with or without tiragolumab (600 mg IV). Non-progressing patients undergo CRT with carboplatin and paclitaxel weekly concurrent with 60 Gray involved-field thoracic radiation in 30 daily fractions delivered Monday to Friday over 6 weeks followed by atezolizumab with or without tiragolumab every 21 days on the same schedule as the neoadjuvant doses, with a plan for one year of therapy absent progression or intolerance.

Correlative science includes tissue and blood-based immune-related biomarkers at baseline and during therapy. This trial utilizes the Alliance Participant Engagement Portal, a patient-facing site designed to provide information and resources to Alliance clinical trial participants. The trial was activated on 12/7/23 and the first patient was screened 1/19/24.

Clinicaltrials.gov Identifier: NCT05798663. Support: Alliance Foundation Trials, Genentech; https://acknowledgments.alliancefound.org

Keywords: Combination immunotherapy, Neoadjuvant therapy, Unresectable NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.14 Quick Start Durvalumab: A Phase II Pilot Study of Early Durvalumab Initiation Following Chemoradiation in Unresectable Stage II-III NSCLC

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Introduction: Durvalumab is the standard consolidation therapy for unresectable stage II-III non-small cell lung cancer (NSCLC) following chemoradiation, based on improved survival reported in the PACIFIC trial. However, optimal timing for initiation remains undefined. Preclinical data and post-hoc analyses suggest that earlier initiation of durvalumab may enhance efficacy, potentially by capitalizing on treatment-induced upregulation of PD-L1 expression. Prior analyses also found no significant difference in incidence of immune-related adverse events with early administration. Despite these findings, in current clinical practice, most patients begin durvalumab more than 14 days after radiotherapy due to a number of barriers (e.g., post-radiation toxicity, logistical barriers, and lack of prospective data). An investigation of patients at our institution with Stage III NSCLC revealed that the majority of patients were started on durvalumab 14 to 42 days post-radiotherapy, and no patients received durvalumab within 14 days of radiotherapy completion. Our study objective is to evaluate the feasibility, safety, and early efficacy of quickly starting durvalumab within 14 days of chemoradiation.

Methods: This open-label, single-arm, pilot phase II trial will enroll approximately 28 patients aged ≥18 years with unresectable or medically inoperable stage II-III NSCLC who have received platinum-based chemotherapy and definitive thoracic radiotherapy (54-66 Gy). Eligible patients must have ECOG performance status 0-2 and no evidence of early disease progression. The study intervention includes the typical one-year course of durvalumab 1500 mg IV every 28 days starting 1 to 14 days post-radiation. The study has IRB approval and is registered as NCT05696782.

The primary endpoint is treatment fidelity to the early initiation of durvalumab within 14 days of the last day of radiotherapy. Secondary endpoints include fidelity to very early initiation (i.e., within 7 days), qualitative assessment of barriers to early initiation, incidence of adverse events, and measures of efficacy (i.e., overall survival, progression-free survival, and objective response rate). Exploratory endpoints include patient-reported outcomes (i.e., quality of life, symptom burden, dyspnea, sleep disruption), immune profiling of peripheral blood mononuclear cells, and feasibility of monitoring circulating tumor DNA (ctDNA).

Blood samples will be collected prior to durvalumab initiation, after cycle 3, and at disease progression if applicable, to assess peripheral immunophenotype and measure ctDNA levels. Imaging and quality-of-life assessments will occur at baseline, throughout treatment, and into surveillance. Participants will be followed for toxicity, progression, and 12-month survival outcomes. Recruitment is currently ongoing.

Keywords: NSCLC, Immunotherapy, Initiation

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.15 Neoadjuvant and Adjuvant Chemoimmunotherapy in Resectable Stage II-IIIA NSCLC: Interim Results of a Prospective Cohort Study

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Introduction: Neoadjuvant and adjuvant immunotherapy combined with chemotherapy have demonstrated promising efficacy in resectable stage II-IIIA non-small cell lung cancer (NSCLC). However, the optimal timing for initiating immunotherapy remains under investigation.

Methods: This is an interim analysis of an ongoing prospective, registered clinical study (ChiCTR2200067160) conducted at a single tertiary center. Eligible patients with resectable stage II-IIIA NSCLC were enrolled between January 2023 and December 2024 and randomized via the envelope method into two groups:Neoadjuvant arm (Group 1): Four cycles of pembrolizumab (200 mg) plus paclitaxel (200 mg/m^2 or genomically guided alternative) and carboplatin (AUC 6) every 3 weeks, followed by surgery and up to one-year pembrolizumab maintenance. Adjuvant arm (Group 2): Upfront surgery followed by four cycles of adjuvant pembrolizumab plus chemotherapy (carboplatin AUC 5 + paclitaxel), and pembrolizumab maintenance for up to 1 year.Progression-free survival (PFS) was analyzed using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) were estimated via Cox proportional hazards regression. The study protocol was approved by the institutional ethics board (No. I-22PJ956).

Results: As of the data cutoff (March 1, 2025), 83 patients were enrolled, and 59 were included in the intention-to-treat population (27 in Group 1; 32 in Group 2). Twenty-four patients were excluded due to protocol deviations or early withdrawal.At the time of analysis, median PFS was not reached in either group. The estimated mean PFS was 21.6 months (95% CI, 19.7-23.4) in the neoadjuvant arm and 24.6 months (95% CI, 19.5-29.6) in the adjuvant arm. The between-group difference in PFS was not statistically significant (log-rank P = 0.150). Cox proportional hazards analysis yielded a hazard ratio (HR) of 0.384 (95% CI, 0.099-1.488; P = 0.166), suggesting a non-significant trend favoring the neoadjuvant arm. Despite the longer mean PFS observed in the adjuvant group, Kaplan-Meier curves consistently showed higher PFS probabilities in the neoadjuvant group across most time points. This apparent discrepancy may be attributable to differential censoring patterns, with a higher censoring rate in the adjuvant group at later follow-up, which may have skewed mean-based estimates. Further follow-up is required to clarify long-term outcomes.

Conclusions: In this interim analysis, neoadjuvant chemoimmunotherapy demonstrated a numerical trend toward improved PFS compared to the adjuvant approach in resectable stage II-IIIA NSCLC, although the difference did not reach statistical significance. These findings are preliminary and should be interpreted with caution. Ongoing follow-up and final analysis are needed to determine the long-term efficacy of each strategy.$$graphic_{8C3EBB44-FF45-4EE1-881A-F289696AF49C}$$

Keywords: Non–Small Cell Lung Cancer, Neoadjuvant Therapy, Randomized study

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.16 CROWD: Chemoradiotherapy With Surgery Followed by Consolidation Durvalumab for Initially Unresectable Stage III NSCLC

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Introduction: The introduction of durvalumab consolidation therapy after chemoradiotherapy (CRT) for patients with unresectable stage III non-small cell lung cancer (NSCLC) resulted in improved overall survival, primarily attributed to enhanced distant control. Additional improvements in locoregional control could lead to better survival outcomes. The phase IV CROWD trial aims to evaluate the feasibility of post-CRT surgery for locoregional control in patients who were initially considered to have unresectable stage III NSCLC.

Methods: This single-center, phase IV feasibility trial conducted at Amsterdam University Medical Center (AUMC, The Netherlands) will enroll adult patients presenting with initially unresectable stage III NSCLC who are planned for definitive CRT followed by consolidation durvalumab. After CRT completion, eligible patients will be re-evaluated for resectability by the multidisciplinary AUMC thoracic oncology tumor board (MDT). If considered resectable, patients will undergo surgery at AUMC followed by consolidation durvalumab (Figure). Key inclusion criteria include a pathologically confirmed stage III (non-N3) NSCLC according to the 8th TNM classification (9th TNM classification: stages IIB-IIIB (excluding T2-3N0-1 or N3)) and an initial nonsurgical treatment recommendation by the referring MDT for concurrent CRT (platinum-doublet, 60 Gy in 30 fractions of 2 Gy once daily) followed by durvalumab. Key exclusion criteria include N3 or M1 disease, tumors with known actionable genomic alterations, and the use of any CRT schemes other than a platinum-doublet and 60 Gy in 30 fractions. After completion of CRT, an 18F-FDG PET/CT-scan and brain-MRI will be performed for restaging. Resectability is considered during MDT discussion in AUMC attended by dedicated thoracic radiologists, nuclear physicians, at least 2 thoracic surgeons, and other specialists. The co-primary study endpoints are safety and the proportion of patients able to proceed to durvalumab. Safety will be assessed by the proportion of patients with severe surgical morbidity and mortality (Clavien-Dindo grades 3-5) and grades 3-5 treatment-related adverse events within 90-days of surgery. With 38 evaluable patients, this study will have 80% power at a one-sided significance level of 0.05 to prove starting durvalumab consolidation after CRT plus surgery is non-inferior (non-inferiority margin of 20%) against a reference of 57% of patients that start with durvalumab after CRT alone (Ronden M et al. JTO-CRR 2021). Secondary endpoints are complete surgical resection (R0) rates and disease-free survival at two years.

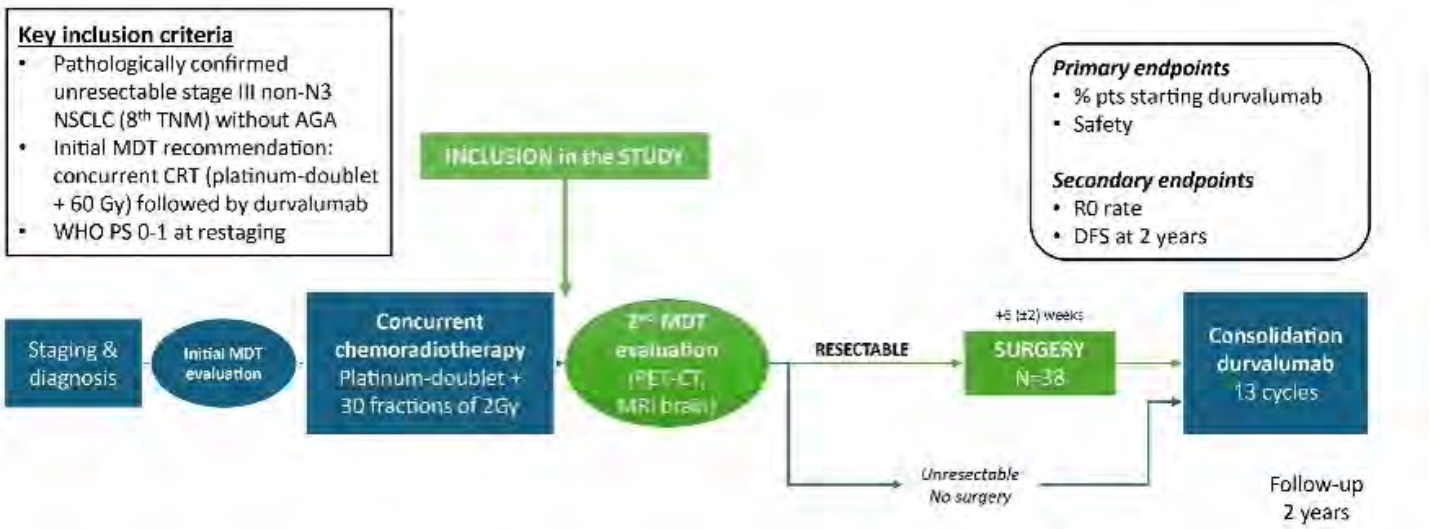

Figure. CROWD study design: Chemoradiotherapy with surgery followed by consolidation durvalumab for initially unresectable stage III NSCLC, a single-arm phase IV feasibility trial

Results:

Conclusions: The first subject was enrolled in December 2024. Primary completion is anticipated in March 2027.

Keywords: Non-Small Cell Lung Cancer, Locally Advanced, Surgery

P3.18.17 Neoadjuvant Chemoimmunotherapy With Immunosensitizing Radiation for Borderline Resectable Non-Small Cell Lung Cancer (NeoRADjuvant)

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Introduction: Neoadjuvant and perioperative chemoimmunotherapy have become the new standard of care for resectable NSCLC without targetable activating mutations in the EGFR/ALK genes, demonstrating significant improvements in pathologic response, event-free survival and overall survival compared to chemotherapy alone. Despite these advancements, ~50% of patients still suffer tumor recurrence within 48 months of surgery, highlighting the need for novel therapeutic approaches. Ongoing efforts seek to augment immune responses and expand benefit to a greater proportion of patients, including strategies for patients with "borderline" resectable disease. Prior studies have evaluated the synergistic role of sub-ablative (8 Gy x 3 fractions) radiation with immune checkpoint blockade, exhibiting encouraging rates of pathologic regression in patients with resectable NSCLC. The NeoRADjuvant study is a phase I trial designed to evaluate the safety, tolerability and preliminary efficacy signal of sub-ablative radiation combined with neoadjuvant chemoimmunotherapy for patients with borderline resectable disease.

Methods: Single-arm, phase I study, planning to enroll up to 18 eligible participants with borderline resectable EGFR/ALK wild-type NSCLC. Patients will receive sub-ablative radiation to the primary tumor (8 Gy x 3 fractions) followed by three cycles of histology specific platinum-doublet chemotherapy and nivolumab. Borderline resectable will be defined as the presence of one or more of the following features: mediastinal invasion, multi-station or bulky N2 disease, contralateral hilar/mediastinal N3 involvement, and/or initial extent of surgery deemed outside the range of a patient's baseline pulmonary function without undergoing tumor downstaging following neoadjuvant therapy. Patients will proceed to definitive treatment within 6 weeks of the last dose of systemic therapy, consisting of either surgical resection if deemed resectable post neoadjuvant chemo-radioimmunotherapy or concurrent chemoradiotherapy and then maintenance immune checkpoint blockade. The primary endpoint of this study is to assess the tolerability of this strategy, with key secondary endpoints being safety and efficacy measured by pathologic response and rate of resection. Surgical outcomes for those patients who undergo definitive resection after neoadjuvant therapy will be reported. Proposed correlate analyses will evaluate circulating tumor DNA (ctDNA) dynamics and minimal residual disease testing as predictors of recurrence after definitive therapy. Spatial transcriptomic profiling on pre- and available post-treatment specimens in resected tumors will be performed to identify patterns of response and resistance to neoadjuvant therapy.

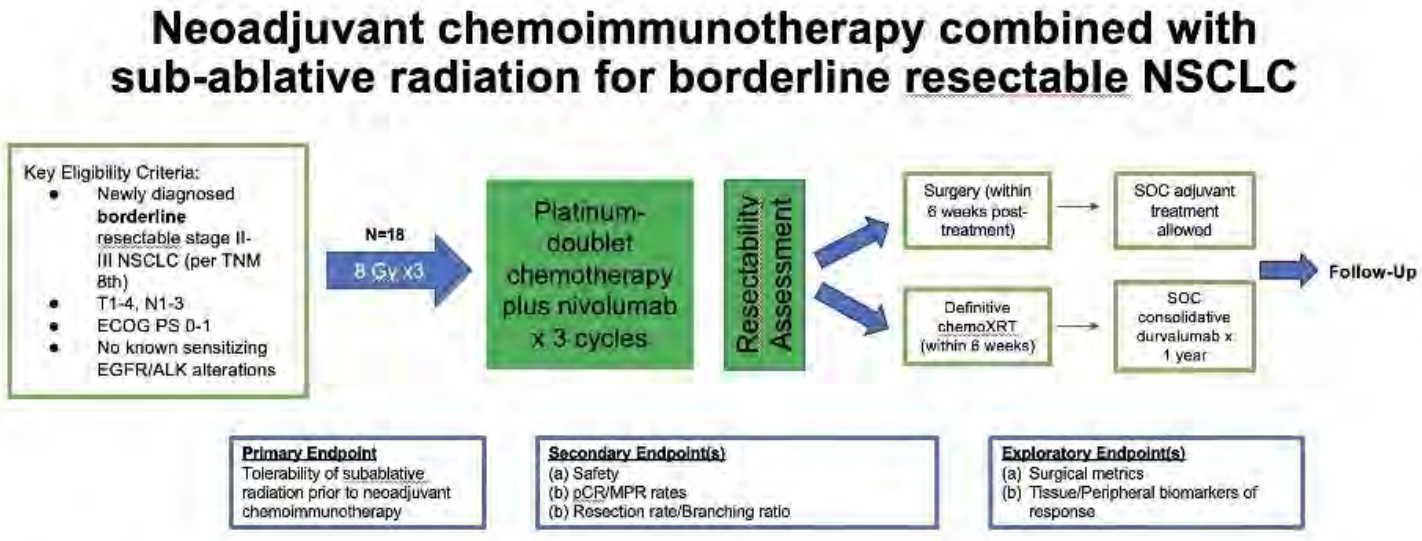

Figure 1: Representative schema for NeoRADjuvant trial

Keywords: Neoadjuvant, Immune checkpoint blockade, Borderline resectable

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.18 Predictive Role of Respiratory Function Tests on Lung Toxicity in Stage III NSCLC Under Chemo-Radiotherapy and Durvalumab: Preludio Trial

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Introduction: Stage III unresectable non-small cell lung cancer (NSCLC) represents a heterogeneous group, for which consolidation immunotherapy with durvalumab, after chemo-radiotherapy, is currently considered the standard of treatment by all national and international guidelines, based on data from the PACIFIC trial. Regarding adverse reactions, pulmonary toxicities represent the most difficult to diagnose and manage.

Methods: It is planned to include 123 patients at 28 sites in Southern Italy experiencing lung cancer in this observational study. The recruitment phase is scheduled to last 24 months (from October 1, 2024, to October 1, 2026) and the follow-up phase is scheduled to last 24-36 months after durvalumab discontinuation. Retrospective data collection can be considered from 09/01/2023. The duration of the study will be 60 months. We propose to estimate the incidence and grading of pulmonary toxicity from radiation therapy and immunotherapy, according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and to investigate the correlation of pulmonary toxicity with pulmonary function tests (PFTs), with a particular focus on forced expiratory volume in one second (%FEV1) and forced vital capacity (%FVC) based on spirometry, diffusing capacity of the lung for carbon monoxide (%DLCO), partial pressure of arterial oxygen (PaO2) based on arterial blood gas (ABG) sampling and maximal distance that patients can walk at their own pace in 6 minutes and minimal oxygen saturation (SpO2) during the 6-minute walking test (6MWT). Pulmonary function tests (basal spirometry, DLCO, 6MWT, ABG) are evaluated at Time 0 (baseline), at Time 1 (post- RT), at Time 2 (after 6 cycles of immunotherapy) and at Time 3 (end of treatment). At data cut-off (31 mar 2025), 45 patients were enrolled and 10 patients were screened failure. Patients were predominantly male (71%) and were a median age of 67 years (range, 49-78 years) and a median PS ECOG of 0 (0-2). 26 of lung cancer cases were adenocarcinoma, 17 cases were squamous-cell carcinoma; 2 subtypes were reported as NSCLC, NOS (not otherwise specified) and as NSCLC with sarcomatoid features. Regarding smoking habits and pre-existing lung diseases, 24 patients (53,3%) were active smokers and 20 patients (44.4%) were previous smokers (p/y 25 - 110); 40% of patients had diagnosis of COPD at baseline. Of 45 patients evaluated at baseline, 19 patients were evaluated also after thoraco-mediastinal RT, 7 patients after 6 administrations of durvalumab. Among the 45 patients enrolled, there were 7 cases of pulmonary toxicity (15.5%). All of the cases showed post-actinic pneumonia (4 cases of grade 2, 2 cases of grade 3 and one case of grade 4 pneumonia).

Keywords: Lung toxicity, Lung function test, Stage III NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.19 The Selective Personalized Radio-Immunotherapy for Locally Advanced NSCLC Trial 2 (SPRINT2)

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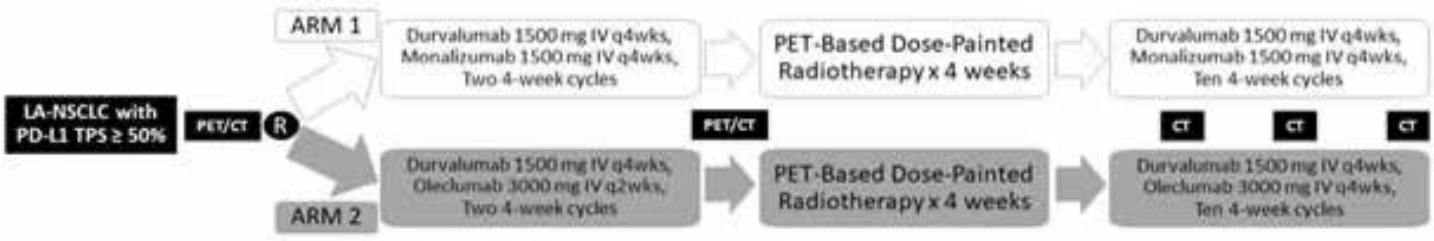
Introduction: In the Selective Personalized Radio-Immunotherapy for locally advanced NSCLC Trial (SPRINT), patients with locally advanced NSCLC (LA-NSCLC) with PD-L1 tumor proportion score (TPS) of ≥50% were treated with induction pembrolizumab, followed by a 20-fraction course of risk-adapted thoracic radiotherapy, followed by consolidation pembrolizumab to complete a 1-year treatment course. This treatment regimen was found to be safe and effective, warranting further study of chemotherapy-free treatment approaches for LA-NSCLC. Additionally, response to induction immunotherapy on FDG-PET, which was observed in 48% of participants, was identified as a promising surrogate endpoint for long-term clinical outcomes. Durvalumab (D) is a PD-L1 antagonist with established activity in NSCLC. Monalizumab and oleclumab are emerging immunotherapeutic agents being developed for the treatment of NSCLC and other malignancies. We hypothesize that dual-agent immunotherapy with durvalumab and either monalizumab or oleclumab will enhance the efficacy of the SPRINT approach.

Methods: Fifty-two patients with a new diagnosis of unresectable stage II or stage III NSCLC and PD-L1 TPS ≥50% will be enrolled on this randomized phase II trial. Participants will be stratified by PD-L1 TPS and disease stage and randomized 1:1 to receive dual-agent immunotherapy with durvalumab + monalizumab or durvalumab + oleclumab. Participants will receive two 4-week cycles of induction immunotherapy, followed by response assessment with FDG-PET. Participants will then receive a 20-fraction course of risk-adapted radiotherapy, where lesions with metabolic tumor volume exceeding 20 cc on FDG-PET receive a dose of 55 Gy, while smaller lesions receive a dose of 48 Gy. Participants will then receive 10 additional cycles of dual-agent immunotherapy. The primary study endpoint is response on FDG-PET after induction immunotherapy, evaluated using PERCIST criteria. Other endpoints include progression-free survival, overall survival, clinician- and patient-reported adverse events, and physical activity metrics captured using wearable devices.



Keywords: locally advanced non-small cell lung cancer, radiotherapy, immunotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.20 PELAGOS: Integrating Surgery and Radiotherapy in EGFR-Mutant N3-Stage III NSCLC After Conversion Therapy

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Introduction: The LAURA trial demonstrated a significant improvement in progression-free survival (PFS) for patients with EGFR-mutant, unresectable stage III non-small cell lung cancer (NSCLC), reporting a median PFS of 39.1 months and 2-year PFS rate of 65%. Additionally, the ADAURA trial demonstrated that adjuvant osimertinib effectively reduces the incidence of distant metastasis in stage IB-IIIA NSCLC from 31% to 13% following surgical resection. Similarly, findings from the POLESTAR study on almonertinib, a third-generation EGFR-TKI, showed promising efficacy in reducing CNS progression and distant metastasis of unresectable stage III NSCLC. Emerging evidence suggests that intrathoracic recurrence represents a major cause of disease progression in stage III NSCLC. This concern is particularly pronounced in more advanced cases, such as stage III disease with N3 involvement (part of IIIB and IIIC), where the optimal treatment strategy remains undefined. To address these challenges, this study evaluates a multimodal approach combining surgery and radiotherapy after induction therapy with almonertinib and chemotherapy, followed by consolidative almonertinib. This approach aims to enhance local disease control and improve survival outcomes in patients with N3 involvement stage III EGFR-mutant NSCLC.

Methods: This is a prospective, multicenter, single-arm phase II clinical trial enrolling 30 treatment-naïve patients with N3 lymph node-positive stage III-NSCLC harboring EGFR mutations (T1-4N3M0, AJCC 9th edition). Eligible patients must be aged ≥18 years, have an Eastern Cooperative Oncolgy Group (ECOG) performance status of 0 or 1, and possess at least one measurable lesion per RECIST 1.1 criteria at baseline. Key exclusion criteria include invasion of critical structures such as the aorta, trachea, esophagus, or heart by the primary tumor or metastatic lymph nodes, as well as the presence of Pancoast tumors. Following induction therapy with three cycles of almonertinib combined with chemotherapy, patients without disease progression will be evaluated by a multidisciplinary team (MDT) and assigned to treatment strategies based on eligibility and patient preference. Patients deemed suitable for surgery will undergo standard lung cancer resection (excluding total pneumonectomy), including removal of the primary tumor and ipsilateral hilar and mediastinal lymph nodes, followed by hypofractionated radiotherapy targeting N3 metastatic lymph nodes concurrent with almonertinib. Patients who are ineligible for or undergo surgery will receive concurrent chemoradiotherapy. After completing local treatment, all patients will continue maintenance therapy with almonertinib until radiographic disease progression, unacceptable toxicity, or completion of one year of treatment. The primary endpoint is the 1-year event-free survival rate (1y-EFS). Secondary endpoints include event-free survival (EFS), overall survival (OS), surgical conversion rate, time to distant metastasis (TTDM), time to local recurrence (TTLR), adverse events (AEs), and the impact of the integrated treatment approach on patient-reported outcomes (PROs). Exploratory analyses will investigate predictive and prognostic biomarkers using tumor tissue and blood samples collected at multiple time points throughout the study. The study protocol was approved by the Ethics Committee of Liaoning Cancer Hospital & Institute (Approval No. 2025302), and written informed consent was obtained from all participants. This trial is prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2400093459).

Keywords: Stage III non-small cell lung cancer, N3 lymph node metastasis, almonertinib

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.21 Durvalumab (D) and Chemotherapy Followed by Either Surgery + D or Chemoradiotherapy + D in Borderline Resectable Stage III NSCLC

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Introduction: Immunotherapy as a component of perioperative treatment has demonstrated survival benefit in resectable non-small-cell lung cancer (NSCLC). Immunotherapy with chemoradiotherapy also showed improvement of outcome for unresectable stage III NSCLC. While the exploration of treatment paradigm for borderline resectable stage III NSCLC is limited.

Methods: This is a multicenter, phase II study assessing the efficacy and safety of neoadjuvant durvalumab and platinum-based chemotherapy, given intravenously, followed by either surgery and adjuvant durvalumab or definitive CRT and consolidation durvalumab in borderline resectable stage III EGFR/ALK wild type NSCLC. Approximately 80 eligible patients will be assessed by multidisciplinary team (MDT), receive two cycles of neoadjuvant durvalumab and platinum-based chemotherapy, then re-assessed by MDT. Patients assessed as having resectable tumors will receive a maximum of 2 cycles neoadjuvant durvalumab and platinum-based chemotherapy (CT) followed by surgery and adjuvant durvalumab for one year (Cohort 1). Patients with tumors deemed unresectable will receive definitive CRT and consolidation durvalumab for one year (Cohort 2). Cross over is allowed if patients were still unresectable after receiving one or two more cycles neoadjuvant durvalumab and platinum-based Chemotherapy. The primary objective is to assess the efficacy of neoadjuvant durvalumab + CT in terms of resection rate in all patients. The secondary objectives include: to assess the efficacy of neoadjuvant durvalumab + CT in terms of pathological complete response (pCR) in cohort 1; to assess the efficacy of neoadjuvant durvalumab + CT followed by definitive CRT and consolidation durvalumab in terms of progression-free survival (PFS) in cohort 2; to assess the efficacy of neoadjuvant durvalumab + CT in terms of objective response rate (ORR) and the efficacy of neoadjuvant durvalumab + CT followed by surgery and then adjuvant durvalumab or definitive CRT and then consolidation durvalumab in terms of event-free survival (EFS).

Keywords: Borderline, Durvalumab, Non-small-cell lung cancer

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.22 TRIPL: Thoracic Radiotherapy and Inhibition of PD-1 and LAG-3 for Locally Advanced Non-Small Cell Lung Cancer

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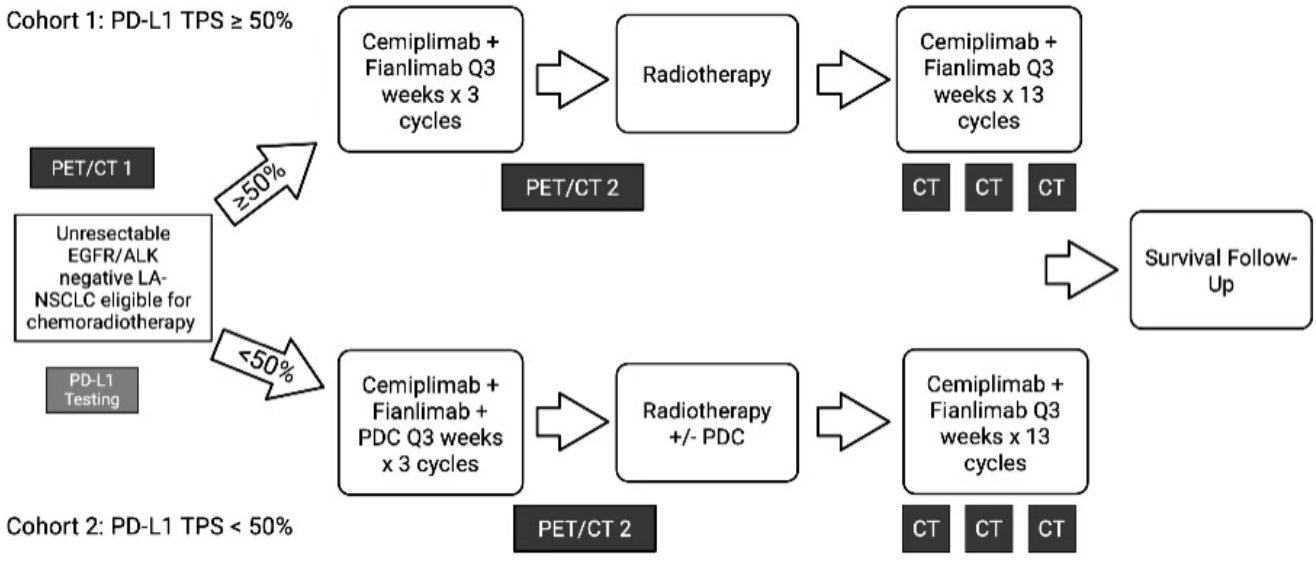
Introduction: SPRINT (NCT03523702) was a multi-center Phase II trial where biomarker-selected (PD-L1 TPS ≥ 50%) locally advanced non-small cell lung cancer (LA-NSCLC) patients were treated with 3 cycles of induction therapy with the PD-1 inhibitor pembrolizumab followed by risk-adapted radiotherapy (RT), then consolidation pembrolizumab to complete a 1-year course while chemotherapy was omitted (PMID: 37988638). The study met its efficacy objectives demonstrating a 1-year progression-free survival (PFS) rate of 76%, 1-year overall survival (OS) rate of 92%, and exploratory analyses suggest that PET response to induction pembrolizumab predicts treatment outcomes best, with a median PFS of 42 months for PET responders. SPRINT demonstrated high treatment efficacy with limited toxicity and introduces PET response to induction immunotherapy (IO) as a novel endpoint allowing for early assessment of treatment activity. An additional advantage of this approach is the ability to clearly evaluate the contribution of treatment components.

Given the promising findings of SPRINT, we now pursue this treatment approach (induction IO followed by RT and consolidation IO) to investigate other novel IO combinations for biomarker-selected LA-NSCLC. One such target is lymphocyte activation gene 3 (LAG-3), which is expressed by immune cells and regulates effector T-cell activation and responses. Thus, we hypothesize that dual IO with the PD-1 inhibitor cemiplimab plus the LAG-3 inhibitor fianlimab administered before and after thoracic RT, as per the SPRINT approach, has valuable potential as a biomarker-driven treatment regimen for LA-NSCLC patients.

Methods: This Phase II study will enroll a total of 76 participants, with at least 32 participants in each of the two cohorts including LA-NSCLC patients with PD-L1 TPS ≥ 50% (Cohort 1) and those with PD-L1 TPS < 50% (Cohort 2). Treatment will be administered in three phases: (1) 3 cycles of induction IO, with histology-specific platinum doublet chemotherapy (PDC) added for subjects with PD-L1 TPS < 50%; (2) risk-adapted thoracic RT (with concurrent PDC recommended for those PD-L1 TPS < 50%); (3) 13 cycles of consolidation IO. The primary endpoint will be objective response rate (ORR) on PET scan via PERCIST criteria following induction IO with 3 cycles of cemiplimab plus fianlimab. Safety will be assessed via a safety-run in phase and extended adverse events collection. Additional endpoints will include ORR on CT, PFS, OS, quality of life assessments, and exploratory analyses focused on tissue and blood-based immune effector signatures.



LA-NSCLC: locally advanced non-small cell lung cancer

PDC: histology-specific platinum-doublet chemotherapy

Keywords: NSCLC, Immunotherapy, Radiotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.23 Management of Synchronous Oligometastatic NSCLC With Surgical Resection of the Primary Tumor: Preliminary Results From the Prospective Trial

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Introduction: Lung cancer ranks among the leading causes of mortality in oncology patients. In the Republic of Belarus, 4,401 new cases of lung cancer were diagnosed in 2023. The standardized incidence and mortality rates were 48.0 and 31.4 per 100,000 population, respectively. Results from several studies have demonstrated the benefits of local consolidation therapy in patients with oligometastatic cancer compared to traditional chemotherapy approaches. Since there is currently no established optimal multimodal treatment strategy, we initiated a prospective non-randomized single-arm phase 2 study at our center.

Methods: The patients with pathologically confirmed oligometastatic NSCLC (T1-3N0-2M1a-c) without activating mutations in EGFR, ALK, ROS1, or BRAF, were included in the study. Patients were selected based on EORTC criteria: number of distant metastases: 1-5; number of metastatic site: 1-3; feasibility of local treatment for all tumor sites. Disease spread was assessed using FDG PET-CT and contrast-enhanced brain MRI. The therapeutic regimen initiates with two cycles of platinum-based induction chemotherapy, followed by surgical resection of the primary tumor and local consolidation therapy for distant metastases. The protocol concludes with two cycles of adjuvant chemotherapy. The protocol prohibits sublobar resections and mandates systematic lymph node dissection in all cases. For patients with brain metastases, treatment initiates with local management of cranial lesions using one of the following approaches: surgical resection, Gamma Knife radiosurgery, or a combination of both modalities.

Results: Since 01.01.2021, 32 patients were enrolled: 18 with brain metastases and 14 with extracranial metastases (adrenal gland [n=2], liver [n=3], bones [n=7], skin and soft tissue [n=2]). Adenocarcinoma was confirmed in 22 (68.7%) patients, while 10 (31.3%) had squamous cell carcinoma. 17 (53,1%) patients showed no regional lymph node involvement (N0). Bronchopulmonary lymph node involvement (N1) was confirmed in 4 (12.5%) cases, and mediastinal lymph node involvement (N2) in 11 (34.4%) patients. Metastatic burden distribution: 20 (62.5%) patients had 1 metastasis, 9 (28.1%) patients had 2 metastases, 3 (9.3%) patients had 3 or more distant metastases. The majority of patients (93.8%, n=30) presented with single metastatic site. Following induction chemotherapy, assessment by RECIST 1.1 criteria revealed partial response in 6 patients (21.4%), stable disease in 20 patients (71.4%), and disease progression in 2 patients (7.1%). Twenty-seven patients underwent surgical resection of the primary tumor: 21 lobectomies (77.8%) and 6 pneumonectomies (22.3%), including 10 VATS procedures (37%). Pathological assessment according to IASLC criteria identified PCR in 2 patients and MPR in 7 patients. The treatment regimen demonstrated satisfactory tolerability with no mortality events observed. Median event-free survival (EFS) was 12.0 months (95% CI 8.3-19.7), with median overall survival (OS) reaching 34.0 months (95% CI 20.6-53.0).

Conclusions: The multimodal treatment approach incorporating induction chemotherapy, primary tumor resection, local therapy for distant metastases, and adjuvant chemotherapy demonstrated satisfactory tolerability. Interim analysis of long-term outcomes reveals superior survival rates compared to historical controls.

Keywords: oligometastatic NSCLC, surgery of the primary site, local consolidation therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.24 A Multicenter, Open Label, Dual Cohort Study: The Efficacy and Safety of Vinorelbine Combined With a First-Line Treatment for Metastatic NSCLC

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Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide. The vinorelbine-cisplatin (NP) regimen has been established as a standard chemotherapy option for advanced non-small cell lung cancer (NSCLC). However, while contemporary first-line treatment paradigms have increasingly incorporated pemetrexed- or taxane-based regimens combined with immune checkpoint inhibitors (ICIs), clinical evidence supporting vinorelbine-based immunotherapy combinations remains scarce. The phase II VinMetAtezo trial provided preliminary insights, demonstrating that metronomic oral vinorelbine combined with atezolizumab, though failing to meet its primary PFS endpoint, maintained an acceptable safety profile with no new toxicity signals. These observations warrant further exploration of vinorelbine-ICI combinations, particularly in the first-line treatment setting where alternative chemoimmunotherapy options are needed. This trial employs a two-stage design to evaluate the efficacy and safety of the NP regimen (vinorelbine plus platinum) in combination with a PD-1 inhibitor, with or without bevacizumab, as a potential first-line therapeutic strategy for metastatic non-squamous NSCLC.

Methods: This multicenter, open-label, dual-cohort trial plans to enroll 87 treatment-naïve patients with metastatic NSCLC lacking actionable driver gene mutations, across 3-5 Chinese centers. Inclusion criteria were: patients with metastatic non-squamous NSCLC without driver gene mutations, has not receive systemic anti-cancer therapy, the occurrence of metastatic disease must be at least 12 months after completion of adjuvant/neoadjuvant treatment, age 18-65 years, ECOG PS 0-1, life expectancy >12 weeks; adequate laboratory-test-documented organ-function results during screening; effective contraception for women of child-bearing potential; available archival tumor tissue or willingness to undergo fresh biopsy, and written informed consent to participate. The main exclusion criteria for both cohorts were: squamous NSCLC, small cell lung, or neuroendocrine cancer; known hypersensitivity to study drugs; currently participating in another clinical trial; received other anti-tumor therapy, major surgery <4 weeks before first dose, lung radiation therapy >30 Gy within 6 months before the first dose, palliative radiotherapy within 7 days before the first dose, live virus vaccination within 30 days before the first dose; active or untreated CNS metastases during screening; uncontrolled pleural effusion, pericardial effusion, ascites requiring recurrent drainage procedures; autoimmune disease; HIV or HBV/HCV positivity; systemic corticosteroid up to 10 mg/day or other systemic immunosuppressant use during the 2 weeks preceding study enrollment; anticipated need for systemic immunosuppressant(s) during the trial; any other severe medical condition that may limit study participation. The exclusion criteria for cohort 2 were: patients with gastrointestinal perforation prior to the first dose or a history of gastrointestinal perforation within 1 year; history of ≥ Grade 2 hemoptysis, laparotomy, thoracotomy, or enterectomy within 28 days prior to the first dose; non-healed wounds; current or recent thromboembolic or cerebrovascular events; hemorrhagic predisposition, coagulation disorders; proteinuria >2+ on dipstick. The study design will be as follows: vinorelbine (60mg/m2 d1, q3w) and cisplatin (75mg/m2 d1, q3w) in combination with Sintilimab (200mg d1, q3w) with/without Bevacizumab (15mg/kg d1, q3w). Patients will be treated until disease progression. Primary endpoint: objective response rate of NP combined with Sintilimab with/without Bevacizumab. Secondary endpoints: efficacy, safety and quality of life. Exploratory endpoint: circulating tumor DNA dynamics and correlation with outcomes.

Keywords: vinorelbine, non-small cell lung cancer, PD-1 inhibitor

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.25 Phase 2 Study of Carboplatin Plus Nab-Paclitaxel Rechallenge for NSCLC With Interstitial Lung Disease: TORG2442/CASTLE Study

T. Itoh[1], G. Saito[1], K. Takahashi[2], Y. Hosomi[3], H. Okamoto[4], T. Suzuki[1]
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Introduction: Interstitial lung disease (ILD), characterized by inflammation and fibrosis of the pulmonary interstitium, is one of the most common comorbidities in patients with non-small cell lung cancer (NSCLC) and is associated with a poor prognosis. The presence of ILD is considered a risk factor for drug-induced lung injury, and outcomes are particularly poor in cases of acute exacerbation of ILD. Although treatment strategies using agents with a lower risk of ILD exacerbation are warranted, patients with ILD are frequently excluded from pivotal clinical trials, and no standard second-line treatment has been established. The combination of carboplatin and nab-paclitaxel is recognized as a standard first-line regimen, and the platinum rechallenge strategy in NSCLC has been suggested as an effective treatment approach based on pooled analyses. Taken together, rechallenge with carboplatin plus nab-paclitaxel is considered a potentially effective and relatively safe therapeutic option for NSCLC with ILD.

Methods: This multicenter, single-arm, phase 2 study will enroll 32 patients with NSCLC and idiopathic ILD previously treated with carboplatin plus nab-paclitaxel. Key eligibility criteria are as follows: patients aged ≥18 years; those with histologically or cytologically confirmed advanced (unresectable stage III or IV) or recurrent NSCLC; and those diagnosed with idiopathic ILD based on high-resolution computed tomography. Patients must have experienced disease progression after receiving 4 to 6 cycles of first-line chemotherapy (carboplatin plus nab-paclitaxel), with a time interval of ≥ 90 days between the last administration of carboplatin and relapse. Eligible patients must also have measurable lesions according to RECIST v1.1 and an ECOG performance status of 0 or 1. Patients with a history of acute exacerbation of ILD, prior thoracic radiotherapy, steroids use of >10mg/day of prednisolone equivalent within 14 days before registration, or symptomatic central nervous system metastases are ineligible. Patients will receive carboplatin (area under the curve 6, on day 1) and nab-paclitaxel (100 mg/m2, on day 1, 8 and 15) of every 4 weeks for 4 to 6 cycles. Tumor imaging will be performed every 6 weeks from registration. Adverse events will be graded according to CTCAE v5.0. ILD imaging evaluations will be conducted by an independent central review, ensuring the diagnostic quality of ILD, classification of ILD imaging patterns, and accurate diagnosis of acute exacerbation of ILD. The primary endpoint is 3-month progression-free survival without acute exacerbation of ILD rate (3m PFS without AE-ILD rate). Progression-free survival without acute exacerbation of ILD (PFS without AE-ILD) is defined as the time from registration to disease progression, death, or the occurrence of acute exacerbation of ILD. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), PFS without AE-ILD, safety and tolerability. Patients enrollment will begin in April 2025. This study has been registered in the Japan Registry of Clinical Trials, jRCTs031240743.

Keywords: NSCLC, interstitial lung disease, carboplatin plus nab-paclitaxel

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.27 An Exploratory Clinical Study of TROP2 ADC SHR-A1921 Combined With Adebrelimab for Advanced NSCLC After Failure of First-line Standard Therapy

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Introduction: Following first-line standard therapy, nearly all patients with advanced non-small cell lung cancer (NSCLC) experience disease progression due to treatment resistance. There is an urgent need to explore safer and more effective second-line treatment strategies beyond single-agent chemotherapy to address resistance after first-line immunotherapy.Antibody-drug conjugates (ADCs), composed of monoclonal antibodies linked to cytotoxic payloads, represent a novel therapeutic approach. Trophoblast cell-surface antigen 2 (TROP2), a transmembrane glycoprotein, plays a critical role in embryonic development and tumor cell proliferation, invasion, and metastatic dissemination.Combining ADCs with PD-1/PD-L1 inhibitors may yield synergistic efficacy, though such combinations remain underexplored in second-line settings. This study aims to evaluate the efficacy and safety of TROP2 ADC (SHR-A1921) combined with PD-L1 inhibitor adebrelimab in patients with advanced NSCLC who progressed after first-line standard therapy.

Methods: This prospective, single-arm, phase II clinical trial (NCT06480136) enrolls patients with advanced oncogenic driver negative NSCLC (stage IIIB-IV per IASLC 8th edition TNM staging) who had progressed after first-line immunotherapy combined with chemotherapy. Participants will receive SHR-A1921 (3 mg/kg, IV, Q3W) plus adebrelimab (1200 mg, IV, Q3W) until disease progression, intolerable toxicity, withdrawal of consent, or other discontinuation criteria (whichever occurs first). Adebrelimab will be administered for a maximum of 35 cycles or 2 years (whichever comes first), after which patients may continue SHR-A1921 monotherapy until discontinuation criteria are met. The primary objective of this study is to evaluate the efficacy of the combination. Secondary objective is to evaluate the safety. And the exploratory objective is to evaluate the dynamic change of biomarkers during treatment. Enrollment began on July 8, 2024, and the study is ongoing.

Keywords: Non-small cell lung cancer, Antibody-Drug Conjugate, Immunotherapy Resistance

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.28 KEYMAKER-U01 Substudy 01G: Pembrolizumab+Patritumab Deruxtecan±Chemotherapy in Previously Untreated Stage IV NSCLC

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Introduction: Pembrolizumab plus chemotherapy is a standard of care, first-line therapy for patients with metastatic non-small-cell lung cancer (NSCLC) with no targetable genetic mutations. Despite advances in treatment for this patient population, there remains an unmet need. Patritumab deruxtecan (HER3-DXd) is an investigational antibody-drug conjugate (ADC) against human epidermal growth factor receptor 3 (HER3), conjugated with a topoisomerase I inhibitor payload, resulting in apoptosis of target cells. HER3 has been shown to be expressed in NSCLC tumors, with an association between HER3 expression and a shorter time to progression. The addition of ADCs to immune checkpoint inhibitors has shown promising antitumor activity. The ongoing phase 1/2 KEYMAKER-U01 umbrella study (NCT04165798) is evaluating investigational agents in combination with pembrolizumab, with or without chemotherapy. We present the study design for KEYMAKER-U01 substudy 01G (NCT06731907), which is evaluating pembrolizumab in combination with HER3-DXd, with or without platinum-based chemotherapy, in previously untreated participants with stage IV NSCLC.

Methods: In this phase 2, rolling-arm, multicenter, open-label, signal-finding substudy, eligible participants are aged ≥18 years with previously untreated stage IV squamous or nonsquamous NSCLC (per American Joint Committee on Cancer v8) with measurable disease per RECIST v1.1 by investigator (verified by blinded independent central review [BICR]) with no EGFR, ALK, or ROS1 alterations, and ECOG PS of 0 or 1. Participants will be randomly assigned 1:2 to Arm 1 and Arm 2, and the number of participants with nonsquamous NSCLC will be limited to 70% per treatment arm. Participants in Arm 1 will receive pembrolizumab 200 mg IV Q3W up to 35 cycles with carboplatin area under the curve 5 mg/ml/min (nonsquamous histology) or 6 (squamous) IV Q3W for 4 cycles, and either paclitaxel 200 mg/m2 IV Q3W or nab-paclitaxel 100 mg/m2 IV QW for squamous histology, or pemetrexed 500 mg/m2 IV Q3W for nonsquamous histology. Participants in Arm 2 will receive pembrolizumab 200 mg IV Q3W up to 35 cycles with HER3-DXd 5.6 mg/kg IV Q3W. Participants can receive HER3-DXd until progressive disease or unacceptable toxicity. Randomization will be stratified by histology (squamous vs nonsquamous) and PD-L1 tumor proportion score (<50% vs ≥50%). The primary objectives are ORR per RECIST v1.1 by BICR, AEs, and treatment discontinuation due to AEs. The secondary objectives are duration of response and PFS per RECIST v1.1 by BICR, and OS. Enrollment for this study will be ongoing globally.

Keywords: Patritumab deruxtecan (HER3-DXd), metastatic non–small-cell lung cancer, antibody-drug conjugate

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.29 NAPISTAR 1-01: An International Phase I/II Trial of the Novel ADC TUB-040 in Advanced/ Metastatic NSCLC Adenocarcinoma

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Introduction: NaPi2b, encoded by SLC34A2, is a sodium-dependent phosphate transporter that is overexpressed in various cancers, with particularly high levels of expression in non-small cell lung cancer (NSCLC) adenocarcinomas. This clinically validated antigen is targeted by TUB-040, a next-generation antibody-drug conjugate (ADC). TUB-040 combines a NaPi2b-specific, Fc-silenced monoclonal antibody with exatecan, a potent topoisomerase-I inhibitor with a robust bystander effect. Antibody-drug conjugation is via a cleavable dipeptide linker (P5) which enables an optimal, homogeneous and stable drug-to-antibody (DAR) ratio of 8 and prevents non-specific interactions with membranes by increasing hydrophilicity. Preclinical studies demonstrated potent anti-tumor activity, including long-lasting tumor regression at doses as low as 1 mg/kg and durable responses in tumors with low NaPi2b expression.

Methods: NAPISTAR 1-01 (NCT06303505) is an ongoing international (EU, UK, US), open-label, multicenter, Phase I/IIa study investigating the safety, tolerability, and efficacy of TUB-040 in patients with recurrent advanced or metastatic NSCLC adenocarcinoma, including those with actionable genomic alteration (AGA) that progressed after targeted therapy, and separately in patients with platinum-resistant ovarian cancer. TUB-040 is administered intravenously every three weeks (Q3W) as a monotherapy until disease progression or unacceptable toxicity. In Phase I, a stepwise dose-escalation strategy is employed using accelerated titration design (ATD), followed by a Bayesian Optimal Interval (BOIN) model to determine the maximal tolerated dose (MTD) and refine dosing as pre-defined safety parameters are met. The dose-escalation framework includes initial double-dosing steps with a 100% increment over the standard dose, transitioning to modified Fibonacci increments (67%, 50%, and 33% dose increments) with intra-patient escalation permissible at low exposure levels. Phase IIa involves the randomization of patients for dose optimization at two or more doses to further characterize the safety profile and identify the optimal therapeutic dose.

Results: This trial will identify the optimal dose for TUB-040, a first-in-class ADC targeting NaPi2b. TUB-040 offers a novel therapeutic strategy for advanced NSCLC adenocarcinoma patients with limited treatment options. The high prevalence of NaPi2b expression in adeno-NSCLC highlights the potential of TUB-040 to address this significant unmet medical need.

Conclusions:

Keywords: advanced metastatic NSCLC adenocarcinoma, ADC, NaPi2b

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.30 A Phase II Clinical Study of Tafolecimab Combined With Sintilimab in the Treatment of Advanced NSCLC Who Failed the Previous Immunotherapy

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Introduction: Lung cancer has emerged as the malignancy with the highest global mortality rate, exhibiting escalating incidence and mortality worldwide. Immunotherapy represents a transformative breakthrough in oncology, particularly in non-small cell lung cancer (NSCLC), where immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies) demonstrate compelling efficacy and manageable safety profiles as monotherapy or combination regimens. However, over 60% of patients experience treatment failure due to acquired resistance despite initial response, with limited therapeutic options post-resistance. Novel strategies are urgently needed to address this clinical challenge.Tafolecimab, a recombinant fully human IgG2 anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) agent, is approved for cardiovascular indications. Emerging preclinical evidence identifies PCSK9 as a potential target to enhance immunotherapy efficacy. Our prior research revealed an inverse correlation between serum PCSK9 levels and immunotherapy outcomes in NSCLC, where elevated PCSK9 predicts inferior responses. This phase II trial investigates the safety and efficacy of Tafolecimab combined with Sintilimab in advanced NSCLC patients after immunotherapy failure.

Methods: This investigator-initiated phase II trial (ChiCTR2400085872) evaluates safety, efficacy, and biomarkers of Sintilimab (200mg, iv, d1, Q3W) plus Tafolecimab (600mg, sc, d1, Q6W) in advanced NSCLC patients with prior immunotherapy failure. Enrolled patients receive combination therapy until disease progression (RECIST 1.1), intolerable toxicity, initiation of new antitumor therapy, withdrawal of consent, loss to follow-up, death, or investigator discretion, whichever occurs first. Sintilimab treatment is capped at 24 months.The primary endpoints are objective response rate (ORR) per RECIST 1.1 and safety profile. Secondary endpoints include progression-free survival (PFS), overall survival (OS), 1-year PFS rate, disease control rate (DCR), and duration of response (DOR).

Keywords: Non-small cell lung cancer, Immunotherapy, combination

P3.18.31 Phase II Study of CBDCA + Nab-PTX + Tremelimumab+Durvalumab for TTF-1 Negative Advanced non-sq NSCLC (WJOG17223L, TURNING)

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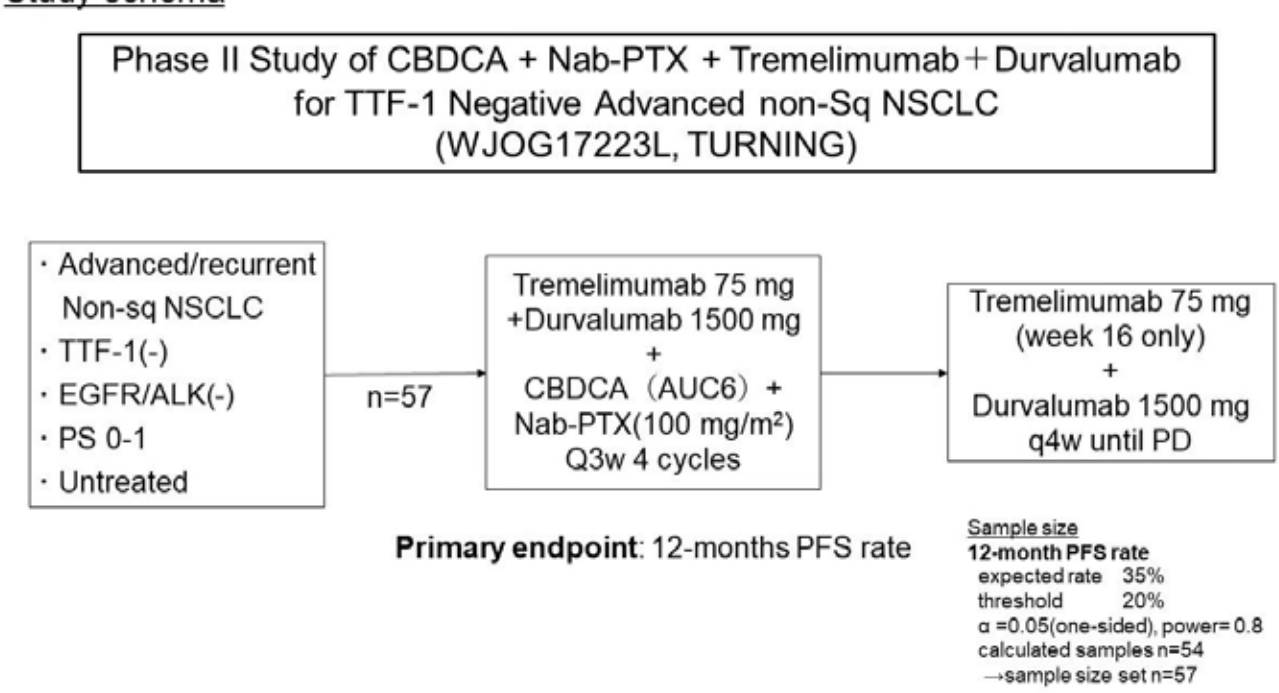
Introduction: Thyroid transcription factor-1 (TTF-1) expression in advanced non-squamous (non-sq) non-small cell lung cancer (NSCLC) has been associated with the efficacy of pemetrexed and PD-1/PD-L1 inhibitor monotherapy. Notably, TTF-1 negative NSCLC demonstrates poor outcomes with platinum + pemetrexed + PD-1/PD-L1 inhibitor therapy, highlighting a critical need for alternative treatments. Given the high unmet need for effective therapies in TTF-1 negative NSCLC, novel treatment strategies are essential. The POSEIDON trial showed that tremelimumab plus durvalumab combined with chemotherapy significantly improved overall survival (OS) and progression-free survival (PFS) versus chemotherapy. We investigate the efficacy and safety of carboplatin (CBDCA) + nab-paclitaxel (nab-PTX) + tremelimumab + durvalumab combination therapy in untreated advanced or postoperative recurrent TTF-1 negative non-squamous (sq) NSCLC.

Methods: This multicenter, single-arm phase II trial enrolls previously untreated advanced or recurrent TTF-1 negative non-sq NSCLC patients aged ≥18 years with ECOG performance status (PS) 0-1. TTF-1 expression is evaluated by immunohistochemical staining of tumor samples at each institute. A specimen is considered TTF-1 negative if none of the tumor cell nuclei exhibit any level of immunoreactivity. Eligible patients have no sensitizing EGFR mutations or ALK rearrangements; stable, treated brain metastases are permitted. The patients receive CBDCA (AUC6, day1) + nab-PTX (100 mg/m2, day1,8,15) + tremelimumab (75 mg/body, day1) + durvalumab (1,500 mg/body, day1) induction therapy for up to four 21-days cycles followed by durvalumab (1,500 mg/body every 4 weeks) until disease progression (PD) or unacceptable adverse events. One additional tremelimumab (fifth dose) is administered at cycle 6/week 16. The primary endpoint is the 12-month PFS rate as assessed by investigators per RECISTv1.1. The secondary endpoints are PFS, OS, objective response rate, and safety. We assumed the threshold of the 12-month PFS rate to be 20% and the expected rate to be 35% with a significant level α=0.05 (one-sided) and power 0.8. The calculated sample size was 54, with a final enrollment target of 57 to account for ineligible patients. Recruitment started in February 2025 at 30 sites in Japan.



Keywords: TTF-1, Tremelimumab, Durvalumab

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.32 Tislelizumab Combined With Bevacizumab and Nab-Paclitaxel as Second-Line Therapy for PD-1/L1 Inhibitor-Resistant Advanced NSCLC

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Introduction: Currently, immunotherapy in combination with chemotherapy has emerged as the first-line standard treatment for advanced non-small-cell lung cancer (NSCLC) patients with negative driver genes. Nevertheless, for these patients who develop resistance following first-line immunotherapy, the standard second-line treatment remains the chemotherapy regimen centered around docetaxel. There is no established standard recommendation regarding the continuation of immunotherapy in the second-line setting after progression during first-line immunotherapy. Both prospective studies and retrospective real-world data analyses have demonstrated that the overall disease response rate of immunotherapy combined with anti-angiogenesis therapy in the second-line and higher-line settings for the population with first-line immunotherapy resistance ranges from 7% to 30%. This study aims to explore the efficacy and safety of Tislelizumab (Tis) in combination with bevacizumab (Bev) and Nab-paclitaxel (Nab) as a second-line treatment strategy for non-squamous NSCLC patients with resistance to first-line PD-1/L1 inhibitor.

Methods: In this single-arm, prospective phase II study, a total of 46 patients with driver gene-negative NSCLC who have developed resistance following first-line immunotherapy combined with chemotherapy will be recruited. Patients who develop disease progression during the first 2 to 4 cycles of first-line treatment with PD-1/L1 inhibitor in combination with chemotherapy will be excluded. Enrolled patients will receive Tislelizumab (Tis, 200 mg, administered every 3 weeks), combined with Bevacizumab (Bev, 7.5 mg/kg, every 3 weeks) and Nab-paclitaxel (Nab, 125 mg/m^2 on day 1 and day 8, every 3 weeks) for 4 to 6 cycles. Subsequently, they will undergo maintenance therapy with Tis plus Bev until disease progression or the occurrence of intolerable toxicity, with a maximum treatment duration of 2 years. The primary endpoint is the objective response rate (ORR) based on the Recist 1.1 criteria in the intention-to-treat (ITT) population. Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR), and safety (evaluated according to CTCAE 5.0). The trial recruitment (ChiCTR2500099531) is currently ongoing.

Keywords: Tislelizumab Combined with Bevacizumab and Nab-pac, Second-Line Treatment for First-Line PD-(L)1 inhib, An Exploratory Study

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.33 Intrapleural Anti-PD-1 Antibody for the Treatment of Advanced Non-Small Cell Lung Cancer With Malignant Pleural Effusion

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Introduction: The presence of malignant pleural effusion (MPE) remains a challenge in clinical treatment. This study aimed to evaluate the safety and efficacy of intrapleural administration of anti-programmed cell death 1 (PD-1) antibody, specifically targeting patients with advanced non-small cell lung cancer (NSCLC) complicated by MPE.

Methods: From May 2019 to December 2023, a total of 16 advanced NSCLC patients with MPE were enrolled. Each patient received a single intrapleural dose of 100 mg of sintilimab. The primary outcome was safety, while secondary outcomes included the proportion of participants who achieved successful pleurodesis by day 35 and day 70 post-intervention; median pleural progression-free survival (mPPFS); the objective response rate (ORR) of extra-pleural tumor at both day 35 and day 70.

Results: Among the 16 patients, the proportion of participants with successful pleurodesis at day 35 was 75.0% (12/16), which decreased to 56.3% (9/16) by day 70. The mPPFS was 10.4 weeks (95% CI: 7.6-13.3 weeks). The ORR of extrapleural tumors at day 35 was 12.5%, with 12.5% (2/16) of patients achieving partial remission (PR), 81.3% (13/16) maintaining stable disease (SD), and 6.3% (1/16) experiencing disease progression (PD). As for safety, the treatment-related adverse events (TRAEs) were well-tolerated. However, 93.8% (15/16) patients experienced treatment-emergent adverse events (TEAEs). The incidence rate of grade 3 TEAEs was 25.0% (4/16), and no grade 4 TEAEs occurred in any patients.

Conclusions: Intrapleural injection of anti-PD-1 antibody demonstrates promising efficacy and a tolerable safety profile as a novel therapeutic strategy for managing MPE in advanced NSCLC.$$graphic_{A677B7CF-5659-4B5B-9F32-996ACC7741C1}$$

Keywords: Malignant pleural effusion, Anti-PD-1 antibody, Intrapleural injection

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.34 TACTI-004, a Phase 3 Trial of Eftilagimod Alfa Plus Pembrolizumab (P) + Chemotherapy (C) vs Placebo + P + C in 1St Line NSCLC

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Introduction: Eftilagimod alfa (E), an antigen presenting cell activator, binds to a subset of MHC class II molecules to mediate T cell (CD4/CD8) recruitment/activation. Prior studies in first line (1L) non-small cell lung cancer (NSCLC) (TACTI-002 [NCT03625323]: combining E + pembrolizumab (P); INSIGHT-003 [NCT03252938] combining E with chemotherapy + P [SoC]) showed encouraging efficacy results across all PD-L1 strata & excellent safety profiles. TACTI-004 is a double-blinded, randomized, placebo-controlled phase 3 study testing E + SoC vs. placebo + SoC in 1L NSCLC patients (pts).

Methods: Approximately 756 pts with 1L NSCLC will be enrolled, irrespective of PD-L1 status, & randomized 1:1 to receive either E + SoC or placebo + SoC. The dual primary endpoint (EP) is overall survival & progression-free survival (RECIST 1.1). Secondary EPs include ORR, disease control rate, duration of response, quality of life, safety & biomarkers. Pts will receive 30 mg E SC q2w for 24 weeks, then q3w and P IV at 200 mg (30 min) q3w both for up to 2 yrs. Chemotherapy choice will be histology-dependent: non-squamous NSCLC pts will receive IV cisplatin (75 mg/m2) or carboplatin (AUC 5 or 6) + pemetrexed (500 mg/m2) q3w for 3 mo, then maintenance pemetrexed q3w. Squamous NSCLC pts will receive carboplatin (AUC 5 or 6) + paclitaxel (175 or 200 mg/m2) q3w for 3 mo.Imaging will be performed q6w until week 18, q9w until week 54 & q12w thereafter. Testing for PD-L1 (22C3) & genetic alterations will be prospectively assessed.Key inclusion criteria: Adults diagnosed with measurable advanced/metastatic (A/M) NSCLC (squamous or non-squamous), not amenable to curative treatment nor locally available oncogenic driver mutation-based 1L therapy. Treatment-naïve for systemic therapy (previous palliative radiotherapy for A/M disease acceptable). Expected survival >3 months & ECOG 0 or 1. Tumour tissue must be available for PD-L1 central testing. Pts may not have tumours with EGFR mutations nor ALK or ROS1 translocations. Stable brain metastasis is acceptable.

Keywords: Advanced/Metastatic NSCLC, Immunotherapy, Chemotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.35 ARTEMIDE-Lung02: A Phase 3 Global Study of Rilvegostomig or Pembrolizumab Plus Chemotherapy for 1L Metastatic Squamous NSCLC

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Introduction: In the United States, squamous histology accounts for approximately 30% of all non-small-cell lung cancers (NSCLCs), with squamous metastatic NSCLC (mNSCLC) associated with a poor prognosis. In this population, immunotherapy targeting programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) represents the standard of care, with the most common first-line (1L) treatment approach being platinum-based chemotherapy combined with anti-PD-1/PD-L1 immunotherapy. Inhibition of the co-inhibitory T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) pathway is being investigated in combination with PD-1/PD-L1 blockade to increase immunotherapy efficacy in NSCLC, as well as other cancer types. Rilvegostomig is a monovalent, bispecific, humanised IgG1 monoclonal antibody targeting both PD-1 and TIGIT receptors that shows antitumor response with a manageable safety profile in NSCLC based on preliminary results (Hiltermann TJN, et al. J Thorac Oncol 2024. Abs OA11.03). ARTEMIDE-Lung02 (NCT06692738) is a phase 3, randomised, double-blind, multicentre study that will assess the efficacy and safety of rilvegostomig versus pembrolizumab, both in combination with platinum-based doublet chemotherapy, as 1L treatment for participants (pts) with squamous mNSCLC.

Methods: Approximately 880 pts will be randomised 1:1 to either Arm A: rilvegostomig + chemotherapy (carboplatin + paclitaxel or nab-paclitaxel) intravenous (IV) every three weeks (Q3W) for 4 cycles followed by rilvegostomig IV Q3W, or Arm B: pembrolizumab + chemotherapy IV Q3W for 4 cycles followed by pembrolizumab IV Q3W. Eligible pts will have histologically confirmed squamous mNSCLC not amenable to curative treatment, tumours expressing PD-L1 (TC ≥1%), no documented mutations in oncogenes with an approved 1L therapy available, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Dual primary endpoints are progression-free survival (Response Evaluation Criteria in Solid Tumors v1.1 by blinded independent central review) and overall survival. Additional endpoints include safety/tolerability and biomarkers. Enrolment is planned across approximately 350 sites in 25-30 countries.

Keywords: Rilvegostomig, Metastatic squamous non-small cell lung cancer, Bispecific antibody

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.36 Peripheral Immune and Hormonal Signatures Associated With Sex Differences in NSCLC Response to Checkpoint Inhibition

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Introduction: Immune checkpoint inhibitors (ICIs) have markedly improved outcomes in non-small cell lung cancer (NSCLC), yet their efficacy varies by sex. Recent research has highlighted sex-based differences in immune function and ICI efficacy, with potential explanations including hormonal variances and distinct inflammatory profiles between sexes. The ALICE (alloimmunization and alloantibodies in male and female NSCLC patients treated with ICIs) study is a prospective, translational cohort study examining gender differences in response to checkpoint inhibition in NSCLC. This branch of the ALICE study aims to investigate the interplay between estrogen signaling and cytokine dynamics in shaping immune exhaustion, tumor progression, and therapeutic response.

Methods: Male and female patients with NSCLC treated with ICI were included in a prospective cohort. Blood and tumor samples were collected for HLA profiling, HLA antibodies, immune cell subpopulations, hormone levels and cytokine profiles. This interim analysis presents hormone levels in the first subcohort of ALICE patients in correlation with gender, tumor diagnosis and response to checkpoint inhibition. The interim analysis includes 59 patients with confirmed diagnosis of NSCLC in disease stage I-IV and current or previous ICI treatment. Peripheral blood samples were collected to measure circulating estrogen concentrations and to profile inflammatory markers using a 15-plex cytokine panel (targeting: IFNγ, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-15, IL-17A, IL-23, TNFα, TNFβ). The main goal is to examine potential associations between hormone and cytokine levels and objective response to ICI treatment. Secondary analyses will assess how these biomarkers relate to clinical parameters such as sex, disease stage, and tumor progression. Progression-free survival (PFS) will be evaluated via Kaplan-Meier estimates and log-rank testing, with Cox proportional hazards modeling to explore predictors of immune response variability following ICI therapy.

Results: This first interim analysis of the ongoing prospective ALICE study includes 59 patients with histologically confirmed NSCLC, comprising 27 females and 32 males. The majority of patients had adenocarcinoma (n=47), while 8 had squamous cell carcinoma and 4 had other histologies, including adenosquamous carcinoma. Participant enrollment and biospecimen collection are ongoing. Final analyses will be conducted upon completion of target accrual in both male and female cohorts to enable adequately powered sex-specific comparisons. In this interim cohort, circulating estrogen levels in female patients were uniformly low, consistent with postmenopausal status. Unexpectedly, two male patients—one with adenocarcinoma and one with adenosquamous carcinoma—demonstrated markedly elevated estrogen levels. These findings warrant further investigation into the potential immunological or tumor-intrinsic implications of aberrant hormone profiles in male NSCLC patients receiving immune checkpoint inhibitors.

Conclusions: This interim analysis of estrogen levels and cytokine profiles during checkpoint inhibition provides a deeper understanding of sex-dependent immune-inflammatory-hormonal signatures which could lead to more effective gender-based medicine strategies. Sex related differences in the immune system and hormone levels influence the response to ICI-therapy and may account for some gender-specific differences in treatment success. These findings could reveal individualized immunotherapy treatment strategies for patients suffering from NSCLC.

Keywords: NSCLC, sex differences, immune checkpoint inhibition

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.37 A Phase 3 Trial of First-Line MK-3475A (Subcutaneous Pembrolizumab) for Stage IV NSCLC With PD-L1 TPS =50%

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Introduction: First-line treatment for patients with stage IV non-small-cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥50% and no targetable genetic alterations includes intravenous (IV) administration of the anti-PD-1 monoclonal antibody (mAb) pembrolizumab. However, evidence suggests that patients prefer subcutaneous (SC) versus IV administration of anticancer therapy, mainly due to reductions in clinic time and improved comfort with the SC administration route. MK-3475A is pembrolizumab with the permeation enhancer berahyaluronidase alfa (MK-5180), a variant of human hyaluronidase developed and manufactured by Alteogen Inc., for SC administration ("pembrolizumab SC"). We present the study design of MK-3475A-F84 (NCT06698042), a phase 3, randomized, active-controlled, open-label study of pembrolizumab SC in participants (pts) with previously untreated stage IV NSCLC and PD-L1 TPS ≥50%.

Methods: Eligible pts are aged ≥18 years with previously untreated histologically or cytologically confirmed stage IV (per American Joint Committee on Cancer v8) squamous or nonsquamous NSCLC with PD-L1 TPS ≥50%; no EGFR, ALK, or ROS1 alterations; and measurable disease per RECIST v1.1 as assessed by the investigator. Additional eligibility criteria include an ECOG PS of 0 or 1 and provision of an archival tumor sample or newly obtained core or biopsy of a nonirradiated tumor. Pts are randomized 1:1 to either pembrolizumab SC 790 mg or pembrolizumab IV 400 mg Q6W for ≤18 cycles or until PD, unacceptable toxicity, or pt/physician decision. Randomization is stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and region (East Asia vs North America/Western Europe/Australia/New Zealand vs rest of world). The dual primary objectives are to compare model-based pembrolizumab cycle 1 area under the curve 0-6 weeks (AUC0-6wk) and steady-state (cycle 3) trough concentration (Ctrough) for pembrolizumab SC vs pembrolizumab IV Q6W; noninferiority will be evaluated with the noninferiority margin of 0.8. Secondary objectives include exposure (cycle 1 maximum concentration [Cmax] and Ctrough, and steady state [cycle 3] Cmax and AUC0-6wk) of pembrolizumab SC vs pembrolizumab IV Q6W, anti-pembrolizumab antibody levels, cycle 1 and steady-state (cycle 3) Ctrough of pembrolizumab SC vs pembrolizumab IV Q3W, ORR, PFS, and duration of response (each per RECIST v1.1 by blinded independent central review), OS, safety, and pt-reported outcomes. Recruitment is ongoing.

Keywords: pembrolizumab SC, anti-PD-1, NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.38 Phase 3 eVOLVE-Lung02 Trial of Volrustomig + Chemotherapy (CT) vs Pembrolizumab + CT in Metastatic NSCLC With PD-L1 TC <50%

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Introduction: Immunotherapies targeting programmed celldeath-1 (PD-1) and its ligand PD-L1 have transformed the treatment of 1Lmetastatic NSCLC (mNSCLC). However, in a subset of patients with PD-L1-low(i.e. TC <50%) or PD-L1-negative (i.e. TC <1%) disease, anti-PD-(L)1therapies alone or in combination with CT are associated with shorter overallsurvival (OS) than in patients with PD-L1 TC ≥50% disease regardless of NSCLChistology. Dual inhibition of PD-(L)1 and CTLA-4has shown survival benefit in patients with PD-L1-low and PD-L1-negative mNSCLCand is used in clinical practice to address the poorer prognosis of thesepatients. Achieving further efficacy improvements with monospecific CTLA-4 inhibitors at higher treatment doses isclinically restrained by toxicity. Volrustomig (MEDI5752) is a monovalent,PD-1/CTLA-4 bispecific, humanized IgG1 monoclonal antibody engineered tospecifically inhibit PD-1 with increased CTLA-4 blockade on PD-1-positiveactivated T cells compared to PD-1-negative T cells. Data from the first-in-humanphase 1/2 study (NCT03530397) showed evidence of T-cell activation andexpansion of new and existing T-cell clones at pharmacodynamic levels exceedingthose clinically feasible with coadministered anti-PD-1 and anti-CTLA-4monospecific antibodies. Encouraging antitumor activity and a manageable safetyprofile were reported in patients with mNSCLC who received 1L volrustomig 750mg with pemetrexed + carboplatin every 3 weeks (Q3W), including those withPD-L1 TC <1% disease. The phase 3, two-arm, randomized, multicenter,open-label eVOLVE-Lung02 study (NCT05984277) will evaluate the efficacy of 1Lvolrustomig plus CT versus pembrolizumab plus CT in patients with PD-L1 TC<50% NSCLC.

Methods: Eligibility criteria include age ≥18 years; ECOG PS 0/1; histologically or cytologically documented squamous or non-squamous stage IV NSCLC not amenable to curative surgery or radiation; PD-L1 TC expression <50%; wild-type EGFR, ALK, ROS1; absence of genomic alterations in other actionable driver oncogenes (e.g. NTRK, BRAF, RET, MET); no prior systemic therapy for mNSCLC or immunotherapy. Exclusion criteria include prior immunotherapy; cardiac disease including but not limited to cardiomyopathy, heart failure, and uncontrolled hypertension; symptomatic brain metastases; and spinal cord compression. Approximately 1200 patients will be randomized 1:1 to receive histology-specific CT (squamous: paclitaxel plus carboplatin; non-squamous: pemetrexed plus carboplatin + pemetrexed maintenance) in combination with either volrustomig or pembrolizumab 200 mg Q3W for 4 cycles; after this volrustomig (Q3W) or pembrolizumab (200 mg Q3W or 400 mg Q6W where locally approved) will be administered until completion of 24 months of treatment or disease progression, or other discontinuation criteria are met. Randomization will be stratified according to histology (squamous vs non-squamous), PD-L1 (TC <1% vs 1-49%), smoking status (never vs former/current), and region (Asia vs rest of world). Primary endpoints are progression-free survival (PFS) per RECIST v1.1 by blinded independent central review and OS in the PD-L1 TC <1% population. Key secondary endpoints are PFS and OS in all randomized patients; other secondary endpoints include objective response rate, duration of response, PFS2 (progression after starting first subsequent therapy or death), safety and tolerability, patient-reported outcomes (including NSCLC Symptom Assessment Questionnaire on disease-related symptoms), pharmacokinetics, and immunogenicity. Enrollment is ongoing at approximately 26 sites in 25 countries/regions.

Keywords: Bispecific antibody, PD-L1-low status, Stage IV NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.39 PRESERVE-003: A Phase 3 Study of Gotistobart Versus Docetaxel in Metastatic NSCLC After Progression on PD-(L)1 Inhibitors

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Introduction: Programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors have improved overall survival of patients with metastatic NSCLC without driver mutations (as first-line monotherapy or in combination with anti-Cytotoxic T-Lymphocyte-Associated Protein 4 [CTLA-4], or in combination with platinum-based doublet agents or as second-line therapy after chemotherapy). However, a significant number of patients do not respond to these immune checkpoint inhibitors or demonstrate disease progression after an initial response. While CTLA-4 is a recognized immunotherapy target in solid tumors, no current anti-CTLA-4 antibodies, including ipilimumab and tremelimumab have demonstrated efficacy as monotherapies to date in NSCLC. Gotistobart (ONC-392/BNT316) is a humanized anti-CTLA-4 mAb with a novel mechanism of action that uniquely preserves CTLA-4 immune checkpoint activity by avoiding lysosomal degradation. A favorable safety profile and anti-tumor activity were previously demonstrated in the first-in-human clinical study (PRESERVE-001) of gotistobart in PD-(L)1 resistant metastatic NSCLC (Kai He et al., JCO 2023;41, 9024-9024).

Methods: PRESERVE-003 (NCT05671510) is a two-stage, randomized, open-label, active-controlled, Phase 3 study of gotistobart versus docetaxel for the treatment of patients with metastatic NSCLC after prior progression on a PD-(L)1 inhibitor. A total of 691 patients will be enrolled, including 213 patients in Stage 1 and 478 patients in Stage 2. In the ongoing Stage 2 of the pivotal study, 478 patients with a histologically or cytologically confirmed diagnosis of metastatic squamous NSCLC will be randomized 1:1 to receive either gotistobart 6 mg/kg Q3W with 2 loading doses of 10 mg/kg Q3W or docetaxel 75 mg/m2 Q3W. Randomization will be stratified by presence of brain metastases (yes or no), ECOG score (0 or 1), and region (US or ex-US). The primary endpoint is overall survival (OS), which will be assessed in the intent-to-treat (ITT) population. OS will be estimated using a Cox Proportional Hazards model, stratified by stratified by the randomization stratification factors, to calculate for the hazard ratio and its 95% confidence intervals (CIs). Kaplan-Meier estimates of median OS will be presented by treatment arm, along with two-sided 95% CIs. Secondary endpoints include objective response rate and progression-free survival based on RECIST 1.1, and safety.

Keywords: NSCLC, CTLA-4, PRESERVE

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.40 KRAS Peptide Vaccine Combined With Chemotherapy, Nivolumab and Ipilimumab in Advanced KRAS Mutated Non-Small Cell Lung Cancer

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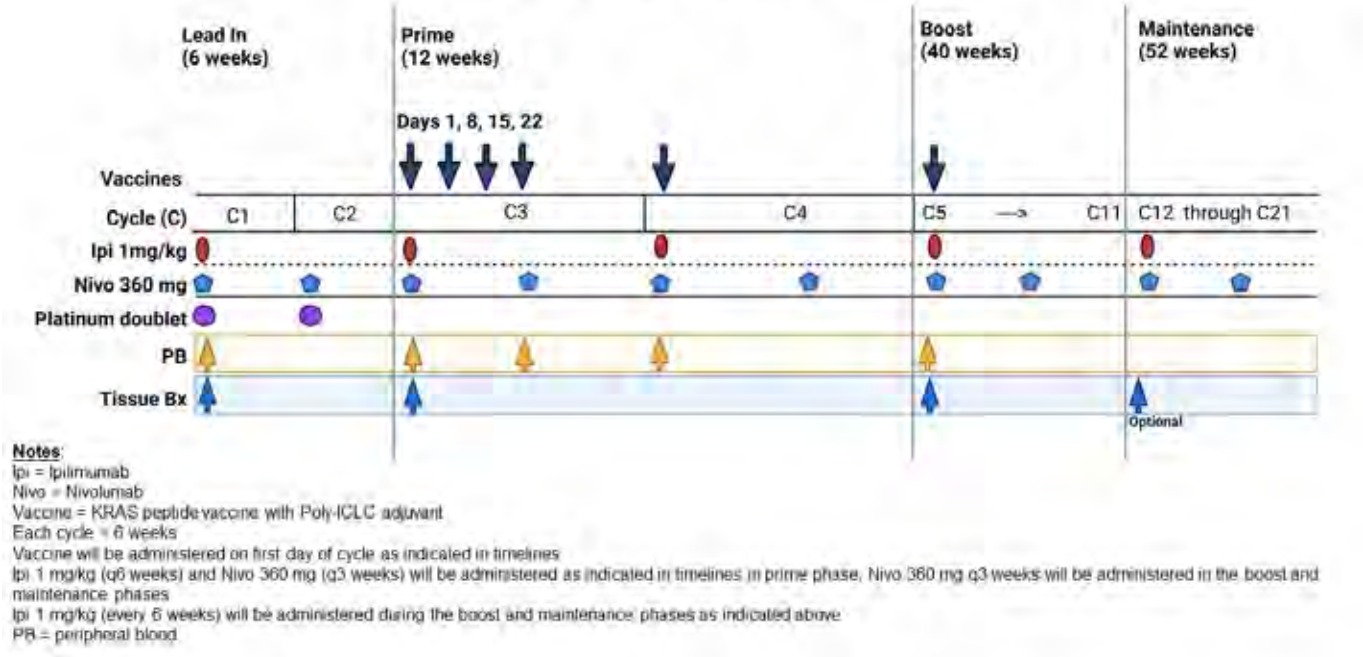
Introduction: KRAS-mutant non-small cell lung cancer (NSCLC) represents a distinct biologic subtype of lung cancer, accounting for around 30% of cases, that has been historically difficult to treat. While some patients with KRAS-mutated tumors derive sustained clinical benefit from immune checkpoint blockade (ICB), others have tumors that appear to have worse clinical outcomes for complex reasons, including co-mutations in certain genes such as STK11 and KEAP1. While chemo-immunotherapy is the most aggressive option for frontline therapy in these patients, many are unable to develop a durable anti-tumor immune response. Given KRAS is an oncogenic driver and less likely to be immunologically edited, it is a prime target for neoantigen-specific vaccination to induce a more effective immune response. In preclinical and early clinical trial data, our group has demonstrated the benefit of combining targeted synthetic peptide vaccines with ICB and adjuvant stimulants in solid tumors. The current study amendment aims to determine the safety and immunogenicity of a novel vaccine in combination with chemotherapy and dual ICB for patients with metastatic KRAS-mutant NSCLC.

Methods: This is a therapeutic amendment to a single institution, phase I trial which will evaluate a pooled mutant-KRAS peptide vaccine in combination with platinum-doublet chemotherapy and nivolumab and ipilimumab in the treatment-naïve metastatic setting. The vaccine consists of poly-ICLC adjuvant admixed with pooled synthetic long peptides (SLPs) corresponding to six common mKRAS subtypes: G12D, G12R, G12V, G12A, G12C, and G13D. Eligible patients must have the presence of a vaccine-targeted KRAS mutation, measurable disease and tumor amenable to biopsy. Treatment is divided into a lead in phase with two cycles of platinum-doublet chemotherapy combined with ipilimumab and nivolumab followed by a priming, boost and maintenance phase (Figure 1). The primary endpoint of the study is to evaluate the safety of administering a mutant KRAS peptide vaccine in combination with chemotherapy and ipilimumab and nivolumab in patients with advanced KRAS-mutant NSCLC. The secondary objectives will be to evaluate efficacy endpoints, and the impact of predicted KRAS mutations on mutant KRAS specific T cell responses in the peripheral blood. Correlative studies will apply multi-omic approaches to identify markers of response and resistance in tumor and plasma samples. The study has enrolled 5 patients to treatment with the combination of ipilimumab and nivolumab with KRAS-mutant vaccine and we will now procced to enroll additional patients to the amendment described herein.

Figure 1: Study Schema



Keywords: KRAS, immunotherapy combination

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.41 A Phase II Study of Second-Line Cadonilimab, Bevacizumab and Docetaxel in Patients With Advanced NSCLC

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Introduction: The second-line treatment options are highly limited for patients with advanced or metastatic non-small cell lung cancer(NSCLC) who have progressed after first-line checkpoint inhibitors(CPI) combined with chemotherapy. Later-line standard treatment recommended by NCCN guidelines are mono-chemotherapy. However, the efficacy is limited with an ORR of 14% -17%, median PFS of 4.0-5.4 months, and OS of 10.5-12 months. Cadonilimab is a humanized immunoglobulin G1 bispecific antibody that simultaneously targets PD-1 and CTLA4. Considering the complex tumor microenvironment after immune resistance, the triplet-regimen of cadonilimab with bevacizumab and docetaxel may exert better anti-tumor effects. Thus, this study aimed to assess the safety and efficacy of the triplet-regimen for the treatment of advanced non-squamous NSCLC without sensitizing EGFR/ALK/ROS1 mutations progressed on CPI.

Methods: AK104-IIT-017 is a single-arm, open-lable, multi-center, phase II trial. Key inclusion criteria are: 1) patients with histologically or cytologically confirmed stage IIIB/IIIC or IV non-squamous NSCLC without sensitizing EGFR/ALK/ROS1 mutations; 2) progressed on not more than one PD-1/L1 inhibitor and one platinum-based chemotherapy (combined or sequential, regardless of sequence); 3) at least two cycles of PD-1/L1 inhibitor (with or without concurrent chemotherapy) with clinical benefits (PFS≥3 months). Other main inclusion criteria include age ≥18 years old, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate organ function. All patients will be simultaneously adminstrated with cadonilimab 10mg/kg Q3W, bevacizumab 7.5mg/kg Q3W, and docetaxel 60 mg/m2 Q3W. Patients will use triplet-regimen for 4 cycles, with continuous maintenance of treatment with cadonilimab and bevacizumab until disease progression, intolerable toxicity, or other reasons. The primary endpoint is 6-month progression-free survival (PFS) rate according to Investigator Assessment (IA). Secondary endpoints include overall survival(OS), PFS, overall response rate(ORR), disease control rate(DCR), duration of response(DoR),etc. We also plan to explore the clinical significance of gene mutations and immunotherapy-related biomarker changes and their correlations with efficacy. Simon's 2-Stage Design is adopted, assuming a 6-month PFS rate of 30% under the null hypothesis and 50% under the assumption that the triplet-regimen is effective. A sample size of 44 patients is required to achieve 80% power at a two-sided significance level of 5%, considering a dropout rate of 10%. All participants would be enrolled simultaneously at three centers in China. So far, one participant has been enrolled. The trial was registered at ClinicalTrials.gov (NCT06793813) and is actively recruiting.

Keywords: bispecific antibody, anti-angiogenesis, later-line combination therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.42 Camrelizumab Combined With Chemotherapy and Local Consolidative Therapy for Untreated Oligometastatic NSCLC With PD-L1 Expression <

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Introduction: In recent years, PD-1/PD-L1 immune checkpoint inhibitors have gained widespread application in the treatment of advanced non-small cell lung cancer (NSCLC), demonstrating significant therapeutic efficacy. Nevertheless, the efficacy of these inhibitors varies among patients with different PD-L1 expression levels. Oligometastatic non-small cell lung cancer (NSCLC) is an intermediate stage between localized and widely metastatic disease. Although local consolidative therapy for oligometastatic NSCLC has demonstrated some benefits, the value of its combination with immunotherapy requires further investigation. This study aims to evaluate the efficacy and safety of camrelizumab combined with chemotherapy and local consolidative therapy in untreated driver-gene-negative and PD-L1 <50% oligometastatic NSCLC patients.

Methods: This prospective, single-arm, phase II study plans to enroll 35 patients aged 18-75 years with pathologically confirmed NSCLC, stage IV oligometastatic disease (≤3 organs and ≤5 metastatic lesions), PD-L1 expression<50%, no driver gene alterations, and no prior systemic treatment for recurrent/metastatic disease. The treatment regimen consists of camrelizumab 200 mg intravenously every 3 weeks plus investigator-chosen chemotherapy for 4-6 cycles, followed by local consolidative therapy (radiotherapy or ablation) .Three weeks after the end of local therapy, maintenance therapy with camrelizumab is initiated, and for non-squamous NSCLC patients, pemetrexed is added to the regimen. The primary endpoint is progression-free survival (PFS). Secondary endpoints include objective response rate (ORR), overall survival (OS), duration of response (DoR), disease control rate (DCR), and safety.Treatment cycles and assessments are scheduled every 3 weeks, with imaging evaluations every 2 cycles during induction and every 3 cycles during maintenance. Safety follow-up occurs 30 days post-treatment, and survival follow-up continues every 2 months. Data analysis will use descriptive statistics, Kaplan-Meier estimation for survival endpoints, and Clopper-Pearson method for response rates.

Keywords: Camrelizumab, Oligometastatic NSCLC, Local consolidative therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.43 A Phase II Study of IDH1 Inhibitor Combined With Serplulimab and Docetaxel in Previously Treated Advanced NSCLC (ChiCTR2400086196)

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases. Over 50% of patients present with advanced disease at diagnosis, and 30-60% of early-stage NSCLC patients experience recurrence after surgery. Although the combination of PD-1/PD-L1 inhibitors and chemotherapy has become the standard first-line therapy for driver mutation-negative advanced NSCLC, most patients progress within 8-10 months. Second-line therapeutic options remain limited: docetaxel demonstrates modest efficacy (objective response rate [ORR] 6-11%; median overall survival [mOS] 5-10 months), while PD-1 inhibitors (e.g., tislelizumab) show improved survival outcomes (ORR 21.9% vs. 7.0%; mOS 17.2 vs. 11.9 months compared to docetaxel). Despite these advances, there remains an urgent need for alternative treatment strategies.Emerging evidence highlights the oncogenic role of isocitrate dehydrogenase 1 (IDH1) in NSCLC progression. Despite low mutation rates (2.01%) in NSCLC, wild-type IDH1 promotes tumor stemness and chemotherapy resistance via enzyme activity-independent serine biosynthesis. Our preclinical studies reveal that IDH1 overexpression drives cancer-associated fibroblast (CAF) activation an enhances TGF-β/CXCL12 secretion, fostering an immunosuppressive “cold” tumor microenvironment. This IDH1-mediated immunosuppressive niche may contribute to immunotherapy resistance, suggesting that IDH1 inhibition could restore immune sensitivity.TQB3454, a novel IDH1 inhibitor, exhibits superior preclinical safety and efficacy compared to AG-120 (ivosidenib). In previous clinical trial ,TQB3454 demonstrated manageable toxicity. Based on these findings, we hypothesize that combining TQB3454, serplulimab, and docetaxel may reverse immunosuppression and enhance antitumor efficacy , thereby overcoming therapeutic resistance in pretreated NSCLC.

Methods:

Design: Single-center, single-arm phase II trial (ChiCTR2400086196).Population:Patients with histologically confirmed locally advanced/metastatic NSCLC,without actionable driver mutations, progression after systemic therapy.Intervention:TQB3454 (600 mg oral QD),Serplulimab (4.5 mg/kg IV Q3W),Docetaxel (60 mg/m^2 IV Q3W).Endpoints: Primary: ORR (RECIST v1.1) and safety (CTCAE v5.0). Secondary: DCR, DOR, PFS, OS.Target accrual: 39 patients. MiniMax two-stage design (α=0.05, power=80%) with H0: ORR=7% (historical docetaxel) vs. H1: ORR=20%.Statistical Design: Survival endpoints analyzed by Kaplan-Meier method.

Keywords: IDH1 Inhibitor, immunotherapy, Combination therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.44 Oral Metronomic Vinorelbine and PD-1 Inhibitors in Elderly Patients With Non-Small Cell Cancer

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Introduction: Immune checkpoint inhibitors have greatly changed the landscape of non-small-cell lung cancer treatment with a significant improvement in survival. There are multiple challenges in the treatment of elderly patients with lung cancer. However, elderly patients are rarely included in clinical studies. We conducted an open-label, non-randomised, phase 2 study to evaluate the efficacy and safety of oral metronomic vinorelbine and PD-1 inhibitors in elderly patients with unoperable, locally advanced or metastatic non-small-cell lung cancer.

Methods: Patients received oral metronomic vinorelbine 40mg every week(20mg for patients over 80 years old), combined with PD-1 inhibitors every 3 weeks. The primary end point was objective response rate (ORR), and the second end points included disease control rate (DCR), progression-free survival (PFS), and safety.

Results: Of the 16 patients enrolled in this study, 12 patients received oral metronomic vinorelbine and PD-1 inhibitors as first-line treatment. The ORR was 31.25% and the DCR was 75%. Median PFS was eight months (95% CI 0-30.651). Median OS was not reached. The median PFS was longer in patients with PD-L1 TPS ≥1% than <1% (not reached versus 5 months(95%CI 0.766-9.234), P=0.046). The most common treatment-related adverse event was immune-related hypothyroidism (31.25%, 5/16) and endocrinopathies (18.75%, 3/16). Only one patient experienced grade 3 or higher adverse event, which were liver function impairment.It was considered to be related to concomitant administration of anti-tuberculosis drugs. No grade 5 treatment-emergent adverse events or death were reported.

Conclusions: The combination of oral metronomic vinorelbine and PD-1 inhibitor is efficient, safe and convenient as treatment for elderly patients with unoperable, locally advanced or metastatic non-small-cell lung cancer.

Keywords: oral metronomic vinorelbine, PD-1 inhibitors, elderly patients with non-small-cell lung cancer

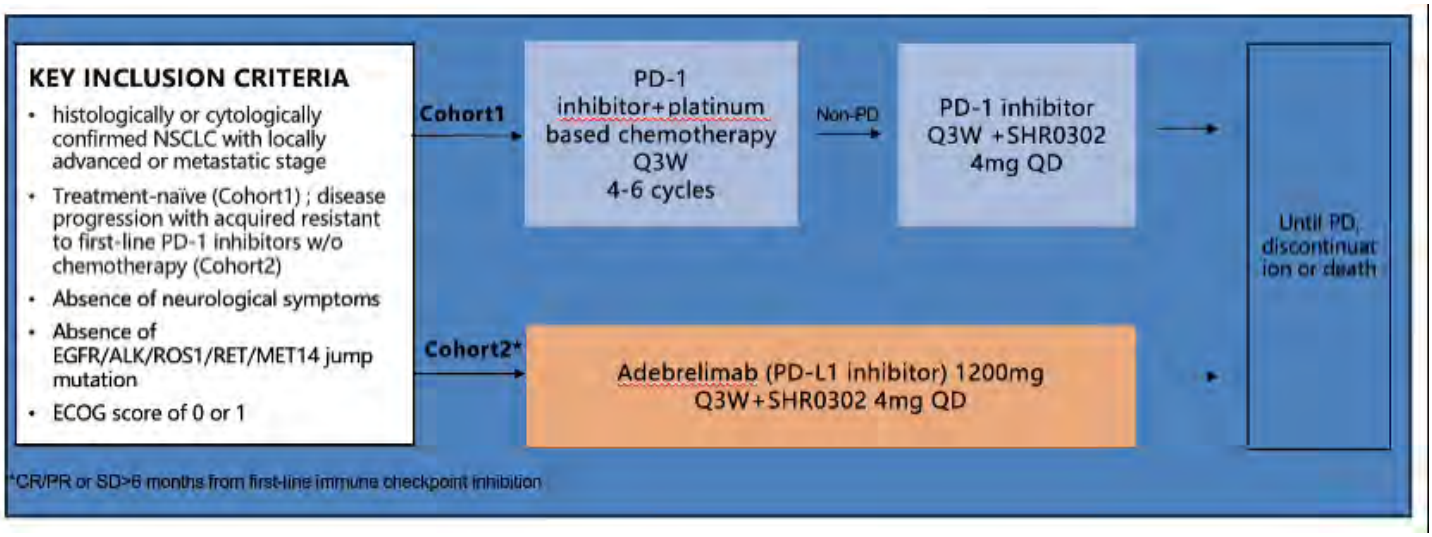
P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.45 A Multi-Cohort, Phase II Study of SHR0302 Combined With PD-1/PD-L1 Inhibitior for Treatment Naïve or Acquired Resistant to Immunology NSCLC

X. Zhang, L. Liu, L. Wang, J. Zhao, J. Wu, C. Su
Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai/CN

Introduction: Recent studies showed that the dysregulated activation of the JAK/STAT pathway, which leads to the prolonged release of IFN-γ, is a significant contributor to the resistance to immune checkpoint inhibitors in cancer immunotherapy. Preclinical and clinical studies have demonstrated that the combination of JAK inhibitors with PD-1 immunotherapy can reverse or delay onset of immunotherapy resistance by modulating the JAK/STAT pathway in Hodgkin's lymphoma and non - small cell lung cancer (NSCLC). SHR0302, being a highly selective JAK1 inhibitor, has shown excellent clinical benefits by effectively inhibiting the JAK/STAT pathway, leading to its approval for the treatment of Ankylosing Spondylitis in China. Preclinical studies also show that the combination of SHR0302 and PD-L1 inhibitor has synergistic potentials for anti-tumor effect in resistant to-immune checkpoint blockade patients. Thus, we conducted a phase 2 clinical trial evaluating SHR0302 combined with PD1/PD-L1 inhibitors as treatment-naïve or acquired resistant to first-line checkpoint inhibitor NSCLC patients.

Methods: Patients will be enrolled into two cohorts. Cohort 1 enrolled first-line metastatic non-small cell lung cancer (NSCLC), who will be administered a combination of anti-PD-1 and SHR0302 in the maintenance treatment after non-PD from 4-6 cycles of anti-PD-1 and platinum-based chemotherapy. Cohort 2 enrolled NSCLC whose disease progressed due to acquired resistance to first-line PD-1 inhibitor, and they will be administered with a combination of Adebrelimab (PD-L1 inhibitor) and SHR0302. Acquired resistance is defined as documented initial objective response (partial or complete response by RECIST or WHO) to therapy or significant and durable (> 6 months) clinical benefit (stable disease defined by RECIST or WHO). Both cohorts will be treated until patients experienced disease progression, intolerable toxicity, or met the criteria for discontinuation of the trial drug. The primary endpoint of this trial is progression - free survival (PFS), while the secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.



Keywords: Immunology, JAK inhibition, NSCLC

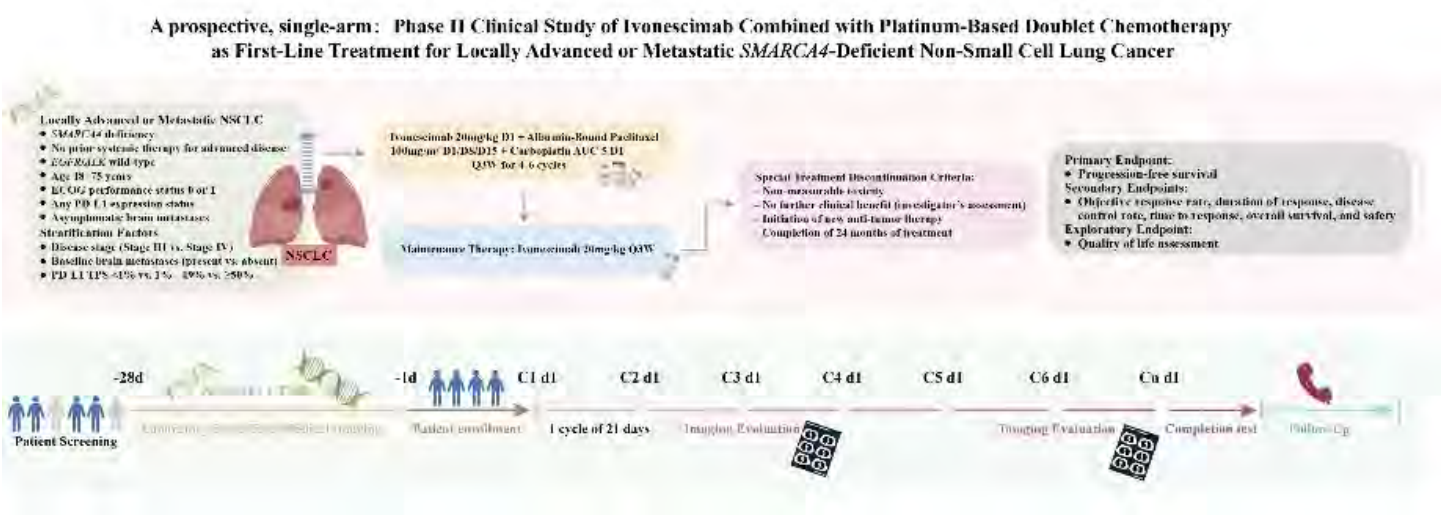
P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.46 Ivonescimab Plus Platinum-Doublet Chemotherapy as First-Line Therapy for Locally Advanced/Metastatic SMARCA4-Deficient NSCLC

Z. Liu[1], J. Li[1], Y. Diao[1], F. Li[1], D. Wang[1], J. Zheng[1], C. Hong[1], J. Liu[2], J. Sun[3], Y. Li[1], Y. Liang[1]
[1]Liaoning Cancer Hospital&Institute, Shenyang/CN ,[2]School of Graduate, Dalian Medical University, Dalian/CN ,[3]China Medical University, Shenyang/CN

Introduction: SMARCA4 deficient non-small cell lung cancer (SMARCA4 -dNSCLC) is a rare primary malignant epithelial tumor originating from the lungs.The incidence of SMARCA4-dNSCLC is about 5% -10%, and it is more common in young or middle-aged male smokers. SMARCA4-dNSCLC grows rapidly, metastasizes quickly, and is insensitive to chemotherapy, targeted drugs, and immunotherapy. Currently, there is no standardized treatment plan.Ivonescimab is a global first-in-class anti-PD-1/VEGF bi-specific antibody, can exert a synergistic effect synergistic effects of vascular endothelial growth factor(VEGF) inhibitors and immune checkpoint inhibitors and may achieve better anti-tumor effects in advanced NSCLC.

Methods: This is a prospective, single arm, exploratory study.Eligible participants are adults aged 18 to 75 years and Histologically or cytologically confirmed, locally advanced (stage IIIB) or metastatic (stage IV) SMARCA4 -dNSCLC that cannot be completely resected by surgery or treated by radical concurrent/sequential chemoradiotherapy (according to the 9th edition of the the International Association for the Study of Lung Cancer, ninth Edition);Group performance status score of 0 or 1 with at least 1 measurable lesion (per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1). Medication regimen:Ivonescimab 20mg/kg D1 + Albumin-Bound Paclitaxel 100mg/m^2 D1/D8/D15 + Carboplatin AUC 5 D1.Q3W for 4-6 cycles.Followed by maintenance therapy with ivonescimab 20mg/kg Q3W.Until disease progression or unacceptable toxicity occurs, or until the 24-month study completion, whichever comes first. Primary endpoint: PFS assessed based on RECIST v1.1. Secondary endpoints: ORR, DoR, DCR, TTR, OS assessed based on RECIST v1.1 and safety assessment. Exploratory endpoints: Health-related quality of life (HRQoL) assessmen.



Keywords: First-line therapy, Ivonescimab, SMARCA4 deficient NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.47 ATTEND: Randomized Phase III Trial of Tislelizumab and Chemotherapy With or Without Diphenhydramine in Advanced Non-Small Cell Lung Cancer

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Tianjin Medical University Cancer Institute and Hospital, Tianjin/CN

Introduction: Despite significant advancements in the treatment of advanced Non-Small Cell Lung Cancer (NSCLC), long-term survival rates continue to be unsatisfactory. While immuno-chemotherapy has been established as a first-line therapy for advanced NSCLC, secondary resistance typically emerges within a few months, posing a critical challenge that urgently requires to be addressed in clinical practice. Histamine, a metabolite of histidine, is released by mast cells and plays a role in allergic reactions, tissue damage, and tumor immunotherapy. Research has demonstrated that the concurrent use of non-steroidal anti-inflammatory drugs can significantly enhance the objective response rate in patients treated with nivolumab. Additionally, the co-administration of aspirin has been shown to lower the mortality rate among patients receiving immunotherapy. Furthermore, the H1 receptor antagonist loratadine has been found to improve survival outcomes for NSCLC. Retrospective studies have indicated that combining immunotherapy with diphenhydramine may not only synergistically boost clinical efficacy but also reduce the incidence of immune-related adverse events. Based on these findings, this prospective study will evaluate the safety and efficacy of diphenhydramine combined with tislelizumab and chemotherapy as the first-line treatment of advanced NSCLC.

Methods: The ATTEND trial is an open-label, multicenter Phase III study that includes patients with Stage IIIB/C NSCLC who are unable to undergo radical surgery or radiotherapy, as well as those with metastatic NSCLC. Patients are randomized (1:1) to receive either tislelizumab (200 mg) plus platinum-based doublet chemotherapy (pemetrexed 500 mg/m^2 for non-squamous cell carcinoma or albumin-bound paclitaxel 260 mg/m^2 for squamous cell carcinoma) every 3 weeks, with or without diphenhydramine (20 mg qd IM on day 0-2). A total of 430 evaluable patients will be enrolled to receive anticancer treatment until disease recurrence or intolerable toxicities. The primary endpoint is progression-free survival. Secondary endpoints include objective response rate, overall survival, and toxicity profile. The ATTEND trial commenced in December 2024, and enrollment is ongoing across 19 centers in China.

Keywords: NSCLC, Tislelizumab, Diphenhydramine

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.48 Phase II Clinical Trial of Trilaciclib in Combination With PD-1 Inhibitor and Chemotherapy as First-Line Treatment for (NSCLC)

Y. Liang[1], Z. Liu[1], J. Li[1], Y. Diao[1], D. Wang[1], J. Zheng[1], C. Hong[1], J. Liu[2], J. Sun[3], Y. Li[1], F. Li[1]
[1]Liaoning Cancer Hospital & Institute, Cancer Hospital of Dalian University of Technology, Shenyang/CN ,[2]School of Graduate, Dalian Medical University, Dalian/CN ,[3]China Medical University, Shenyang/CN

Introduction: This is an exploratory clinical trial evaluating the efficacy and safety of Trilaciclib in combination with PD-1 monoclonal antibody and first-line chemotherapy in patients with advanced non-small cell lung cancer. In the study, Major inclusion age ≥18 years old , and the histology and cytology confirmed late drive gene mutation negative non-small cell lung cancer, all subjects who meet the enrollment criteria will receive Trilaciclib combined chemotherapy and PD-1 monoclonal antibody as the first-line treatment according to the study plan. Trilaciclib will be used before each chemotherapy cycle and will be treated with chemotherapy for 4-6 cycles. Trilaciclib should also be discontinued after chemotherapy. Imaging evaluation was performed every 2 cycles during treatment. The primary endpoint was progression-free survival (PFS), and the key secondary endpoints were antitumor efficacy (ORR, DCR, OS, etc.) and bone marrow protection efficacy (incidence of grade 3 neutropenia during chemotherapy; Incidence of ≥ grade 3 thrombocytopenia; Incidence of grade 3 anemia, etc.), safety and tolerability.

Methods: Medication plan is Trilaciclib 240mg/m2 intravenously for 30 minutes and administered within 4 hours before chemotherapy; Pembrolizumab 200mg Q3W; Or Camrelizumab 200mg Q3W; Or Tislelizumab 200mg Q3W; Or Sintilimab 200mg Q3W; Or Toripalimab 240mg Q3W;Pemetrexed (non-squamous cell carcinoma) is 500mg/m2 Q3W;Paclitaxel Albumin-bound (squamous cell carcinoma) is 260mg/m2 Q3W;Carboplatin is AUC=5, up to 750mg Q3W; At present, this study has passed the Medical Ethics Committee of Liaoning Cancer Hospital, and has completed registration in the Chinese Clinical Trial Registry, The registration number is ChiCTR2500098340.It is expected to take 12 months to complete the enrollment and 24 months to complete the study.

$$graphic_{59E52DFA-741F-443A-BC09-9D4B69989FBC}$$

Keywords: Trilaciclib, Non-small cell lung cancer, Immunotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.49 Efficacy and Safety of Tislelizumab Combined With Tofacitinib and Docetaxel for NSCLC After Failure of First-Line Immunotherapy

W. Xie, L. Cao, J. Zhang
The First Affiliated Hospital of USTC, Hefei/CN

Introduction: Immune checkpoint inhibitors (ICIs), either as monotherapy or in combination, have significantly improved outcomes in patients with driver gene-negative advanced non-small cell lung cancer (NSCLC). However, disease progression is inevitable in most patients, after which options are limited. Overcoming the inherent poor antigenicity and immunosuppressive tumor microenvironment post-immunotherapy may represent a critical strategy for achieving durable responses to ICIs. Recent evidence suggests that Janus kinase inhibitors (JAKi) may enhance antitumor immunity, and combination with ICIs could potentially overcome resistance to prior immunotherapy and restore antitumor immune responses. This study aims to evaluate the efficacy and safety of tislelizumab (a PD-1 inhibitor) in combination with tofacitinib (a JAK inhibitor) and docetaxel, with the goal of optimizing rechallenge strategies in patients with ICI-resistant NSCLC.

Methods: This is an open-label, single-arm, prospective, multicenter phase II trial designed to assess the efficacy and safety of tislelizumab in combination with tofacitinib and docetaxel as second-line treatment for patients with advanced NSCLC who experienced disease progression after first-line immunotherapy. Eligible patients will receive tofacitinib orally at a dose of 5 mg daily, followed by tislelizumab (200 mg) and docetaxel (75 mg/m2) intravenously at day 8 and then every 3 weeks for 2 years or until progression. The primary endpoint is the objective response rate (ORR) as assessed by the investigator using RECIST 1.1 criteria. Secondary endpoints include progression-free survival (PFS), 6-month PFS rate, disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. Exploratory objectives will focus on identifying potential biomarkers through blood, urine, and tumor tissue analyses. Adverse events will be monitored throughout the trial and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Keywords: NSCLC, JAK inhibitor, immunotherapy rechallenge

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.50 Induction Tislelizumab With Chemotherapy Followed by Surgery and Radiotherapy in Stage III-N3 Unresectable NSCLC (HURRICAN

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Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang/CN

Introduction: The current standard of care for patients with unresectable locally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CRT) followed by immunotherapy consolidative. However, up to 30% of patients are ineligible for immunotherapy consolidation. Furthermore, intrathoracic local recurrence remains the predominant mode of treatment failure. Therefore, optimizing local control is a critical priority, particularly for more advanced N3 lymph nodes involvement (part of IIIB and IIIC) patients. To address these challenges, preliminary investigations have explored surgical intervention following immunotherapy-based conversion therapy in N3 patients. However, the feasibility of radical surgery for N3 disease remains constrained. In response, this study aims to evaluate a comprehensive treatment strategy integrating surgery and hypofractionated radiotherapy following induction immunotherapy and chemotherapy, with subsequent immunotherapy consolidation. The objective is to optimize individualized treatment selection, improve local control, and ultimately enhance long-term survival outcomes.

Methods: This is a prospective, multicenter, single arm phase 2 clinical trial enrolling 30 newly diagnosed stage III NSCLC patients with N3 lymph-node metastasis (T1-4N3M0, AJCC 9th edition). Mainly eligible patients must be negative for sensitive gene mutations, treatment-naive for systemic or local therapy, aged ≥18 years, and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with at least one measurable lesion according to RECIST 1.1 criteria at baseline. Key exclusion criteria include invasion of critical structures such as the aorta, trachea, esophagus, or heart by the primary tumor or metastatic lymph nodes, as well as the presence of Pancoast tumors. Following induction therapy with 3-4 cycles of Tislelizumab combined with platinum-based chemotherapy, patients without disease progression will be evaluated by a multidisciplinary team (MDT) and assigned to treatment strategies based on eligibility and patient preference. Patients deemed eligible to surgery will receive standard lung cancer resection (excluding total pneumonectomy), including removal of the primary tumor, ipsilateral hilar, and ipsilateral mediastinal lymph nodes, followed by hypofractionated chemoradiotherapy targeting N3 metastatic lymph nodes. Patients ineligible for or unwilling to undergo surgery will receive definitive conventional CRT. After completion of local treatment, all patients will continue Tislelizumab maintenance therapy until radiographic disease progression, unacceptable toxicity, or completion of one year of treatment. The primary endpoint is the 1-year event-free survival rate (1y-EFS rate). Secondary endpoints include EFS, overall survival (OS), surgical conversion rate, time to distant metastasis (TTDM), time to local recurrence (TTLR), adverse events (AEs), and the impact of the integrated treatment approach on patient-reported outcomes (PROs). Exploratory analyses will be conducted to identify predictive and prognostic biomarkers using tumor tissue and blood samples collected at multiple time points during the study.

Keywords: Stage III-N3 Unresectable NSCLC, Tislelizumab, surgery or chemoradiotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.51 Anlotinib Combined With PD-1 Blockade and Platinum Doublet Chemotherapy for PSC as First Line Treatment

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Nanjing Drum Tower Hospital, Nanjing/CN

Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a unique, highly invasive pulmonary malignancy with a poor prognosis, representing approximately 0.5% of all malignant lung cancers. Many retrospective clinical trials demonstrated good response to imunnotherapy, and ORR was about 30-60%. In this trial, we try to demonstrate the efficacy and safety of Penpulimab combined with anlotinib and platinum doublet chemotherapy as first line treatment for PSC.

Methods: The study included patients with histologically confirmed sarcomatoid carcinoma of the lung; who had not received systemic therapy previously; with measurable lesions (according to RECIST 1.1 criteria); ECOG score 0-1; and aged ≥18 years. The treatment regimen included albumin-bound paclitaxel (100 mg/m^2, d1, d8, d15/q3w or 260mg/m2 d1/q3w), carboplatin (AUC=5, d1/q3w), anlotinib (12 mg, po, qd, d1-14/q3w), and penpulimab (200 mg, d1/q3w) for 4 cycles, following penpulimab and anlotinib for maintenance therapy until progression of disease(PD) or intolerable toxicity. The primary endpoint is PFS, and secondary endpoint included ORR, OS, DCR and safety.

Results: Till March 20, 2025, we enrolled 5 patients. All 5 patients can be evaluated. The ORR is 80% (4/5), and DCR is 100% (5/5). Any grade AE is 100%. The incidence of adverse events at any level is 100%, mainly decreased white blood cells, hypertension, decreased neutrophils, skin reaction of hands and feet, stomatitis, weight loss, and rash.The incidence of adverse events above grade 3 is 40%, mainly increased hypertension, stomatitis, and decreased white blood cells.

Conclusions: Anlotinib combined with PD-1 blockade and platinum doublet chemotherapy is efficacious and AE can be manageable as first line treatment for PSC.$$graphic_{09237E65-9163-43D9-8B75-0AA065617818}$$$$graphic_{18E045F6-7A79-4B06-B56B-DD3E9089524A}$$

Keywords: anlotinib, PD-1 blockade, Pulmonary sarcomatoid carcinoma

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.52 Phase 3 Trial ResQ201A of NAI Plus Tislelizumab and Docetaxel Vs. Docetaxel Monotherapy for Advanced or Metastatic NSCLC Resistant to ICI Therapy

S. Reddy[1], L. Sender[1], R. Blanton[1], A. Malhotra[1], K. He[2], D. Morgensztern[3], J. Wrangle[4], A. Greystoke[5], M. Vincent[6], D. Breadner[6], T. Weitz[1], P.R. Spilman[1], P. Bhar[1], H. Zhang[1], P. Soon-Shiong[1], L. Drusbosky[1]
[1]ImmunityBio, Inc., Culver City/CA/USA ,[2]The Ohio State University Comprehensive Cancer Center, Columbus/OH/USA ,[3]Washington University, St. Louis/MO/USA ,[4]Medical University of South Carolina, Charleston/SC/USA ,[5]Newcastle University, Newcastle/GB ,[6]London Health Sciences Centre, London/ON/CA

Introduction: Immune checkpoint inhibitors (ICIs) that target PD-1 or PD-L1 are approved for use as monotherapy and in combination with chemotherapy in advanced NSCLC. Unfortunately, a majority of patients experience progressive disease with limited treatment options, warranting better options following progression on an ICI. Findings from Phase 2 studies [Wrangle Lancet Oncol. 2018;19(5):694-704; and J. Thorac. Oncol. 2024; 19(10) Suppl.] have demonstrated the potential for the IL-15 receptor superagonist nogapendekin alfa inbakicept (NAI; or N-803) as a novel lymphocyte stimulating agent (LSA) to enhance ICI efficacy, prolonging progression-free survival (PFS) and overall survival (OS) when used in combination with an ICI. ResQ201A is specifically informed by the trial QUILT3.055 wherein median OS was prolonged at 14.3 months overall, and further prolonged to 15.8 months in the 80% of participants wherein NAI increased or maintained absolute lymphocyte counts (ALC) > 1200, and to 21.1 months in those with ALC ≥ 1500. In ResQ201A, monotherapy docetaxel, standard 2nd line therapy for NSCLC, is being compared to combination therapy with NAI, anti-PD-1 tislelizumab [Wang 2021 JAMA Oncol 7], and 2 cycles of docetaxel. NAI, acting as LSA that proliferates and activates NK and T cells, is anticipated to contribute to the efficacy of docetaxel plus tislelizumab therapy in ICI-resistant NSCLC and prolong survival as shown in QUILT 3.055 when administered without chemotherapy.

Methods: In this randomized, open-label phase 3 trial ResQ201A (NCT06745908), up to 462 participants are being enrolled 2:1 in an experimental arm to receive NAI, tislelizumab, and docetaxel or a control arm to receive docetaxel monotherapy. Participants are stratified based on histology, presence of actionable genomic alterations, and geographical region. Experimental arm treatment consists of two 3-week cycles NAI [SC 1.2 mg], tislelizumab [IV 200 mg] plus docetaxel [IV 75 mg/m2] followed by repeated 3-week cycles of NAI (1.2 mg) and tislelizumab (200 mg) without chemotherapy; control arm treatment consists of repeated 3-week cycles with docetaxel (IV 75 mg/m2). Key inclusion criteria are: age ≥ 18 years, ability to provide informed consent, pathologically-confirmed stage IV NSCLC with acquired resistance to an ICI (PD after an initial response or stable disease (SD) (≥ 6 mo. duration) to a single line of anti-PD-(L)1 with or without anti-CTLA-4 or chemotherapy, ECOG performance status of 0 to 2, and measurable tumor lesions according to RECIST v1.1. Key exclusion criteria are: systemic autoimmune disease, history of organ transplant, and positive actionable genomic alterations (AGA) such as ALK AGA. The primary efficacy endpoint is OS by Kaplan-Meier with treatment arm comparison based on the stratified log-rank test and OS hazard ratio (and 95% CI) summarized based on the stratified Cox proportional hazard model, both stratified by the randomization strata. Secondary efficacy endpoints are the immune disease control rate (iDCR - iCR + iPR + iSD [≥ 2 months]) per iRECIST; progression-free survival (iPFS), overall response rate (iORR) and duration of response (iDOR). Safety is assessed by AEs and SAEs graded using the NCI CTCAE v5.0.

Keywords: nogapendekin alfa inbakicept, NAI, lymphocyte stimulating agent

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.53 Phase 3 Clinical Trial ResQ201A of N-803 (NAI), Tislelizumab and Docetaxel Vs. Docetaxel Monotherapy for Advanced NSCLC Resistant to ICI Therapy

P.R. Spilman[1], S. Reddy[1], L. Sender[1], A. Malhotra[1], R. Blanton[1], M. Vincent[2], D. Breadner[2], T. Weitz[1], P. Bhar[1], H. Zhang[1], P. Soon-Shiong[1]
[1]ImmunityBio, Inc., Culver City/CA/USA ,[2]London Health Sciences Centre, London/ON/CA

Introduction: This is a description of the phase 3 clinical trial ResQ201A-NSCLC (USA: NCT06745908 and EU: 2025-521221-32-00) for people with advanced or metastatic nonsmall cell lung cancer (NSCLC). A phase 3 clinical trial looks at how well a possible new treatment works, as well as its side effects, in many people. The participants in this trial have NSCLC and have previously received a type of immunotherapy called an 'immune checkpoint inhibitor' (or ICI) for which the therapy stopped working overtime. ICIs block proteins that prevent immune cells from actively killing tumor cells. In this study, an ICI called tislelizumab will be used with a new treatment called nogapendekin alfa inbakicept (NAI) that is very good at activating immune cells called natural killer and T cells. It is thought these 2 treatments together with docetaxel - a standard chemotherapy used for NSCLC - will be more effective than docetaxel alone. Tislelizumab has already been approved by the U.S.A. FDA for 2 types of esophageal cancer and NAI has already been shown to be effective for a particular type of bladder cancer, for which it was approved by the FDA in 2024.

Methods: The trial is open label, which means the people running the trial and the participants receiving treatment in the study will know the treatment received. Up to 462 participants will be enrolled and assigned to either the group (or 'arm') that receives the experimental combination of the 3 treatments or to the 'control' arm, where they would receive docetaxel alone. In the experimental arm, participants will receive two 3-week cycles of NAI (1.2 mg) by subcutaneous injection, tislelizumab (200 mg) by intravenous (IV) infusion, and docetaxel (75 mg/m2) also by IV, followed by repeated 3week cycles of only NAI and tislelizumab at the same dosage. Participants in the control arm will receive repeated 3-week cycles of docetaxel alone (IV 75 mg/m2). Participants must be at least 18 years of age, be able to understand what will happen on the study (informed consent). and have stage 4 NSCLC that was previously treated with an ICI that either was not effective or that became less effective over time. Participants need to be relatively healthy (ECOG score of 0 to 2). Tumors will be scanned by CT or MRI and measured using systems called RECIST v1.1 and immune RECIST. People who have immune diseases, are receiving treatment after an organ transplant, or who have a genetic alteration termed 'ALK' cannot participate in the study. An important objective is the time a participant survives, called 'overall survival. This will be analyzed using a statistical method called KaplanMeier. Important assessments are changes in the tumor size, if any, and how long it lasts, referred to as the disease control rate, the objective response rate, and progression-free survival. Determination of safety is very important, therefore vital signs and changes in laboratory tests will be recorded, as well as adverse events (AEs) of all severity using the NCI CTCAE v5.0 system.

Keywords: nogapendekin alfa inbakicept, Non-small cell lung cancer, immune checkpoint inhibitor

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.54 Increasing the Dosing Interval of Osimertinib in Patients With EGFR-Mutated Advanced NSCLC (OSI-SAVE Study Design)

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Introduction: Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), is approved as a first-line treatment for locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). At the registered dosage of 80 mg once daily (QD), up to 98% of patients experience adverse events, most frequently diarrhea and rash, while severe toxicity occurs in up to 34% of cases. Phase 2 studies suggest that reducing the dose to 40 mg QD maintains efficacy while decreasing toxicity. Given osimertinib's half-life of 44 hours, extending the dosing interval to 80 mg every other day (QOD) is pharmacokinetically justifiable, as it provides an area under the curve (AUC) equivalent to that of 40 mg QD. This adjusted dosing regimen could reduce adverse events without compromising therapeutic effectiveness. Furthermore, a non-daily regimen will reduce the cost of osimertinib by approximately €3,000 per patient per month in Europe. Given a median progression-free survival (mPFS) of 18.9 months, this could yield substantial savings.

Objective: The primary objective of this trial is to investigate the effectiveness of osimertinib 80 mg QOD compared to the registered 80 mg QD regimen. The primary endpoint is PFS defined as the time from randomisation to clinical or radiological disease progression. Secondary endpoints include overall survival, patient-reported toxicity, quality of life, the cumulative incidence of central nervous system (CNS) metastases and economic assessment. Exploratory endpoints include pharmacokinetics, pharmacogenetics, and circulating tumor DNA.

Methods: This international, randomized controlled, non-inferiority trial (EU trial number: 2024-514693-47-00) will enroll 383 patients to achieve 80% power with a 10% non-inferiority margin. Eligible patients must have received osimertinib 80 mg QD, with or without platinum-pemetrexed chemotherapy, for at least three months to treat EGFR-mutated (exon 19 deletion or L858R), locally advanced or metastatic NSCLC. Secondly, they must have demonstrated a radiological response to treatment. Patients with baseline CNS metastases will be excluded. Patients will be randomized in a 1:1 ratio to receive either osimertinib 80 mg QOD or continue 80 mg QD, with or without chemotherapy, and will be monitored in routine clinical care for up to two years.

Relevance: This is the first large-scale clinical trial to determine whether increasing the dosing interval of osimertinib in NSCLC patients is both safe and effective. If non-inferiority is demonstrated, the results will provide robust evidence to support the adoption of osimertinib 80 mg QOD as a standard-of-care regimen.

Keywords: osimertinib, non-small cell lung cancer, treatment optimization

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.55 A Phase II Study of Repotrectinib in ROS1-Positive Non-Small Cell Lung Cancer Patients With Active Brain Metastasis - REPOSE

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Introduction: A subset of patients with metastatic NSCLC (mNSCLC) have tumors that harbor driver genetic alterations, including ROS1 rearrangements, which are detected in 0.9-2.6% of mNSCLC cases. ROS1-targeted tyrosine kinase inhibitors (TKIs) have transformed the disease course. However, given that up to 50% of patients develop brain metastases (BM), and current treatment options are limited for overcoming acquired resistance, novel ROS1 inhibitors with enhanced intracranial (IC) efficacy are needed. Preclinical studies reported that repotrectinib, a next-generation ROS1 inhibitor, is a highly selective ROS1 inhibitor with favorable properties for enhanced intracranial activity. The TRIDENT-1 (NCT03093116) study reported meaningful IC activity of repotrectinib in patients with advanced solid tumors harboring ROS1, or NTRK1-3 rearrangements and asymptomatic BM. The limited treatment options for patients with BM, particularly those with symptomatic lesions, and the promising IC overall response rate (ORR) observed in TRIDENT-1 underscore the need for further research.

Methods: REPOSE (NCT06315010) is an international, multicenter, open-label, single-arm, phase II trial using Simon's two-stage design in patients with mNSCLC with ROS1 fusion and active BM. Eligible adult patients must have histologically proven advanced NSCLC with ROS1 fusion and untreated or progressing BM after local treatment, with no immediate indication for neurosurgery or radiotherapy. Prior anti-ROS1 therapy is not allowed. Participants must have at least one measurable brain lesion (≥10 mm) confirmed by T1-weighted, gadolinium-enhanced MRI, meeting RANO-BM criteria. There is no limit on prior chemotherapy, immunotherapy, or non-ROS1 TKI therapy. ECOG performance status must be ≤2, with adequate bone marrow and organ function.Twenty patients will be enrolled to receive repotrectinib 160 mg orally once daily for 14 days, then twice daily until unacceptable toxicity, disease progression, death, or discontinuation for any reason. The first stage includes 10 patients, expandable to 20 in the second stage.The primary endpoint is IC-ORR at any time, based on the best CNS response per RANO-BM criteria. Main secondary endpoints include ORR (RECIST v1.1 for extracranial (EC)/overall lesions), clinical benefit rate, disease control rate, time to response, duration of response, best tumor burden change and progression-free survival (RANO-BM for IC lesions, RECIST v1.1 for EC/overall lesions), overall survival (OS), neurological function (NANO scale), patient reported outcomes, and safety (NCI-CTCAE 5.0). The sample size follows Simon's two-stage design. An IC-ORR ≥50% is the alternative hypothesis, while ≤20% is unmeaningful (null hypothesis). The design has a 10% one-sided type I error rate and 93.8% power to reject the null hypothesis. The study will stop for futility if <2 (20%) intracranial responses occur in stage 1 (N=10). The primary endpoint is met if ≥7 of 20 patients show intracranial responses. Primary analysis will use Koyama & Chen's (2008) methods. Enrollment is expected to take 17 months. The steering committee will decide on continuation based on efficacy and safety. Trial activation is expected in April 2025 for Spain and Austria, and in June 2025 for Germany, with about 15 sites across the three countries.Clinical Trial Identification: NCT06315010Support and funding: Bristol-Myers Squibb (BMS)

Keywords: Lung cancer, Brain metastasis, ROS1 inhibitors

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.56 EGFR-Mutated Lung Cancer in Randomized Investigator-Initiated Study (ERIS): A National Phase III Trial From the Swedish Lung Cancer Study Group

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Introduction: Advanced EGFR-mutated non-small cell lung cancer (NSCLC) should be treated with a tyrosine kinase inhibitor (TKI) in first line. Current Swedish guidelines recommend either a third-generation inhibitor, osimertinib, or one of the second-generation EGFR-inhibitors, afatinib or dacomitinib. Given differences in complexity of resistance at tumor progression during treatment with these agents (that have not yet been compared in a head-to-head trial), the optimal sequence of EGFR-inhibitors is still under debate. In this nation-wide randomized trial, ERIS, we will evaluate progression free survival, total time on TKI treatment, overall survival, tumor responses, adverse effects, quality-of-life, and molecular profiles in blood and tumor samples aimed for improving treatment decisions and management of resistance mechanisms.

Methods: The main inclusion criteria is advanced EGFR-mutated NSCLC accepted for first-line treatment with an EGFR-TKI. Exclusion criteria include e.g. presence of second primary malignancy without radical treatment option. Study participants are randomized to second or third generation EGFR-inhibitor, i.e. afatinib/dacomitinib or osimertinib. Randomization is stratified according to occurrence of CNS metastases and according to EGFR mutation type. Cross-over to osimertinib in second line is recommended in the event of T790M-positive progression during treatment with a second-generation inhibitor. Choice of regimen in all subsequent lines of treatment is made by the local investigators. The study includes a structured assembling of clinical data, tumor evaluation, and laboratory tests. The longitudinally sampled blood and tumor tissue will be used for explorative analyses on the DNA, RNA, and protein level. An inclusion of minimum 200 patients over a three year-period in Sweden is planned and the study will end 36 months after the last inclusion.

Results: At abstract submission, a total of 82 patients at 11 different hospitals in Sweden have been randomized.

Conclusions: There is a need to identify who will benefit most from second vs. third generation EGFR-TKI:s in first line. Early treatment prediction and monitoring through biomarkers may lead to more individualized treatment. In ERIS, we address these questions by randomization between osimertinib and dacomitinib/afatinib and by longitudinal sampling of blood and tumor tissue.

Keywords: First line EGFR-TKI, Blood-based monitoring, Resistance mechanisms

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.57 Phase 1/2 Clinical Trial of JIN-A02, a 4th Generation EGFR-TKI in EGFR Mutant Advanced/ Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Epidermal growth factor receptor (EGFR) mutations are the predominant drivers of NSCLC. While EGFR tyrosine kinase inhibitors (TKIs) are the primary treatment for EGFR-mutant NSCLC patients, resistance inevitably develops, leading to disease progression. JIN-A02, a novel 4th generation EGFR-TKI, intended for oral administration, selectively and reversibly binds to EGFR mutations, including the C797S and/or T790M mutation that causes resistance to 3rd generation of EGFR-TKIs. Preclinical studies with EGFR C797S and/or T790M mutated cell lines and C797S+ xenograft mice model showed that JIN-A02 inhibits cell and tumor growth in a dose dependent manner and exhibits high selectivity over wild-type EGFR. Moreover, JIN-A02 has been shown to penetrate the blood-brain barrier and exhibit anti-tumor activity in an intracranial tumor model. This phase 1/2 study is designed to evaluate the safety and anti-tumor activity of JIN-A02 in EGFR-mutant NSCLC patients.

Methods: JIN-A02 is under evaluation in Phase 1/2, multicenter, an open-label trial (NCT05394831) for subjects with advanced NSCLC harboring C797S and/or T790M mutation as a monotherapy. The primary objective is to assess safety, tolerability, pharmacokinetics, and anti-tumor effect for determining the recommended phase 2 dose (RP2D) of JIN-A02. Inclusion criteria are that the subject (≥ 18 years) must have advanced or metastatic NSCLC showing progressive disease post-treatment with approved standard EGFR-TKIs and/or platinum-based anticancer chemotherapy, with ECOG status 0 or 1.The study consists of 3 parts: dose escalation (Part A), dose exploration (Part B), and dose expansion (Part C). In Part A, JIN-A02 is administered orally once daily from 12.5 mg, and at least 3 subjects are recruited per cohort conducted over 28 days cycles to evaluate the maximum tolerated dose. Dose escalation between cohorts is made at up to twice the prior dose level. Dose-limiting toxicities (DLTs) are assessed over 21 days. Part B aims to further evaluate JIN-A02 safety to determine the RP2D using two preliminary effective dose levels from Part A. In Part C, subjects are divided into 5 cohorts based on the EGFR mutation status (both or single positive for C797S and T790M), and the anti-tumor activity of JIN-A02 is evaluated according to RECIST v1.1 at the RP2D.

Results: As of April 01, 2025, Part A is still in progress at Cohort 6 of 300 mg daily. A total of 20 subjects received JIN-A02 over 6 dose levels and 4 subjects are still on study treatment (2 subjects with 150mg, 2 subjects with 300mg). No DLT has been reported in any of these 6 cohorts in Part A. Three patients with EX19DEL/T790M/C797S exhibited partial responses (50 mg OD, 100 mg OD, and 300 mg OD, respectively). The median duration of response among these responders was 414 days (range: 106 days - 539 days). Of these, the patient on 300 mg showed a sustained response with shrinkage of lung (-39.7%) and brain lesions (-19.4 %). Furthermore, in the ctDNA analysis of this patient, C797S and EX19DEL mutations were completed cleared and more than 90% of T790M mutation was cleared after JIN-A02 treatment.

Conclusions: Further dose escalation is warranted to comprehensively assess both safety and anti-tumor efficacy of JIN-A02.

Keywords: NSCLC, EGFR, C797S

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.58 Trastuzumab Deruxtecan + Pembrolizumab as First-Line Treatment in HER2-Overexpressing, PD-L1 Tps <50% NSCLC (DESTINY-Lung06)

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Introduction: Non-small cell lung cancer (NSCLC), driven by diverse molecular alterations, is the leading cause of cancer-related deaths globally. Human epidermal growth factor receptor 2 (HER2) overexpression (immunohistochemistry score [IHC] 3+ or IHC 2+) occurs in ~13%-20% of patients with NSCLC and is associated with poor prognosis. Programmed death ligand 1 (PD-L1) is expressed in ~60%-70% of patients with NSCLC and predicts immunotherapy response. Pembrolizumab + platinum-based chemotherapy is a first-line treatment option for patients with HER2-overexpressing nonsquamous NSCLC without actionable genomic alterations (AGAs), regardless of PD-L1 expression. However, survival outcomes are modest in patients with PD-L1 tumor proportion score (TPS) <50%. Additionally, no first-line HER2-directed therapies are approved for HER2-overexpressing NSCLC, highlighting an unmet medical need. Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate, has shown efficacy in HER2-overexpressing tumors. DESTINY-Lung01 was conducted to investigate T-DXd in patients with previously treated HER2-overexpressing NSCLC. Findings from DESTINY-Lung01, DESTINY-PanTumor02, and DESTINY-CRC02 led to the approval of TDXd monotherapy as the first tumor-agnostic HER2-directed therapy for unresectable/metastatic HER2-positive (IHC 3+) solid tumors after prior systemic treatment and no satisfactory alternative treatment options. Preclinical evidence suggests T-DXd enhances antitumor immunity and may have synergistic effects with immune checkpoint inhibitors. Preliminary data from the phase 1b DS8201-A-U106 trial showed encouraging efficacy with T-DXd + pembrolizumab (confirmed objective response rate [ORR], 54.5%) in immuno-oncology treatment-naive patients with HER2-expressing NSCLC, supporting a larger phase 3 investigation of this treatment combination. DESTINY-Lung06 aims to enhance first-line standard-of-care, immuno-oncology by replacing standard chemotherapy with TDXd + pembrolizumab for patients with HER2 overexpressing, PD-L1 TPS <50% NSCLC.

Methods: DESTINY-Lung06 (NCT06899126) is a global, open-label, randomized, phase 3 trial designed to evaluate the safety and efficacy of T-DXd + pembrolizumab versus platinum-based chemotherapy + pembrolizumab in patients with HER2-overexpressing, PD-L1 TPS <50%, unresectable/metastatic, nonsquamous NSCLC. Patients (≥18 years) should have centrally confirmed HER2 overexpression and PD-L1 TPS <50% and no known AGAs that have locally available therapies targeting their AGAs in the first-line advanced/metastatic setting. Patients should have an Eastern Cooperative Oncology Group performance status of 0 or 1, left ventricular ejection fraction ≥50%, and not have received prior systemic anticancer therapy in the metastatic setting. Patients with a history of myocardial infarction, interstitial lung disease/pneumonitis, or other lung-specific illnesses will be excluded. The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR). The key secondary endpoint is overall survival. Additional secondary endpoints include investigator-assessed PFS, ORR and duration of response by BICR and investigator assessment, safety, and patient-reported outcomes. Approximately 686 patients will be randomized 1:1 to receive T-DXd 5.4 mg/kg + pembrolizumab 200 mg every 3 weeks (Q3W) or pemetrexed 500 mg/m2 + platinum-based chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 5 mg/mL/min) + pembrolizumab 200 mg Q3W. Randomization will be stratified by prior neoadjuvant/adjuvant therapy (yes vs no), smoking history (ever smoked vs never smoked), PD-L1 expression (TPS <1% vs 1%-49%), and HER2 IHC expression (IHC 3+ vs non-3+).

Keywords: non–small cell lung cancer, HER2-overexpressing, trastuzumab deruxtecan

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.59 Resistance Mechanisms and Sequential Therapies Following 1St Line Lorlatinib in ALK+ NSCLC: A Real-World Study (LORES CTONG2501)

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of cases. Approximately 3-7% of NSCLC patients harbor anaplastic lymphoma kinase (ALK) gene rearrangements. ALK-positive NSCLC is characterized by unique molecular features and a high propensity for brain metastases, contributing to suboptimal clinical outcomes. Lorlatinib, a third-generation ALK tyrosine kinase inhibitor (TKI), has demonstrated unprecedented progression-free survival (PFS) and intracranial efficacy in first-line treatment of locally advanced and metastatic ALK-positive NSCLC. Despite its effectiveness, resistance to lorlatinib inevitably emerges in some cases, and the mechanisms underlying resistance in real-world populations after first-line use are poorly characterized. Furthermore, evidence guiding sequential therapies post-lorlatinib progression is limited. This study aims to address these critical gaps by prospectively investigating resistance mechanisms and evaluating the clinical utility of subsequent treatment strategies in a real-world cohort, thereby informing personalized therapeutic approaches, optimizing patient management and improving overall survival.

Methods: This is a multicenter, prospective, observational real-world study enrolling approximately 100 adults with locally advanced/metastatic ALK-positive NSCLC who progressed after first-line treatment with lorlatinib. Patients will be recruited from 10 sites in China. Key inclusion criteria include histologically or cytologically confirmed NSCLC, ALK gene rearrangement confirmed by approved tests, and documented disease progression after first-line lorlatinib treatment. Exclusion criteria include prior treatment with other ALK-TKI and concurrent participation in other interventional clinical studies. The primary objective is to explore the resistance mechanisms to first-line lorlatinib. Secondary objectives include evaluating the efficacy and safety of sequential treatment strategies post-lorlatinib progression. Resistance mechanisms will be investigated using next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) and tissue biopsy DNA and RNA (when feasible). If possible, the detection of stereo-seq(RNA) will be further carried out. Patients will be followed up for 24 months to assess the outcomes of post-progression therapies. Descriptive statistical analyses will be conducted, and Kaplan-Meier curves will be used to summarize time-to-event variables.

Keywords: ALK+ NSCLC, Resistance Mechanisms, Real-world Study

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.60 The COALA (Cure Oncogene-Addicted Lung Adenocarcinoma) Network: A Nationwide Consortium to Improve Lung Cancer Outcome

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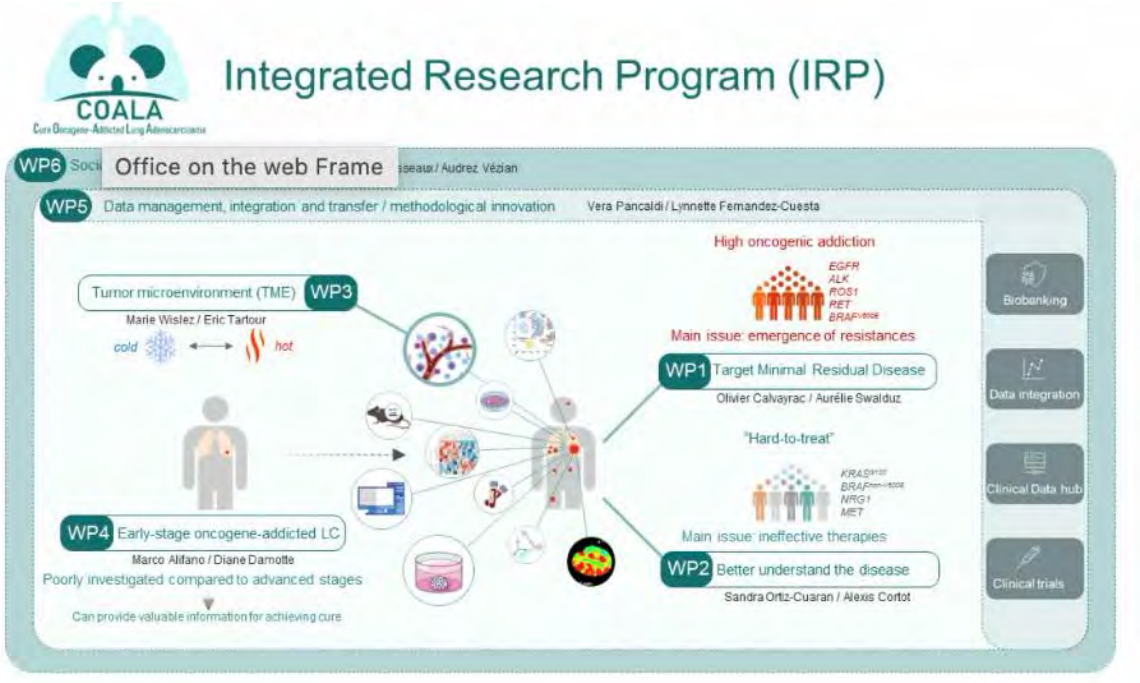
Introduction: The French National Cancer Institute has proposed funding for research networks focused on cancers with poor prognosis. The COALA network, dedicated to oncogene-addicted lung adenocarcinoma, received funding of 3 M€ in 2024 for a period of five years, with the goal of improving the prognosis of this group of patients. One of the main challenges in thoracic oncology is to increase the survival of patients with oncogenic addiction. A better understanding of tumor biology has allowed the development of targeted therapies that are highly effective in terms of response rates and progression-free survival without being able to definitively eradicate the disease. The objective of COALA is to bring together physicians, surgeons, biologists, computer scientists, mathematicians and sociologists from 15 expert centers in France. By enhancing our understanding of treatment resistance and identifying strategies to overcoming it, the network aims to offer patients a better prognosis.

Methods: Our aim is to radically improve the outcome of oncogene-addicted lung cancer by setting up a national network with the following goals: - Overcome the molecular resistance to targeted therapies in highly oncogene-addicted lung cancer (EGFR, ALK, ROS1, BRAF V600E) with a focus on the residual disease. - Improve the targeting of hard-to-treat alteration (KRAS, MET, HER2) or emergent biomarkers (BRAF nonV600, NRG1). - Address the role of the immune and non-immune environment in molecularly characterized lung cancer to refine the role of immunotherapy and non-targeted agents. - Extend our findings and hypotheses on early-stage lung cancer to improve the potential to radically cure oncogene-addicted NSCLC. - Address the sociological aspect of building such a network including multiple partners. - Harmonize and organize all the clinical and biological databases to fuel all the projects. - Create a consortium around the theme including patients, academic and industrial partners. - Develop specific clinical trial based on our preclinical findings - Disseminate the knowledge to inform the community and to recruit more researchers to this cause, enabling French research on lung cancer to cross new boundaries. The COALA network aims to bring together expert teams in France to focus on this ambitious integrated research project. Our goal is to identify new vulnerabilities in resistance mechanisms to targeted therapy. The objective is to implement our therapeutic strategies, particularly to target residual disease and significantly improve the prognosis of lung cancer associated with oncogenic addiction, in both advanced and early stages.



Keywords: Oncogenic addiction, Targeted therapy, Research Network

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.61 KRYSTAL-4: Phase 3 Study of Adagrasib Plus Pembrolizumab and Chemotherapy Intreatment-Naïve, Advanced KRAG12C-Mutated NSCLC

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Introduction: Adagrasib is a potent, orally available, small molecule covalent KRASG12C inhibitor that has received accelerated/conditional approval as monotherapy in the United States, European Union, and United Kingdom for patients with previously treated KRASG12C-mutated locally advanced/metastatic NSCLC based on results from the phase 1/2 KRYSTAL-1 study. Adagrasib further demonstrated significant improvements in progression-free survival (PFS) and objective response rate (ORR) compared with docetaxel in the phase 3 KRYSTAL-12 study in patients with KRASG12C-mutated advanced/metastatic NSCLC previously treated with chemotherapy and immunotherapy. For patients with previously untreated KRASG12C-mutated advanced/metastatic NSCLC, the standard of care remains immunotherapy with or without chemotherapy. However, in patients with advanced NSCLC (not selected for KRAS mutation status), this first-line approach results in a median PFS of 6-9 months and a 5-year overall survival (OS) rate of approximately 20% (de Castro G, et al. J Clin Oncol 2022; Garassino MC, et al. J Clin Oncol 2023). Adagrasib is currently being evaluated in the first-line setting in combination with pembrolizumab, a PD-1 inhibitor, vs pembrolizumab monotherapy in patients with KRASG12C-mutated advanced/metastatic NSCLC and PD-L1 ≥50% in the phase 3 portion of the KRYSTAL-7 study (NCT04613596), following promising results from the phase 2 portion of the study (ORR, 59%; median PFS, 27.7 months; Garassino MC, et al. ELCC 2025). First-line adagrasib is also being evaluated in combination with pembrolizumab and chemotherapy in the single-arm, phase 2 KRYSTAL-17 study (NCT05609578). The phase 3 KRYSTAL-4 study (NCT06875310) aims to evaluate the efficacy and safety of first-line adagrasib in combination with pembrolizumab and chemotherapy vs placebo with pembrolizumab and chemotherapy in patients with KRASG12C-mutated advanced/metastatic non-squamous NSCLC, regardless of PD-L1 expression level.

Methods: KRYSTAL-4 is a randomized, double-blind, placebo-controlled, phase 3 study of adagrasib plus pembrolizumab and platinum-doublet chemotherapy vs placebo plus pembrolizumab and platinum-doublet chemotherapy in patients with treatment-naïve, locally advanced/metastatic non-squamous NSCLC with a KRASG12C mutation (detected in tumor tissue and/or circulating tumor DNA centrally or locally using a sponsor-approved test). Patients may have any level of tumor PD-L1 expression (determined centrally or locally using a sponsor-approved immunohistochemistry test). Patients with stable and asymptomatic brain metastases, including untreated brain metastases (≤20 mm in diameter), are eligible for inclusion. Randomization (1:1) will be stratified according to tumor PD-L1 expression (<1% vs 1-49% vs ≥50%) and presence of brain metastases (yes vs no). Patients will receive adagrasib 400 mg or placebo orally BID (until disease progression or unacceptable toxicity), pembrolizumab 200 mg intravenously Q3W (up to a total of 24 months), and pemetrexed 500 mg/m2 (until disease progression or unacceptable toxicity) plus cisplatin 75 mg/m2 or carboplatin AUC 5 mg/ml/min intravenously Q3W (four cycles). The study has dual primary endpoints of PFS (per RECIST v1.1 according to blinded independent central review [BICR]) and OS. Secondary endpoints include ORR and duration of response per RECIST v1.1 according to BICR, PFS according to investigator assessment, safety, and patient-reported outcomes. Intracranial efficacy and investigator-assessed PFS2 will also be evaluated as exploratory endpoints.

Keywords: adagrasib, NSCLC, KRAS

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.62 TRUST-III: Phase 3 Head-To-Head Study of Taletrectinib vs Crizotinib in Patients With ROS1+ Non-Small Cell Lung Cancer

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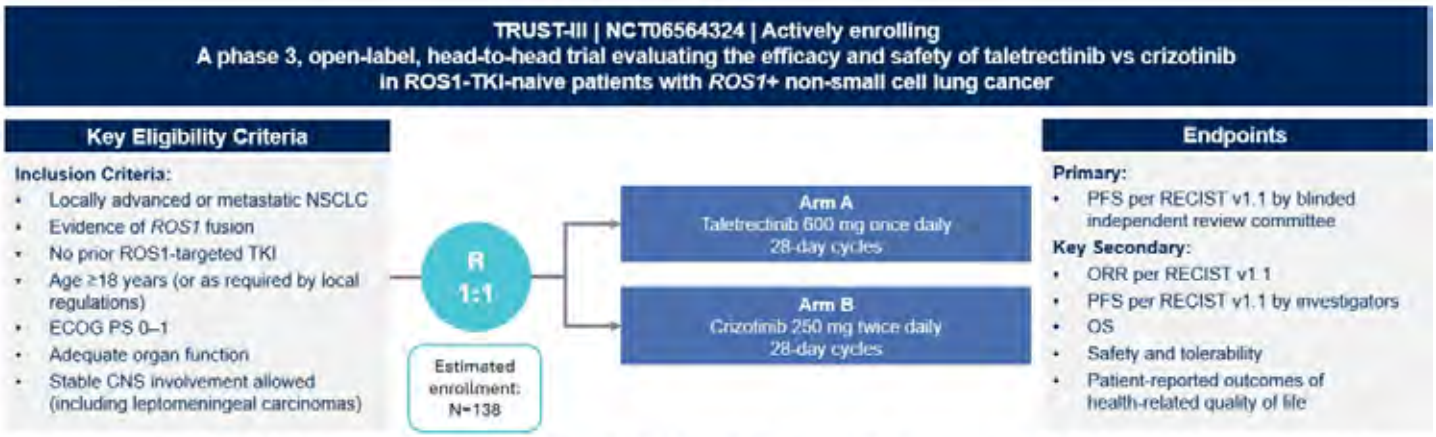
Introduction: ROS1 gene fusions, oncogenic alterations that result in constitutive activation of the ROS1 kinase domain leading to dysregulated cell differentiation, proliferation, and survival, occur in ~2% of patients with non-small cell lung cancer (NSCLC). Patients with ROS1+ NSCLC tend to be female, younger, never-smokers, diagnosed at an advanced stage, and have adenocarcinoma. Crizotinib, a tyrosine kinase inhibitor (TKI) approved by the US Food and Drug Administration (FDA) for ROS1+ NSCLC in 2016, transformed clinical outcomes (objective response rate [ORR], 72%; median progression-free survival [PFS], 19.3 months; Shaw et al, Annals of Oncology 2019) for patients with ROS1+ NSCLC; however, ~50% of crizotinib-treated patients developed central nervous system (CNS) metastases, and ~30%-40% developed the acquired resistance mutation G2032R. Taletrectinib, an oral, potent, CNS-active, selective, next-generation, ROS1 inhibitor, has shown high and durable responses and favorable safety in patients with ROS1+ NSCLC. In the pooled analysis of the two pivotal phase 2 clinical trials, taletrectinib demonstrated a high confirmed ORR (cORR) in both TKI-naive (n=160; 88.8%) and TKI-pretreated (n=113; 55.8%) patients. Among TKI-naive patients, median duration of response (DOR) was 44.2 months and median PFS was 45.6 months. In crizotinib- or entrectinib-pretreated patients, median DOR and PFS were 16.6 and 9.7 months, respectively. Intracranial-ORR was 76.5% in 17 TKI-naive patients and 65.6% in 32 TKI-pretreated patients. Taletrectinib is active against the most common acquired resistance mutation to crizotinib, G2032R (n=13; cORR, 61.5%). In December 2024, the US FDA granted Priority Review of the New Drug Application for taletrectinib for advanced ROS1+ NSCLC; a Prescription Drug User Fee Act goal date of June 23, 2025, was assigned.

Methods: TRUST-III (NCT06564324) is a phase 3, open-label, head-to-head trial evaluating the efficacy and safety of taletrectinib vs crizotinib in an estimated 138 patients with locally advanced or metastatic ROS1+ NSCLC (Figure). Adults without prior ROS1-targeted TKI will be randomized 1:1 to receive taletrectinib or crizotinib. Patients will be stratified by the presence of baseline CNS metastases and prior use of chemotherapy. Taletrectinib 600 mg (recommended phase 2 dose) will be administered once daily; crizotinib 250 mg will be administered twice daily. Patients will be treated in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint is PFS per RECIST v1.1 by blinded independent review committee. Key secondary endpoints include ORR; PFS per investigator; overall survival; safety and tolerability; and patient-reported outcomes of health-related quality of life. This trial is currently enrolling.



Keywords: ROS1+, Non-small cell lung cancer (NSCLC), Taletrectinib

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.63 Phase 1 Study of FHND5071, a Novel Selective RET Inhibitor, in RET Fusion-Positive Advanced NSCLC

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Introduction: FHND5071 is a novel, oral, selective RET inhibitor that demonstrates strong tissue and brain penetration. In preclinical studies, FHND5071 exhibited significantly higher tumor and brain tissue exposure: the AUC_{0-t} of FHND5071 in tumor tissue was approximately 28-time higher than that of selpercatinib, and its brain concentration was ~33-time higher at 4 hours post-dose. These favorable distribution characteristics translated into robust antitumor activity and CNS efficacy in the ongoing Phase 1 multi-center, open-label trial (NCT05818917).

Methods: Eligible patients (≥18 years) with histologically or cytologically confirmed advanced RET fusion-positive non-small cell lung cancer (NSCLC) who had progressed after standard therapy or had no available standard treatment options were enrolled in dose escalation (40-400 mg QD) and dose expansion cohorts (160 or 240 mg QD). FHND5071 was administered orally QD in continuous 28-day treatment cycles. A total of 48 NSCLC patients were enrolled (N=15 in dose escalation; N=33 in dose expansion). At baseline, 29% (14/48) had brain metastases and 77% (37/48) had received prior treatment. One enrolled patient did not receive study drug and was excluded from the intent-to-treat (ITT) population.

Results: Among the ITT population (N=47), ORR was 68.1% (32/47; 95% CI: 53.6-80.1), and the DCR was 89.4% (42/47; 95% CI: 77.4-96.0). In the pooled high-dose group (≥240 mg, N=27), the ORR was 70.4% (19/27). The median DoR was not reached (95% CI: 11.0-NE), with 68.8% (22/32) of responders still on treatment at cutoff. Median PFS was also not reached (95% CI: 12.8-NE) with a censoring rate of 59.6%. Among 14 patients with baseline brain metastases, 4 had measurable brain metastases. All 4 pts achieved brain metastases shrinkage after the treatment, with reduction of 100%, 85.7%, 48.3% and 32.5% respectively. The CNS ORR reached 100%, consistent with its high brain tissue penetration observed preclinically. Two dose-limiting toxicities (DLTs) were reported in the 400 mg dose group (N=6) during the dose-escalation phase, including one case of Grade 3 proteinuria and one case of Grade 3 elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST); both events resolved with supportive care. No treatment-related Grade ≥3 adverse events (TRAEs) occurred in ≥10% of patients. Among Grade ≥3 treatment-emergent adverse events (TEAEs), infectious pneumonia was the only event occurring in ≥10% of patients (5/47, 10.6%).

Conclusions: FHND5071 demonstrated robust antitumor activity, including meaningful intracranial responses. The compound's strong CNS efficacy, along with its manageable safety profile supports its continued development as a promising therapy for patients with RET fusion-positive advanced NSCLC.

Keywords: RET fusion, NSCLC, brain metastasis

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.64 Phase 1 Study to Evaluate the Safety and Tolerability of CVHNLC Plus Pembrolizumab in Patients With Squamous NSCLC

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Introduction: Programmed cell death protein 1 (PD-1) or PD-ligand 1 (PD-L1) blockade has become an important pillar of standard treatment for patients with metastatic squamous cell non-small cell lung cancer (sqNSCLC). However, the overall prognosis remains poor for these patients, highlighting a high unmet need for new treatment options. Messenger ribonucleic acid (mRNA)-based cancer immunotherapies represent a promising strategy to increase the therapeutic efficacy of immune checkpoint blockade. CVHNLC is an LNP-encapsulated mRNA-based cancer immunotherapeutic encoding eight tumor-associated antigens expressed in sqNSCLC. Our study will assess the safety and tolerability of CVHNLC plus pembrolizumab in patients with sqNSCLC.

Methods: CV-HNLC-001 is a first-in-human, phase 1, dose-finding, open-label trial of CVHNLC in patients with advanced sqNSCLC. The trial comprises a dose-escalation part (Part A) of first-line pembrolizumab maintenance treatment plus CVHNLC followed by an optional dose-expansion part (Part B) of first-line treatment of CVHNLC in combination with pembrolizumab and platinum-based chemotherapy. In Part A, patients with histologically confirmed metastatic stage IV sqNSCLC will be eligible if they have received 3-6 months of treatment with pembrolizumab either as monotherapy or in combination with ≥2 cycles of platinum-based chemotherapy as first-line treatment, with no documented disease progression and eligible for pembrolizumab maintenance therapy. CVHNLC doses between 100 µg and 400 µg will be investigated, guided by a Bayesian Logistic Regression Model. Patients will initially receive 4 weekly intramuscular injections of CVHNLC followed by 3-weekly injections plus pembrolizumab for up to 12 months or until disease progression or undue toxicity. The primary endpoint of Part A includes the number of dose-limiting toxicities and incidence of treatment-related and -emergent adverse events; secondary endpoints include overall response rate per RECIST 1.1, progression-free survival, duration of response, and disease control rate. Exploratory endpoints include antigen-specific immune responses against the encoded antigens, changes in cytokine/chemokine profiles and other biomarker signals detectable in peripheral blood. At the end of Part A, an independent Data and Safety Monitoring Board will recommend the CVHNLC dose for Part B.

Keywords: mRNA, Cancer immunotherapeutic, NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.65 Trial in Progress - RAsolve 301: A Phase 3 Study of Daraxonrasib (RMC-6236) Vs. Docetaxel in in Patients With Previously Treated RAS Mutant NSCLC

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide, with previously treated non-small cell lung cancer (NSCLC) patients representing a significant unmet medical need. In this setting, after patients have received platinum-based chemotherapy and/or immune checkpoint inhibitors, docetaxel monotherapy is often the main stay of treatment, with reported objective response rates (ORRs) of 9.2% to 14.7%, median progression-free survival (mPFS) of 3.0 to 4.5 months, and median overall survival (mOS) of 9.1 to 11.8 months across multiple studies. RAS mutations occur in approximately 30% of NSCLC cases, with non-G12C variants making up 60% of these mutations. The majority of these are G12X mutations (such as G12D, G12V, etc.), for which there are currently no approved targeted therapies. Daraxonrasib (RMC-6236) is an oral, RAS(ON) multi-selective, tri-complex inhibitor of GTP-bound mutant and wild-type RAS. In an ongoing Phase 1 monotherapy trial (NCT05379985), daraxonrasib at 120-220 mg daily showed manageable safety and preliminary efficacy in patients with NSCLC. As of a September 30, 2024 data cutoff (N=73), Grade ≥ 3 treatment-related adverse events (TRAEs) reported in ≥2 patients included rash (n=5, 7%), vomiting (n=2, 3%), and anemia (n=2, 3%), with no Grade 4 or Grade 5 TRAEs. In 40 patients with RAS G12X-mutant NSCLC, previously treated with immunotherapy and platinum-based chemotherapy, treatment with daraxonrasib at 120-220 mg resulted in a confirmed ORR of 38%, median duration of response (DOR) of 15.1 months (95% CI: 11.1, Not Estimable [NE]), mPFS of 9.8 months (95% CI: 6-12.3), and a mOS of 17.7 months (95% CI: 13.7-NE). These preliminary results provide strong rationale for the continued development of daraxonrasib in patients with previously treated, locally advanced or metastatic, RAS-mutant NSCLC.

Methods: RASolve 301 is a global, multicenter, open-label, randomized Phase 3 study (NCT06881784) designed to evaluate the efficacy and safety of daraxonrasib compared to docetaxel in patients with previously treated, locally advanced or metastatic, RAS-mutant NSCLC. Patients are randomized 1:1 to receive either docetaxel or daraxonrasib. Key eligibility criteria include histologically confirmed NSCLC, age ≥ 18 years, ECOG performance status of 0 or 1, previous treatment with an anti-PD(L)-1 agent and platinum-based chemotherapy, and a documented RAS mutation based on local testing. Eligible RAS mutations are defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61). Key exclusion criteria include untreated central nervous system metastases, prior RAS-directed therapy, or the presence of an actionable driver mutation for which an approved targeted therapy is available. The dual primary endpoints are PFS and OS in patients with RAS G12X mutations excluding G12C (G12X-C). Secondary endpoints include PFS and OS in patients with all RAS mutations, ORR per RECIST v1.1, DOR, time to response, quality of life, safety and tolerability, and further characterization of daraxonrasib's pharmacokinetic profile. The study will enroll approximately 420 patients globally across North America, Europe, and Asia.

Keywords: metastatic NSCLC, RAS inhibition, daraxonrasib (RMC-6236)

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.66 Preliminary Safety and PK of the MET-TKI Do-2 in Advanced Solid Tumors With MET Aberrations: Phase I Study

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Introduction: DO-2 is a potent (0.2nM Kd) highly selective (>3000 fold vs 450+ kinases tested), deuterated MET Tyrosine Kinase Inhibitor that was designed to have 'fast on' and 'fast off' binding kinetics. The resulting short residence times requires drug exposure to be above a threshold for MET inhibition. Here, we report the safety pharmacokinetics (PK) and preliminary efficacy data from the dose escalation phase (Part 1) of the first-in-human phase 1 trial of DO-2 in patients with advanced solid tumors harboring MET aberrations.

Methods: Eligible patients with tumors harboring proven MET activating mutations or MET amplification (≥10 copies) received DO-2 once (QD) or twice (BID; 4hr interval) daily orally, under fasting conditions. The primary endpoint was safety and tolerability; secondary objectives included PK of DO-2, the primary metabolites DO-5 and M3 and anti-tumor activity according to RECIST 1.1. Dose-escalation followed a Simon stage 3 accelerated titration design starting at 5mg QD, enrolling one patient per cohort until grade 2 toxicity. Thereafter, dose-escalation followed a "3+3" design. Blood samples for PK were collected pre-dose and at multiple time points post-dose on days 1 and 22. The dose limiting toxicity (DLT) observation period was 4 weeks. Response assessment was performed every 8 weeks.

Results: Thus far, 26 evaluable cancer patients have been included at ten dose levels (5, 10, 20, 40, 60 and 80 mg QD and 20+20, 30+30, 40+20 and 40+40mg BID). There were 19 exon14 skipping mutant and 3 MET amplified (>10fold) Non-Small Cell Lung Cancer (NSCLC) patients 1 ovarian, 1 rectal and 1 gastroesophageal cancer with MET Amp (>10fold) and 1 renal cancer with another MET mutation. The pre-clinically determined DO-2 exposure (AUC0-24; >1000ng.h/ml) and target Time over Threshold (ToT; 160ng/ml) were reached with all the BID dosing levels tested. Treatment Related Adverse Events were mainly grade 1 or 2, with grade 3 adverse events (18%) being limited to 2 cases of nausea, and 1 each of reversible creatinine increase, fatigue and vomiting. No peripheral oedema, expected with MET inhibition, was seen. Anti-tumor activity included one confirmed partial response (cPR), a disease control rate (DCR) at week 8 of 76% in all the 21 fully evaluable patients and 100% in the six evaluable 1st line exon14 skipping mutant NSCLC patients. One patient without RECIST target lesions had complete resorption of malignant pleural effusion and related symptoms after 20wks. This patient remains on treatment (65wks +) with no reported adverse events of note.

Conclusions: DO-2 was well tolerated with an expected safety profile and no drug-induced edema as typical for other MET inhibitors. The dose for the expansion cohort will be selected based on all available data after review by the safety evaluation team.Based on the promising DCR and DOR, the expansion cohort will recruit patients with locally advanced, treatment naïve unresectable or metastatic NSCLC MET exon 14 skip who are ineligible for standard of care treatment.

Keywords: DO-2, MET TKI, Pharmacokinetics

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.67 First-In-Human Phase I/II Trial of PFL-002/VERT-002 in Locally Advanced or Metastatic Solid Tumors Including NSCLC With MET Alterations

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Introduction: Non-small cell lung cancer (NSCLC) represents 85% of lung cancer cases, with 47% to 55% diagnosed at Stage IV. Around 2% to 4% of NSCLCs have MET exon 14 (METex14) skipping alterations, the median Overall Survival (OS) is 8 to 11 months without MET inhibitor treatment. Although approved MET TKIs are efficacious in NSCLC with METex14 mutation, they have limited efficacy in NSCLC with MET amplification. Moreover, the safety profile has limitations that affect treatment tolerance. Therefore, there is still a high unmet medical need in patients with solid tumors including NSCLC with MET alterations, more specifically those with de novo MET amplification, in the absence of approved or suitable therapies. VERT-002 is a monoclonal antibody targeting the MET receptor. Unlike classical antagonistic antibodies inducing target internalization, VERT-002 has a unique mechanism of action based on the enhancement of MET ECD intrinsic shedding, inducing near complete profound MET degradation, thus, leads to loss of MET signaling and eventual death of tumor cells, whose survival has become dependent on MET signaling, termed “MET-addiction”.In addition, VERT-002 has demonstrated anti-tumor activities in relevant tumor models in vitro and in vivo. These observations make VERT-002 an interesting therapeutic development candidate for the treatment of MET-altered tumors.

Methods: PFL-002 (NCT06669117) is an open-label, first-in-human (FIH) Phase I/II trial designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), preliminary antitumor activity and efficacy of VERT-002. The trial consists of 3 parts: In Part 1, patients with solid tumors, including NSCLC with MET alterations, will be enrolled to reach up to 30 evaluable patients. The Bayesian Optimal Interval (BOIN) design will guide the dose escalation to determine the MTD (or the MAD if the MTD cannot be reached) based on the safety data of VERT-002. In Part 2, safety, anti-tumor activity, PK and PD of VERT-002 will be further characterized. In Part 2a, up to 20 patients with NSCLC harboring METex14 mutation will be enrolled and treated at a dose where safety is acceptable, and activity may be expected. In Part 2b, up to 90 evaluable patients with NSCLC harboring METex14 mutation and/or MET amplification will be randomized to 2 or 3 doses. The Part 2 main goal is to define VERT-002 recommended phase 2 dose (RP2D).Part 3 will be added at the end of Part 2 once sufficient data will be available to support its design. Dose level 1 has been completed without DLT. Enrollment to dose level 2 began in December 2024.

Keywords: MET alterations, Non-small cell lung cancer (NSCLC)

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.68 First-In-Human Trial of PFL-241/STX-241 in Patients With Locally Advanced or Metastatic NSCLC Resistant to EGFR Tyrosine Kinase Inhibitors

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Introduction: Activating mutations of the epidermal growth factor receptor (EGFR) gene occur in 15-20% of non-small-cell lung cancer (NSCLC) patients (pts). About 7-18% pts develop resistance due to EGFR C797X mutations after treatment with third-generation EGFR TKI, often presenting with brain metastases. There is a need for new treatments in this setting, including inhibitors selective for these resistance mutations. PFL-241/STX-241, an orally bioavailable fourth generation EGFR targeted, brain-penetrant small-molecule inhibitor addressing C797X mutations, may provide benefit in NSCLC patients (pts) progressing after third-generation EGFR TKI treatment. Preclinical studies show that PFL-241/STX-241 has activity against double mutants (EGFR ex19del/L858R mutation founder mutations and acquired C797X resistance). PFL-241/STX-241 is highly selective for EGFR mutants over wild-type, and has brain penetrance comparable to osimertinib. In in vivo double mutant models, PFL-241/STX-241 has demonstrated tumor regression supporting further clinical exploration.

Methods: PFL-241 is a First-In-Human (FIH) open label, international, multicenter phase I/II trial designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), preliminary anti-tumor activity and efficacy of PFL-241/STX-241. The trial is comprised of 3 Parts: Part 1 Dose Escalation, Part 2 Dose Optimization for Recommended Phase 2 Dose (RP2D) selection, and Part 3 Dose Expansion at RP2D. In Part 1, successive cohorts of pts with locally advanced or metastatic NSCLC who have previously progressed on a third generation EGFR TKI at any line of treatment, will be treated with PFL-241/STX-241, administered orally as single agent, until the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) is reached. In Part 2, pts with locally advanced or metastatic NSCLC harboring C797X mutation who have previously received a third generation EGFR TKI at any line of treatment, will be randomly assigned in a 1:1 ratio into at least 2 dose cohorts to receive PFL-241/STX-241 at OBD and MTD to identify the RP2D. Part 3, will assess the efficacy of PFL-241/STX-241 at the RP2D. PFL-241 is approved for enrollment in 5 countries globally with 10 actively recruiting patients

Keywords: EGFR mutations, Non-small cell lung cancer (NSCLC), TKI resistance

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.69 Efficacy and Safety of Befotertinib Plus Icotinib in Advanced NSCLC With Uncommon EGFR Mutations: A Phase II Study (Icombine)

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Introduction: EGFR mutations, one of the most common driver mutations in non-small cell lung cancer (NSCLC), are present in up to 51.4% of Asian NSCLC patients. The advent of targeted therapies has significantly improved survival outcomes for NSCLC patients. However, current targeted therapies are predominantly indicated for or investigated in patients harboring classical EGFR mutations, such as exon 19 deletions (19Del) and L858R (exon 21). Although uncommon EGFR mutations (accounting for 10-15% of EGFR-mutant NSCLC, such as G719X, L861Q, and S768I) show partial efficacy to approved EGFR tyrosine kinase inhibitors (TKIs) like afatinib and osimertinib, the optimal therapeutic strategy for these mutations remains undetermined, with no consensus in clinical practice. Preclinical and clinical evidence has shown that combining first-/second- and third-generation EGFR-TKIs may delay resistance (e.g., osimertinib plus gefitinib demonstrated an 88.9% objective response rate [ORR] in phase I/II trials), but such strategies remain unexplored in uncommon mutations. Befotertinib, a third-generation TKI approved for classical EGFR mutations, has demonstrated superior progression-free survival (median PFS: 22.1 vs. 13.8 months) compared to icotinib. This study investigates the novel combination of befotertinib and icotinib to address unmet therapeutic needs in NSCLC patients with uncommon EGFR mutations.

Methods: This prospective, phase II, single-arm trial (NCT06517953) employs a Simon's optimal two-stage design to evaluate the efficacy and safety of befotertinib combined with icotinib in treatment-naïve advanced NSCLC patients harboring uncommon EGFR mutations (G719X, L861Q, or S768I). In Stage I, eight patients receive befotertinib 75 mg once daily (QD) plus icotinib 125 mg three times daily (TID). Dose escalation of befotertinib to 100 mg QD will occur after the first 21-day cycle if no grade ≥2 thrombocytopenia or grade ≥2 headache (per CTCAE v4.03) is observed; otherwise, the dose remains at 75 mg. If ≥2 patients achieve an objective response, the trial will proceed to Stage II, enrolling an additional 15 patients (total evaluable N=23). Treatment continues until disease progression, intolerable toxicity, or patient withdrawal. The primary endpoint is ORR assessed by RECIST v1.1, with secondary endpoints including PFS, disease control rate (DCR), overall survival (OS), and safety evaluations (incidence and severity of adverse events). Recruitment for this trial is currently ongoing.

Results: The clinical trial is ongoing.

Conclusions: The clinical trial is ongoing.

Keywords: Uncommon EGFR mutations, Befotertinib, Icotinib

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.70 Combination of Osimertinib and Carotuximab for Advanced, EFGR-Mutated Non-Small Cell Lung Cancer Patients

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Introduction: CD105 is a transmembrane receptor found on non-small cell lung cancer (NSCLC) cells that promotes bone morphogenic protein (BMP) signaling and inhibits transforming growth factor-beta (TGF-β). Inhibition of epidermal growth factor (EGFR) with tyrosine kinase inhibitors (TKIs) like osimertinib and gefitinib were found to further promote CD105 expression. In mouse models, the suppression of BMP signaling downstream of CD105 by a monoclonal neutralizing antibody, carotuximab (ENV105), was found to restore osimertinib sensitivity. Although carotuximab was originally developed as an anti-angiogenic agent due to its known expression in proliferative endothelial cells, the studies demonstrated no clinical benefit. However, together with the preclinical findings and an acceptable safety profile suggested that carotuximab may support sensitivity in patients with EGFR mutant NSCLC developing resistance to osimertinib in a synthetic lethality strategy. We initiated a phase I trial with osimertinib and carotuximab in advanced EGFR mutant NSCLC to evaluate the ability of CD105 inhibition to overcome resistance to osimertinib safely.

Methods: This phase I study (NCT05401110) will assess safety and tolerability and RP2D of carotuximab and osimertinib in patients with recurrent or metastatic NSCLC with EGFR activating mutations. In part 1, dose escalation, the RP2D, toxicity and tolerability of the combination will be assessed by adverse events as graded by CTCAE 5.0. The number of dose-limiting toxicities (DLTs) experienced within the first two treatment cycles will be assessed to determine the RP2D. Dose escalation will use an adaptive Bayesian design. In part 2, we will evaluate 2 patient cohorts: those with progressive disease on osimertinib or other prior EGFR (TKIs) (n = 25) and those receiving front line osimertinib for less than 12 weeks with detectable ctDNA (n = 25). Patients must have finished chemotherapy at least three weeks or radiotherapy at least two weeks before enrollment. A history of interstitial lung disease, small cell lung cancer histology, as well as recent thrombotic and/or cardiovascular events are exclusion criteria. Carotuximab is given through an intravenous infusion once a week for the first 4 weeks, then every 2 weeks at a dose based on dose-finding study, and osimertinib 80 mg is given orally once daily. Secondary objectives include assessment of objective response rate, duration of response, progression free survival and disease control rate. Exploratory endpoints are included to identify companion biomarkers in tumor tissue, circulating DNA and extracellular vesicles. Clinical trial information: NCT05401110. Support for this trial has been provided by the William and Anna Tenenblatt Foundation and the Cancer Clinical Trials Office of Cedars-Sinai Cancer Center.

Keywords: Non-small cell lung cancer, EGFR-mutant, CD105

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.71 CA240-0007: BMS-986504 With Anti-PD-1 or Chemotherapy as Treatment for Advanced Solid Tumors With Homozygous MTAP Deletion

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Introduction: BMS-986504 selectively binds to the PRMT5-MTA complex, which represents a synthetic lethal target in MTAP-deletion (MTAP-del) cancer cells, while sparing MTAP-wild-type cells. CA240-0007 (NCT05245500) is a phase 1/2 multiple expansion cohort trial of BMS-986504 in patients with advanced, unresectable or metastatic solid tumors with homozygous MTAP-del. Preliminary antitumor activity has been shown in multiple advanced solid tumors with BMS-986504 monotherapy. Based on emerging preclinical data, combining BMS-986504 with standard of care treatment (anti-programmed death-1 [PD-1] or chemotherapy [chemo]) is expected to increase efficacy in advanced solid tumors. Phase 1b combination substudies from the dose escalation and expansion phases will evaluate the safety, pharmacokinetics (PK), and clinical activity of BMS-986504 with anti-PD-1 treatment or chemo.

Methods: BMS-986504 will be evaluated with anti-PD-1 treatment in MTAP-del non-small cell lung cancer and other solid tumors, and with chemo in pancreatic ductal adenocarcinoma (PDAC). Eligibility criteria for the combination substudies will meet all enrollment criteria specified for the phase 1/1b parts of the main study but with specific criteria for the substudies. Patients with measurable disease are eligible. Patients with active brain metastases or carcinomatous meningitis, select cardiac abnormalities, or prior PRMT5 or MAT2A inhibitor treatment will be excluded. Exclusion criteria for these respective substudies differ based on prior treatment history, comorbidities, and recently or currently administered concomitant medications. Exclusion criteria specific to the BMS-986504 with anti-PD-1 treatment substudy include lung radiation (> 30 Gy) within 6 months before the first treatment dose, active or prior documented autoimmune disease, immunosuppressant use within 28 days before the first treatment dose, history of primary immunodeficiency or allogeneic transplant, or receipt of a live vaccine within 30 days before the first treatment dose. Exclusion criteria specific to the PDAC substudy include a history of select lung diseases, connective tissue disorders, peripheral artery disease, chronic leukemias, or the ongoing need for warfarin or for a treatment known to inhibit or induce cytochrome P450 3A4 or 2C8 that cannot be switched to an alternative treatment prior to study entry. Treatment will begin with BMS-986504 400 mg QD with anti-PD-1 Q3W in solid tumors or BMS-986504 200 mg QD with chemo in PDAC. Starting doses of BMS-986504 are based on safety, preliminary antitumor activity, and potential dose-dose interactions. Evaluation of subsequent dose levels will be in accordance with the Modified Toxicity Probability Interval-2 method. The substudy objectives include safety, clinical activity, PK, and recommended phase 2 dose of BMS-986504 in combination regimens. Further substudies with BMS-986504 combination regimens are planned. The combination substudies are currently recruiting, and approximately 155 patients will be enrolled across all substudies.

Keywords: PRMT5, MTAP deletion

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.72 Liquid Biopsy Guided Addition of Chemotherapy With TKI in Advanced EGFR Mutated NSCLC (LiquiACT)

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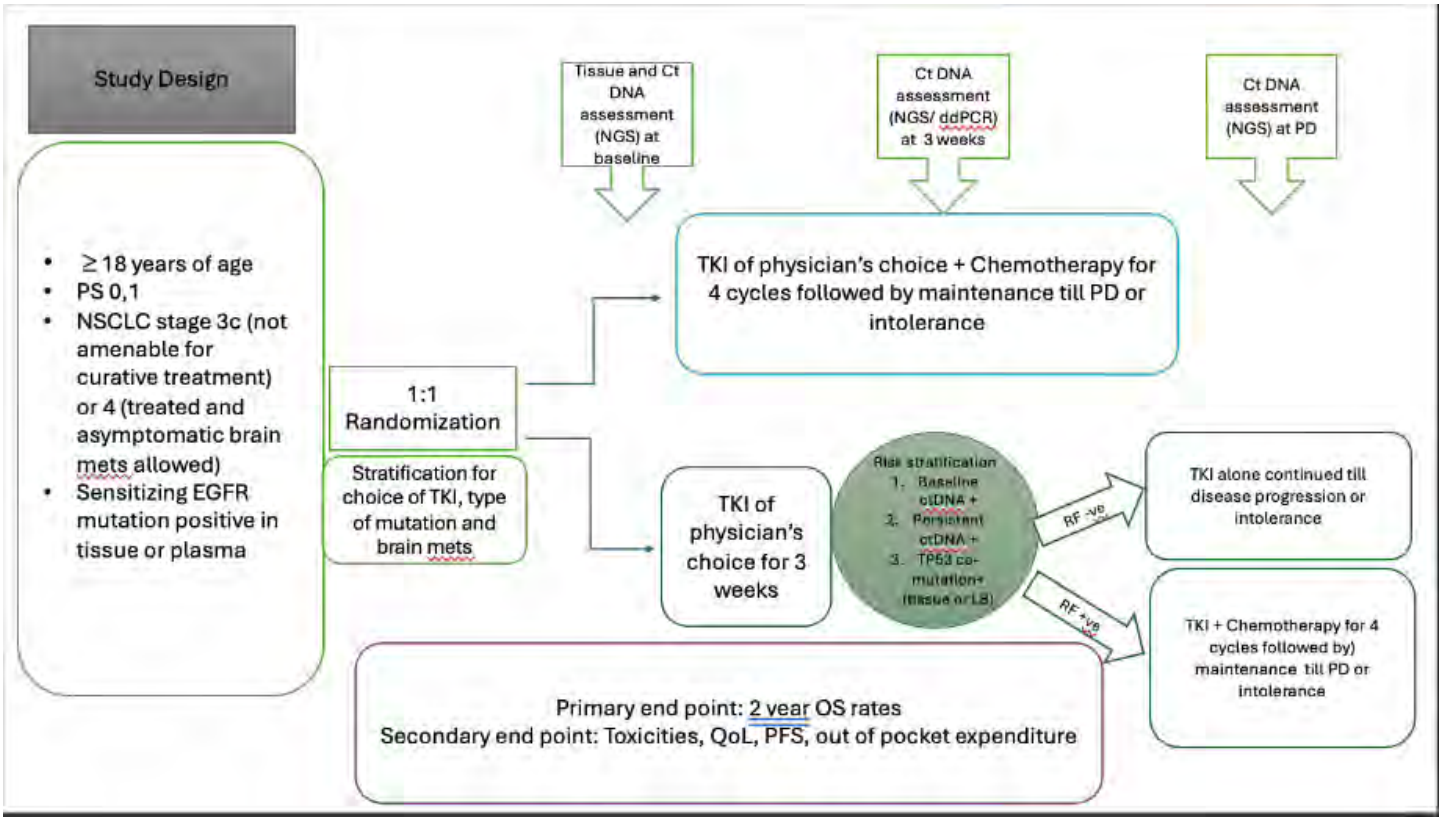
Introduction: Combination of tyrosine kinase inhibitors (TKIs) with chemotherapy is emerging as a new standard of care for the treatment of EGFR mutated non small cell lung cancer (NSCLC) which has shown to improve progression-free survival but at the cost of higher toxicity. Baseline ctDNA positivity, failure to clear ctDNA at 3 weeks after TKI and presence of co-existing TP53 mutations have been considered poor risk factor for TKI monotherapy. Whether we can avoid the addition of chemotherapy and associated toxicities in patients who do not have these high risk features, is largely unknown. In this study, we aim to evaluate if the risk adapted ctDNA guided addition of chemotherapy to TKI is non-inferior to TKI- chemotherapy combination in EGFR mutated advanced NSCLC

Methods: This is an open label, multicentric, phase 3, randomized control trial including patients 18 years of age and above, having advanced NSCLC with sensitizing EGFR mutations and ECOG PS 0 and 1. Patients with treated and asymptomatic brain metastasis are allowed. Patients are being randomized in 1:1 ratio to receive either TKI of physician choice (osimertinib or gefitinib) with platinum based chemotherapy or TKI of physician's choice for 3 weeks and addition of chemotherapy at 4th week only in cases with any of the risk factors namely baseline ctDNA positive status, failure to clear ctDNA at 3rd week sample or presence of TP53 co-mutations. Patients without any of the risk factors in the experimental arm are being continued on TKI as monotherapy. The primary end point is 2-year overall survival rates. The secondary end points are toxicity profiles, Quality of life assessed by EORTC QLQ-C30 and LC13 questionnaires, progression free survival and cost analysis. This is a non-inferiority trial. Assuming that the 2 year OS rates in the control group (TKI+ chemotherapy) are 60% and hazard ratio defining non-inferiority margin of 1.3, with 5% alpha and 90 percent power we will require 321 patients for this study over 2 years. Expecting a 10% drop outs due to loss to follow up, total number required will be 354 (177 in each arm). Enrolment in the study has been started in March 2025.



Keywords: Liquid biopsy, ctDNA, EGFR mutated NSCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.73 A Phase 1b/2 Study of Gocatamig and Ifinatamab Deruxtecan for Relapsed or Refractory Extensive-Stage Small Cell Lung Cancer

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Introduction: Gocatamig (MK-6070; HPN328) is a delta-like ligand 3 (DLL3)-targeted T-cell engager. Ifinatamab deruxtecan (I-DXd) is an antibody-drug conjugate (ADC) comprising a B7-H3 monoclonal antibody covalently linked to a potent topoisomerase I inhibitor. Both DLL3 and B7-H3 are highly expressed on the cell surface of small cell lung cancer (SCLC). Gocatamig monotherapy has shown manageable safety and encouraging antitumor activity in participants with SCLC that is relapsed or refractory after one or more prior lines of platinum-based chemotherapy. I-DXd monotherapy has been well tolerated and shown promising efficacy as second- or later-line treatment in participants with extensive-stage (ES) SCLC. The distinct mechanisms of action and minimally overlapping toxicities of gocatamig and I-DXd suggest that their combination may enhance efficacy yet remain tolerable.

Methods: The 6070-002 study (NCT06780137) is an ongoing, open-label, multicenter two-part study. Adults ≥18 years old with ES SCLC and ECOG PS 0 or 1 who had prior platinum-based chemotherapy (with or without PD-(L)1 inhibitors) are eligible. Part 1 includes a safety run-in phase of different dosing schedules of gocatamig combined with I-DXd, as well as I-DXd alone, followed by a dose-expansion phase. Target doses and schedules of gocatamig and I-DXd in part 1 will be determined based on the findings of the ongoing 6070-001 study (NCT04471727). Participants will be allocated to treatment arms during the dose-expansion phase using an interactive response technology if more than one cohort is enrolling at the same time. Part 2 consists of a Japan-only arm, in which participants receive gocatamig monotherapy. The primary objectives are to evaluate safety and tolerability (parts 1 and 2), including the incidence of adverse events (AEs), dose-limiting toxicities, and treatment discontinuations due to AEs, and to evaluate the objective response rate per RECIST v1.1 (part 1). Secondary objectives are to evaluate duration of response and progression-free survival per RECIST v1.1 (part 1) and to characterize the pharmacokinetics and immunogenicity of gocatamig plus I-DXd combination therapy (part 1), I-DXd monotherapy (part 1), and gocatamig monotherapy (part 2). The 6070-002 study will enroll participants in Australia, Chile, China, Israel, Japan, the Republic of Korea, Spain, Türkiye, and the United States of America.

Keywords: extensive-stage small cell lung cancer, DLL3-targeted T-cell engager, B7-H3-targeted antibody-drug conjugate

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.74 BNT324-01: A Phase 1b/2 Trial of BNT324/DB-1311 (B7H3 ADC) With BNT327 (PD-L1 x VEGF-A bsAb) in Lung Cancer (SCLC or NSCLC)

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Introduction: BNT327 is an investigational anti-PD-L1 x VEGF-A bispecific antibody (bsAb) that is designed to restore effector T-cell function by binding PD-L1, while localizing VEGF-A neutralization within the tumor microenvironment, leading to tumor growth inhibition. BNT324/DB-1311 is an investigational topoisomerase-I-inhibitor-based anti-B7H3 antibody-drug conjugate (ADC) with a cleavable linker and a drug-to-antibody ratio of ~6.

We hypothesize that combining BNT327 and BNT324/DB-1311 will improve efficacy since targeting VEGF-A can facilitate ADC penetration, which in turn can increase sensitivity to PD-L1 inhibition. Moreover, B7H3, an immune checkpoint protein, is overexpressed in tumor tissues and promotes tumor progression through immune-dependent and nonimmune pathways. In preclinical in vivo models, BNT327+BNT324/DB-1311 demonstrated superior anti-tumor effects compared to each drug alone. Encouraging early efficacy results and safety profile have been reported separately for BNT327 and BNT324/DB-1311 in both small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC); the combination is anticipated to improve patient outcomes with a manageable safety profile.

	1L SCLC	2L SCLC	2L/3L EGFRm NSCLC	1L NSCLC	2L+ SCLC	2L+ nsq NSCLC	2L+ sq NSCLC
Treatment	BNT327 + carbo/etop	BNT327 + paclitaxel	BNT327 + carbo/pem	BNT327	BNT324	BNT324	BNT324
N efficacy	48	65	64	17	73	41	25
ORR	87.5%	56.9%	60.9%	47.1%	56.2%	22.0%	16.0%
DCR	97.9%	87.7%	95.3%	100%	89.0%	80.5%	60.0%
mPFS, months	6.9	5.5	NR	13.6	3-mo PFS 73.6%	3-mo PFS 74.5%	3-mo PFS 50.5%
mOS, months	16.8	14.3	NR	13.9	NR	NR	NR
N safety	50	70	64	61	277 (across all tumor types)		
Grade ≥3 TRAEs	86.0%	78.6%	60.9%	19.7%	41.5%		
TRAE leading to discontinuation	6.0%	7.1%	7.8%	8.2%	5.4%		
TRAE leading to death	0	2.9%	1.6%	0	0.4%		
Reference	Cheng Y ELCC 2025 #302	Cheng Y. ELCC 2025 #332	Wu YL. ESMO 2024 #1255MO	Wu C. ASCO 2024 #8533	Cheng Y. ESMO Asia 2024 #57O		

Unconfirmed ORR is reported. TRAEs reported in BNT327 studies are related to BNT327 and/or chemotherapy.
DCR, disease control rate; EGFRm, epidermal growth factor receptor mutated; mo, month; NR, not reported; NSCLC, non-small-cell lung cancer; nsq, non-squamous; ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival; SCLC, small-cell lung cancer; sq, squamous; TRAE, treatment-related adverse events.

Methods: This global Phase 1b/2, open-label, two-part multicohort trial will evaluate efficacy, safety, pharmacokinetics, and the recommended Phase 2 dose (RP2D) of BNT324/DB-1311+BNT327 (NCT06892548). Inclusion criteria include: ≥18 years, ECOG PS 0-1, histologically or cytologically confirmed advanced/metastatic SCLC or NSCLC.

In Part 1, patients with SCLC or NSCLC will receive BNT324/DB-1311+BNT327 using a Bayesian optimal interval dose escalation (BOIN) design. Three dose levels with be explored for BNT324/DB-1311 (DL0, DL1, DL2) and 2 dose levels for BNT327 (DL0, DL1). Part 1 primary endpoint is safety, including dose-limiting toxicities to determine RP2D.

Part 2 will consist of 7 Cohorts (2 for dose optimization [DO] and 5 for signal-seeking), with Cohort-specific enrollment criteria: • non-squamous NSCLC, without actionable oncogenic alterations (AGA negative), any PD-L1 expression, treatment-naïve for advanced/metastatic disease (DO Cohort 1) • SCLC, post-chemotherapy +/- immunotherapy (DO Cohort 2) • non-squamous NSCLC, AGA negative, post-chemotherapy +/- immunotherapy (Cohort 3) • squamous NSCLC, AGA negative, treatment-naïve for advanced/metastatic disease (Cohort 4) • squamous NSCLC, AGA negative, post-chemotherapy +/- immunotherapy (Cohort 5) • non-squamous NSCLC, AGA positive, post-TKI (Cohort 6) • ES-SCLC, treatment-naïve (Cohort 7). Both DO Cohorts 1 and 2 will randomize patients 1:1 to RP2D vs a lower-dose combination (RP2D−1) and Cohorts 3-7 will receive RP2D until disease progression or up to 24 months (BNT327 monotherapy may continue for 12 additional months). Part 2 primary endpoint is safety and ORR in DO Cohorts 1&2 to determine the optimal dose, and ORR in Cohorts 3-7. Enrollment is ongoing.

Results:

Conclusions:

Keywords: B7H3 ADC, PD-L1, VEGF-A

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.75 Tislelizumab in Combination With EP/EC Chemotherapy and Sequent Anlotinib Followed by Radiotherapy as First-Line Treatment for ES-SCLC

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Introduction: The combination of immunotherapy with chemotherapy has greatly improved the efficacy of first-line treatment for extensive-stage SCLC(ES-SCLC) patients, but compared to NSCLC, the benefits are still relatively limited. Therefore, the exploration of how to expand the benefits of immunotherapy for SCLC is ongoing. Adding anti-angiogenic to the foundation of immunotherapy combined with chemotherapy can further improve the prognosis of patients with ES-SCLC. Additionally, previous studies have shown that after induction therapy, the addition of thoracic radiation therapy (TRT) following remission leads to an increase in survival rates and a significant reduction in the recurrence rate of thoracic lesions. Therefore, this study aims to explore the efficacy and safety of first-line treatment for ES-SCLC with Tislelizumab in combination with the EP/EC chemotherapy and sequential Anlotinib followed by radiotherapy.

Methods: This was an open-label, single-arm, phase 2 trial. Eligible patients were aged 18 years or older with histologically or cytologically documented untreated ES-SCLC (VALG staging). Patients received induction treatment with Etoposide (100mg/m2, d1-3) and Carboplatin (AUC 5, d1) or Cisplatin (75 mg/m2, d1) plus Tislelizumab (200 mg, d1) and Anlotinib(10mg, d1-14) of each 21-day cycle, for 4 cycles. Subsequently, investigators assessed patients who were suitable for radiotherapy (a total dose of 50Gy-51Gy for the primary chest lesion, and 30Gy or 45-50Gy for brain metastases). Patients suitable for radiotherapy include those with Complete Response (CR), Partial Response (PR), and those with Stable Disease (SD) whom the investigators deem likely to benefit from the treatment. During the maintenance treatment, patients will receive Tislelizumab in combination with Anlotinib until disease progression. The primary endpoint is the Progression-Free Survival (PFS) as assessed by the investigators according to RECIST v1.1. The Secondary endpoints were 6-month PFS rate, OS, 1-year OS rate and ORR. Safety was assessed in the intention-to-treat population. This study is registered with medicalresearch.org.cn, PID: 241871, and is ongoing.

Keywords: ES-SCLC, Radiotherapy, Combination therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.76 Efficacy and Safety of Cross-Line Adebrelimab Combined With Apatinib and Nab-Paclitaxel in Recurrent Small Cell Lung Cancer

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Introduction: Treatment options for relapsed small cell lung cancer (SCLC) remain limited, with second-line standard regimens (e.g., topotecan) demonstrating an objective response rate (ORR) of <25% and a median overall survival (OS) of 6-8 months. The CAPSTONE-1 study established adebrelimab combined with carboplatin and etoposide as the first-line standard of care for patients with extensive-stage SCLC in China. However, the clinical value of continuing immune checkpoint inhibitors (ICIs) beyond progression after first-line immunotherapy remains unclear. Here, we present the first evaluation of effectiveness and safety of cross-line adebrelimab (i.e., continued use after progression on first-line immunotherapy) combined with apatinib (a VEGFR-2 inhibitor) and nab-paclitaxel in relapsed SCLC.

Methods: This prospective, multicenter, single-arm study enrolled patients with histologically confirmed relapsed SCLC who progressed after first-line adebrelimab combined with chemotherapy. Key eligibility criteria included age ≥18 years, ECOG performance status 0-1, at least one measurable disease per RECIST v1.1, and progression-free survival (PFS)≥3 months for first-line treatment. Patients received induction therapy comprising adebrelimab (1200 mg q3w), apatinib (250 mg qd), and nab-paclitaxel (200 mg/m^2 q3w) for 2-4 cycles, followed by maintenance therapy with adebrelimab and apatinib until disease progression or intolerable toxicity. The primary endpoint was ORR, the secondary endpoints included PFS, OS, disease control rate (DCR),duration of response and safety assessed by CTCAE v5.0.

Results: Between December 10, 2023 to February 12, 2025, 12 patients were included (median age 61.5 years [range 48-74], 4 [33.3%] with ECOG PS 1, 3 [25.0%] with brain metastasis, 2 [16.7%] with liver metastasis, 6 [50.0%] with first-line PFS ≥6 months). As of March 25, 2025, the median follow-up was 6.4 months (95% CI: 3.2-9.5). Among the 12 patients, 10 were evaluated, the unconfirmed ORR was 66.7% (8/12; 95% CI: 34.1-89.7%) and DCR was 83.3% (10/12; 95% CI: 54.4-99.5%). The median PFS was 6.2 months (95% CI: 4.9-7.5). Treatment- related adverse events (TRAEs) of any grade were reported in 9 (75.0%) patients, and grade 3 or worse TRAEs occurred in 5 (41.7%) patients. The most common grade 3 or worse TRAEs were neutropenia and decreased white blood cell count.

Conclusions: Cross-line adebrelimab combined with apatinib and nab-paclitaxel showed promising efficacy and manageable safety in relapsed SCLC, providing a novel treatment strategies for post-immunotherapy progression.

Keywords: cross-line immunotherapy, recurrent small cell lung cancer, Adebrelimab

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.77 Efficacy and Safety of Adebrelimab Plus Irinotecan Liposome in ES-SCLC After First-Line Therapy: A Phase II Study (AIPATH)

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Introduction: Platinum-based chemotherapy or immunochemotherapy is the standard first-line treatment for extensive-stage small-cell lung cancer (ES-SCLC). Despite inducing significant tumor responses, most patients experience disease progression. Second-line options, mainly traditional chemotherapy, offer limited survival benefit. This study evaluates the efficacy and safety of adebrelimab combined with irinotecan liposome (II) in ES-SCLC patients after progression on first-line therapy.

Methods: This multicenter, multicohort prospective phase II trial in China enrolls ES-SCLC patients aged 18-75 years with histologically or cytologically confirmed diagnoses, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, progression after first-line treatment with etoposide and platinum-based chemotherapy, at least one measurable, non-irradiated target lesion per RECIST version 1.1, a life expectancy ≥ 12 weeks, and adequate organ function. Exclusion criteria include clinically significant brain or meningeal metastases, and interstitial pneumonia. Patients are stratified into two cohorts: cohort A (prior immune checkpoint inhibitors) and cohort B (no prior immune checkpoint inhibitors), with 30 patients each. All patients receive adebrelimab 1200 mg plus irinotecan liposome (II) 100 mg/m2 intravenously every 3 weeks until disease progression and/or intolerable toxicity. Primary endpoint is objective response rate.Secondary endpoints include overall survival (OS), 6-month OS rate, progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and safety. Exploratory endpoints include biomarker analysis, quality of life assessments, and long-term survivor characteristic.Trial registration: ChiCTR2400089170.

Keywords: ES-SCLC, adebrelimab, irinotecan liposome

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.78 A Prospective Study of Lurbinectedin Plusivonescimab Assecond-Line Treatment for Extensive-Stage Small Cell Lung Cancer

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Introduction: Extensive-stage small cell lung cancer (ES-SCLC) is a highly aggressive malignancy with limited therapeutic options. Patients undergoing second-line and subsequent systemic therapies typically have a survival of only 4-5 months. Lurbinectedin, a novel chemotherapy agent, has been approved for the treatment of adult patients with metastatic SCLC with disease progression during or after platinum- based chemotherapy. Recent advances in immunotherapy and anti-angiogenic therapies have shown promise for improving patient outcomes. Preliminary data from two phase 1/2 single-arm studies (2SMALL and LUPER) have demonstrated significant anti-tumor activity of lurbinectedin in combination with immunotherapy as second-line treatment for ES-SCLC. Ivonescimab (AK112), a bispecific antibody against programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF), has shown potential in improving survival when combined with chemotherapy in ES-SCLC. This study aims to evaluate the efficacy and safety of lurbinectedin combined with ivonescimab (AK112) in patients with ES-SCLC who have progressed after first-line chemoimmunotherapy.

Methods: This is a prospective, multi-center, open-lable, single arm phase 2 clinical trial. Key inclusion criteria include: 1) patients with histologically or cytologically confirmed ES-SCLC; 2) disease progression on or after first-line immunotherapy combined with platinum-based chemotherapy; Other main inclusion criteria include aged 18-75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and adequate organ function. The study consists of two phases: a safety run-in phase and an expansion phase. All participants will be simultaneously adminstrated with lurbinectedin 3.2 mg/m^2 every three weeks (Q3W) and ivonescimab (AK112) 20 mg/kg Q3W until disease progression or intolerable toxicity. The safety run-in phase will initially enroll 6 participants. If the treatment is deemed safe and tolerable, the study will proceed to the expansion phase. Our study aims to enroll a total of 53 participants. Sample size calculations were based on a power of β=0.8 and a two-sided significance level of α=0.2, with the 6-month progression-free survival (PFS) rate estimated at 32.9% under the null hypothesis of ineffectiveness and 45% under the alternative hypothesis of effectiveness, considering 10% dropout rate. The primary efficacy endpoint is the 6-month PFS rate, while secondary endpoints include objective response rate (ORR), median PFS, duration of response (DOR), disease control rate (DCR), and overall survival (OS). Safety will be evaluated based on the incidence and severity of adverse events (AEs) graded according to the NCI-CTCAE v5.0. Exploratory analyses will include biomarkers assessments of PD-L1 expression, tumor mutational burden (TMB), and immune cell infiltration in tumor tissues and plasma samples. In conclusion, this study aims to provide valuable insights into the efficacy and safety of lurbinectedin combined with ivonescimab (AK112) as the second-line treatment for ES-SCLC, potentially offering a new therapeutic option for patients. The trial has been registered at www.chictr.org.cn.

Keywords: ivonescimab, lurbinectedin, SCLC

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.79 Contralateral Esophageal-Sparing Technique Reduces High-Grade Esophagitis in Locally Advanced Small Cell Lung Cancer

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Introduction: Acute esophagitis, especially grade 3 or higher, is a major limiting toxicity in the concurrent chemoradiotherapy for locally advanced small cell lung cancer (LS-SCLC) , which can severely impact patient quality of life and treatment outcomes. The primary objective of this study was to evaluate whether the contralateral esophageal-sparing technique (CEST) could reduce the incidence and severity of high-grade esophagitis in LS-SCLC patients. The secondary objectives included assessing esophageal dose-volume parameters and overall treatment efficacy.

Methods: This single-center, prospective, randomized controlled trial enrolled 70 eligible LS-SCLC patients with tumors a within 1 cm of the esophagus. They were randomly assigned to the standard therapy group (CON) and the CEST group in a 1:1 ratio. All eligible patients received concurrent chemoradiotherapy (45 Gy radiotherapy in 30 fractions, twice-daily for 3 weeks with chemotherapy). In the CEST group, the CE was contoured as an avoidance structure with specific dose-volume constraints (CE maximum dose < 42 Gy, V36 < 0.5 cc, V30 < 3.5 cc). Acute esophagitis (AE) events were graded in line with the RTOG acute toxicity grading system. Ethical approval was obtained, and all patients provided informed consent.

Results: In this study, 70 patients were recruited (34 in CEST group, 36 in CON group). Eventually, 62 patients (31 in each group) were included in the analysis due to patient withdrawals and incomplete radiotherapy. In the CEST group (n=31), the incidence of acute esophagitis was 19.4%, and no cases of grade 3 or higher adverse events (AE) were observed. In the CON group (n=31), the incidence rate was 83.9%, including 4 cases (12.9%) of grade 3 AE. Dosimetric analysis revealed that the median maximum esophageal dose in the CEST group was 38.0 Gy, which was significantly lower than that in the CON group (47.8 Gy). The CEST group had better volume parameters, such as V45 of 0 cc, V36 of 0.01 cc, and V30 of 0.30 cc, compared to the CON group's 3.15 cc, 7.88 cc, and 9.31 cc, respectively (all P < 0.01). For treatment efficacy, analyses of progression-free survival (PFS) and overall survival (OS) showed no significant differences between the two groups (all P>0.05).

Conclusions: This study shows that the application of CEST in LS-SCLC patients can significantly reduce the incidence and severity of acute esophagitis, making it worthy of further clinical promotion. CEST helps improve the quality of life for patients undergoing concurrent chemoradiotherapy and may optimize treatment standards.$$graphic_{5060127F-EE3D-48CC-B655-447DEEED8184}$$

Keywords: Contralateral Esophageal-Sparing Technique, Locally Advanced Small Cell Lung Cancer, Esophagitis

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.80 A Phase 3 Study of Sacituzumab Govitecan in Patients With Previously Treated Extensive Stage Small Cell Lung Cancer

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Introduction: There are limited options for the treatment of extensive-stage small cell lung cancer (ES-SCLC) that has progressed after platinum-containing therapy with or without anti-programmed cell death protein (ligand) 1 (anti-PD-[L]1) therapy. Due to the toxicities and poor clinical outcomes associated with the current fully approved standard of care (SOC), topotecan, there remains an unmet need for novel agents in this patient population. Sacituzumab govitecan (SG), a Trop-2-directed antibody-drug conjugate, has demonstrated encouraging antitumor activity and manageable safety as a second-line treatment for ES-SCLC in the open-label, phase 2 TROPiCS-03 study. At a median study follow-up of 12.3 months in TROPiCS-03, investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 42% and median overall survival (OS) was 13.6 months. Neutropenia (44%) and diarrhea (9%) were the most common grade ≥3 treatment-emergent adverse events (TEAEs), and no TEAEs led to discontinuation of SG; one treatment-related TEAE led to death. EVOKE-SCLC-04 (NCT06801834) is a global, multicenter, randomized, open-label, phase 3 study evaluating the efficacy and safety of SG versus SOC (topotecan or amrubicin [Japan only]) in previously treated patients with ES-SCLC.

Methods: Key eligibility criteria for EVOKE-SCLC-04 include age ≥18 years, confirmed SCLC diagnosis, Eastern Cooperative Oncology Group Performance Status score of 0-1, measurable disease per RECIST v1.1, disease progression after 1 prior line of platinum-containing therapy with or without anti-PD-(L)1 therapy, and no untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients will be randomized 1:1 to either SG (10 mg/kg on Days 1 and 8) or SOC: topotecan (1.5 mg/m2 daily on Days 1-5) or amrubicin (40 mg/m2 daily on Days 1-3) administered as intravenous infusion in 21-day cycles, until progressive disease as assessed by blinded independent central review (BICR) per RECIST v1.1, unacceptable toxicity, or death. Randomization will be stratified by chemotherapy-free interval (≥90 vs <90 days), CNS involvement (yes vs no), geographic region (East Asia vs non-East Asia), and prior anti-PD-(L)1 therapy (yes vs no). The primary endpoints are ORR as assessed by BICR per RECIST v1.1 and OS. Secondary endpoints include progression-free survival, duration of response, patient-reported outcomes (time to first deterioration in shortness of breath and physical functioning), and safety/tolerability. This study is open and actively recruiting as of February 2025 and is planning to enroll 695 patients from approximately 200 sites globally.

Keywords: Sacituzumab govitecan, Extensive stage small cell lung cancer, Phase 3

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.81 A Phase II Study of First-Line Sintilimab Combined With Anlotinib and Platinum-Based Chemotherapy in Unresectable MPM

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Introduction: Malignant pleural mesothelioma (MPM) remains an aggressive thoracic malignancy with limited therapeutic advancements. Current first-line platinum-pemetrexed chemotherapy demonstrates modest efficacy (objective response rate (ORR) 20-40%, median overall (OS) 12-18 months). Recent studies have explored the role of anti-angiogenic agents and immune checkpoint inhibitors in MPM. BEAT-meso trial showed that the addition of atezolizumab to chemotherapy-bevacizumab result in a significant improvement in PFS (9.2 versus 7.6 months, HR 0.72, p = 0.0021); however, it did not translated into a significant increase in median OS (20.5 versus 18.1 months, p = 0.14). Anlotinib, a multi-target tyrosine kinase inhibitor, potently inhibits VEGFR2/KDR, along with PDGFRβ and C-kit, showing promising anti-tumor activity in various malignancies. Previous studies suggested that compared to bevacizumab, Anlotinib demonstrate both anti-angiogenses and regulation of cell proliferation, along with the modulation of immunosuppressive tumor microenvironment (TME). Sintilimab, a fully humanized IgG4 PD-1 monoclonal antibody, has demonstrated efficacy and manageable safety in advanced lung cancer, suggesting its potential in MPM. Building on these findings, this trial investigates the novel combination of sintilimab, anlotinib, and platinum-based dual-agent chemotherapy, hypothesizing synergistic effects through PD-1 blockade, VEGF pathway inhibition, and chemotherapy-induced immunogenic modulation.

Methods: This single-arm, open-label, phase II trial enrolls treatment-naïve patients aged ≥18 years with histologically confirmed unresectable or advanced MPM (stage IIIB/IV), ECOG 0-1, and measurable lesions per mRECIST 1.1. Key exclusion criteria include prior systemic therapy for advanced disease (excluding platinum-containing adjuvant therapy >6 months prior), active autoimmune diseases, and uncontrolled CNS metastases. Patients receive sintilimab 200mg IV (D1, Q3W), anlotinib 12mg PO (D1-14, Q3W), pemetrexed 500mg/m^2 IV (D1, Q3W), and cisplatin 75mg/m^2/carboplatin AUC5 IV (D1, Q3W) for 4-6 cycles, followed by sintilimab/anlotinib/pemetrexed maintenance until disease progression or intolerable toxicity. The primary endpoint is investigator-assessed ORR per mRECIST 1.1. Secondary endpoints include duration of response(DOR), disease control rate(DCR), progression-free survival (PFS), OS, and safety (NCI-CTCAE v5.0). Using a Simon two-stage design, 29 patients will be enrolled across two Chinese centers, taking into account an approximately 20% dropout rate. In the first stage, 13 participants would be recruited. If the number of responders among these 13 participants was less than 5, the study would be terminated. Otherwise, the enrollment would continue. We also plan to explore predictive biomarkers through serial blood samples detection and tumor tissue analysis. The trial was registered at ClinicalTrials.gov (NCT05188859) and is actively recruiting. As of March 27th , 2025, 8 patients have been enrolled.

Results: Between September 1, 2024, and March 27, 2025, 8 patients were enrolled in the study. Of these, 5 were evaluable for efficacy, with 3 achieving partial response (PR) and 2 stable disease (SD), resulting in an ORR of 60% and a DCR of 100%. Treatment-related adverse events (TRAEs) included 1 patient discontinuing anlotinib due to pulmonary embolism, 1 requiring dose reduction to 8 mg for intestinal obstruction, and 1 reducing to 10 mg for diarrhea.

Conclusions: No conclusions to report for this trial in progress abstract.

Keywords: Immunotherapy, Multi-target tyrosine kinase inhibitor, First-line combination therapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.82 Towards Harmonization of Clinical Care and Promoting Research for Thymic Epithelial Tumors: THETIS (THymic Cancers NETwork in Switzerland)

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Introduction: Thymic epithelial tumors (TETs) are rare tumors, with an incidence of 0.15 per 100,000 person-years. In Switzerland, the number of diagnosis has increased in recent years, particularly in women, according to data from our national cancer registry. Due to their rarity, management of TET patients should include dedicated multidisciplinary discussion at expert centers. Diagnosis is often delayed, preventing curative treatments. Furthermore, due to a high interobserver variability and limited pathology expertise diagnostic changes often occur upon review at specialized centers. Treatment protocols are based on retrospective series, expert opinion, and a limited number of prospective trials, emphasizing the importance of expert centers and multidisciplinary teams (MDT) for optimal care.

Methods: THETIS is a Swiss national network that includes the following Swiss cities and regions: Ticino, Lausanne, Geneva, Baden, Bern, St Gallen, Lucerne, Chur, Basel, Winterthur, Thurgau, Zurich and Fribourg. Key components include regular MDT discussions for all confirmed or suspected TET cases to ensure accurate diagnosis and management, and pathological review for standardizing diagnostic practices. The network will develop evidence-based treatment guidelines to uniform management across Switzerland. Furthermore, we will start a multi-center, ambispective observational study aiming at collecting clinical, epidemiological, and biological data on TETs in Switzerland. The registry will include data for all patients treated in the participating centers, focusing on diagnosis (imaging techniques, histology, clinical staging), treatment history (systemic therapies, radiotherapy, surgery), and patient outcomes. A data warehouse will integrate clinical data with biological samples, such as tumor biopsies, enabling translational research and informing future clinical trials. Clinical data will be collected prospectively during MDT and retrospectively from patients electronic charts. Relevant information will be entered into a dedicated electronic Case Report Form (eCRF), using validated software (5DBase® or Redcap®) for remote data collection, ensuring compliance with data protection, access control, and traceability standards. The database will be based on datasets from ITMIG (www.itmig.org). The TETHIS registry will enable the identification of epidemiological trends, treatment outcomes, and therapy effectiveness for TETs. Integrating clinical data with biological samples potentially uncovers novel biomarkers for diagnosis, prognosis and novel therapies. MDT discussions and expert reviews will improve diagnostic accuracy, ensuring timely and appropriate treatment. Additionally, treatment guidelines will ensure consistent, high-quality care across Switzerland. TETHIS network is a collaborative effort to improve the diagnosis, treatment, and research for thymic malignancies in Switzerland. We will collaborate with international research networks, including ITMIG and Euracan, to enhance global research, broaden access to clinical trials, and support novel therapies. Ultimately, it will provide a valuable resource for clinical trials and informed decision-making in TET treatment, eventually improving patient outcomes. We will present number of cases discussed and activities implemented during the first months following network activation.

Keywords: multidisciplinary network, thymic epithelial tumors, rare cancers

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.83 Efficacy and Safety of Ivonescimab Plus Chemotherapy for Recurrent/Metastatic Thymic Carcinoma: A Phase II Study (iThyme)

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Introduction: Thymic carcinoma (TC) is a rare malignancy with an increasing incidence in Asia. Despite surgical resection being the cornerstone for early-stage disease, advanced or metastatic thymic carcinoma poses significant therapeutic challenges. Platinum-based chemotherapy is the current standard of care, yet its efficacy is limited with response rates ranging from 30% to 60%. Emerging evidence suggests that dual targeting of immune checkpoints and angiogenesis may enhance antitumor activity. Ivonescimab, a novel bispecific antibody targeting PD-1 and VEGF, has demonstrated promising results in non-small cell lung cancer. This study aims to evaluate the efficacy and safety of ivonescimab in combination with chemotherapy as a first-line treatment for recurrent or metastatic thymic carcinoma.

Methods: This prospective, single-arm, Simon' s two-stage phase II study (NCT06750952) enrolls patients with histologically confirmed, untreated, unresectable TC. Key inclusion criteria: ECOG PS 0-1, measurable lesions (iRECIST), and adequate organ function. Patients receive ivonescimab (20 mg/kg, intravenously every 3 weeks) in combination with paclitaxel (175 mg/m^2) or albumin-bound paclitaxel (260 mg/m^2) and carboplatin (AUC 5) for 4-6 cycles, followed by maintenance therapy with ivonescimab until disease progression or unacceptable toxicity. The primary endpoint is the 6-month progression-free survival rate (PFS6m). Secondary endpoints include PFS, overall response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety assessments. Exploratory biomarker analyses will assess tumor tissue and blood samples. Using Simon' s optimal design (α=0.05, β=0.20), 8 patients are enrolled in Stage I; if ≤3 progressions occur by 6 months, Stage II proceeds to total 24 patients. Success is defined as ≤10 progressions at 6 months in the full cohort.

Results: The clinical trial is ongoing.

Conclusions: The clinical trial is ongoing.

Keywords: Thymic carcinoma, Ivonescimab, Chemotherapy

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.84 A Randomized Comparative Effectiveness Trial of Perioperative Physical Activity in Older Adults With Lung Cancer and Their Family Caregivers

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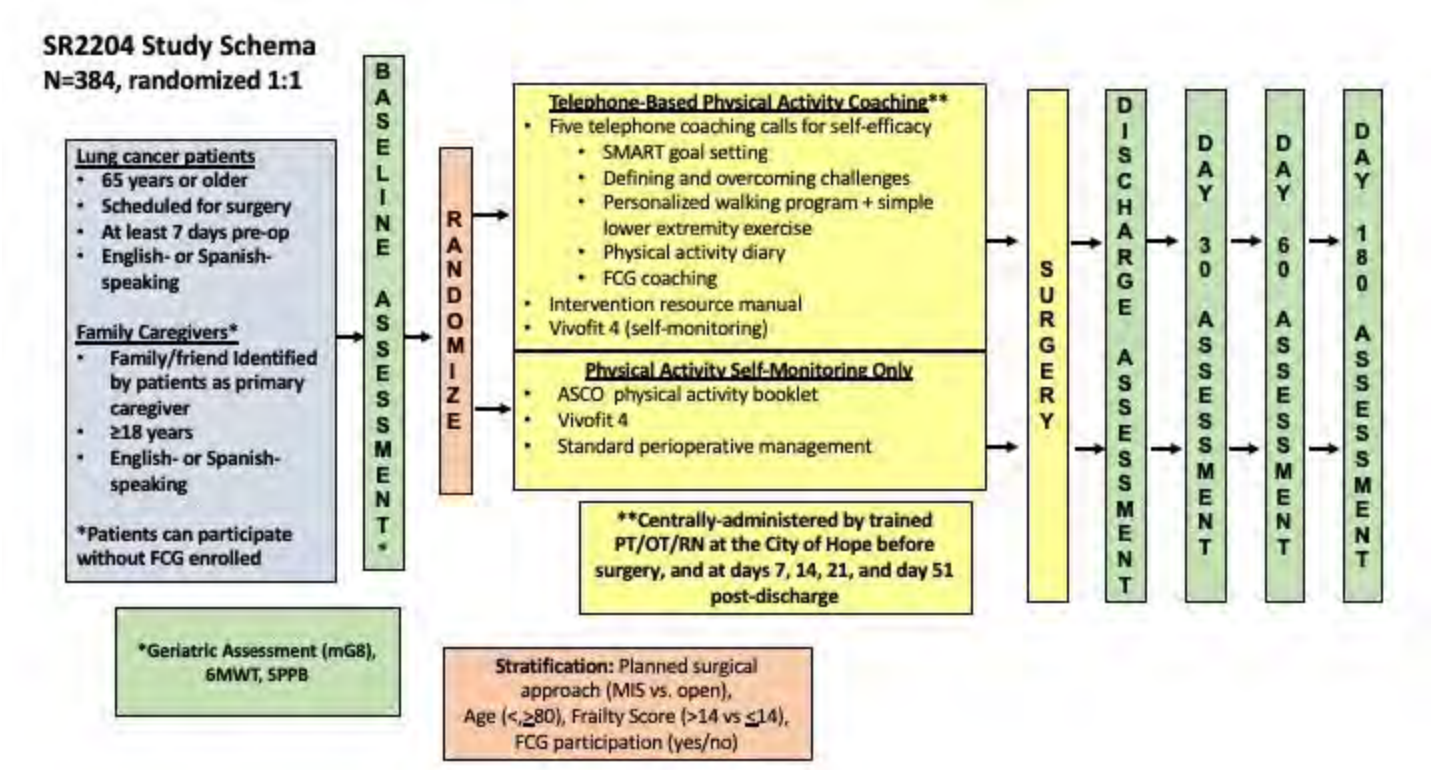
Introduction: With a median age at diagnosis of 70, lung cancer is a major public health issue for older adults worldwide. Surgery plays a crucial role in the treatment of most patients with non-metastatic lung cancer. However, patients often face postoperative challenges such as pain, fatigue, reduced pulmonary function, and diminished physical capabilities. Despite the importance of these issues, there are limited data on how to best improve the functional recovery of older adults after lung cancer surgery, and few interventions specifically address the needs of older patients and their family caregivers (FCGs). This pragmatic comparative effectiveness trial aims to assess whether telephone-based physical-activity coaching, provided both before and after surgery, offers greater benefits than physical-activity self-monitoring without coaching for older adults and their FCGs.

Methods: SR2204 is a phase 3, multi-center, randomized comparative effectiveness trial. 382 older adults (aged 65 and above) with a lung cancer diagnosis and planned surgical resection, along with their family caregivers (FCGs), will be recruited prior to surgery and randomly assigned to one of two groups: telephone-based physical activity coaching or physical activity self-monitoring without coaching. Participants in the coaching group engage in 5 telephone sessions with rehabilitation coaches (1 before and 4 after surgery), receive an intervention resource manual, and are provided with a wristband pedometer. Those in the self-monitoring group are given physical activity guidelines from the American Society of Clinical Oncology (ASCO) and wristband pedometers. All participants are evaluated prior to surgery (baseline), at discharge, and at 30-, 60-, and 180-days post-discharge. The primary outcome measure is the change in 6-minute walk distance at 30 days after discharge compared to baseline. Secondary endpoints include geriatric assessment, lower extremity function, self-reported physical function, self-efficacy, and quality of life. The trial is open to enrollment at 12 sites throughout the United States. Enrollment commenced on January 10, 2024. The trial has enrolled 118 patient participants at the time of submission, among whom 64% enrolled along with FCGs in the study. Clinical trial information: NCTN06196008.



Keywords: Lung cancer surgery, Rehabilitation, Older Adults

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.85 A Personalized Nutrition and Physical Exercise Intervention to Enhance Early-Stage NSCLC Outcomes: The STARLighT Study

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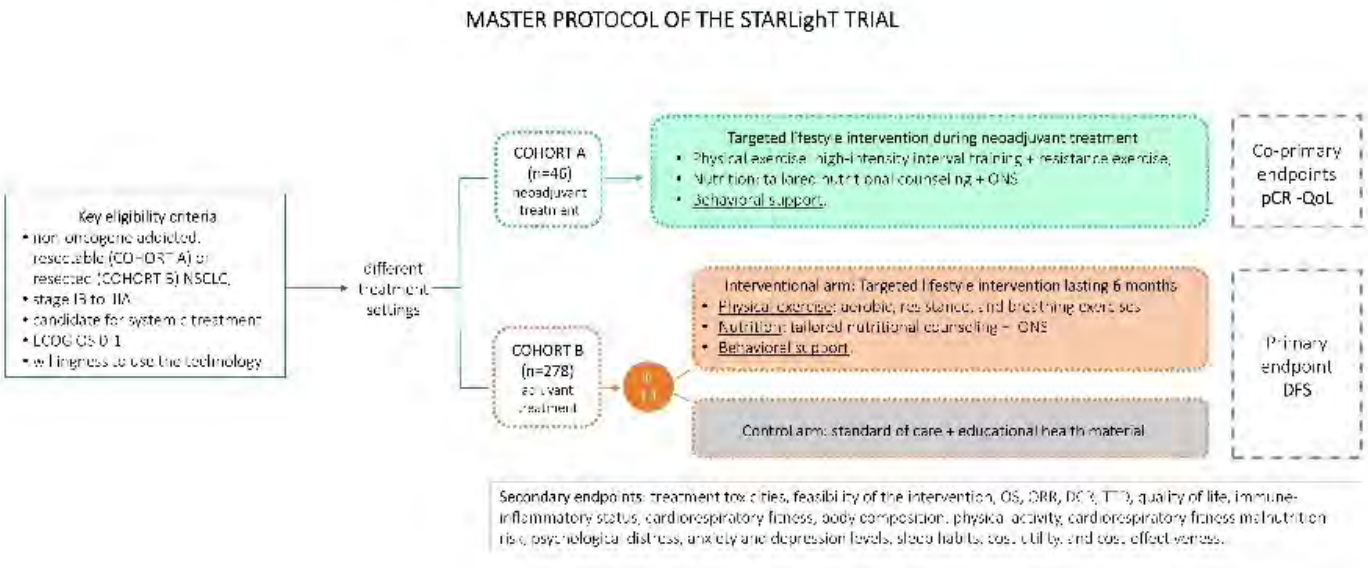
Introduction: A healthier lifestyle could have avoided >1,600,000 lung-cancer-related deaths in 2019. Lifestyle interventions have a positive impact on the natural history of lung cancer across all disease stages. However, solid clinical evidence of the impact of lifestyle interventions on hard clinical endpoints in early-stage disease is currently lacking. The STARLighT study builds on the hypothesis that implementing a structured lifestyle intervention together with systemic treatment would significantly improve clinical outcomes in patients with early-stage lung cancer while substantially improving patients' quality of life. The primary aim of the STARLighT trial is to test the impact of a structured and evidence-based lifestyle intervention delivered by a telemedicine platform on pathological complete response (pCR) in patients undergoing neoadjuvant treatments and on disease-free survival (DFS) in patients undergoing adjuvant therapies. We expect that a tailored lifestyle intervention will result in a higher pCR rate and longer DFS in patients in the neoadjuvant or adjuvant setting, respectively, thereby potentially increasing cure rates in early NSCLC.

Methods: A master clinical protocol will be set up to evaluate the lifestyle intervention in different cohorts of patients diagnosed with non-oncogene addicted with early-stage non-small cell lung cancer (NSCLC), stages IB to IIIA. COHORT A will accrue 46 patients undergoing neoadjuvant chemo/immunotherapy and exploit a single-arm phase II design to detect an increase in the proportion of pCR from 20% to 40%; COHORT B will accrue 278 patients undergoing physician's choice of adjuvant treatment and exploit a 1:1 randomized controlled design to detect an increase in 2-year DFS rates from 55% to 70% in the control and experimental arms, respectively. All patients in COHORT A will receive a personalized physical exercise intervention thrice a week, tailored nutritional counseling by a skilled dietitian, and immunonutrients, two bottles/day. The intervention in COHORT A will last for the entire neoadjuvant treatment period. In COHORT B, whereas patients randomized in the controls will receive the current standard of care and dedicated educational health material, those allocated in the experimental arm will undergo physical exercise twice a week, nutritional counseling, and oral supplementation (whey protein, 20 gr/day). The intervention for the COHORT B will last 6 months. Translational studies will encompass baseline assessment of genomic and transcriptomic features and longitudinal assessment of circulating immuno-inflammatory profiles and tumor microenvironment composition, to be correlated with clinical and lifestyle data to build a comprehensive predictive model.



P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.86 Efbemalenograstim Alpha Prophylaxis for Intermediate-Risk FN Chemotherapy in NSCLC: A Multicenter Exploratory Study

M. Li[1], D. Huang[1], C. Liu[2], H. Lan[3], J. Ge[4], F. Ran[5], X. Tang[6], C. Rao[7], W. Zheng[8], T. Gao[9], Z. Li[10], Z. Zhao[11], Y. Mao[12], W. Cui[13]
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Introduction: Neutropenia represents a frequently observed dose-limiting toxicity of chemotherapy, with its severity and persistence significantly influencing treatment efficacy. In non-small cell lung cancer (NSCLC) management, while high-risk febrile neutropenia (FN) chemotherapy remains relatively uncommon, real-world data indicate suboptimal utilization of granulocyte colony-stimulating factor (G-CSF) prophylaxis among patients with risk factors receiving intermediate-risk FN regimens. This study aims to evaluate the clinical effectiveness and safety profile of efbemalenograstim alpha in maintaining absolute neutrophil count (ANC) levels during chemotherapy cycles for NSCLC patients undergoing intermediate-risk FN treatment protocols with coexisting risk factors.

Methods: This randomized, multicenter, exploratory clinical study (NCT06143735)enrolled non-small cell lung cancer (NSCLC) patients undergoing intermediate-risk febrile neutropenia (FN) chemotherapy with additional risk factors. Participants were stratified into two groups: the primary prophylaxis arm (Group A) received subcutaneous efbemalenograstim alfa (20 mg) within 48±4 hours after each chemotherapy, starting from the first cycle, while the secondary prophylaxis arm (Group B) initiated treatment only if grade ≥3 neutropenia (CTCAE v5.0) occurred in the preceding cycle. All patients were required to receive at least 4 cycles of platinum-based chemotherapy. The primary objective was to compare the incidence of grade ≥3 neutropenia during the first chemotherapy cycle between primary and delayed secondary prophylaxis strategies. The secondary objectives included FN incidence, grade ≥3 neutropenia during other chemotherapy cycles, and adverse events or serious adverse events. Here,we present, after the first analysis, the updated results of Guard-03.

Results: As of March 31, 2025, 53 subjects were enrolled (median age: 69 years; 64.15% with ECOG 0-1; 90.57% male), with 35 assigned to Group A and 18 to Group B . The incidence of grade ≥3 neutropenia during the first treatment cycle was 23.08% (6/26) in Group A versus 64.71% (11/17) in Group B. Febrile neutropenia (FN; defined per CTCAE v5.0 as ANC <1.0×10^9/L with single temperature >38.3°C [101°F] or sustained temperature ≥38°C [100.4°F] for >1 hour) occurred in 1 and 2 patients in Groups A and B, respectively. Safety analysis showed 11 patients (28.2%) experienced TRAEs (4 cases [10.3%] with pain symptoms such as ankle soreness or neuropathic pain), while 23 patients (59.0%) developed grade ≥3 AEs, predominantly chemotherapy-related.

Conclusions: Efbemalenograstim alfa demonstrated promising clinical efficacy in the prophylactic management of chemotherapy-induced neutropenia, reducing the risk of infection and enhancing patients' quality of life.

Keywords: Efbemalenograstim alfa, Chemotherapy-induced neutropenia, Intermediate-risk FN regimens

P3.18 CLINICAL TRIALS IN PROGRESS
TUESDAY, SEPTEMBER 9, 2025 - 10:00 - 11:30

P3.18.87 EVEREST-2: Phase 1/2 Study of Logic-Gated Tmod CAR T A2B694 in Lung Cancer and Other Tumors Expressing MSLN With HLA-A*02 LOH

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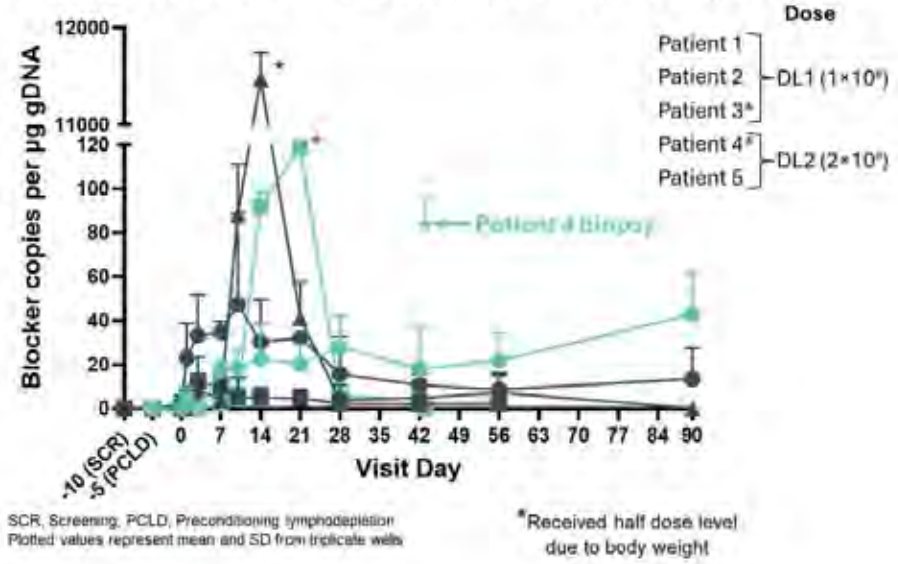
Introduction: Mesothelin (MSLN) is commonly overexpressed in lung cancer, with minimal expression in normal tissues. Unacceptable toxicities, including death, have limited MSLN-targeted programs. A2B694 is an autologous, logic-gated Tmod chimeric antigen receptor T cell (CAR T) therapy designed to improve tumor selectivity and decrease toxicity by integrating an MSLN CAR T activator with a human leukocyte antigen (HLA)-A*02 blocker. Loss of heterozygosity (LOH) may provide a means to target tumors instead of normal cells.

Methods: EVEREST-2 (NCT06051695) is a first-in-human, open-label, phase 1/2 study evaluating the safety and efficacy of A2B694 in patients with recurrent or metastatic cancers with MSLN expression (non-small cell lung cancer [NSCLC], colorectal cancer, pancreatic cancer, ovarian cancer, and mesothelioma) and tumor-associated HLA-A*02 LOH. Eligible patients are identified in the master prescreening study, BASECAMP-1 (NCT04981119). BASECAMP-1 enrollees have their leukapheresis product cryopreserved. When clinically appropriate, A2B694 is manufactured on demand and administered after lymphodepletion. The primary objective of phase 1 is to evaluate the safety and tolerability of A2B694 and identify a recommended phase 2 dose. The phase 2 primary objective is to assess overall response rate.

Results: As of 6 March 2025, 5 patients were enrolled in phase 1: 4 women/1 man, median age 59 years, 4 non-Hispanic White, 1 Hispanic. Tumor types included ovarian cancer (Patients 1-3), pancreatic cancer (Patient 4), and NSCLC adenocarcinoma (Patient 5). A2B694 doses were 0.5×108 (n=1), 1×108 (n=3), and 2×108 (n=1) cells. Lymphodepletion was well-tolerated by all patients, with no clinically significant cytopenias. All patients had ≥1 adverse event, most commonly decreased appetite (n=3; 1 serious) and fatigue (n=3). There were no dose-limiting toxicities, cytokine release syndrome, or related neurotoxicity noted, and no new safety signals after ≤8.9 months of follow-up. A2B694 was detected post-infusion in peripheral blood in all treated patients (Figure) and present in a tumor biopsy in 1 patient (Patient 4) 42 days (D) post-infusion. Patient 5 has KRAS G12V/STK11 co-mutated NSCLC adenocarcinoma that progressed on carboplatin, pemetrexed, and pembrolizumab. They achieved a partial response at D90 post-infusion and continue on observation. Patients 1-3 had stable disease at D28 and progressive disease by D90 and Patient 4 had progressive disease at D28.

Conclusions: A2B694 has manageable safety and tolerability in patients with advanced solid MSLN-expressing tumors with tumor-associated HLA-A*02 LOH. The dose-escalation phase continues to enroll patients. All patients exhibited CAR T expansion, and there is an ongoing partial response in a patient with NSCLC.

Figure. EVEREST-2 Dose Levels (DL) 1 and 2: A2B694 (MSLN Tmod) Levels in Peripheral Blood (droplet digital PCR) Over Time



Keywords: Mesothelin, CAR-T, Loss of Heterozygosity

09 | ePOSTER LISTINGS

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.01 Exercise Training Modalities in Patients With Lung Cancer: A Protocol for Systematic Review and Network Meta-Analysis

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Introduction: Lung cancer is a common malignancy and a major cause of cancer-related deaths worldwide, ranking high in terms of morbidity and prevalence. Exercise is a well-established recovery aid for many chronic respiratory conditions and lung cancer. However, it is difficult to determine the superiority of different exercise training modalities using randomised controlled trials (RCTs) or pairwise meta-analyses. Our Bayesian network meta-analysis (NMA) aimed to compare the impact of different perioperative exercise training modalities on lung function, exercise capacity, adverse events, health-related quality of life and mortality in patients undergoing lung cancer surgery, including preoperative and postoperative patients.

Methods: We will perform a comprehensive literature search using PubMed, EMBASE, Cochrane Library and Web of Science, from inception to May 2022, to identify studies that potentially provide data regarding exercise training modalities for patients with lung cancer. We will assess the risk of bias according to the Cochrane risk-of-bias tool and certainty of evidence for the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation framework. Pairwise meta-analyses will be conducted using a random effects model and Stata software, and the NMA will be analysed using R software.

Results: We will focus on the following outcomes of interest: ► Lung function (eg, volumes and diffusing capacity). ► Exercise capacity (measured either by the 6min walk test or peak oxygen consumption during a maximal incremental exercise test). ► Adverse events. ► Quality of life, determined using the Medical Outcomes Study Short Form 36 General Health Survey, the European Organization for Research and Treatment of Cancer Quality of Life, the Functional Assessment of Cancer Therapy-Lung scale or HRQoL. ► Mortality.

Conclusions: Different exercise training modalities will be considered in our systematic review, including aerobic, strengthening, breathing and combined exercises. Supervised, unsupervised or a combination of both exercise sessions will be considered. Aerobic exercise will be defined as a regimen that contains aerobic components. Aerobic components include, but are not limited to, walking, cycling, yoga (only yoga that meets the definition of aerobic exercise), jogging and swimming.26 Strengthening exercise will be defined as a regimen consisting of some type of progressive resistance to increase muscle strength, endurance or power, which includes, but is not limited to, bench press, seated row, shoulder press, leg press and weight strength.27 Breathing exercises will be defined as a broad range of respiratory strategies, including, but not limited to, pursed-lip, abdominal and thoracic breathing exercises. Combined aerobic and resistance training (combined exercise) will be defined as performing an aerobic training programme plus a resistance training programme to ensure an adequate dose of each type of exercise.

Keywords: Exercise training modalities, lung cancer

EP.01.02 Long-Term Survival After Curative Surgery for Stage I-III NSCLC Patients in British Columbia, 2005-2021: A Population-Based Study

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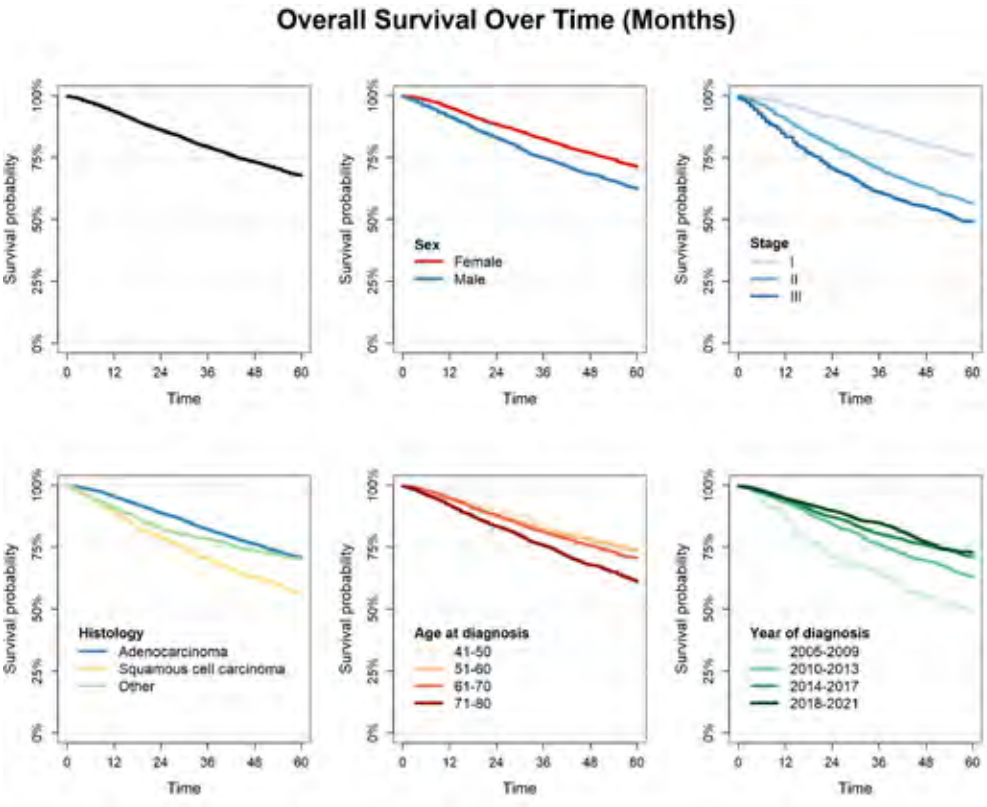
Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide. In British Columbia (BC), Canada, curative-intent surgical resection is the cornerstone treatment for stage I-III non-small cell lung cancer (NSCLC). Real-world data on long-term survival across demographic and clinical subgroups is essential to measure the impact of adopting novel treatment modalities and early detection interventions. Here, we evaluated overall survival (OS) among stage I-III NSCLC patients diagnosed from 2005 to 2021 who underwent curative-intent surgery in BC, to characterize patterns of survival before the implementation of the provincial lung cancer screening program in 2022.

Methods: We conducted a population-based retrospective cohort study using data from the BC Cancer Registry. We included patients aged 40-80 at diagnosis, with stage I-III NSCLC, who received curative-intent surgery between 2005 and 2021. Demographic (age, sex) and clinical (stage, histology, year of diagnosis) variables were obtained. Kaplan-Meier methods estimated OS probability (with 95% confidence intervals, CIs) at 12, 36, and 60 months. We used Fine and Gray's subdistribution hazard model to estimate sub-hazard ratios (sHRs) for lung-cancer-specific mortality by prognosis factors, accounting for the competing risk of death from other causes. The University of British Columbia Research Ethics Board approved this study.

Results: A total of 3,614 patients met inclusion criteria (57.8% female; mean age at diagnosis 67.3 years). Overall, 12-, 36-, and 60-month OS estimates were 93.2% (CI 92.7-93.7), 80.2% (CI 79.1-81.3), and 68.6% (CI 67.1-70.2), respectively. Females had higher OS than males (60-month OS 72.4% vs. 63.5%). By stage, 60-month OS was 76.0% for stage I, 57.5% for stage II, and 50.9% for stage III. Adenocarcinoma demonstrated the most favorable OS (60-month OS 71.3%), while squamous cell carcinoma (58.9%) fared the worst. Patients diagnosed in later years experienced higher 60-month OS than those diagnosed in 2005-2009 (49.9%). In competing risk analysis, earlier years of diagnosis were associated with higher risk of lung-cancer-specific death (2005-2009: sHR=3.27, CI=2.48 to 4.31; 2010-2013: sHR=1.90, CI=1.55 to 2.34; 2014-2017: sHR=1.44, CI=1.17 to 1.77) compared to 2018-2021, after adjusting for age, sex, stage, and histology.

Conclusions: Survival after curative-intent surgery for stage I-III NSCLC has improved in BC over time, with early stage, adenocarcinoma histology, and female sex associated with better prognosis. Future analyses will explore how treatment modality has driven these improvements. Our findings provide a benchmark for future assessments of the BC lung cancer screening program's impacts on lung cancer mortality and survival.



Keywords: NSCLC, Survival, Prognostic factors

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.03 Young Patients With Non-Small Cell Lung Cancer in Poland - a Comprehensive Epidemiological, Molecular and Prognostic Analysis

M. Knetki-Wróblewska[1], B. Tomasik[2], L. Grono[2], W. Bortnowski[2], B. Sobocki[2], M. Sekuła[3], J. Chwatko[3], M. Krzakowski[1]
[1]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw/PL ,[2]Medical University of Gdansk, Gdansk/PL ,[3]Medical Univeristy in Warsaw, Warsaw/PL

Introduction: The incidence of non-small cell lung cancer (NSCLC) in Young Caucasian Patients (<50 years) is low, and knowledge clinical features, molecular landscape, and treatment outcomes is still incomplete. This study presents the clinicopathological, molecular characteristics, and survival of young-onset NSCLC in a real-world setting in two cancer centres in Poland.

Methods: Patients aged 18 to 50 years with a diagnosis of NSCLC who were treated between 2010 and 2023 were identified using electronic medical records. The included patients were reviewed for demographics including age, sex, smoking history, histology, molecular analysis, staging, treatment history, and survival data. Survival was analysed using the Kaplan-Meier method.

Results: Of 234 included Caucasian patients, the median age was 42.8 years, 55% (n = 129) were female, 38% (n = 90) were never smokers. Most of the patients had adenocarcinoma (74%, n = 173) and presented metastatic disease (73%, n = 171). In patients with non-squamous metastatic NSCLC (n = 130), next-generation sequencing (NGS) was performed in 60% (n = 78). Molecular aberrations were found in 79% (n = 62) of the patients, which is a significantly higher percentage than in the general population of patients. Among them in the majority (n = 47, 76%) molecular targeted therapy was introduced. Median overall survival (OS) in metastatic NSCLC was 17.6 months (95% CI 14.7-21.1 months), with a higher median overall survival in those with a targeted therapy option (23.6 months) compared to those without (12.9 months; p < 0.001). In patients with non-metastatic NSCLC, median OS was 81.1 months (95% CI 77.3-152.9 months).

Conclusions: Young Caucasian patients with NSCLC have predominantly advanced stage adenocarcinoma and exhibit a high prevalence of actionable molecular aberrations. Integration of NGS and targeted therapies significantly influences treatment outcomes, highlighting the need for personalised approaches in this rare population.

Keywords: Young Patients, NSCLC, NGS

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.04 Features, Demographics and Treatment Profiles of Primary Lung Cancer Cases in Nigeria: The Largest Single Centre Report in West Africa

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Introduction: Lung cancer leads the cancer incidence and mortality chart globally, yet it is not among the top 10 cancer cases in Nigeria. This is likely due to underdiagnosis, partly due to similar clinical presentations to endemic diseases such as tuberculosis, as well as limited infrastructure for robust data storage and analysis. This study aims to unravel lung cancer in Nigeria by examining the database of cases treated at a leading comprehensive cancer center in Lagos, the most populous city in West Africa.

Methods: Primary lung cancer cases treated at the Centre between 2019 and 2024 were retrospectively reviewed. Patient data, including demographics, tumor characteristics, medical imaging, comorbidities and histological subtypes, diagnosis and treatment options, were analyzed.

Results: The search revealed 175 confirmed cases (Scan QR Code to see study cohort demographics table). The average patient age was 59 years (range: 27 - 85), of which 49.7% were females and Adenocarcinoma the most common histological subtype (57.1%). Only 4% of cases presented at an early stage (I and II). Despite lung cancer's strong global association with tobacco use, 14.9% of cases had a history of smoking, suggesting the possible role of environmental and genetic factors. Cross modality imaging was available to 77% of the patients for diagnosis. Radiotherapy was provided to 31% of patients, most of which for palliative intent. Immunohistochemistry testing was performed in 14.3% of cases, while 8% of patients received immunotherapy, reflecting limited access to advanced molecular diagnostics and targeted therapies. Representative CT images of the cases are shown in Figure 1.

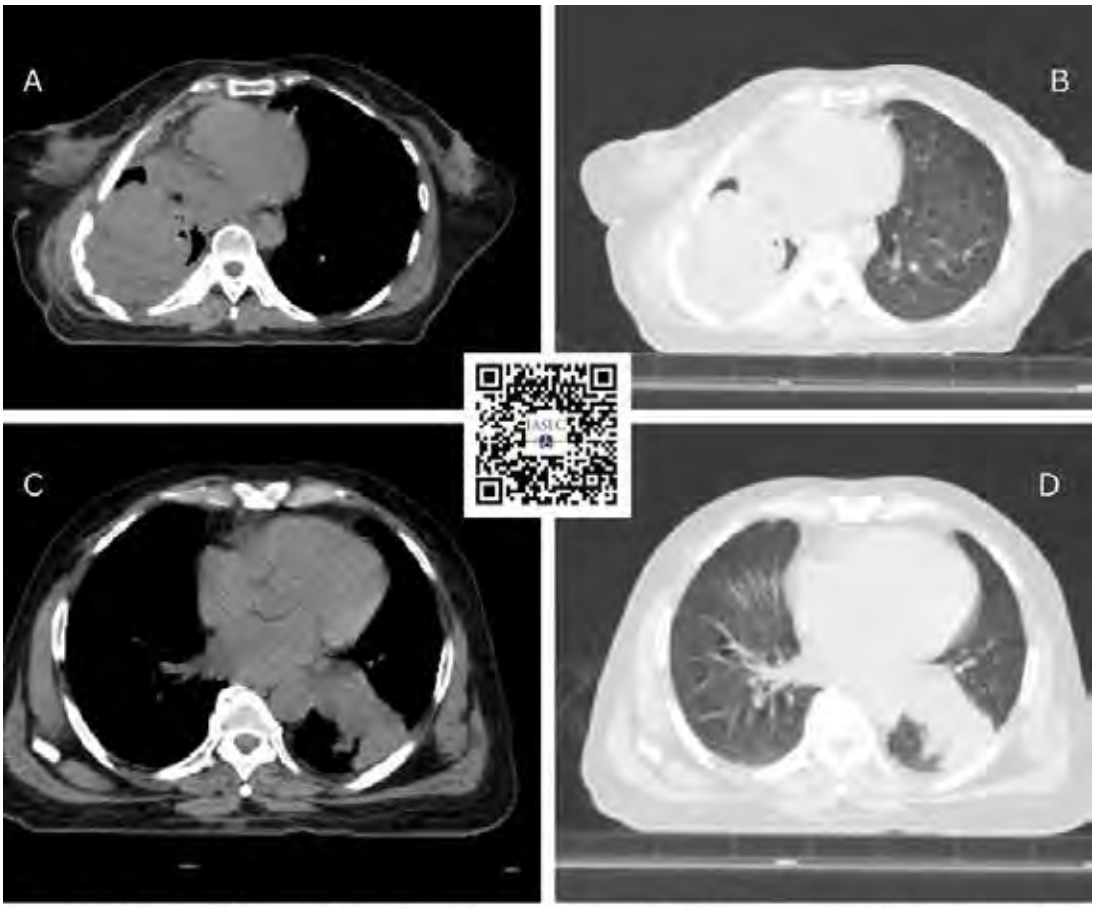

Figure 1: Study Cohort Sample CT Images (A and C in soft tissue window, B and D in lung window). A and B shows right lung mass with associated atelectasis and pleural effusion. C and D demonstrate left lower lobe mass with associated atelectasis. Scan the QR code to see the full demographic table

Conclusions: This study, representing the largest single center lung cancer report from West Africa, highlights a predominance of late-stage lung cancer presentation and heavy reliance on palliative care in Nigeria. Importantly, lung cancer in this cohort showed a weak association with smoking, with nearly equal male and female representation, differing from global patterns. Defining and targeting high-risk groups and improved understanding of cancer biology in African populations is needed to improve regional and global lung cancer outcomes.

Keywords: Lung Cancer, Nigeria, Clinicopathological features and Demographics

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.05 Mapping the Clinical Pathways in Lung Cancer: Evaluating the Inspire Program in the Brazilian Public Healthcare System

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Introduction: Understanding the clinical pathway of cancer patients is fundamental for optimizing the management of tracking programs and driving strategies for improving clinical outcomes within the public healthcare system. The purpose of this study has been to map the clinical pathways of patients treated by the Inspire Program, in Botucatu, Brazil, analyzing the healthcare flows and identifying critical factors that directly impact the efficiency and the results in lung cancer care.

Methods: This retrospective study analyzed patient data who were treated by the Inspire Program, implemented in Botucatu, São Paulo, Brazil in the period from January 2023 to October 2024. The program focuses on early diagnosis and treatment of chronic respiratory conditions, especially focused on vulnerable populations, integrated between primary care and specialized networks. The information was extracted from clinical and administrative records, ranging from demographic, smoking history, diagnostic exams, treatment performed, and clinical outcomes. The clinical flows were analyzed by process mining, generating detailed maps that revealed the frequency of transitions, the temporal efficiency between steps and critical factors that directly impacted the quality of patient care for lung cancer patients.

Results: The data analysis revealed that the patients' mean age was 63.5, with (62.5%) female gender predominance, and with a mean tobacco load of 79 packs/year, indicating a significant history of smoking. Most patients were diagnosed with an advanced stage of cancer (37.5% in stage IV). Before beginning treatment, the most common activities included primary healthcare (17.8%), laboratory exams (13.4%), and miscellaneous medical care (12.2%). After diagnosis, laboratory exams were the most common (22.91%), radiotherapy (16.59%), and primary healthcare (9.16%) as the most frequent interventions. An analysis of the clinical pathways demonstrated differences based on the staging of the disease: patients in the initial stages were mainly treated with thoracic surgery, while those whose stages were locally advanced and advanced were treated with combined radiotherapy, chemotherapy, and multidisciplinary support, including palliative and nutritional care.

Conclusions: This study mapped the clinical pathways of patients with lung cancer treated by the Inspire Program, revealing the complexity of treatment pathways and emphasizing the importance of specialized and multidisciplinary interventions.

Keywords: Lung Cancer Screening, Clinical Pathways, Healthcare Management

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.06 Clinical Characteristics, Molecular Profile and Survival Outcomes in Young Lung Cancer Patients From Western India

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Introduction: Lung cancer in individuals under 50 years presents distinct clinical characteristics and poses unique diagnostic and therapeutic challenges. This study aims to evaluate the demographic profile, molecular characterization and survival outcomes in young lung cancer patients in India

Methods: This retrospective study included consecutive patients from community oncology centres diagnosed Lung cancer NSCLC (age ≤50) between March 2018 and September 2024. Progression-free survival and overall survival were calculated using the Kaplan-Meier analysis

Results: A total of 2281 patients were diagnosed with lung cancer, of whom 297(13%) were young patients(age ≤ 50 years); among them, n=83 were classified as very young (age≤40 years), and n=214 were aged between 41 and 50 years. The median age at presentation was 45 years(IQR 40-48), with a M:F of 1.14:1 and distribution by stage was 3.4%(n=10) in stageI/II, 17.2%(n=51) in stageIII, and 77.8%(n=231) in stageIV. Among the cohort, smoking history was reported in 32.2% of males and 13.7% of females(p<0.001). The cohort comprised 90.9% of Non-small cell lung cancer(NSCLC) cases, with adenocarcinoma being the predominant subtype (84.1%). Most common sites of metastasis were bone(134/231), brain(75/231), lymph nodes(52/231), and liver (49/231). Molecular testing was performed in 66.3%(197/297) of patients, out of which Next-generation sequencing(NGS) was done in 104/197 patients wherein 45.2% were comprehensive NGS panel and 54.8% were short NGS panel while 93/197 were tested by Polymerase chain reaction(PCR) method. Actionable molecular alterations(EGFR/ALK/ROS1) were detected in 55.3%(109/197) of tested patients, with EGFR mutations in 40.6%(80/197), ALK rearrangement in 12.7%(25/197), and ROS1-rearrangement in 5.1%(10/197), while Tumor mutational burden(TMB) >10 Mut/Mb was reported in n=4/197. Prevalence of ALK rearrangement was significantly higher in patients ≤ 50 years (12.7%) compared to overall cohort of lung cancer patients (5.6%)p<0.001. Among the 44.7%(88/197) of patients with EGFR/ALK/ROS1 wild-type, PD-L1 expression was 1-49% in 27 patients and >=50% in 8 patients. Mutational alterations were identified in 36.1% of males and 38.8% of females(P=0.624), with a similar distribution across both genders. The median overall survival(mOS) of the cohort was 38.1 months(95 % CI 32.0- 44.1) with a median follow-up duration of 21.3 months(95% CI: 17.1-25.5). The mOS for the very young cohort(age≤40 years) was 24.2 months (95%CI: 2.2-46.5). Survival analysis was limited to stage IV patients to evaluate the impact of driver mutations and targeted therapy, showed a significantly improved mOS of 49 months(95%CI: 34.7-63.2) in those who received targeted therapy compared to 17.2 months(95%CI: 11.4-22.9) in those who did not(p=0.000). Additionally, mOS was longer in females at 57.2 months (95%CI: 29.9-84.5) compared to 32.9 months in males(95%CI: 19.8-46.1)(p=0.114)

Conclusions: This study provides valuable insights into the clinical characteristics and survival outcomes of young lung cancer patients in Western India, with a distinct focus on the very young population (≤ 40 years). The findings emphasize the unique disease biology in this subgroup, highlighting the importance of early molecular profiling and personalized treatment strategies to improve outcomes in this demographic

Keywords: Young Lung cancer, Western India, Molecular Profile

EP.01.07 Lung Cancer in Young: A Descriptive Study From Thoracic Oncology Clinic in Northern India

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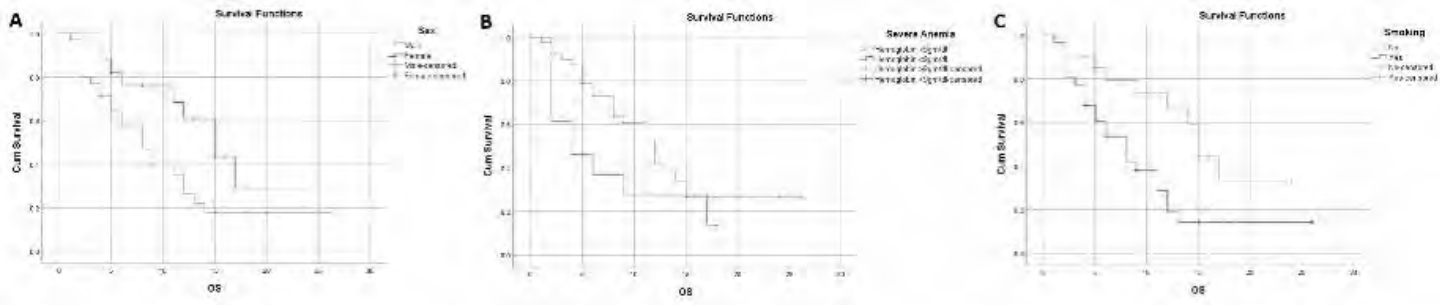
Introduction: Lung cancer has been considered as disease of the old. However, there has been a steady rise in lung cancer incidence among younger population throughout the globe. Young lung cancer patients exhibit unique risk factors, molecular traits, and clinical behaviour. In this study we intended to study the clinico-demographic characteristics of young lung cancer patients from northern India.

Methods: This was a retrospective study including lung cancer patients under 45 years of age (at the time of diagnosis) and attending the thoracic oncology clinic in a tertiary care hospital in northern India. Data on demographics, smoking-history, histology, stage, treatment, laboratory investigations and survival (overall survival- OS) were collected.

Results: Between January 2022 and March 2025, a total of 844 patients were registered in the clinic. Among them, 52 patients (6.2%) were younger than 45 years (with 17 below 36 years of age). Males constituted 67% (n=35) of this cohort, and overall mean age was 38.5±6.5 years. A history of smoking was present in 60% (n=31, all current smokers) with mean pack years of 11.9±4.1. The majority cases were diagnosed through ultrasound-guided-biopsy, followed by endobronchial biopsy. Non-small cell lung carcinoma was the predominant histological type (83%, n=43), with adenocarcinoma (n=21) being the most common subtype, followed by squamous cell carcinoma (n=12). Most patients had an Eastern-Cooperative-Oncology-Group (ECOG) performance status of 1 at presentation (48.1%). At diagnosis, 63.5% of patients had metastatic disease. 24 patients were classified as stage IVa, while 11 patients (each) had stage IIIc and IVb disease. Financial constraints prevented most patients from undergoing comprehensive molecular testing. 17 adenocarcinoma patients had data of basic (EGFR-mutation/ALK-rearrangement/ROS1-rearrangement) molecular-analysis available: 6 had EGFR mutations, 8 harboured ALK rearrangements, and 3 showed no targetable genetic alterations. Only 5 of 14 eligible patients received targeted therapy. All remaining patients were treated with chemotherapy and radiation as appropriate. Using Kaplan Meier Survival analysis, OS was found to be significantly higher in never-smokers compared to smokers (15±0.9 versus 8±1.5 months; p<0.05). Survival outcomes were also better in females compared to males (p=0.046). OS was also lower in patients who had an haemoglobin of less than 9gm/dl at the time of presentation (12±1.4 versus 4±2.2 months; p=0.041). However, OS was independent of histological subtype, ECOG and albumin levels.(figure 1)

Conclusions: Majority young lung cancer cases often presented late and genetic alterations especially ALK-rearrangement were common. Smoking and presence of anaemia contributed significantly to survival outcomes.



Keywords: Young, Lung Cancer, Epidemiology

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.08 Lung Cancer in Elderly Patients: Insights From a Community Oncology Setting in Western India

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Introduction: Lung cancer remains a major cause of cancer-related deaths, with elderly patients facing unique clinical challenges. This study addresses the limited data on lung cancer outcomes in elderly patients (≥80 years) in Western India, focusing on survival trends, treatment patterns, and the impact of molecular mutations in community oncology settings.

Methods: This retrospective study included consecutive patients from community oncology centres diagnosed Lung cancer NSCLC (age ≥80) between March 2018 and September 2024. Baseline characteristics including patient demographics, disease stage, and treatment modalities were retrieved from the EMR. Progression-free survival and overall survival were calculated using the Kaplan-Meier analysis

Results: A total of 2281 patients were diagnosed with lung cancer, of whom 189 patients who were aged ≥80 years were analyzed and found to have Median age of 82 years (IQR: 81-85) with M:F ration being 2:1. Distribution by stage is as follows, stage I/II - 6.9% (n=12), stage III - 22.8% (n=43), and stage IV - 69.3% (n=131), while the Common metastatic sites included bone (61/131), brain (22/131), liver (22/131) and lymph nodes (17/131). The cohort comprised of 82% Non-small cell lung cancer (NSCLC) cases, with adenocarcinoma being the predominant subtype (72.3%). Molecular testing was performed in 57.7% of patients, with EGFR mutations being the most common (31.1%), followed by KRAS (9.7%), TP53 (8.7%), MET (3.9%), RET, ROS1, PIK3CA (1.9% each) and BRAF, ALK, and HER2 (each 0.97%). PD-L1 testing was conducted in 38% of patients, with PD-L1 expression of 1-49% observed in 27 of 72 cases and ≥50% in 12 of 72 cases. The Median overall survival (mOS) of the cohort was 10.3 months (95% CI: 6.7-13.9) with median follow up time of 32.8 months (95% CI: 25-40.5). Patients with identified mutations had significantly improved mOS (14.95 months) compared to non-mutated patients (7.3 months) p<0.001. Mutation-positive patients in this subgroup also had improved survival outcomes 14.95 months (95% CI: 12.1-16.9) compared to 4.7 months in non-mutated patients (95% CI: 0.1-9.2) p = 0.025. Among 189 patients, 52.9% (100/189) received first-line treatment, with mutations detected in 42% (42/100); among these, 80.9% (34/42) received TKI, 14.2% (6/42) chemotherapy, and 4.7% (2/42) a combination of chemotherapy and TKI. Among mutation-negative patients (58/100), 10.3% (6/58) had PD-L1 expression of 1-49%, 8.6% (5/58) had ≥50% expression, and 45.4% (5/11) received immunotherapy

Conclusions: Elderly lung cancer patients (≥80 years) are known to have poor survival and lesser prevalence of actionable mutation however, targeted treatment with respect to these molecular aberrations can help to improve survival in this subset of patients

Keywords: Elderly Lung Cancer, Western India, Molecular Profile

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.09 NSCLC Epidemiology and Survival in Denmark, Finland, and Norway: A Decade of Real-World Insights From the LANDSCAPE Study

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Introduction: Despite comparable healthcare systems and cancer care, Nordic countries have different overall survival (OS) rates in lung cancer. Healthcare registries enable for longitudinal, population-based, lung cancer studies with real-world data to examine survival variations in Nordic populations. Here we describe a NSCLC population and survival rates in non-metastatic and metastatic settings in Denmark, Finland, and Norway to better understand differences in course of disease in the Nordic region and provide insights for improved lung cancer management.

Methods: This observational study was conducted in three Nordic countries (January, 2011-December, 2022). In Denmark and Norway, NSCLC cohorts were established by linking nationwide, population-based healthcare registries. The Finnish NSCLC cohort comprised patients from the Helsinki and Uusimaa (Helsinki University Hospital data lake) regions (~30% overall NSCLC population). The study population included patients with NSCLC during the study period. Demographic data were summarized at NSCLC diagnosis (index date). Annual 1-, 3-, 5-year survival estimates were reported by country and metastatic status at diagnosis (M0, no metastases; M1, metastases). Age-standardized survival analyses were conducted to determine median OS by metastatic status.

Results: Analysis cohorts comprised 45,298 (Denmark), 6,986 (Finland), and 25,480 (Norway) patients with NSCLC aged, 70 years on average (standard deviation ~ 9.5 years) at time of diagnosis across all countries and metastatic status. Approximately 50% (Denmark), 55% (Finland), and 55% (Norway) of respective cohorts were male. During the study period, 1-, 3-, and 5-year survival numerically improved for M0 and M1 in all countries (Figure 1). One-year survival increased between 2011-2022 from 66.2%, 63.6%, and 69.5% to 79.8%, 71.2%, and 80.9% (M0 group), and from 23.1%, 23.7% and 25.9% to 31.5%, 30.0% and 36.9% (M1 group) in Denmark, Finland and Norway, respectively, with similar trends for 3- and 5-year survival. Median survival times during the study period for the M0 group were 35, 28, and 44 months in Denmark, Finland, and Norway, respectively. In the M1 group, median OS was 6 (Denmark), 5 (Finland), and 7 (Norway) months.

Conclusions: Survival rates for NSCLC patients improved over this decade-long, observational study in Denmark, Finland, and Norway at 1-, 3-, and 5-years' follow-up and by metastatic status. The large survival differences in patients with and without metastases at diagnosis highlight the need for early diagnosis and prevention metastatic disease to improve outcomes. These data enable additional research on NSCLC-care management in patient subgroups for further insights that may guide future healthcare decisions.

Keywords: Survival, epidemiology, NSCLC

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.10 Young Onset Lung Cancer: Clinical, Pathologic and Molecular Profile From a Tertiary Care Centre in Indi

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Introduction: Lung cancer in young patients is a rare entity. This subset of patients may have a biologically distinct behaviour compared to their older counterparts. Studies done so far in this age group have a higher proportion of females and adenocarcinomas on histology. A higher frequency of positive family history and driver mutations have also been observed. Data is scarce in this population especially in the Indian setting.

Methods: Records of lung cancer patients aged ≤40 years and gender and smoking status matched patients aged ≥ 60 years, registered at Lung Cancer Clinic at AIIMS New Delhi and NCI Jhajjar between 01/01/2018 and 30/07/2024 were collected and analysed. Clinical, pathologic, molecular, treatment and outcome details were collected

Results: Records of 201 young onset lung cancer cases and gender and smoking status matched late onset lung cancer cases were analysed. In the young onset group median age at presentation was 36 years (20-40) and 66 years (60-83) in the late onset group. Adenocarcinoma was the most common histology in both groups. In the young onset group, 115 patients (57.21%) were males and 85 patients (42.79%) were female and majority were non-smokers (81.59%). In the late onset group prevalence of comorbidities was significantly higher (15.92% vs 44.27%, p < 0.001). Young patients were more likely to present with metastatic disease (92.04% vs 84.08%; p= 0.014), higher number of metastatic sites (2 vs 1; p< 0.001), brain metastases (41.08% vs 18.34%; p<0.001), adrenal metastases (18.92% vs 11.24%; p= 0.049) and ALK rearrangement positivity (26.98% vs 8.76%; p< 0.001). There was no difference in PFS1, TKI-PFS or OS between the age groups. In the young onset group metastatic disease was associated with a detrimental outcome (HR = 5.38; p= 0.002) and TKI use was associated with a better outcome (HR = 0.41; p = 0.008).

Conclusions: In conclusion, younger lung cancer patients exhibited a higher prevalence of metastatic disease, particularly brain and adrenal metastases, and a greater frequency of ALK mutations, while older patients had more comorbidities but fewer metastatic sites. Despite these differences, performance status was comparable across age groups. Although younger patients showed a higher prevalence of driver mutations, this was not statistically significant. The use of tyrosine kinase inhibitors (TKIs) significantly improved survival outcomes in both age groups, emphasizing the importance of targeted therapies in lung cancer management regardless of age.

Keywords: Young Onset Lung Cancer, India

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.11 Impact of Demographics and Smoking on Driver Gene Mutations Development in Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Lung cancer is the most common type of cancer. Non-small cell lung cancer (NSCLC), is known to have a variety of genetic mutations. Behavioral and demographic factors cause an increased risk of development of driver gene mutations, including KRAS, EGFR, ERBB2, and ALK, which leads to a higher incidence of lung cancer. This study aims to explore the impact of smoking, sex, race, and ethnicity on the development of driver mutations in non-small cell cancer patients.

Methods: We queried the AACR Project GENIE BPC NSCLC v2.0 dataset and included 537 patients diagnosed with stage I-III NSCLC. We tested for significant associations using Chi-square test. Effect sizes were measured using Cramer V and Phi coefficients. A p-value of <0.05 was considered statistically significant.

Results: A total of 537 patients diagnosed with NSCLC were included, with a median age of 68.2 years (35.5-87.5). The majority were female (55.7%) and White (86.6%), with 93.5% identified as non-Hispanic. Smoking status was significantly associated with EGFR mutations ($p<0.001$, Cramer V = 0.333, moderate association) but not with KRAS, ERBB2, or ALK mutations. Female sex was significantly associated with EGFR mutations ($p=0.006$, phi = 0.118); but no significant associations were observed for ERBB2, KRAS, or ALK mutations. White race was significantly associated with EGFR ($p<0.001$, Cramer V = 0.192) and ERBB2 mutations ($p=0.003$, Cramer V = 0.171), both indicating small associations, while no associations were found for KRAS or ALK mutations. Ethnicity showed no significant association with any of the studied mutations: ERBB2, KRAS, EGFR, or ALK.

Conclusions: This study showed significant association between smoking, female sex and white race and the development of EGFR, but not with KRAS, ALK or ERBB2 gene mutations. However, ethnicity had no correlation to the occurrence of any of the studied driver gene mutations. These findings highlight the role of demographics and lifestyle factors in development of driver mutation in non-small cell lung cancer, emphasising the need for personalised approaches in risk assessment and treatment.

Keywords: NSCLC, Epidemiology, Genetic mutations

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.12 A Causal Machine Learning Approach for the Prediction of Immune-Related Adverse Events in Lung Cancer Patients Receiving Immunotherapy

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Introduction: Immune-Related Adverse Events [irAEs] are a diverse set of toxicities associated with immunotherapy affecting multiple organ systems, ranging in severity from mild to life-threatening. Whilst awareness of irAE incidence is growing, current research gaps mean that risk factors are often not well understood. Although RCTs are viewed as the gold standard for clinical evidence, they must generally exclude individuals with comorbities, certain lifestyle factors, concomitant medication, and other characteristics commonly present in real-world populations, limiting their generalisability. Meanwhile, observational studies which include individuals with these characteristics are limited by challenges in establishing causality. These shortcomings contribute to uncertainty in facilitating shared decision making between provider and patient as well as human factors such as considerations around Quality of Life, with irAEs being a common concern for both parties. In clinical practice, decisions must be based on explainable reasoning, not only correlations found by associative black-box models. Therefore, this research aims to bridge the gap between RCTs, observational studies, and clinical practice by utilising State-of-the-Art machine learning models capable of efficiently discovering causal relationships in observational data, aiming towards actionable decision support for both clinicians and patients regarding irAEs. We apply these methods to a retrospective clinical dataset of patients with lung cancer who received immunotherapy, incorporating detailed records of treatment history, demographics, irAEs, laboratory results, comorbidities, and concomitant medications.

Methods: To identify potential causal relationships between observational variables and the development of irAEs, we apply a machine learning framework based on causal discovery methods. These approaches are underpinned by well-established statistical theory and allow us to move beyond traditional association-based models, enabling the identification of variables which may play a causal role in the onset of irAEs. The causal outputs of the models are represented by a causal Directed Acyclic Graph (DAG), which makes interpretability intuitive.

Results: To validate our approach, we tested our proposed model on synthetic datasets with known ground truth, finding that it consistently outperformed existing state-of-the-art causal discovery methods as measured by Structural Hamming Distance.

On real-world data, combination chemotherapy was found to be a causal factor influencing irAE incidence, as well as patient gender. Other logically-sound causal relationships were found, such as between Primary Site and Surgery Type. Causal effects downstream from irAEs included haemoglobin, Billirubin, White Blood Count, Random Glucose, and Random Cortisol counts, all of which can be affected by the action of specific irAEs on various organs.

However, many spurious relationships were also found by our model, such as an indication that Surgery Type can affect a patient's Age Group.

Conclusions: Preliminary application of our causal discovery model to a dataset of lung cancer patients treated with immunotherapy reveals some promising findings consistent with clinical expectations. However, the dataset is currently limited in size and completeness, restricting predictive accuracy for both causal and associative models. These initial findings should be viewed as exploratory. Data collection is ongoing, and updated analyses based on more complete data will be presented at the Conference, allowing more robust conclusions to be drawn.

Keywords: Adverse Events, Immunotherapy, Causal Inference

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.13 Lung Cancer Burden in Latin America and the Caribbean, 1990-2021: A Comprehensive Analysis

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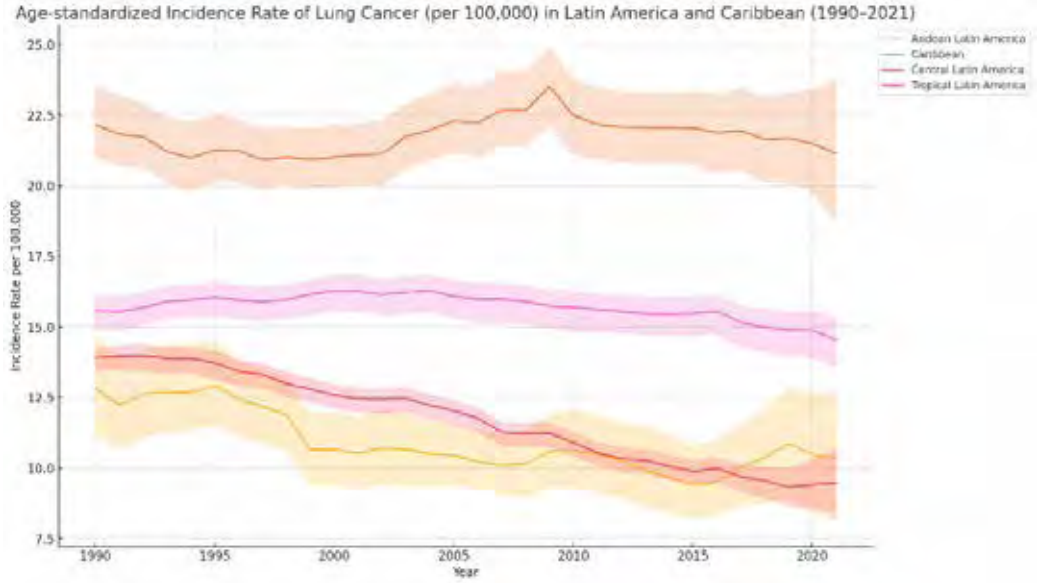
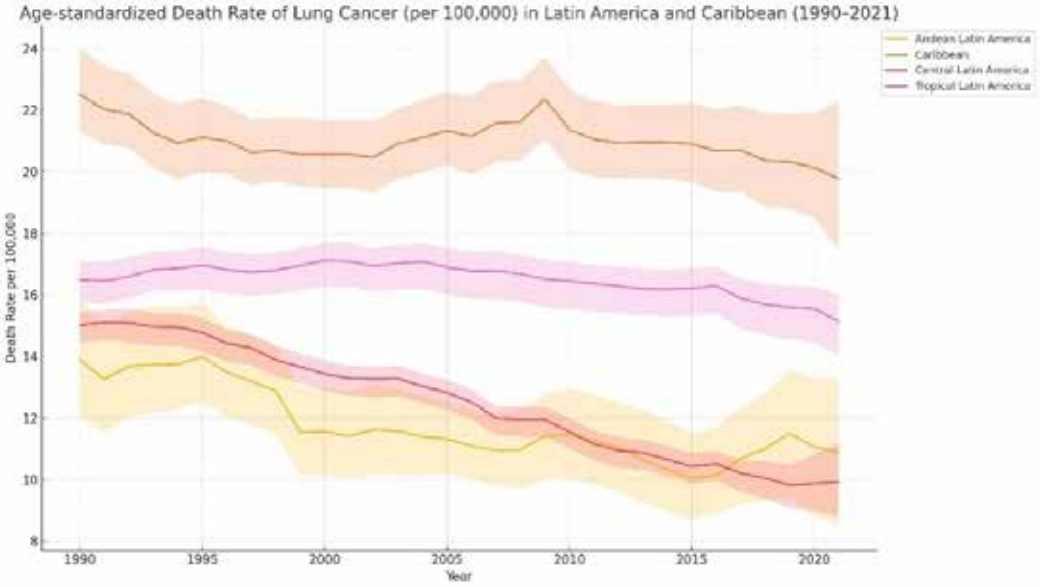
Introduction: Lung cancer remains a leading cause of cancer-related morbidity and mortality globally. In Latin America and the Caribbean (LAC), the epidemiological transition and rising exposure to risk factors such as tobacco use have contributed to a changing burden. This study aims to quantify and analyze trends in incidence, mortality, and disability-adjusted life years (DALYs) attributable to lung cancer in LAC from 1990 to 2021.

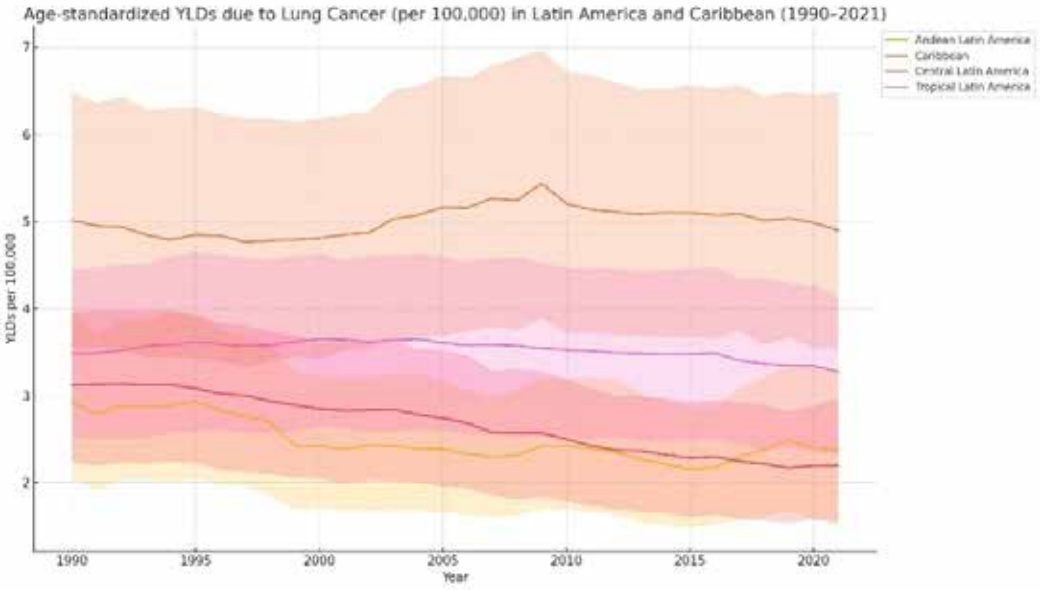
Methods: Utilizing global burden of disease 2021 methodology, focusing on 33 countries in the LAC region, we estimated age-standardized rates (ASR) per 100,000 population for incidence, mortality, and DALYs. Trends were evaluated using estimated annual percentage change (EAPC), stratified by sex and country.

Results: Between 1990 and 2021, the number of new lung cancer cases in LAC increased from 52,400 to 108,900, representing a 107.7% rise. However, the ASR of incidence showed a modest increase from 14.8 to 15.6 per 100,000 (+5.4%). Mortality ASR declined slightly from 13.2 to 12.6 per 100,000 (−4.5%), with a significant reduction in males (EAPC −0.6%) but a marginal increase in females (EAPC +0.3%). The total DALYs rose from 1.3 million to 2.4 million, largely driven by population aging. Countries like Cuba and Uruguay had the highest incidence rates in 2021 (above 25 per 100,000), while countries like Guatemala and Haiti had the lowest (below 8 per 100,000).

Conclusions: While age-standardized mortality rates have decreased slightly, the overall burden of lung cancer in LAC has increased due to population growth and aging. Gender-specific trends suggest progress among males, but emerging concerns among females. Strengthening tobacco control, early detection strategies, and access to care is essential to reduce the growing health and economic burden in this region.







Keywords: Global burden, Lung cancer, Epidemiological trend

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.14 Pulmonary Pure Ground-Glass Nodule Follow-Up During Pregnancy and Lactation: A Case Repor

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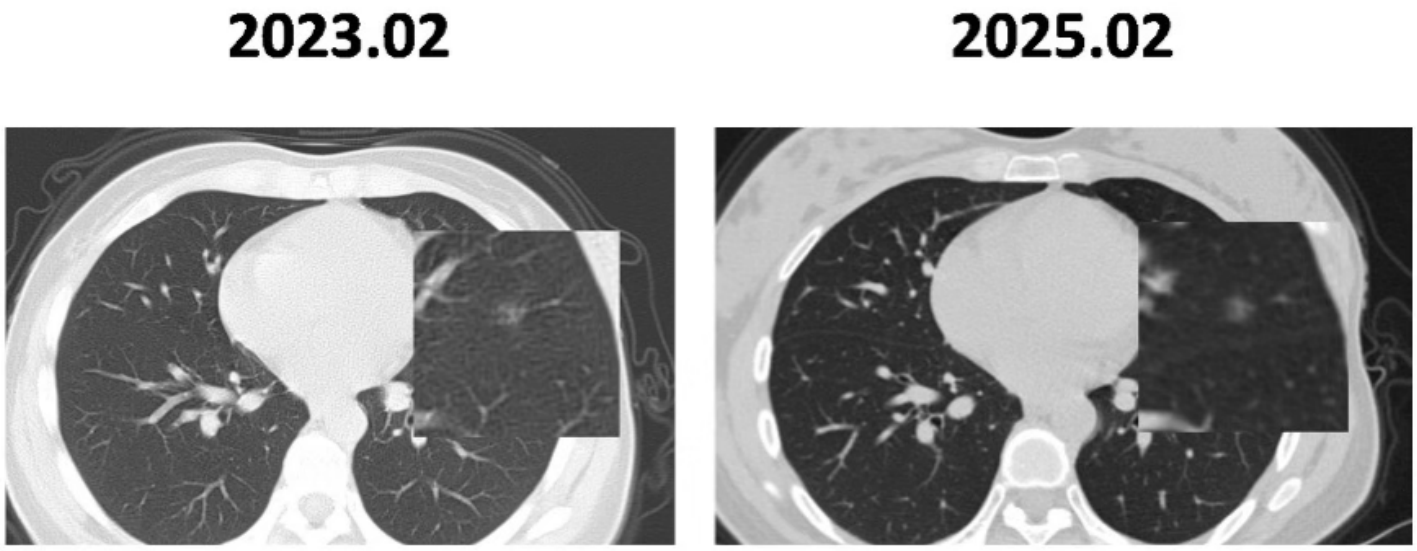
Introduction: The prevailing consensus advocates observation as the primary management strategy for pure ground-glass nodules (pGGNs) until morphological alterations necessitate surgical intervention. However, significant controversy persists regarding special populations, particularly concerning the pre-gestational resection of pGGNs in young women. The central debate focuses on whether dynamic hormonal fluctuations during pregnancy and lactation might influence nodular progression. We present a case of a 31-year-old woman with a left upper lobe pGGN followed through pregnancy and lactation.

Methods: A previously healthy 31-year-old woman was incidentally found to have a 6-mm pGGN in the left upper lobe during a routine health examination in February 2023. The lesion had a CT attenuation of -570 HU (Figure). Given the absence of concerning features, active surveillance was recommended. She subsequently conceived in 2023, gave birth in 2024, and breastfed for nearly one year. In 2025, a follow-up chest CT was performed to assess any changes in the nodule.

Results: Follow-up CT in 2025 showed that the nodule remained 6 mm in size but exhibited increased attenuation, with a CT value of -450 HU (Figure). A multidisciplinary team (MDT) discussion suggested two options: surgical resection or continued surveillance. The patient opted for continued follow-up rather than immediate surgery. No new solid components or significant dimensional changes were observed during the latest evaluation.

Conclusions: Hormonal fluctuations during pregnancy and lactation have been linked to significant changes in certain malignancies, but their impact on pGGN progression remains unclear. In this case, despite prolonged exposure to hormonal changes, the nodule remained stable in size, with only a mild increase in attenuation. While surgical resection was considered, the patient chose close monitoring instead. Long-term follow-up is required to further elucidate the natural history of pGGNs in pregnancy and lactation.



Keywords: Pulmonary Pure Ground-Glass Nodule, Pregnancy, Lactation

EP.01.15 Gender Disparities in Survival Outcomes of "Minimally Invasive Lung Squamous Cell Carcinoma"

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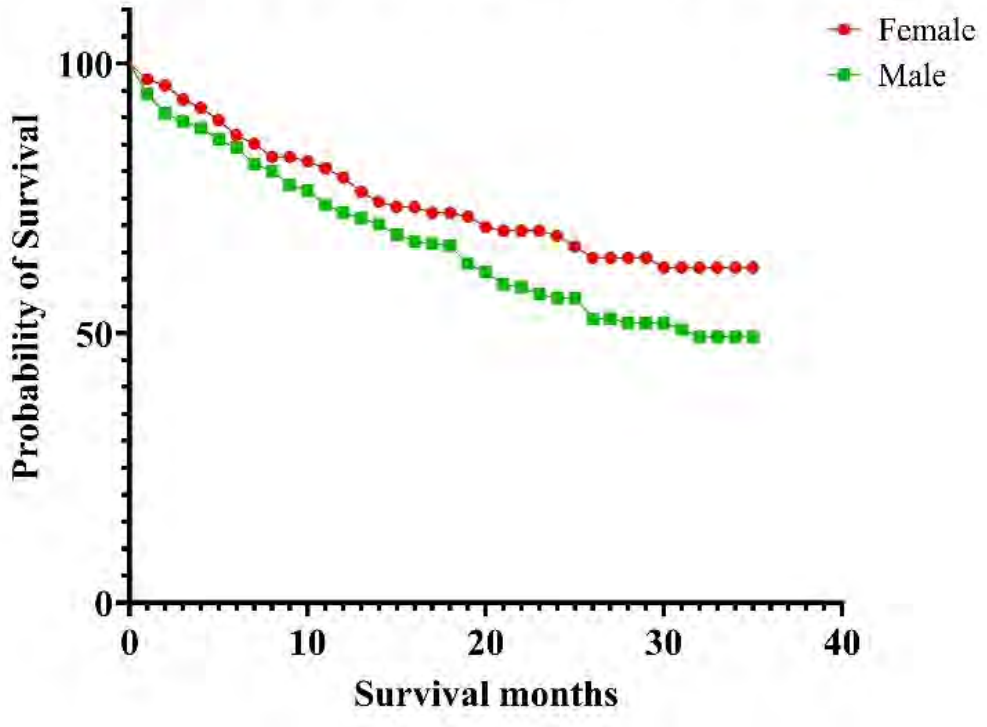
Introduction: Lung cancer exhibits marked gender disparities in both incidence and survival outcomes. Females demonstrate a higher incidence of lung adenocarcinoma (LUAD), while males are higher of lung squamous cell carcinoma (LUSC). Male patients exhibit poorer survival outcomes compared to females in both pathological types. Survival outcomes vary across pathological types: patients with LUSC show inferior survival outcomes relative to LUAD. The refinement of pathological classification in LUAD has enabled more precise treatment approaches, but LUSC still lacks similarly refined subclassifications. The study aims to investigate gender-stratified survival outcomes in LUSC patients with tumors ≤3 cm in diameter and invasion depth ≤5 mm (The study defines such LUSC as "minimally invasive LUSC"). The findings may contribute to refining the LUSC classification system and the precision of therapeutic strategies.

Methods: Surveillance, Epidemiology, and End Results (SEER) database is an authoritative database in the United States that provides detailed data on cancer incidence, survival, and treatment. Based on the SEER database, the study analyzed 654 cases of "minimally invasive LUSC" diagnosed between 2018 and 2020. The study performed life table analysis, Kaplan-Meier analysis, and univariate and multivariate Cox regression analysis, while adjusting for confounding factors, to assess the patients data. The nomogram was constructed to guide the prognosis judgment.

Results: The survival analysis showed that male patients (n = 374) with "minimally invasive LUSC" exhibited a shorter survival period than female patients (n = 280). In univariate analysis, the study found that gender, laterality, primary site, stage, and chemotherapy were potential factors influencing patients' survival. The results of multiple Cox regression analysis demonstrated an increased risk of death in males compared to females (HR = 1.40), especially in the groups of 60-69 years (HR = 2.09), middle lobe (HR = 2.28), moderate differentiation (HR = 2.31), single tumor (HR = 1.61), postoperative systemic therapy (HR = 5.89) and chemotherapy (HR = 3.16). Based on receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) value for the survival prognostic model developed in this study was 0.73.

Conclusions: The study proposes the concept of "minimally invasive LUSC" firstly and reveals that male patients with such LUSC exhibit a worse prognosis compared to females, thereby contributing to refining the pathological classification framework of LUSC. It is a retrospective analysis utilizing the SEER database with relatively limited sample size, so our center is prospectively collecting supplementary cases to be incorporated into future research.

Figure1. Survival curves of "minimally invasive LUSC" of different genders



Keywords: gender disparities, survival, lung squamous cell carcinoma

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.16 Differential Effect of Neoadjuvant Therapy in Locally Advanced Non-Small Cell Lung Cancer Based on Sexis

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Introduction: Patients with locally advanced non-small cell lung cancer (LA-NSCLC) experience disease progression rates of 60-70% at 2 years despite numerous modern approaches to treatment. This highlights the need for predictive biomarkers to identify at-risk patients and improve patient selection. Prior laboratory and clinical research suggests that sex may be a possible predictive and prognostic biomarker for survival in lung cancer, particularly following radiotherapy (RT). In this study, we seek to investigate sex as a biomarker for overall survival (OS), progression-free survival (PFS), and pathologic complete response (pCR) in patients receiving neoadjuvant chemotherapy (chemo), chemo-RT, or chemo-immunotherapy (IO) prior to surgery for LA-NSCLC.

Methods: We accessed the NSCLC data in the Flatiron Health Research Database. Adults (age ≥ 18) with stage II-IIIA NSCLC diagnosed from 1/1/2019 to 3/4/24 and treated with neoadjuvant chemo, chemo-RT, or chemo-IO, with chemotherapy consisting of at least two cycles of a platinum doublet. First, we analyzed OS, PFS, and pCR in males versus females using Cox proportional hazards regression in the entire cohort. We analyzed these outcomes based on treatment within subgroups of sex and based on sex within subgroups of treatment. We conducted Fine-Gray competing risk analysis for PFS.

Results: Our cohort consisted of 150 patients, including 62 females and 88 males with similar characteristics except for higher proportion of squamous cell histology in males. Most (62%) received chemo-IO (n=93), followed by 22% with chemo alone (n=33), and 16% with chemo-RT (n=24). Among those receiving chemo-RT, females had significantly higher OS (HR 0.085, 95% CI 0.009-0.725, p=0.006) and borderline significantly higher PFS (HR 0.247, 95% CI 0.055-1.104, p=0.051) than males. Males receiving chemo-RT had significantly worse OS than those getting chemo alone (HR 5.721, 95% CI 1.321-24.781, p=0.009). These differences were not observed in females. On cumulative incidence analysis, an increased hazard of death and not progression was observed in males undergoing chemo-RT. These results were maintained when adjusting the Cox models for histology, with males undergoing chemoRT having worse OS than those getting chemo alone (HR 5.424, 95% CI 1.023-24.462, p=0.0278). Despite higher pCR rates among males (29.5% versus 27.4%), multivariable analysis did not indicate an association between sex or treatment type with pCR.

Conclusions: In this cohort of patients with LA-NSCLC undergoing neoadjuvant therapy before surgery, males who received chemo-RT have significantly lower OS than females. Furthermore, treatment of males with chemo-RT results in significantly worse OS when compared to chemo alone, without significant differences in other subgroups. Further research is needed to test the hypothesis that sex may be a biomarker for increased radiation toxicity following neoadjuvant therapy for LA-NSCLC

Keywords: Sex differences, Sex biomarker, Non-small cell lung cancer

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.17 Association Between Cigarette Smoking History and Germline Rare Variant Burden in a Cohort of Lung Cancer Patients

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Introduction: Lung cancer is the global leading cause of cancer-related mortality. While cigarette smoking is the strongest risk factor, incidence of lung cancer among persons who have never smoked cigarettes is increasing, highlighting the etiologic role for other environmental and genetic risk factors. Most large-scale genetic studies of lung cancer to date have focused on common germline genetic variants, while the role of rare variants remains understudied. This study compared germline rare variant burden among 23andMe Lung Cancer Genetics Study participants with and without a history of cigarette smoking.

Methods: 1220 individuals diagnosed with lung cancer provided informed consent to participate in the study and were genotyped on a custom chip that included 1023 rare (minor allele frequency <0.001) coding (frameshift, missense, and stop-gain) variants in 45 genes previously implicated in germline genetic susceptibility to lung cancer. Data on lung cancer diagnosis, cigarette smoking, and other relevant covariates were collected via web-based surveys. Smoking history was defined as self-report of either current smoking or of a lifetime total of at least 100 cigarettes smoked. Associations between rare germline variants and smoking history were assessed using Fisher's exact test as well as logistic regression adjusted for age, sex, and ancestry principal components. A Poisson regression was fit to compare the counts of rare germline mutations between individuals with and without a history of smoking, adjusted for age, sex, ancestry principal components, and genotyping chip version.

Results: Among the 1010 consented 23andMe Lung Cancer Genetics Study participants who provided exposure data, 536 (53%) had self-reported a history of cigarette smoking. Of the 1023 rare SNPs, 56 had the variant allele in the study sample. A nominal association was observed between the history of smoking and a missense variant in the RET gene (rs77724903, Fisher's exact test p=0.05). However, none of the rare variants was associated with smoking history after adjustment for age, sex, and ancestry principal components. Further, the counts of rare variant mutations were not statistically different between individuals with and without a history of smoking (β= 0.03, p-value= 0.67).

Conclusions: Our findings do not support a significant difference in rare germline variant burden by history of cigarette smoking. Future larger-scale studies including individuals without cigarette smoking history may be able to detect associations with specific rare variants that can elucidate lung cancer etiology in that population.

Keywords: genetics, rare variants, smoking

EP.01.18 Family History of Lung Cancer in Lung Cancer in Never-Smokers, a Matched Case-Control Study

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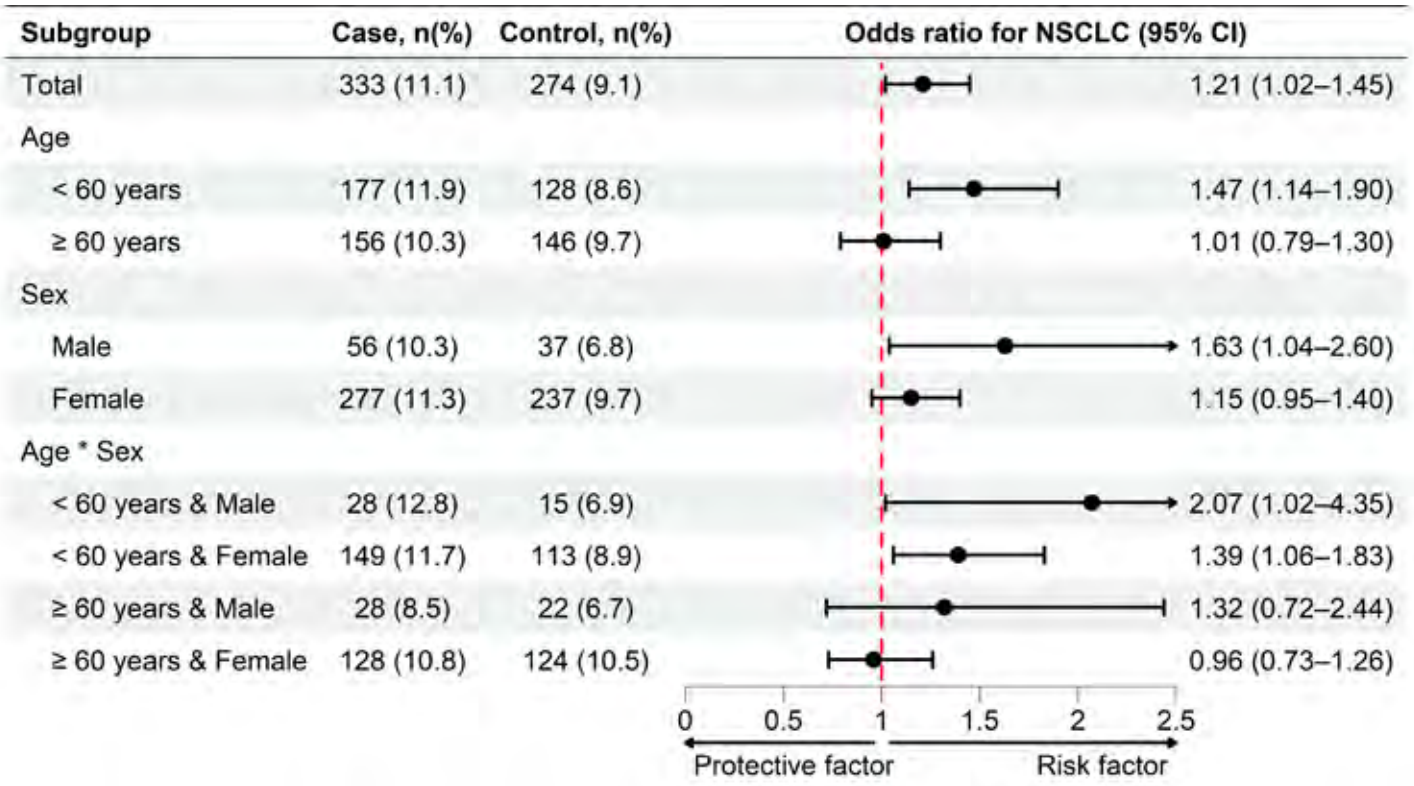
Introduction: Lung cancer in never-smokers (LCINS) accounts for over 50% of newly diagnosed lung cancer cases in East Asia. However, current lung cancer screening programs are based on high-risk smokers, and risk factors for lung cancer among never-smokers are not well established.

Methods: This was a multicenter, case-control study matching on age and sex in never-smokers. Case patients were diagnosed with non-small cell lung cancer (NSCLC) between 2016 and 2020 in tertiary centers in South Korea, while control individuals underwent opportunistic chest CT screening with negative findings in the same center's health screening department during the same period. The clinical characteristics of case patients and risk factors for NSCLC were analyzed.

Results: The number of case patients and matched control individuals was 3,000 each, totaling 6,000. The median age of the study population was 60 years, and females accounted for 81.1%. Among case patients, the adenocarcinoma subtype was the most common form of NSCLC (95.0%). The mutation rates of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) were 63.1% and 3.3%, respectively. In multivariable logistic regression models, a first-degree family history of lung cancer (adjusted odds ratio [aOR]: 1.21; 95% confidence interval [CI]: 1.02-1.45; P = 0.032) and chronic lung disease (aOR: 2.95; 95% CI: 2.42-3.61; P < 0.001) were significant risk factors for NSCLC. In a subgroup analysis by age, a family history of lung cancer remained a significant risk factor among individuals younger than 60 years (aOR: 1.47; 95% CI: 1.14-1.90; P = 0.003) but not in those older than 60 years (aOR: 1.01; 95% CI: 0.79-1.30; P = 0.913). In the sex-stratified analysis, this association remained significant in males (aOR: 1.63; 95% CI: 1.04-2.60; P = 0.036) but not in females (aOR: 1.15; 95% CI: 0.95-1.40; P = 0.148).

Conclusions: A first-degree family history of lung cancer and a history of chronic lung disease were significant risk factors for NSCLC in never-smokers. Among younger individuals and males, the risk associated with a first-degree family history of lung cancer was more pronounced. Further studies are needed to identify high-risk groups among never-smokers and to expand lung cancer screening programs beyond smokers to include never-smokers.



Keywords: Non-small cell lung cancer, never-smoker, famil history of lung cancer

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.19 Characteristics of Lung Cancer in Never- and Light-Smokers: A Retrospective Study From Greece

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Introduction: Lung cancer (LC) in never- and light-smokers accounts for 10-20% of all LC cases. Recent studies estimate that its incidence is rising worldwide. However, clinicopathologic and molecular data of patients with LC with no/light smoking history are scarce and do not reflect the heterogeneity of demographic and molecular features of different populations worldwide.

Methods: This is a retrospective study enrolling all patients with LC from the Oncology Unit of a tertiary academic hospital in Athens between 2010-2024. Medical records were reviewed to identify never-smokers (<100 cigarettes during lifetime) and light-smokers (<5 cigarettes/day). Demographic, clinicopathologic and molecular data were recorded. Air quality index (AQI) was searched in https://www.iqair.com/.

Results: We identified 67 cases of never- and light- smokers with LC in a total of 1280 LC patients (prevalence= 5.2% n=67/1280, never-smokers=39, light-smokers= 28, mean age±SD=69.1±12.0). Females constituted 64.1% (25/39) of never smokers. Professional exposure (silica dust and radon) was reported in 4.47% (3/67) of patients and 10.5% (7/67) had family history of at least one first-degree relative with LC. AQI of the patients' residence was moderate (51-100) in 53.7% and good (0-50) in 46.3% of the cases. Adenocarcinoma subtype was diagnosed in 83.5% of the patients; other subtypes included squamous (n=4), LCNEC (n=2), adenosquamous (n=1), NOS (n=1) and SCLC (n=1). The TNM stage at initial diagnosis was stage I in 4.5% (3/67), stage II in 10.5% (7/67), stage III in 15.0% (10/67) and stage IV in 70.1% (47/67) of the patients. There were 20.9% of the patients who were initially diagnosed with stage IVA due to malignant pleural or pericardial effusion or pleural metastases. PD-L1 expression (TPS) was available in 38 patients and was negative (<1%) in 21, low (1-49%) in 12 and high (>50%) in 5 patients. NGS was available in 15 patients and PCR testing of main driver genes in 31 patients. Oncogenic alterations were identified in 21 patients and were: EGFR exon 19 del/L858R point mutations (n=11), EGFR exon 20 insertion (n=1), ERBB2 amplification (n=1), RET fusion (n=1) and KRAS G12 mutations (n=7, 6 light-smokers/1 never-smoker).

Conclusions: Our data validate the need for multicenter national registries of never- and light-smokers with LC to identify the distinct characteristics of this subgroup in different patient populations.

Keywords: Lung cancer, never smokers, light smokers

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.20 Non-Smoking Lung Adenocarcinoma: Implications for Predominant Growth Patterns, Tumor Heterogeneity and Prognosis

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Introduction: In pulmonary adenocarcinoma, several growth patterns can be discriminated, including lepidic, acinar, papillary, micropapillary, solid, and complex glandular. The individual tumor composition and occurrence of the different growth patterns is associated with significant differences in prognosis. Patients with predominantly lepidic tumors have a favorable long-term survival compared to patients with solid- or micropapillary-predominant tumors. Smoking is the main risk factor for the development of lung adenocarcinoma, but it remains unknown if smoking-associated and non-smoking lung adenocarcinomas differ in respect to the occurrence of different growth patterns.

Methods: This retrospective cohort study included 501 patients with pathologic stage I non-mucinous pulmonary adenocarcinoma who underwent curative surgery with complete resection (R0) between 2010 and 2020. Differences between patients with a history of smoking and non-smokers were analyzed by Chi-Square test and Mann-Whitney U test. Patient survival was determined using the Kaplan-Maier method with log-rank test.

Results: 403 (80.4%) patients were active or former smokers, 98 (19.6%) non-smokers. Non-smokers were significantly more likely to be female (75.5%, p<0.001). The median age of never-smokers at the time of surgery was 69.8 years compared to 65.8 years for smokers (p< 0.001). Based on the current IASLC grading system, non-smokers had a higher proportion of tumors with favorable tumor grading (grade 1: 19.4% vs. 9.9%; grade 3: 26.5% vs. 41.9%; p = 0.003). The T-stage did not differ significantly between the groups. Lepidic-predominant tumors were almost twice as common in non-smokers as in smokers (19.4% vs. 10.4%, p = 0.042). The opposite was true for solid-predominant tumors (6.1% vs. 14.1%, p = 0.042). The median follow-up time was 61 months. We observed a trend for favorable 5-year recurrence-free survival in non-smokers at 80.3% vs. 72.5% in smokers (p = 0.104; log-rank test).

Conclusions: Smoking status has a significant influence on tumor heterogeneity and the occurrence of different growth patterns within adenocarcinoma. Non-smokers develop the disease at an older age, have more lepidic tumor components, lower tumor grade and tend to have better recurrence-free survival. Further studies with a larger patient cohort are necessary to validate the results shown here and to clarify the biological basis of the different tumor proportions in non-smokers.

Keywords: lung adenocarcinoma, non-smokers, growth pattern

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.21 Mapping Persistent and Irreversible Arsenic Effects on Lung Epithelium Using Integrated Transcriptome and Methylome Analysis

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Introduction: Arsenic, a well-established environmental carcinogen, contaminates underground water sources worldwide and poses a significant public health threat through chronic low-dose exposure. In Nova Scotia (Canada), elevated arsenic levels in drinking water, particularly in rural well water systems, are believed to contribute to the province's rising lung cancer incidence, even among non-smokers. Arsenic undergoes biotransformation in the body through methylation processes, which paradoxically can both detoxify arsenic and generate reactive intermediates that alter DNA methylation patterns and disrupt epigenetic regulation, leading to aberrant gene expression. Despite substantial evidence connecting arsenic exposure to lung carcinogenesis, the molecular mechanisms and early biomarkers of damage remain poorly understood. Our research aims to identify specific biomarkers of early arsenic-induced molecular damage using lung models exposed to environmentally relevant arsenic concentrations that mirror those found in Nova Scotia's high-risk regions.

Methods: We established an in vitro experimental system using human bronchial epithelial cells (HBECs), a key target of arsenic-induced carcinogenesis. These cells were systematically exposed to relevant concentrations of sodium arsenite (0.08µM and 2µM) to represent both low and moderate-high exposure levels observed in human populations. Cells underwent treatment following a controlled exposure protocol with treatment cycles of 48-96 hours between passages over a period extending up to 12 days, creating a chronic exposure model. We included experimental groups where arsenic was removed to assess recovery dynamics and irreversible molecular changes. Both DNA and RNA were isolated from treated cells to enable characterization using next-generation sequencing, with a comprehensive coverage of the transcriptome and assessment of DNA methylation patterns. This approach allows for the detection of alterations in methylation profiles, subtle (likely tissue-specific) changes in gene expression, and alternative splicing events potentially relevant to arsenic-induced carcinogenesis.

Results: The first cohort of 18 samples has been successfully sequenced and processed through our analytical pipeline. Data quality assessment and normalization procedures are currently being completed for differential expression analysis using DESeq2. Our initial focus is identifying arsenic-induced persistent gene expression changes that develop in response to exposure and are maintained throughout the treatment period, with particular attention to expression changes occurring in regions with differential methylation patterns. Subsequent phases will investigate irreversible molecular changes by removing arsenic after exposure and allowing cells to grow. Additionally, we will co-treat cells with arsenic-chelating agents to identify arsenic-dependent molecular alterations specifically and distinguish them from general stress responses. We will validate identified molecular signatures in human lung tumors from individuals in high-arsenic regions using the Nova Scotia Lung Tumour Biobank (the largest lung tumor biobank in Canada), and in lung organoids to evaluate chronic exposure effects in a more complex lung model.

Conclusions: Identifying specific biomarkers of arsenic-induced lung damage will contribute to developing prevention strategies and early detection methods for arsenic-related lung cancer. The molecular signatures we characterize may serve as screening biomarkers for high-risk populations, addressing a significant public health concern in Nova Scotia and globally.

Keywords: Arsenic, bioinformatics, molecular damage

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.22 The Effectiveness of Offering Repeated Co-Located, Opt-Out Smoking Cessation Support Within Lung Cancer Screening

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Introduction: The UK National Screening Committee has recommended the implementation of targeted lung cancer screening with integrated smoking cessation service provision. The Yorkshire Enhanced Stop Smoking (YESS) study showed the acceptability and efficacy of a co-located stop smoking service (SSS) comprising NRT/e-cigarettes and behavioural support delivered on an opt-out basis to all eligible smokers attending for baseline lung cancer screening within the Yorkshire Lung Screening Trial (YLST), however the impact of offering SSS for subsequent screening rounds is unknown.

Methods: In March 2021 YLST commenced its second round of screening, two years after individuals had attended for their baseline screen, as well as re-inviting those who had not responded to their baseline invitation in the previous round. Stop smoking support was offered on the same basis as delivered in YESS (behavioural support plus nicotine replacement therapy/vapes/pharmacotherapies for up to 12 weeks). Here we report preliminary analyses of the uptake of this offer, and self-reported quit rates at 4 and 12-weeks post attendance at screening.

Results: Of 1498 current smokers eligible for SSS, 1138 (76.0%) were attending for their second screening visit. Of re-attendees, 864 (75.9%) accepted a consultation with a smoking cessation practitioner (SCP): 498 (57.6%) had received SSS in the previous round, 306 (35.4%) had declined in the previous round, and 60 (6.9%) had not been eligible. Of the 360 attending for the first time, 297 (82.5%) accepted an SCP consultation. Overall, 843 of the 1161 (72.6%) individuals meeting the SCP accepted ongoing SSS. Of those accepting ongoing SSS, 25.7% reported abstinence from smoking at 4 weeks, (14.5% of all eligible smokers) and 37.0% reported abstinence from smoking at 12 weeks (20.8% of all eligible smokers) (similar to overall quit rates seen during the first round of screening in YLST).

Conclusions: Co-located, opt-out, specialist stop smoking support was shown to be effective during a second screening round, with good engagement and encouraging 4 and 12 week quit rates.

Keywords: Smoking cessation, Lung cancer screening

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.23 Tobacco Smoking, Quit Attempts and Vaping Among an Online Sample of South African Cancer Survivors

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Introduction: Studies have demonstrated that tobacco smoking may negatively affect cancer survivors' health and survival, including raising the risk of having poor cancer treatment outcomes, developing subsequent primary cancer, and having cardiovascular and respiratory comorbidities. Smoking cessation is therefore a priority in caring for cancer survivors who smoke. With limited access to smoking cessation services, the use of e-cigarettes or vaping has been promoted as a cessation aid in South Africa, and elsewhere. However, only limited information is available on quitting behaviour and use of e-cigarettes among cancer survivors in South Africa and low- and middle-income countries in general. This study therefore sought to describe quit attempts and intention to quit smoking and pattern of e-cigarette use among a population of self-identified cancer survivors who currently smoke cigarettes.

Methods: Methods: This was a secondary analysis of data obtained from an online sample of 13,675 South African adults aged ≥18 years, including 381 cancer survivors (self-reported having been diagnosed with cancer). The online survey conducted in 2021 during the COVID-19 pandemic used a non-probability sampling, but an appropriate weight was applied to the sample to provide a more representative sample of the South African population. Information collected included participants' diagnosis of cancer and other potential comorbidities (asthma, hypertension and diabetes), ever tobacco and e-cigarette use and sociodemographic characteristics.

Results: Of the cancer survivors, 84.2% were older than 45 years and 65.2% were males. 74.8% have greater than high school education but 40.2% were not employed. Of the cancer survivors, 15.7% (95%CI=10.2- 23.4) currently smoke cigarettes and 1.3% (0.8 - 2.3) currently use e-cigarettes. Of those who smoke, 50.7% reported having attempted to quit in the past 12 months while only 44.5% contemplate quitting in the coming 6 months. Of those who have ever attempted to quit in the past, 50% reported using cold-turkey, 16.3% reported using one or a combination of approved cessation aids (counselling/NRT/medication), while only 2.2% reported using e-cigarettes as cessation aid. Of the participants, 10.2% reported having been diagnosed with a mental health condition, while 11.5% reported a chronic respiratory disease as comorbidity.

Conclusions: This study showed that tobacco smoking is prevalent among South African cancer survivors, but the use of e-cigarettes or vaping remains uncommon, highlighting the urgent need to provide smoking cessation services to this priority population with significant comorbidities.

Keywords: Cigarette smoking, Vaping, cancer survivor

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.24 Determinants Influencing Smoking Cessation Implementation in an Oncology Setting: Canadian Healthcare Provider Perspectives

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Introduction: Smoking after a cancer diagnosis contributes to adverse health outcomes, including the risks of second primary cancers and cancer recurrence, poorer treatment responses, and increased treatment-related toxicities. For individuals with cancer, quitting smoking increases survival and reduces risk of recurrence and second primaries. In Canada, Ontario Health recommends SC support (SCS) to all individuals with cancer. However, an implementation gap remains in the provision of SCS within Ontario regional cancer centres (RCCs). Our qualitative study aimed to identify determinants influencing the implementation of SCS in oncology settings through semi-structured interviews with healthcare providers (HCPs) at four of the 14 Ontario RCCs.

Methods: Our study was conducted at the Centre for Addiction and Mental Health in collaboration with Ontario Health (Cancer Care Ontario), the Canadian Partnership Against Cancer, and patient advisors. Ontario Health employed purposive sampling to select participating RCCs, ensuring diversity in centre parameters and patient populations served. Snowball sampling was used to recruit adult, patient-facing HCPs in the RCCs. Semi-structured interviews were framed using the Consolidated Framework for Implementation Research (CFIR), which explores multiple factors affecting the implementation of evidence-based practice, including aspects related to the intervention itself, the individuals involved, the implementation process, and the inner and outer settings. Interviews were conducted virtually and HCPs were compensated with a 30 Canadian dollar gift card. Thematic analysis guided our data analysis, deductively using CFIR, and inductively as new themes emerged.

Results: Of the 27 HCPs who participated in our study, 41% were radiation therapists, 15% each were registered dental hygienists and registered nurses, 11% were registered practical nurses, and 19% were physicians, nurse practitioners, social workers, and advanced practice nurses. HCPs were generally experienced in providing SCS to patients, as 74% of providers had 5-14 years of experience. From the HCP perspective, five themes emerged: 1. Patient engagement with SCS is shaped by both clinical and personal factors, including their cancer stage, cancer type, age, quit motivation, and perceived stigma. 2. HCPs tailored SCS based on the patient's context, sometimes avoiding the discussion in response to poor prognosis, emotional distress, or resistance. 3. Empathy is critical to providing smoking cessation support, yet training gaps leave HCPs feeling unprepared. 4. The 3As (Ask, Advise, and Act) approach to smoking cessation presents challenges with advising and acting, alongside mixed perceptions of the opt-out referral model. 5. System-level constraints, including limited HCP time, lack of continuity in patient care, unclear prescribing roles for varenicline and bupropion, insufficient communication about RCC's performance metrics and lack of feedback on impact of SCS on patients referred for SC.

Conclusions: These findings highlight the complex interplay of patient-level, interpersonal, and structural factors that influence the provision of SCS in oncology settings. Addressing these challenges will require a multifaceted approach, including tailored interventions, enhanced HCP training, and system-level changes to better integrate smoking cessation support into oncology settings.

Keywords: Smoking cessation, Determinants of implementation, Canadian HCP perspective

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.25 Identifying Effective Strategies to Support Smoking Cessation in Ontario Cancer Care Settings: A Consensus-Building Approach

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Introduction: In 2012, Cancer Care Ontario introduced a smoking cessation (SC) program in its 14 regional cancer centers. The program targeted patients receiving ambulatory cancer care who were recent or current tobacco users. Despite the presence of a guiding framework for SC in Regional Cancer Centers, and numerous initiatives to disseminate the growing body of literature demonstrating that smoking cessation after a cancer diagnosis improves treatment outcomes, reduces complications, and enhances survival rates, program delivery and performance has varied widely amongst treatment centers. Of greatest concern is the variability in the performance metric 'Percentage of current or recent tobacco users who accepted referral to SC support" ' where some centers perform exceptionally well, others struggle to reach target (30%) This study, supported by the Canadian Cancer Society Research Institute, aimed to identify the most viable implementation strategies to support smoking cessation within Ontario's cancer treatment facilities.

Methods: To establish consensus on feasible and impactful strategies to address the observed variability, we conducted a modified Delphi panel, a structured consensus-building methodology, engaging a diverse panel of oncology HCPs and individuals with lived cancer and tobacco use experience. We conducted two rounds of rating 13 potential implementation strategies previously identified in systematic reviews as effective in facilitating SC within oncology settings. In Round 1, 15 panelists (10 HCPs, 5 patients) rated each strategy on a five-point scale (1 = Very Low Likelihood of Success; 5 = Very High Likelihood of Success). Strategies were categorized based on consensus levels: "Appropriate" (≥70% agreement on high likelihood of success), "Inappropriate" (<50% agreement), and "Partial Consensus" (between 50% and 69%). Strategies lacking consensus advanced to Round 2, during which panelists reviewed summarized feedback from Round 1 before re-rating the most promising strategies.

Results: In Round 1, no strategy achieved full consensus as Appropriate. On the other hand, four strategies were deemed Inappropriate: 1. Adding electronic medical record alerts for smoking cessation counselling. 2. Distributing smoking cessation pamphlets. 3. Posting educational materials for staff. 4. Providing real-time feedback to HCPs. Seven strategies fell into the partial consensus category, requiring further discussion. In Round 2, 12 panelists (9 HCPs, 3 patients) reassessed these strategies, incorporating feedback from Round 1. Four strategies achieved full consensus as viable for implementation: 1. Revising clinical roles to establish expectations for HCPs to offer smoking cessation referrals. 2. Increasing the number of smoking cessation champions within regional cancer centres. 3. Distributing free smoking cessation medication onsite at cancer centres. 4. Mailing free SC medication directly to patients' homes.

Conclusions: This consensus-building study highlights the importance of stakeholder engagement in identifying contextually appropriate SC strategies. While some commonly employed approaches were deemed unlikely to succeed, the panel identified four strategies with strong potential for implementation in Ontario's cancer treatment facilities. These findings will inform future efforts to integrate evidence-based smoking cessation support into oncology care.

Keywords: smoking cessation, strategies, concensus-building

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.26 Achievements and Future Directions of Tobacco Control in Lung Cancer Prevention in China

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Introduction: As the largest tobacco consumer globally, China faces persistently high incidence and mortality rates of lung cancer. Recent years have witnessed significant progress in lung cancer prevention through legislative actions, health education, and multi-dimensional tobacco control strategies. This study synthesizes China's achievements in tobacco control and their impact on lung cancer epidemiology and early detection.

Methods: We analyzed national policy documents, epidemiological data, and clinical studies (2023-2025) to evaluate the effects of tobacco control measures (e.g., public smoking bans, increased tobacco taxes, health campaigns) and the integration of low-dose computed tomography (LDCT) screening.

Results: 1. Policy Effectiveness: Adult smoking rates decreased by 14.2% compared to 20154, with a 35% reduction in public smoking in Beijing post-implementation of the 2015 smoking control ordinance10. Nationwide smoke-free legislation now covers 78% of public spaces5. 2. Early Detection: LDCT combined with AI improved early-stage lung cancer detection to 80%, achieving a 5-year survival rate near 100% post-surgery10. Revised 2024 guidelines lowered the screening age threshold to 45, targeting high-risk non-smoking women10. 3. Public Awareness: Health education campaigns via social media and science popularization projects (e.g., the 2025 "Scientific Tobacco Control, Shared Health" initiative) increased public awareness of smoking risks to 92%15. 4. Integrated Medicine: Traditional Chinese medicine (TCM) reduced chemotherapy-induced side effects, enhancing patient compliance16.

Conclusions: China's multi-faceted tobacco control strategies and technological innovations have effectively mitigated lung cancer risks and improved early diagnosis. Sustained integration of policy, healthcare, and societal resources is crucial to achieving the "Healthy China 2030" goals.

Keywords: Tobacco control policy, Lung cancer screening, Healthy China

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.27 Gender and Tobacco Use Status Shape Support for Endgame Strategies in India

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Introduction: In India, where tobacco use remains a leading public health concern, there is limited research on public preferences and support levels for tobacco endgame strategies and policies aimed at eliminating tobacco use. Furthermore, the interaction between gender and tobacco use status in shaping these support levels remains unexplored. This study aimed to assess preferences for various tobacco endgame strategies and examine support levels among Indian adults, with a focus on the interactive effects of gender and tobacco use status

Methods: A cross-sectional survey was conducted using a convenience sample of 250 Indian adults,for 2 years between 2022 and 2024, 45.3% of whom were female. Participants were asked how much they agreed or disagreed upon use of standardised packaging,type of tobacco and bans on minors. Preferences for tobacco endgame policies were assessed across demographic variables using chi-square tests. Levels of support were compared by gender and tobacco use status using bootstrapped regression models, adjusting for relevant covariates.

Results: Policy preferences varied significantly across subgroups.Overal , 55 % of adults(63% of and 47% of women $p < 0.001$)showed preference for standardized packaging. 69% of female participants favored nicotine reduction strategies. There were 51.2% of never, 59.4% of past ,25.3% of current smokers($p < 0.001$) were supportive of taxation measures, import bans, bans for both minors and adults, and flavor bans. Overall, never and past tobacco users expressed significantly greater support for endgame policies compared to current users. Notably, among males, those who had never used tobacco or had quit demonstrated higher support levels than their currently using counterparts.

Conclusions: he findings suggest that strong support for tobacco endgame strategies among never and former tobacco users, particularly among males, suggests a favorable climate for advancing such policies in India. These findings can guide targeted advocacy and policy formulation.Perceived difficulties in gaining public support should not impede the introduction of rigorous tobacco control measures needed to achieve a tobacco-free India.

Keywords: Tobacco endgame, smokers, targeted advocacy

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.28 Changes in Respiratory Function in a Patient Undergoing Two Lung Resections

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Introduction: Owing to recent advancements in CT imaging and lung cancer treatment, opportunity of detecting new pulmonary lesions after lung cancer surgery has become increasingly common. We investigated changes in postoperative pulmonary function in patients undergoing repeated lung resections.

Methods: A total of 86 patients underwent pulmonary resection twice at our institution between January 2010 and December 2024. Among them, 35 patients received pulmonary function test one year after the second surgery. Predicted postoperative pulmonary function was calculated assuming a 3% decrease for partial resection, while segmentectomy and lobectomy were calculated based on the number of resected subsegments. In order to compare the difference between predicted and actual pulmonary function, the discrepancy (%) was analyzed by Pearson's correlation coefficient analysis.

Results: There were ten patients who underwent lobectomy for both surgeries and 17 patients who underwent one lobectomy and one sub-lobar resection, and 8 patients who underwent limited resection for both surgeries. Indication for lung resection was primary lung cancer, metastatic tumor, and lymph node involvement. The number of cases in which actual values exceeded predicted values was 32 for VC and 31 for FEV1.0%. The mean discrepancy between actual and predicted values was 42.7% for VC and 43.1% for FEV1.0% in the group that underwent two lobectomies, 26.6% for VC and 36.1% for FEV1.0% in the lobectomy and sub-lobar resection group, and 10.9% for VC and 86.0% for FEV1.0% in the group that underwent two sub-lobar resections. The Pearson's correlation coefficients between the discrepancy of actual versus predicted values and the extent of lung resection were 0.665 for VC and 0.787 for FEV1.0%, with both of P-values being <0.001. There were 20 past or current smokers and using a t-test to compare the discrepancy in pulmonary function between smokers and non-smokers, no significant difference was found.

Conclusions: These findings suggest that in cases of two-stage lung resection, the greater the volume of lung resected, the smaller the decline in postoperative pulmonary function relative to predicted values. Additionally, smoking history does not contribute to this discrepancy. Further studies with a larger sample size are expected to provide more insights into postoperative pulmonary function.

Keywords: Postoperative Respiratory Function, Repeated Lung Resection

EP.01.29 Association of the Cholesterol-Modified Prognostic Nutritional Index With the Survival After Lung Resection for Elderly Patients With NSCLC

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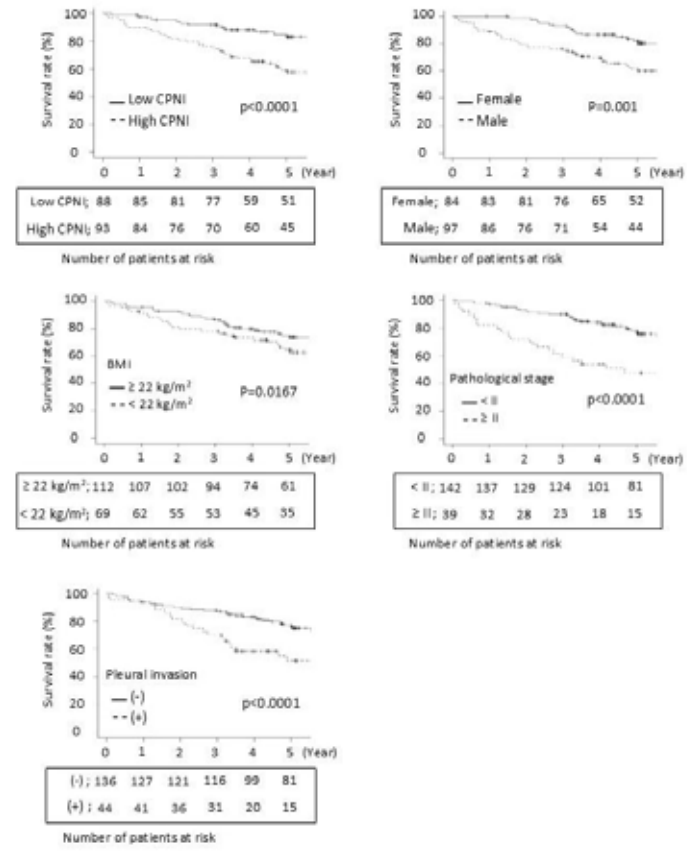
Introduction: Malnutrition has been considered a prognostic predictor of various diseases. Several nutritional indicators, including the prognostic nutritional index (PNI), and neutrophile-lymphocyte ratio (NLR), C-reactive protein-albumin ratio (CAR), the controlling nutritional status (CONUT) and are known as an independent prognostic predictor for non-small cell lung cancer (NSCLC). Furthermore, high cholesterol levels have been reported to increase the risk of cancer as well as cardiovascular and cerebrovascular disease and intensify tumor aggressiveness. Recently, the cholesterol-modified PNI (CPNI), which was proposed as a new nutritional assessment based on PNI, has shown greater predictive accuracy for overall survival (OS) in breast and liver cancer patients than other indices, but the association with this in patients with NSCLC is unknown. The purpose of this study was to verify the effectiveness of CPNI in determining the nutritional status and predicting OS in elderly patients with NSCLC, comparing it with several previously proposed nutritional indicators.

Methods: This retrospective single-center study enrolled 181 patients aged 75 years or older with first-episode NSCLC patients who underwent curative lung resection from April 2006 through December 2021. All data used in this study were preoperative. With respect to the cut-off values for each factor, including BMI, CPNI, PNI, NLR, CAR, and CONUT, those with standard values were statistically analyzed at those values, and those without were calculated based on ROC curves. The association between baseline characteristics, including the blood collection items, histology, pathological stage, nutritional indexes and OS was examined using Kaplan-Meier curves and Cox proportional hazard regression models.

Results: 97 patients (53.6%) were male, and the most common histology was adenocarcinoma in 140 patients (77.3%). The median follow-up period was 61 months. During follow-up, 79 patients (43.6%) died and 40 patients (22.1%) recurrenced. Univariate and multivariate analysis showed that patients with high CPNI had lower OS than those with low CPNI (p<0.0001 and 0.004, respectively). In addition, male (HR 2.28, 95% CI 1.08-4.82, p=0.0306), low BMI (HR 1.97, 95% CI 1.21-3.20, p=0.0063), pathological stage (≥II) (HR 1.92, 95% CI 1.12-3.28, p=0.017), and pleural invasion (HR 1.99, 95% CI 1.14-3.48, p=0.016) were also significant predictors of OS. Among evaluated analyzed objective nutritional assessments, CPNI demonstrated the greatest prognostic predictive power for predicting OS.

Conclusions: CPNI may be a new instrument for evaluating nutritional status and forecasting survival in elderly NSCLC patients who underwent lung resection, potentially offering advantages over other several previously proposed objective nutritional assessments.

Fig. Kaplan-Meier survival curve



Keywords: cholesterol-modified prognostic nutritional index, malnutrition, non-small cell lung cancer

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.30 Beyond Smoking: Exploring Risk Factors for Lung Cancer in Women

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Introduction: Lung cancer is the leading cause of cancer-related deaths in females, with incidence rates declining more slowly in women than in men. While smoking remains the primary risk factor, it does not fully explain the increasing burden of lung cancer in women. Emerging evidence suggests that reproductive factors, including hormonal fluctuations, metabolic disorders, and family history of cancer and their interaction, may influence lung cancer susceptibility. However, the risk factors and their interaction remain poorly understood, particularly across diverse populations. To address this gap, we conducted a case-control study using the All of Us Research Program cohort to explore the complex interplay between these factors and lung cancer risk in adult females.

Methods: Using de-identified data from the All of Us Research Program, we conducted an age-matched case-control study to investigate the association between sociodemographic, reproductive, and metabolic disorders and family history with lung cancer risk in adult females. We identified cases and controls using SNOMED-CT codes and applied a 1:1 stratification (n=5,500) to ensure statistical power. Descriptive statistics, chi-square tests, and two-sample t-tests were used to compare characteristics between cases and controls. Multivariable logistic regression was performed to assess the likelihood of lung cancer occurrence, adjusting for potential confounders.

Results: Lung cancer patients had a mean age of 67.9 years (SD ± 11.9) and a BMI of 28.9 (SD ± 7.1). Non-Hispanic Whites comprised 63.4%, followed by non-Hispanic Blacks (14.5%) and Hispanics (12.2%). Overweight individuals had lower odds (adjusted OR = 0.78, p = 0.0003), while obesity was insignificant. Smoking increased the risk (adjusted OR = 1.28, p = 0.0023), but alcohol had no effect. Postmenopausal bleeding (adjusted OR = 1.59, p < 0.001) and menopause (adjusted OR = 1.47, p < 0.001) were significant, while estrogen use was borderline (p = 0.063). Smoking interactions with estrogen use (p = 0.043) and menopause (p < 0.001) increased risk, as did menopause in Asians (adjusted OR = 2.12, p = 0.001). Hyperlipidemia (adjusted OR = 1.62, p < 0.001) and hypothyroidism (adjusted OR = 1.65, p < 0.001) were significant, with hyperlipidemia-smoking interaction further increasing risk (adjusted OR = 1.71, p < 0.001). Breast (adjusted OR = 0.84, p = 0.038) and ovarian (adjusted OR = 0.61, p = 0.007) cancer family history were protective. Risk increased with smoking in lung cancer family history (adjusted OR = 1.94, p = 0.03), breast cancer family history with hypothyroidism (adjusted OR = 1.64, p = 0.0038), and postmenopausal bleeding with family history of breast (adjusted OR = 1.82, p = 0.017) or lung cancer (adjusted OR = 2.10, p = 0.033).

Conclusions: Beyond smoking, factors such as sociodemographic factors, reproductive history, metabolic conditions, and family history of lung, breast, or ovarian cancer and their interactions contribute to risk. Identifying these factors can improve early detection and prevention strategies for female lung cancer.

Keywords: Female lung Cancer, Beyond smoking, Risk Factors

EP.01 RISK FACTORS, RISK REDUCTION & TOBACCO CONTROL

EP.01.31 Vaping, Smoking and Lung Cancer in Adults Under Age 50: A Case-Control Study

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Introduction: Lung cancer in young adults (under 50 years of age) is increasingly recognized as a distinct clinical entity with potentially unique risk factors. While nicotine exposure through electronic delivery systems (vaping) has been associated with vaping-related lung injury, its contribution to lung cancer risk in younger populations remains largely unexplored. We examined the association between vaping, cigarette smoking, and lung cancer risk in young adults in a case-control study conducted at The Ohio State University Medical Center.

Methods: Electronic medical records from the James Cancer Hospital and Solove Research Institute were analyzed, focusing specifically on patients under 50 years of age with newly diagnosed, pathologically confirmed lung cancer during 2013-2021. A total of 256 lung cancer cases were compared to 2,946 controls without cancer matched to the cases by age, gender, race, and year of ascertainment. Unconditional logistic regression analyses were performed to estimate odds ratios (OR) with 95% confidence intervals for vaping, smoking, and lung cancer in this younger population.

Results: Among individuals under 50 years of age, the distribution of cigarette smoking and vaping differed dramatically between cases and controls. Traditional smokers who did not vape made up 69.9% of cases and 22.3% of controls, OR=5.1 (95% CI: 3.8-6.9, p<0.0001). Most notably, 7.8% of cases both vaped and smoked compared to only 1.6% of controls, with an OR=7.8 (95% CI: 4.2-14.5, p<0.0001) for those who both smoked and vaped versus OR=3.0 (95% CI: 2.2-4.2, p<0.0001) for those who smoked only. Thus, younger adults who both vaped and smoked had an 8-fold increased risk of lung cancer compared to non-smokers, and approximately 2.6 times higher risk than those who only smoked.

Conclusions: Our findings suggest an increased risk of lung cancer among young adults who both vape and smoke compared to those who only smoke. While smoking alone remains a significant risk factor, the addition of vaping appears to further accelerate carcinogenesis in younger populations. These results highlight the potentially harmful synergistic effect of vaping and smoking in young adults and underscore the importance of targeted preventive strategies for both habits. Further research is needed to confirm these results and to elucidate biological mechanisms that may contribute to heightened lung cancer risk among those who combine vaping with cigarette smoking.

Keywords: Lung cancer, Vaping, Young Adults

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.01 Investigating the MET Exon 14 Interactome in Lung Adenocarcinoma

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Introduction: Lung cancer is the leading cause of cancer death worldwide, with lung adenocarcinoma (LUAD) being the most common subtype. In 3-4% of cases, LUAD patients present with mutations in the hepatocyte growth factor receptor (MET) resulting in skipping of exon 14 (METex14); these mutations may be associated with a worse prognosis and a more invasive phenotype. Exon skipping affects receptor degradation, leading to increased receptor half-life and subsequent hyperactivation of downstream signaling pathways which contribute to METex14's transforming potential. While targeted therapies against METex14 have been developed, patient response is poor, necessitating the development of more robust treatment strategies. Our lab has previously demonstrated that METex14 preferentially drives KRAS signaling, hyperactivating the RAS-MAPK signaling pathway relative to its wildtype counterpart. Disruption of signaling through this pathway impeded cell proliferation and colony formation in a METex14-addicted model, while KRAS activation restored cell viability following treatment with MET inhibitors. The increased reliance upon the RAS-MAPK pathway by METex14 compared to the wildtype receptor suggests that this mutant displays altered affinity for downstream effectors which results in differences in signaling activity.

Methods: To investigate, cell lines overexpressing either V5-tagged wildtype or mutant receptor were made; overexpression is inducible following treatment with doxycycline. Lysates from these cell lines were then collected and used for co-immunoprecipitation, followed by mass spectrometry, to identify binding partners which preferentially interact with METex14 and contribute to its oncogenic potential.

Results: Interactors were identified for both the wildtype and mutant receptor, including both known and novel interactors. The interactome comprised various proteins involved in facilitating MET signaling. Effectors mediating Ras activation were also detected and found to preferentially interact with the mutant form of MET.

Conclusions: Together, this work will lead to a better understanding of METex14 signaling, as well as elucidate potential vulnerabilities which can be exploited therapeutically in combination with METex14 targeted therapies to improve patient prognosis.

Keywords: Lung Adenocarcinoma, Interactome, MET

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.02 YB-1 Is a Survival Factor for Mesothelioma-Associated Fibroblasts

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Introduction: Pleural mesothelioma (PM) is a rare malignancy mainly caused by the inhalation of asbestos fibers, with a poor outcome due to a long latency period with nonspecific initial symptoms, leading to late diagnosis. Moreover, treatment options are limited and show a relatively low efficacy, resulting in a median survival of less than 12 months. PM is characterized by a lack of oncogenic mutations, suggesting that the signals driving growth and migration of pleural mesothelioma cells (PMCs) are mainly induced by the tumor microenvironment (TME). Over the last decades, cancer-associated fibroblasts (CAFs) have gained attention for their ability to promote pro-oncogenic traits such as proliferation, migration, invasiveness, and therapy resistance. It has been previously demonstrated that mesothelioma-associated fibroblasts (Meso-CAFs) induce PMCs proliferation and migration through the secretion of signaling molecules. Additionally, Y-box binding protein 1 (YB-1) has emerged as a key pro-oncogenic and multifunctional protein involved in multiple hallmarks of cancer, promoting tumor growth and metastasis in multiple cancer types. Recent studies demonstrated that YB-1 inhibition in PMCs significantly reduces their malignant traits and enhances cisplatin sensitivity. The aim of the present study is to investigate the role of YB-1 in Meso-CAFs and determine whether this molecule is one of the main TME signals driving PMCs malignancy.

Methods: YB-1 depletion was achieved by treating cells with the specific inhibitor SU056 or by siRNA. Cell proliferation was assessed using SYBR Green staining. YBX-1 RNA levels and Meso- CAF differentiation markers (ELN and CTGF) were analyzed by qRT-PCR. YB-1 protein expression and phosphorylation were quantified via western blot. The stimulatory effect of Meso-CAFs on YB-1 expression in PMCs was evaluated by treatment with conditioned media. Cell migration and cell fate were assessed by live cell videomicroscopy, followed by single-cell tracking and image analysis.

Results: YB-1 targeting siRNA treatment was able to achieve a strong reduction of YBX-1 mRNA and protein levels in Meso-CAFs. SU056 resulted in a more moderate reduction of YB-1 protein without an effect on mRNA. Both methods of YB-1 targeting decreased the viability and migration capacity of Meso-CAFs and resulted in an increase of cell death. In contrast, no consistent regulation of the Meso-CAF differentiation markers ELN and CTGF levels by YB-1 targeting was observed. Treatment with Meso-CAF-conditioned medium had only a minimal effect on YB-1 expression in PMCs.

Conclusions: YB-1 plays a key role for the survival of Meso-CAFs. Targeting YB-1 with specific drugs, such as SU056, or via knockdown may thus not only reduce growth, migration, and invasion of PMCs directly, as previously demonstrated, but also indirectly by removing the stimulating effect of Meso-CAFs on PM growth, potentially resulting in a more pronounced overall treatment efficacy.

Keywords: YB-1, Mesothelioma, Cancer-Associated Fibroblasts

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.03 Investigating the Therapeutic Potential of DUSP4/6 Inhibition in Lung Adenocarcinoma

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Introduction: Lung cancer (LC) is the principal cause of cancer mortalities due to limited treatment options with curative potential. Non-small cell lung cancer (NSCLC), of which lung adenocarcinomas (LUADs) are the predominant variant, make up around 80% of all LC cases. The epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma virus (KRAS) oncogenes are often mutated within this subtype. Resistance eventually develops to all current therapeutics for EGFR and KRAS-mutated LUADs, highlighting a need for novel treatment options. KRAS and EGFR mutations promote oncogenesis by activating the mitogen activated protein kinase (MAPK) signalling pathway and its key effectors, the extracellular signal regulated kinases (ERK1/2). We have previously demonstrated that excessive activation of ERK1/2 can also be toxic to cancer cells. The dual specificity phosphatases (DUSP) 4 and 6 negatively regulate ERK signalling, and their inhibition has been proposed as a strategy to hyperactivate ERK and induce cancer cell death. However, combined inhibition of DUSP4 and 6 has not been evaluated in LUAD. This project aims to investigate the effects of DUSP4/6 knockout in drug sensitive and drug resistant cell lines to evaluate the therapeutic potential of DUSP4/6 inhibition in LUAD.

Methods: Using CRISPR and RNAi, we depleted DUSP4 and DUSP6 in LUAD cell lines, including models that are sensitive and resistant to common targeted therapies. Clonogenic assays were conducted to determine the impact of DUSP deletion on cell proliferation and viability, as well as changes in sensitivity to targeted therapies including osimertinib and trametinib. A kinase translocation reporter assay and Western blots assessed the impact of gene knockout on ERK activity.

Results: Findings show that combined knockout of DUSP4/6 impairs LUAD cell viability and induces ERK hyperactivation. Certain drug resistant LUAD cell lines were more sensitive to combined knockout than their parental counterparts.

Conclusions: Given the challenges of resistance to targeted therapies in LUAD, novel approaches are urgently needed. This study demonstrates that DUSP4/6 knockdown can overcome drug resistance, supporting the potential for therapies targeting DUSP4/6 as a viable treatment strategy.

Keywords: Lung adenocarcinoma, Oncogene, Signaling Pathways

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.04 Identification of a Novel Immunotherapy Target in EGFR-Mutant Lung Cancer Resistant to Immune Checkpoint Inhibitors

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Introduction: Immunotherapy is the standard of care for non-small cell lung cancer (NSCLC). However, EGFR-mutant lung cancer exhibits high resistance to immune checkpoint inhibitors (ICIs). This resistance has been attributed to low PD-L1 expression and low tumor mutation burden (TMB). Recently, an immunosuppressive tumor microenvironment (TME) has been proposed as a contributing factor, but the mechanisms underlying this phenomenon remain unclear. This study aims to identify novel therapeutic targets for ICI therapy in EGFR-mutant lung cancer.

Methods: We analyzed The Cancer Genome Atlas (TCGA) and Cancer Cell Line Encyclopedia (CCLE) databases to compare gene expression between EGFR-mutant and non-EGFR-mutant lung cancers, identifying a significantly upregulated gene, "Gene X," in EGFR-mutant lung cancer. Further analysis of the EGFR-mutant lung cancer cell line HCC2279, which harbors an exon 19 deletion, revealed bimodal expression of Gene X, leading to the classification of high-expression (X-High) and low-expression (X-Low) groups. To investigate the functional role of Gene X, we conducted RNA sequencing (RNA-seq) in X-High and X-Low groups. Additionally, we co-cultured HCC2279 cells with NK92 cells and compared protein X knockout in X-High cells to control groups. To further assess immune cell dynamics, we utilized a three-dimensional microfluidic system to evaluate NK cell migration towards tumor spheroids in response to Gene X modulation.

Results: Enrichment analysis revealed that X-Low cells exhibited higher enrichment of interferon and inflammatory markers, suggesting increased immunogenicity. In co-culture experiments with NK92 cells, X-knockout HCC2279 cells exhibited increased granzyme B levels, indicating enhanced NK cell activity. Furthermore, in the microfluidic assay, X-knockout HCC2279 cells significantly accelerated NK-92 cell migration towards tumor spheroids from the side channel, further supporting the role of Gene X in immune modulation.

Conclusions: These findings suggest that Gene X expression in EGFR-mutant lung cancer contributes to an immunosuppressive tumor microenvironment by modulating NK cell recruitment and activation. Targeting Gene X may serve as a novel immunotherapeutic approach for overcoming ICI resistance in EGFR-mutant lung cancer.

Keywords: Lung cancer, EGFR, immune

EP.02.05 Three-Dimensional Visualization of Spreading Tumor Cell Through Air Spaces (STAS) Using High Resolution Phase-Contrast Imaging Method

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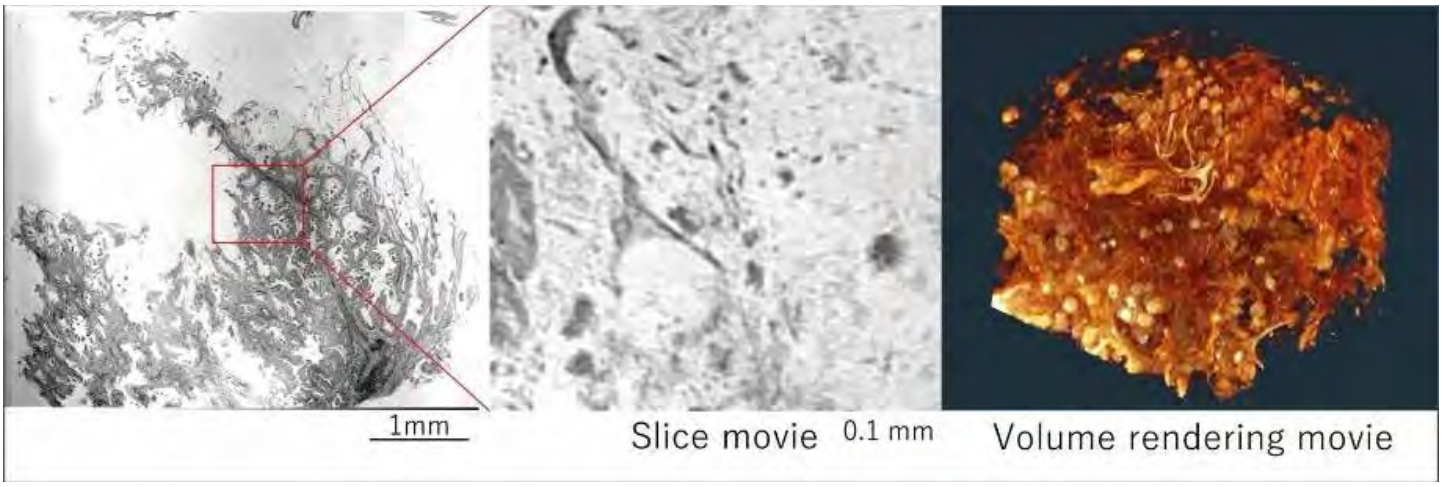
Introduction: The presence of spreading tumor cell through air spaces (STAS) above the edge of tumor margin inside lung cancer has been proved to be one of important prognostic factors for recurrence. However, there still no definite diagnostic tools for the detection of STAS unless proceeding precise pathologic examination. Synchrotron radiation phase-contrast tomography techniques applying specially designed crystal optics could be an optimal imaging method for visualizing STAS from lung cancer samples. The aim of this study is to visualization of STATS over the edge lung adenocarcinomas using synchrotron radiation tomography apply analyzer-based optics for identification of STAS over the edge of lung adenocarcinoma, therefore, enhancing three-dimensional comprehension of invasive mechanism.

Methods: Parts of human lung cancer tissue harvested from a patient who underwent surgical resection for curative purpose were used to acquire high resolution phase-contrast CT using synchrotron radiation. The experiment was performed using analyzer-based optic devices configured at Photon Factory BL 14B affiliated in High Energy Accelerator Research Organization in Japan. Obtained images were reconstructed to three-dimensional tomography. Segmentation was also performed. Used specimen was made to a formalin-fixed Paraffin Fixed block, sliced and stained with hematoxylin and eosin (H&E) for conventional light-microscopic examination

Results: Parts of human lung cancer tissue harvested from a patient who underwent surgical resection for curative purpose were used to acquire high resolution phase-contrast CT using synchrotron radiation. The experiment was performed using analyzer-based optic devices configured at Photon Factory BL 14B affiliated in High Energy Accelerator Research Organization in Japan. Obtained images were reconstructed to three-dimensional tomography. Segmentation was also performed. Used specimen was made to a formalin-fixed Paraffin Fixed block, sliced and stained with hematoxylin and eosin (H&E) for conventional light-microscopic examination

Conclusions: Synchrotron radiation phase-contrast tomography imaging techniques applying analyzer-based optics are useful for achieving higher resolution enough to visualize the actual three-dimensional characteristics of STAS. This approach has the potential to establish a fundamental framework for 3D virtual histopathology as an imaging-based diagnostic tool for lung cancer.



Keywords: Lung cancer, Synchrotron, Diagnosis

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.06 Natural Multiple Serine Synthase Inhibitors Modulate Tumor Microenvironment Polarization and Inhibit the Growth of Lung Cancer

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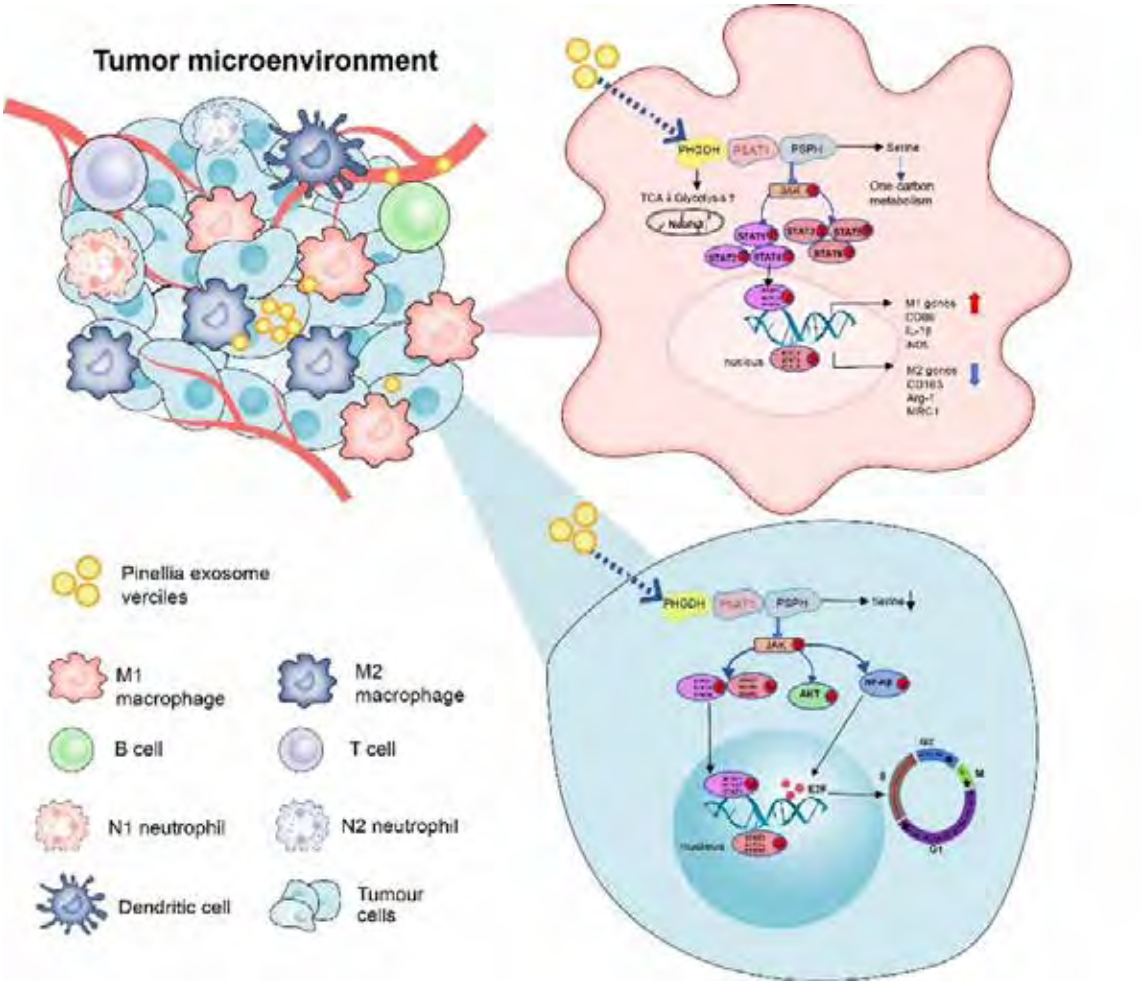
Introduction: Cancer cells exhibit a high level of metabolic activity and strongly rely on exogenous amino acid resources, especially serine and glycine. The Chinese herb Pinellia ternata has been reported to improve cellular lipid metabolism, regulate cellular immunity, and possess anti-tumor properties. In this study, we reported that the nano-therapeutic drugs prepared from Pinellia ternata simultaneously inhibited multiple serine synthesis enzymes and targeted both tumor cells and macrophages in the tumor microenvironment and declined the growth of lung cancer.

Methods: Pinellia exosomes were extracted by ultracentrifugation and detected by electron microscopy. In pinellia exosomes treated THP1 macrophages, the M1 and M2 cellsubtye markers were detected by Q-PCR. In pinellia exosomes treated lung cancer cells, cell proliferation, cell apoptosis and cell cycle were detected by CCK8 and flow cytometry. The regulated gene expression and signaling pathway by pinellia exosomes were detected by transcriptome sequencing.

Results: Electron microscopy examination showed that pinellia exosomes were vesicles with spherical and bilayer membrane structures. It was unexpectedly found that Pinellia exosomes simultaneously caused decrease expressions of multiple serine synthesis-related genes PHGDH, PSAT1, and PSPH in macrophages, the members of the JAK/STAT signaling pathway were regulated by serine synthesis enzyme genes. Further studies showed that Pinellia exosomes inhibited lung cancer growth by promoting M1 polarization of tumor-associated macrophages through affecting serine synthesis, and also had a direct inhibitory effect on lung cancer cells, especially in lung cancer cells with high expression of PHGDH, PSAT1, and PSPH genes.

Conclusions: Natural Chinese herbal medicine Pinellia exosomes inhibit the expression of serine synthesis-related genes, exert dual effects on lung cancer cells and macrophages in the tumor microenvironment, thereby suppress lung cancer growth. This provides a new approach for tumor treatment by combining natural Chinese herbal medicine with modern nanotechnology.



Keywords: Lung cancer, Pinellia ternata exosomes, Tumor immune microenvironment

EP.02.07 Enhancing Alectinib Efficacy in ALKPositive Non-Small Cell Lung Cancer by Targeting Mtor

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Introduction: Alectinib, a powerful ALK tyrosine kinase inhibitor (TKI), has greatly enhanced treatment outcomes for patients with ALK-positive non-small cell lung cancer (NSCLC). However, a major challenge is the inevitable development of resistance, with nearly 50% of cases driven by the activation of parallel signaling pathways, such as the mTOR pathway. The mTOR pathway, a central regulator of key cellular processes of cell growth, metabolism, and survival plays a pivotal role in tumor progression and cellular adaptation to therapeutic pressure. Given the important role of mTOR in promoting tumor survival, integrating mTOR inhibition with Alectinib holds potential to optimize treatment efficacy and impact of ALK-targeted therapies. This combination approach holds potential not only to optimize outcomes for patients with advanced ALK-positive NSCLC but also to broaden the impact of ALK-targeted therapies by combating therapeutic resistance.

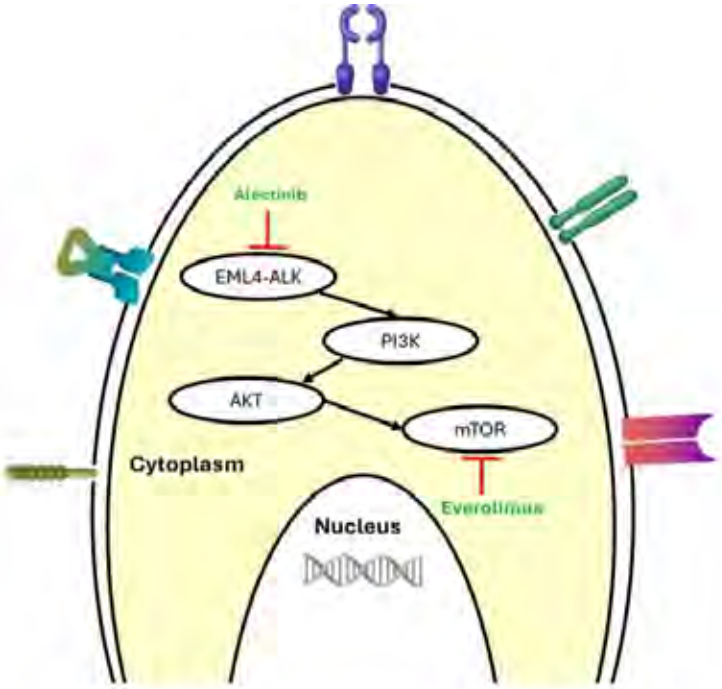
Methods: ALK-rearranged cancer cell lines CUTO8, CUTO9, CUTO29.1, CUTO39, CUTO41, CUTO43, CUTO46, DFCI032, NCI-H2228, NCI-H3122, SNU2292, SNU2535, and EA2 were treated with Alectinib alone or in combination with Everolimus. Cell viability was assessed using a 3D Cell-titer Glo viability assay and a BioTek BioSpa Live Cell Analysis System. Synergistic interactions were quantitatively evaluated using the Chou-Talalay method.

Results: The combination of Alectinib and Everolimus demonstrated strong synergistic effects, significantly reducing cell viability across all tested ALK-rearranged NSCLC cell lines, demonstrating increased sensitivity when mTOR was co-targeted. This profound synergy suggests that dual inhibition effectively disrupts key oncogenic adaptive signaling pathways that contribute to tumor cell plasticity that favors survival and proliferation. The observed reduction in cell viability was not only consistent across multiple ALK-rearranged NSCLC models, but also exhibited a greater magnitude of effect compared to Alectinib monotherapy, reinforcing the therapeutic potential of this combination approach from the onset of treatment.

Conclusions: These findings provide strong evidence that mTOR inhibition is a promising strategy to enhance the effectiveness of Alectinib, potentially overcoming some resistance mechanisms in ALK-positive non-small cell lung cancer (NSCLC) and enhancing Alectinib efficacy. Taken together, these studies in multiple cell models provide a strong rationale for further in vivo validation and clinical exploration to improve outcomes for patients.

	Alectinib+Everolimus	
Cell Lines	ED50	ED75
SNU2535	0.29	0.40
SNU2292	0.01	0.05
NCI-H3122	0.25	0.24
NCI-H2228	0.16	0.24
DFCI032	0.65	0.39
CUTO46	0.46	0.18
CUTO43	0.55	0.10
CUTO41	0.29	0.24
CUTO39	0.23	0.11
CUTO29.1	0.31	0.43
CUTO9	0.24	0.28
CUTO8	3.55	0.08
EA2	0.28	0.26

Combination index values at therapeutically relevant doses (ED50 and ED75) of combining alectinib with Everolimus in ALK+ lung cancer cell lines



Keywords: ALK-positive lung cancer, mTOR, combination

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.08 Exploratory Effect of Cisplatin on Autophagic Pathway in Human Lung Adenocarcinoma Cell Line

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Introduction: Cisplatin, an antineoplastic agent acts through various mechanisms like apoptosis, DNA damage and cell cycle arrest. Recently, cisplatin was found to induce autophagy, a cell recycling pathway in breast, prostate, pancreatic and oral cancer. This study aims to determine the effect of cisplatin on autophagic pathway in human lung adenocarcinoma (A549) cell line.

Methods: Cell viability assay was performed at 7.5-250 µM cisplatin against A549 cell line (NCCS, Pune) at 24 h, 48 h and 72 h and half - maximal inhibitory concentration (IC50) was determined. Cell cytotoxicity assay and cell cycle analysis were performed using flow cytometry. Additionally, reactive oxygen species (ROS) and nitric oxide (NO) levels were determined. Hoechst staining was performed using confocal microscopy. Autophagy - related protein 5 (ATG5) and sequestosome 1 (SQSTM1) were determined using Western blotting. Additionally, sequestosome 1 was semi-quantitatively determined using immunofluorescence. Ultrastructural changes in A549 cells were determined using transmission electron microscopy (TEM).

Results: IC50 of cisplatin at 24 h, 48 h and 72 h were 43.6 µM, 19.8 µM and 9.6 µM, respectively. At 20 µM there was 11.9 fold increase in early apoptotic cells and 3.8 fold increase in late apoptotic cells ($p<0.0001$). At 40 µM, there was 11.9 fold increase in early apoptotic cells and 6.9 fold increase in late apoptotic cells ($p<0.0001$). Cisplatin caused arrest in G2M phase of cell cycle as compared to control cells ($p<0.0001$). Mean fluorescence intensity (MFI) of ROS was higher in cisplatin treated groups as compared to control [cisplatin 20 µM: 13.8 ± 0.4 ($p=0.0003$), cisplatin 40 µM: 24.2 ± 2.1 ($p=0.0002$), control: 4.4 ± 1.3] but NO release was lower in cisplatin treated groups compared to the control group [cisplatin 20 µM: 15.1 ± 0.6 ($p <0.0001$), cisplatin 40 µM: 15.1 ± 0.6 ($p <0.0001$), control: 24.2 ± 0.5]. Using Hoechst staining, there was increase in the MFI in the cisplatin treated groups as compared to the control group 7 ($p <0.0001$). There was downregulation of proteins, ATG5 and SQSTM1 in the cisplatin treated groups. Additionally, decrease in MFI of SQSTM1 was observed in cisplatin treated groups as compared to the control group [cisplatin 20 µM: 7017.5 ± 5048.3 ($p=0.001$), cisplatin 40 µM: 4467.6 ± 2245.4 ($p <0.0001$), control: 22073.9 ± 12715.6] using immunofluorescence. On electron microscopy, increased number of autophagosomes and residual bodies were observed in cisplatin treated groups as compared to the control group.

Conclusions: Cisplatin, an anticancer drug, was observed to downregulate key proteins involved in autophagic pathway leading to increased accumulation of autophagosome and residual bodies in cisplatin treated groups. It implies that autophagy plays a crucial role in the anticancer activity of cisplatin in human lung adenocarcinoma. Hence, further studies with autophagy inducer and inhibitor will help in elucidating the conclusive effect of cisplatin activity through autophagic pathway.

Keywords: Cisplatin, Autophagy, Lung cancer

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.09 Deciphering CD47-Mediated Platelet-Tumor Crosstalk and Its Role in NSCLC Metastasis

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Introduction: CD47 is overexpressed and associated with poor prognosis in non-small cell lung cancer (NSCLC). Most studies of CD47 in cancer have focused on its role in promoting tumor immune evasion, although we and others have found that it influences cancer metastasis. Since platelets can promote tumor cell dissemination and they can bind to other cells through homotypic CD47 interactions, we aimed to investigate the hypothesis that CD47 promotes NSCLC metastasis through interactions with platelets.

Methods: CRISPR/Cas9 was used to knockout (KO) CD47 in murine (LLC) and human (H1299) NSCLC models. The effects of CD47 KO on cancer cell binding to platelets after co-incubation and platelet activation induced by cancer cell supernatants in vitro were measured by flow cytometry. Binding assays utilized GP1b-b and CMFDA as markers for platelets, while JON/A and Pac-1 were used as activation markers. An in vivo study to assess the influence of platelets on cancer metastasis was performed using the LLC model. Luciferase-tagged LLC cells were intravenously delivered into mice by tail vein injections, and platelet depletion was achieved using an anti-GPIb antibody administered by intraperitoneal injection every 3 days. Metastasis to the lungs was monitored using bioluminescence imaging of mice to detect luciferase activity. RNA-sequencing (RNA-seq) data for LLC cells sorted from wildtype and CD47 KO tumors grown in mice was also analyzed to investigate how CD47-associated transcriptomic changes might influence platelet-mediated metastasis.

Results: In vitro assays revealed decreased binding of platelets to LLC cells with CD47 KO compared to wildtype controls. Results for H1299 cells were variable and additional replicates are needed to confirm the trend towards reduced platelet binding to CD47-deficient cells in this model. Supernatants from LLC and H1299 cells with CD47 KO exhibited a reduced ability to activate platelets relative to supernatants from cells with wildtype CD47. In vivo, platelet depletion did not affect metastasis of wildtype LLC cells to the lungs, but CD47 KO together with platelet depletion completely abolished metastasis. Gene set enrichment analyses on RNA-seq data for cancer cells isolated from LLC tumors revealed that genes downregulated in CD47 KO relative to wildtype tumors were significantly enriched for coagulation pathways. Moreover, several genes encoding factors that bind to platelet receptors were upregulated in CD47 KO relative to wildtype cells.

Conclusions: Our findings suggest that CD47 regulates lung cancer cell interactions with platelets, which could affect the ability of lung cancer cells to metastasize and/or contribute to other hallmarks of cancer influenced by platelets. As such, CD47 blockade could antagonize lung tumor growth and progression through multiple mechanisms. Future experiments will include studies to characterize platelet activating factors secreted by wildtype and CD47 KO cells, and in vivo experiments to understand the effects of platelet depletion on cancer cell metastasis in additional NSCLC models.

Keywords: CD47, NSCLC, Platelets

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.10 Fumarate and Ass1 in KRAS-Mutant NSCLC: The Influence of Cetuximab in Combination With KRAS G12C Inhibitors (Sotorasib and Fulzerasib)

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Introduction: Clinical trials using KRASG12C inhibitors as monotherapies have exhibited brief responses. It has been identified that EGFR is involved in a dominant resistance mechanism to KRASG12C inhibitors in colorectal cancer. Therefore, targeting EGFR activation with cetuximab, a key component of the adaptive resistance mechanism, is of significant interest. Notably, in KRASG12C-mutant lung cancer patients, fulzerasib plus cetuximab attained an 80% response rate (KROCUS).

Beyond its role in oncogenic signalling, KRAS has been implicated in the remodelling of aspartate metabolism and the urea cycle, directly affecting the expression of argininosuccinate synthetase 1 (ASS1) and fumarate accumulation. Interestingly, in colorectal cancer, specific KRAS mutations can lead to ASS1 overexpression, facilitating cell proliferation and generating key intermediates of the TCA cycle, such as fumarate. These findings suggest that ASS1 expression and fumarate levels could serve as key prognostic biomarkers in different cancer types.

In this study, we evaluated the synergistic effects of fulzerasib or sotorasib (KRASG12C inhibitors) in combination with cetuximab in KRAS-mutant lung cancer cell lines, along with analysis of RAS signaling rebound. In addition, identification of a wide range of proteins and assessment of fumarate levels.

Methods: A panel of KRAS G12C-mutant cell lines, including H358, H23, H2122, H1792, H2030 and Mia-PaCa-2 were used. Reagents, antibodies, cetuximab and sotorasib were purchased. Fulzerasib was provided by Genfleet. Cell viability was assessed by MTT. The following primary antibodies were used for western blot analysis: EGFR Y1068, HER3 Y1289, FASN, EphA2 S897, YAP Y357, MIG6, ASS1, ERK1/2 T202/Y204, MRAS and Hsp90. Fumarate levels were quantified using a spectrophotometric kit.

Results: The IC50 values for both fulzerasib and sotorasib were notably low in H358, H2122, and Mia PaCa-2 cells, whereas they were high in H2030 cells and moderately elevated in the H23 cell line. The combination with cetuximab enhanced cytotoxicity. H358 cells showed a high synergistic effect, with a combination index of 0.53 when paired with fulzerasib. Other cell lines exhibited slightly synergistic effects (values below 1), while H23 cells showed an additive response.Western blot analysis revealed that the ERK1/2 rebound, typically induced by fulzerasib or sotorasib alone, was effectively abolished in H358 cells. Suppression of ERK1/2 resulted in attenuation of YAP Y357 phosphorylation. ASS1 expression appeared to increase more substantially in the more resistant cell lines, H23 and H2030, following treatment with sotorasib or fulzerasib. In contrast, ASS1 expression levels remained largely unaffected in H358 by KRASG12C inhibitors treatment. Fumarate levels seem to be higher in H358 compared to more resistant cell lines. Fulzerasib and sotorasib seem to increase levels of fumarate in a similar extent.

Conclusions: Cetuximab combined with fulzerasib or sotorasib inhibits cell viability in H358 cell line, preventing ERK1/2 rebound and YAP1 activation. Levels of ASS1 in H358 cells were stable before treatment. In contrast, ASS1 levels were low and upregulated after sotorasib treatment in H23 cells. Low ASS1 expression is shown to harbour a poor prognosis. Further research could clarify the relevance of ASS1 and fumarate as a biomarker and therapeutic target.

Keywords: Fumarate, ASS1, KRASG12C inhibitors

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP.02.11 Clinical and Biological Significance of Cystathionine Gamma-Lyase in Pulmonary Adenocarcinoma

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Introduction: Cystathionine gamma-lyase (CTH) is an enzyme that catalyzes endogenous hydrogen sulfide and involved in physiological processes, such as cell proliferation and migration. However, the significance of CTH expression in lung adenocarcinoma remains unclear. This study aimed to evaluate CTH expression in invasive pulmonary adenocarcinoma and clarify its prognostic significance in patients.

Methods: CTH expression was analyzed by immunohistochemistry to evaluate its clinicopathological significance in 103 patients with p-Stage IA-IIIA invasive pulmonary adenocarcinoma who underwent surgical resection between 2016 and 2021. To clarify the role of CTH expression, the effects of CTH knockdown in human lung adenocarcinoma cell lines ABC-1 and VMRC-LCD were examined using proliferation, scratch, and invasion assays. To investigate the involvement of CTH in tumor cell aggressiveness, growth factor antibody array was performed.

Results: In patients with p-Stage IA-IIIA invasive pulmonary adenocarcinoma, CTH expression in tumor cells was significantly associated with tumor recurrence ($p = 0.014$), histological subtype ($p < 0.001$), and microvessel invasion ($p = 0.001$). Patients with higher CTH expression levels had significantly lower relapse-free survival rates than those with lower CTH expression levels ($p = 0.005$). In vitro assays, the CTH knockdown did not affect the proliferative activities of A549, ABC-1, and VMRC-LCD cells. The migratory and invasive activities of these tumor cells were significantly reduced by CTH knockdown. The growth factor antibody array revealed that the protein level of platelet-derived growth factor-A (PDGF-A) was significantly decreased by CTH knockdown in tumor cells.

Conclusions: CTH promotes tumor cell motility via PDGF-A expression in pulmonary adenocarcinoma. In p-Stage IA-IIIA invasive pulmonary adenocarcinoma, CTH expression could serve as a predictor of tumor recurrence.

Keywords: Pulmonary adenocarcinoma, Cystathionine gamma-lyase

EP.02 TUMOR BIOLOGY – PRECLINICAL BIOLOGY

EP02.12 Identifying Acquired Resistance Mechanisms to Sotorasib in G12C Lung Adenocarcinoma (LuAD) Cell Lines (CL)

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Introduction: KRAS mutations are responsible for approximately 20% of lung adenocarcinomas (LuAD). Most of these mutations consist of a glycine to cysteine transversion at codon 12 (G12C), trapping KRAS on its GTP-bound active state and consequently activating downstream singnaling pathways. The first effective strategies are G12C inhibitors (sotorasib and adragrasib) that are bound to mutant cysteine, therefore trapping KRAS on its inactive state. Sotorasib and adagrasib trials showed promising response rates but short duration of response (11 and 8 months, respectively). We assessed the possible mechanisms of acquired resistance to sotorasib and tried to identify possible strategies to overcome this resistance.

Methods: To generate sotorasib-resistant models we selected two different commercial lung cancer cell lines (H355 and H2030) and exposed them to increasing doses of sotorasib. We characterized the parental cancer cells and the derived-resistant genetically and molecularly by exome (WES) and RNA sequencing and performed analysis of signaling pathways and of the KRAS activation status by western-blot and RAS assay test. We also exposed the resistant cells to a SHP2 inhibitor (TNO155) and to a MEK inhibitor (trametinib), with and without sotorasib, and determined efficacy using cell viability and colony formation assays. We also tested these drug combinations in other commercial and in a patient-derived lung cancer cells with a KRASG12C mutation.

Results: The H2030 cells showed partially intrinsic resistance to sotorasib and we couldn't find acquired resistant mechanisms at a genetic level, although there were changes in gene expression. Three of the H358 derivate resistant cells showed KRAS G12C amplification. One model harbored a secondary G12V mutation. AKT activation was present in two models. TNO155 was not effective in overcoming resistance but trametinib was. One of the resistant models was addicted to sotorasib as drug combinations weren't effective without sotorasib.

Conclusions: Mutant allele amplification and secondary KRAS nonG12C mutations could be on target acquired resistance mechanisms. AKT pathway activation could be an off-target resistance mechanism. SHP2i could be synergic in combination with sotorasib in partially resistant cell lines.

Keywords: KRAS, sotorasib, resistance

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.01 Identification and Validation of Recurrence-Associated Proteins in Stage I Lung Adenocarcinoma

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Introduction: In the evolving landscape of treatment for resectable lung cancer patients, better understanding of tumor biology is necessary. We have previously identified proteins associated with survival in surgically resected stage I-III lung adenocarcinoma (LUAD) patients. We sought to perform proteomic analysis in resected stage I LUAD patients to determine 1) proteins associated with recurrence and 2) whether there are shared proteins compared with our previously identified survival-associated proteins.

Methods: From our retrospective database of resected LUAD between 2016-2022, we selected pathologic stage I patients. We then selected 10 early recurrent cases (recurrence within 3 years of surgery) and 10 cases with long disease-free interval (more than 3 years). Laser microdissection was used to selectively harvest tumor epithelium from the formalin-fixed, paraffin-embedded LUAD tumor tissues, which were analyzed using a quantitative proteomics workflow employing tandem mass tags and high-resolution liquid chromatography-tandem mass spectrometry. Significant proteins were then compared with previously identified survival-associated proteins.

Results: Among the 10 early recurrent cases, the median age was 70.5, and 2 were females. By procedure, 6 received wedge resections and 4 received lobectomies. By stage, there were 6 stage IA2 and 4 IA3. By morphology, there were 6 acinar, 2 papillary, 1 lepidic, and 1 solid. Among the long disease-free interval cohort, the median age was 74, and 2 were females. By procedure, 5 received wedge resections and 5 received lobectomies. By stage, there were 1 stage IA1, 6 IA2, and 3 IA3. By morphology, there were 4 solid, 3 acinar, 2 mucinous, and 1 uncategorized. Between the two cohorts, we identified 880 proteins that were significantly altered ($p<0.05$). We then compared these to the 1041 significantly ($p<0.05$) altered proteins associated with survival in stage I-III LUAD in our previous study. We identified 109 proteins that are shared between the two studies that are highly quantitatively correlated (correlation ~0.8, $p<0.0001$, Figure 1).

Conclusions: Our study identified proteins significantly associated with recurrence in resected stage I LUAD patients. Furthermore, some of these proteins are shared with our previously identified proteins associated with survival in stage I-III LUAD. Current and future work will focus on pathway analysis and performing similar analysis on preoperative biopsy specimens.

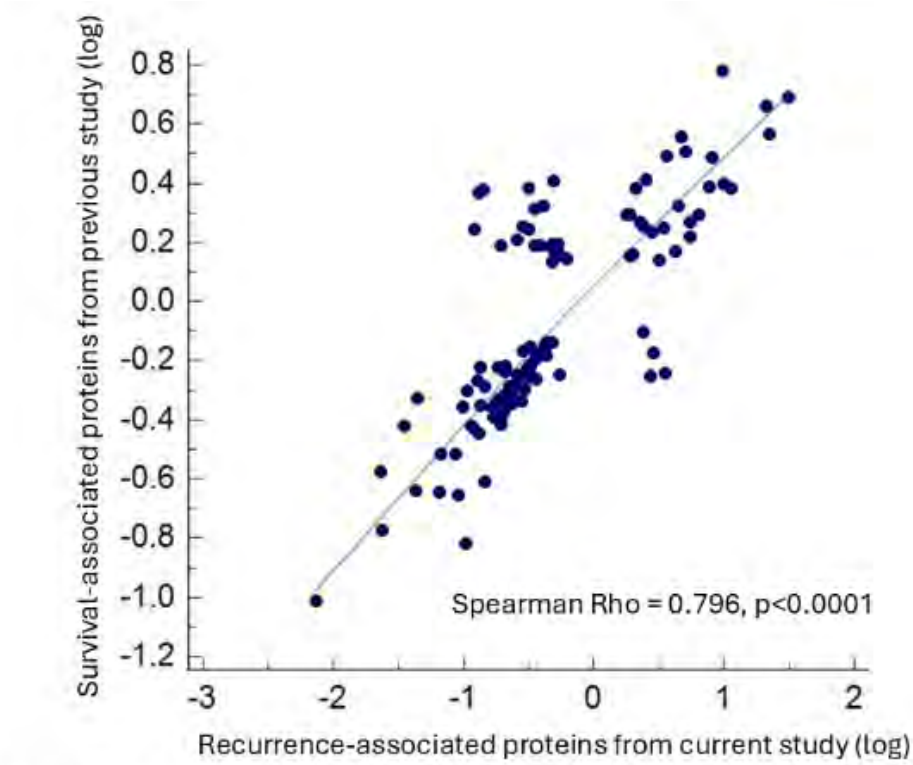

Figure 1. Correlation of recurrence-associated proteins from stage I lung adenocarcinoma and survival-associated proteins from previous study in stage I-III lung adenocarcinoma

Keywords: proteomic, recurrence, stage I lung adenocarcinoma

EP.03.02 An Integrating Multiomic Approach to Chart the Tumor Immune Microenvironment Associated to Immunotherapy Response in Non-Small Cell Lung Cancer

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Introduction: The organization and composition of the Tumour Immune Microenvironment (TIME) are crucialdeterminants of patient clinical outcomes. This evidence highlights the importance of profiling cellidentity, functionality, and tissue architecture for the development of novel and more effectivetherapeutic strategies. Distinct TIME subtypes have been characterized, each exhibiting uniquefeatures that influence tumour invasiveness, modulate immune responses, and impact theeffectiveness of therapeutic interventions. Among these, a TIME enriched in tertiary lymphoidstructures (TLS), ectopic lymphoid hubs where B and T cells interact to produce high-affinityimmune responses and durable immune memory, has recently emerged as a prognostic andpredictive biomarker of responsiveness to immune checkpoint blockade (ICB) therapy.Concurrently, cancer-associated fibroblasts (CAFs), a highly heterogeneous and dynamic cellularcomponent of the TIME, have gained increasing interest for their pivotal role in shaping TIMEarchitecture, influencing tumor progression, and modulating immune cell functionality. Ourprevious work has shown that, in CAFs, the high expression of hMENA, an actin cytoskeletonregulator, modulates the expression of Lymphotoxin β Receptor (LTβR) and secretion of CXCL13,critical initiators of TLS development. Furthermore, we identified a gene signature, includinghMENA, fibronectin, and LTβR, that is predictive of response to ICB in NSCLC and is associatedwith the presence of a TLS-enriched TIME.

Methods: We collected tumor, adjacent non-tumor tissue, and peripheral blood from six treatment-naïveNSCLC patients who underwent curative surgery in our Institute. Patients who later recurred andreceived ICB were classified as good or poor responders. We integrated spatial transcriptomics, by10X Visium, and single-cell RNA sequencing (scRNA-seq) to in-depth profile the composition andfunctionality of patients' TIME and focused on TLS maturation, also in relation to surroundinghMENA-expressing CAFs

Results: By integrating publicly available single-cell atlases of T and B cells, and the in-house generatedCAF atlas with our spatial transcriptomic datasets, we identified key TIME programs likelyassociated to clinical response to ICB therapy. Comparative analysis between ICB responder andnon-responder patients revealed significant differences in TLS cellular composition and maturationstages. Specifically, NSCLC patients with a good response to ICB exhibited a higher TLSmaturation score, also characterized by an increased abundance of activated and germinal center Bcells, along with antibody-secreting plasma cells. Additionally, integrating the lung CAF single-cellatlas with spatial transcriptomic data highlighted a higher presence of immunosuppressive hMENA-overexpressing CAFs within and around TLS in poor ICB responders compared to good responders,suggesting that hMENA-expressing CAFs may hinder the formation of fully functional antitumorTLS. In parallel, ongoing scRNA-seq profiling of peripheral lymphocytes aims to uncover systemicimmune signatures that could further aid in stratifying patients based on their likelihood to benefitfrom ICB.

Conclusions: Our findings emphasize the value of combining complementary spatial and single-celltranscriptomic technologies to uncover predictive biomarkers of ICB response in NSCLC and toreveal novel mechanisms of immune evasion, critical for developing more precise and effectiveimmunotherapeutic strategies

Keywords: Immune microenvironment, Spatial transcriptomics, Immumotherapy

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.03 Tumor Heterogeneity Consisting of SCLC With RB1 Exon 19 Deletion and L718V Mutation-Positive Adenocarcinoma in EGFR-TKI Resistant Lung Cancer

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Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are widely used as targeted therapies for EGFR-positive non-small cell lung cancer (NSCLC). However, acquired resistance, such as secondary mutations and histological transformation to small cell lung cancer (SCLC), remains a significant clinical challenge. In this study, we investigated the mechanisms of resistance to osimertinib by analyzing sequential biopsy specimens obtained over time following the development of resistance.

Methods: We established cell lines from cancerous pleural effusions and mediastinal lymph node biopsies obtained from patients with EGFR L858R mutation-positive lung cancer who had been treated with osimertinib at the time of disease progression. EGFR and other gene mutations, as well as gene expression profiles, were analyzed using RNA sequencing and whole-exome sequencing. In addition, we assessed the drug sensitivity of the established cell lines and examined the effects of the drugs on cell proliferation signaling pathways by Western blot analysis.

Results: The patient-derived cell lines JFCR330-4 and JFCR330-7, established from pleural effusions after the development of resistance to osimertinib, were classified as lung adenocarcinoma. Both L858R and L718V mutations in the EGFR gene were identified in these lines. In contrast, JFCR330-5, which was established from mediastinal lymph node biopsy specimens, exhibited characteristics of SCLC, and harbored only the EGFR L858R mutation. Cell viability assays and Western blot analyses demonstrated that JFCR330-4 and JFCR330-7 were resistant to osimertinib but showed high sensitivity to afatinib, a second-generation EGFR-TKI. Notably, JFCR330-7 cells exhibited partial sensitivity to gefitinib, whereas they were resistant to erlotinib, which shares a high degree of structural similarity with osimertinib. RNA sequencing revealed that genes regulated by ASCL1, as well as synaptic and nervous system-related genes, were enriched in JFCR330-5, which had undergone small cell transformation. Both RNA sequencing and whole-exome sequencing detected TP53 mutations in all cell lines derived from this patient. However, only in JFCR330-5 was a deletion of exon 19 in the RB1 gene identified, suggesting that a DNA region of approximately 10 kb or less, including exon 19, was deleted. Such a single-exon deletion at the DNA level is likely to be missed by next-generation sequencing (NGS) of tumor tissues when a high proportion of nucleic acids are derived from surrounding normal tissues. These subtle genetic alterations may underlie SCLC transformation even in cases lacking obvious RB1 mutations or deletions.

Conclusions: In this case, SCLC transformation and the acquisition of the L718V mutation occurred simultaneously but in distinct tumor sites. In the pleural effusion, the L718V mutation emerged, suggesting that afatinib may be a potential therapeutic option to overcome this resistance. In contrast, in the mediastinal lymph node metastasis, microdeletion of the RB1 gene led to small cell transformation and subsequent drug resistance. These findings highlight the temporal and spatial heterogeneity of resistance mechanisms in EGFR inhibitor-treated lung cancer.

Keywords: SCLC transformation

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.04 PD-L1-Regulated c-Met Phosphorylation Contributes to MET Amplification in EGFR Mutation NSCLC

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Introduction: Programmed death-ligand 1 (PD-L1) is a well-recognized predictive biomarker for immunotherapy in non-oncogene-addicted non-small cell lung cancer (NSCLC). However, its role in epidermal growth factor receptor (EGFR)-mutant NSCLC remains unclear. Some retrospective analyses suggested that PD-L1 expression is associated with lower response rate and shorter survival to EGFR tyrosine kinase inhibitors. This study aims to investigate the impact of PD-L1 on the signaling pathways in EGFR-mutant NSCLC.

Methods: The regulatory role of PD-L1 was investigated through in vitro manipulation of PD-L1 expression across several EGFR-mutant cell lines, followed by analysis via human receptor tyrosine kinase (RTK) array, Western blotting, protein tyrosine phosphatase (PTPs) activity assays. Anti-PD-L1 antibodies atezolizumab and durvalumab were added to evaluate the location of regulation. In vivo experiments were carried out using xenograft mice implanted with parental, PD-L1 knock-out and PD-L1 overexpression NCI-H1975 cells. Osimertinib was orally administered to the mice until tumor progression to evaluate the impact of PD-L1 on osimertinib resistance. Progression-free survival (PFS) of the mice were compared using log-rank test and plotted on Kaplan-Meier curve. MET copy number variation was assessed by RT-PCR-based TaqMan assay.

Results: In human RTK array screening, c-MET phosphorylation was found to be increased in EGFR-mutant PD-L1 overexpression cells. We found that PD-L1 overexpression upregulated c-MET phosphorylation, while PD-L1 knock-out and knock-down resulted in downregulation of c-MET phosphorylation. Atezolizumab and durvalumab did not reduce c-MET phosphorylation in PD-L1 overexpression cells. Furthermore, we showed that PD-L1 upregulates c-MET phosphorylation by suppressing PTP activity. In xenograft mice, PFS was significantly shorter in mice implanted with PD-L1 overexpression tumor, compared with mice implanted with PD-L1 knock-out and parental NCI-H1975 tumor cells. MET amplification only developed in PD-L1 overexpression, but not in PD-L1 knock-out and parental NCI-H1975 cells, at the time of osimertinib resistance.

Conclusions: In EGFR-mutant NSCLC, PD-L1 regulates c-MET phosphorylation and promotes MET amplification, contributing to osimertinib resistance and shorter survival.

Keywords: programmed death-ligand 1, epidermal growth factor receptor mutation, MET alterations

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.05 The Study on the Mechanism of OM-85 in Regulating the Immune Microenvironment in Early-Stage Lung Adenocarcinoma

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Introduction: Early-stage lung adenocarcinoma (LUAD) in clinical practice predominantly manifests as ground-glass pulmonary nodules, exhibiting an incidence rate of 10%-20% in China, with about 5% progressing to invasive malignancy. Current management strategies are restricted to serial CT surveillance or invasive resection, lacking effective pharmacological interventions. OM-85 Broncho-Vaxom (BV), a standardized bacterial lysate with documented immunomodulatory capacity, was investigated for its therapeutic potential in remodeling the immune landscape of incipient LUAD, aiming to establish a paradigm for early pharmacological intervention.

Methods: A KrasG12DTgfbr2-/- (KT) genetically engineered mouse model recapitulating human early LUAD pathology was employed. Sixteen age-matched male mice (8-10 weeks) were randomized into two cohorts: Cohort A (vehicle control, PBS oral gavage) and Cohort B (OM-85 treatment). Longitudinal tumor dynamics were quantified via micro-CT volumetry and survival Kaplan-Meier analysis. Multi-parametric immunophenotyping (IHC/IF, flow cytometry) mapped immune infiltrate spatial-kinetic profiles. Systemic and compartmental immune responses were decoded through scRNA-seq of lung parenchyma and cytokine profiling (ELISA: peripheral blood, BALF). Functional validation included NK-tumor co-culture systems and transwell invasion-migration assays.

Results: OM-85 administration conferred significant survival advantage coupled with attenuated tumor burden. scRNA-seq unveiled clonal expansion of CX3CR1+NK cells within tumor niches, exhibiting enriched cytokine-cytotoxic effector pathways. In vitro, OM-85-primed NK cells demonstrated CX3CR1/IFN-γ axis activation, which mediated potent suppression of LKR cell invasiveness. CX3CR1 knockdown abrogated OM-85's anti-tumor efficacy.

Conclusions: OM-85 orchestrates tumor-immune crosstalk by potentiating CX3CR1+NK cell effector functions, characterized by IFN-γ-driven suppression of metastatic priming and stromal remodeling. This study mechanistically deciphers how oral OM-85 administration restrains early LUAD progression via NK-centric immunomodulation, proposing a novel oral immunomodulatory regimen for intercepting premalignant evolution.

Keywords: early-stage lung adenocarcinoma, bacterial lysate products, NK cells

EP.03.06 Blocking JNK Signaling as a Strategy to Fight EGFR-Driven Lung Cancer

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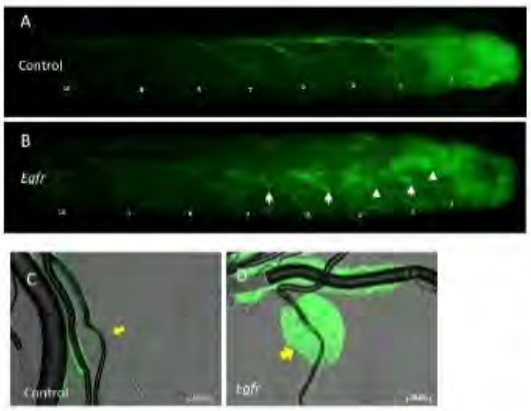
Introduction: Mutations in the Egfr gene are among the most important drivers of lung tumor development. However, the success of personalized therapies still needs to be improved due to the development of resistance. We comprehensively analyzed the signaling pathways involved in tumor development in a tailored Drosophila model to identify novel intervention stategies.

Methods: In suitable Drosophila models, tumors were induced by constitutive activation of the EGFR receptor, and both tumor volume and survival rate or mean survival time were quantified.

Results: Our research underscores the pivotal role of the EGFR-activated signaling system in tumor growth. Through targeted genetic and pharmacological interventions, we demonstrated the significant contributions of different arms of this system, the canonical MAPK pathway and the PI3K/Akt pathway. The JAK/STAT pathway emerged as a critical factor in cancer cell migration. Notably, JNK inhibition via RNAi or dominant-negative constructs significantly reduced tumor growth (6.92-fold decrease in T6 tracheoblast area, $p < 0.0001$), suppressed proliferation, and promoted apoptosis. Importantly, our findings indicate that the JNK pathway acts as a central coordinator of these signaling pathways, influencing their activation. This aligns with our observation that JNK signaling blockade can be effective in inhibiting tumor growth.

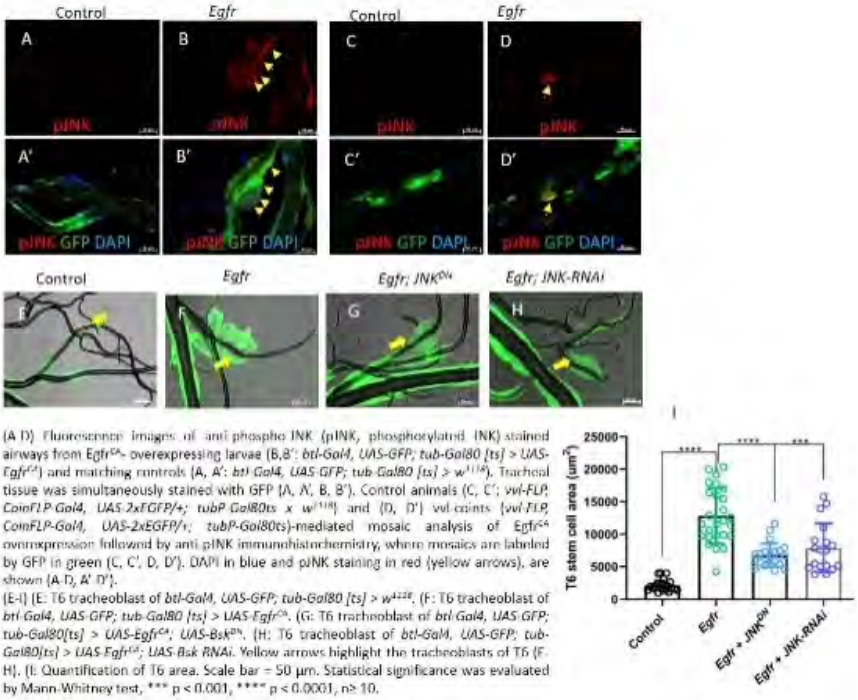
Conclusions: The implications of our findings are promising, a targeted, intelligent combination therapy focusing on different signaling pathways could be a highly effective approach for treating lung tumor patients. Notably, the inclusion of JNK inhibition holds particular potential.

Figure 1. Targeted expression of an Egfr induced larval death and tumor-like growth of tracheal stem cells



(A) *btl-Gal4, UAS-GFP; tub-Gal80[ts] > w[1118]*.
(B) *btl-Gal4, UAS-GFP; tub-Gal80[ts] > UAS-Egfr[CA]*. White arrows highlight tumor-like growths of tracheoblasts. White arrows highlight tumor-like growths of tracheoblasts.
(C) T6 tracheoblast from (A). (D) T6 tracheoblasts from (B). Yellow arrows highlight the tracheoblasts of T6.

Figure 2. Ectopic expression of Egfr activates the JNK signaling and blocking the JNK inhibits the growth of Egfr-induced tumors



(A-D) Fluorescence images of anti phospho JNK (pJNK, phosphorylated JNK) stained airways from Egfr[CA]- overexpressing larvae (B,B': *btl-Gal4, UAS-GFP; tub-Gal80 [ts] > UAS-Egfr[CA]*) and matching controls (A, A': *btl-Gal4, UAS-GFP; tub-Gal80 [ts] > w[1118]*). Tracheal tissue was simultaneously stained with GFP (A, A', B, B'). Control animals (C, C'; *vvl-FLP, CoinFLP-Gal4, UAS-2xEGFP/+; tubP-Gal80ts x w[1118]*) and (D, D') vvl-cells (*vvl-FLP, CoinFLP-Gal4, UAS-2xEGFP/+; tubP-Gal80ts*)-mediated mosaic analysis of Egfr[CA] overexpression followed by anti pJNK immunohistochemistry, where mosaics are labeled by GFP in green (C, C', D, D'). DAPI in blue and pJNK staining in red (yellow arrows), are shown (A-D, A'-D').
(E-I) (E: T6 tracheoblast of *btl-Gal4, UAS-GFP; tub-Gal80 [ts] > w[1118]*. (F: T6 tracheoblast of *btl-Gal4, UAS-GFP; tub-Gal80 [ts] > UAS-Egfr[CA]*. (G: T6 tracheoblast of *btl-Gal4, UAS-GFP; tub-Gal80[ts] > UAS-Egfr[CA]; UAS-Bsk[DN]*. (H: T6 tracheoblast of *btl-Gal4, UAS-GFP; tub-Gal80[ts] > UAS-Egfr[CA]; UAS-Bsk RNAi*. Yellow arrows highlight the tracheoblasts of T6 (F-H). (I: Quantification of T6 area. Scale bar = 50 µm. Statistical significance was evaluated by Mann-Whitney test, *** $p < 0.001$, **** $p < 0.0001$, $n \geq 10$.

Keywords: EGFR, JNK signaling, Drosophila model

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.07 The Role of Tumour Intrinsic Inflammasome Mutations in Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma (LUAD) is the most common form of lung cancer and the leading cause of cancer related death. In 2017, immune checkpoint inhibitors (ICI)s were approved as part of the front-line LUAD treatment regime. However, only about 20% of non-stratified LUAD patients respond to ICI monotherapy, and predicting the response of individual patients remains challenging. The innate immune system is critical and necessary for maturation and activity of the adaptive immune system and offers opportunities to enhance the response to ICIs. Indeed, the importance of the innate immune cytokine, IL-1b in the development of LUAD was revealed by the phase III CANTOS trial which recorded a staggering 67% and 77% reduction in lung cancer incidence and mortality respectively. However, IL-1b neutralization in patients with existing LUAD failed to meet primary efficacy endpoints. Together this highlights the potential of harnessing the innate immune system in the treatment of LUAD but to do so requires a deep understanding of the inflammatory environment throughout the development of LUAD.

Methods: We combine patient data with autochthonous mouse models of LUAD and spatial transcriptomics to interrogate the importance of the inflammasome in Kras driven LUAD development.

Results: Our data show activating mutations in the inflammasome are prevalent in LUAD, which are accompanied by transcriptomic changes in tumor microenvironment. Tumor intrinsic deletion of the inflammasome significantly delays disease onset.

Conclusions: The inflammasome plays a key role in the development of lung adenocarcinoma and offers a novel therapeutic opportunity.

Keywords: Lung Adenocarcinoma, Innate immunology, Inflammasome

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.08 Tumor Treating Fields (TTFields) Concomitant With Antiangiogenic Therapy in Non-Small Cell Lung Cancer in Vivo Model

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Introduction: Angiogenesis is a hallmark of disease progression and poor prognosis in non-small cell lung cancer (NSCLC). Ramucirumab, an antiangiogenic antibody that binds the vascular endothelial growth factor receptor (VEGFR), is approved as second line treatment for metastatic NSCLC, in combination with docetaxel. Angiogenic inhibitors function by normalizing tumor vasculature, hence improving drug delivery and immune cell infiltration to the tumor. Tumor Treating Fields (TTFields) are electric fields that disrupt cellular processes critical for cancer cell survival. TTFields therapy, together with immune checkpoint inhibitors or docetaxel, is approved for treatment of metastatic NSCLC following progression on or after platinum-based therapy. In the current study, we examined the effects of TTFields concomitant with docetaxel and anti-VEGFR treatment in an orthotopic NSCLC mouse model.

Methods: C57Bl/6 mice were injected orthotopically with LL/2 lung carcinoma cells, and tumors were allowed to grow for 7 days. The mice were then treated with TTFields (150 kHz) or sham (heat) continuously for 8 days. Vehicle or the murine anti-VEGFR DC101 (10mg/kg) were intraperitoneally administered on days 1, 4, and 7 of treatment. Vehicle or docetaxel (3mg/kg) were intraperitoneally administered on days 2, and 6 of treatment. Overall, there were 6 study groups: control, docetaxel alone, docetaxel plus DC101, TTFields alone, TTFields plus docetaxel, and TTFields plus docetaxel plus DC101. At treatment end, tumors were weighed and analyzed by immunohistochemistry, with anti-CD31 for vessel staining and additional functional markers.

Results: TTFields concomitant with docetaxel and DC101 significantly decreased tumors size relative to all other treatment groups. Tumors from this treatment group also presented with higher levels of apoptosis, as indicative from TUNEL assay. Staining for αSMA and CD8 demonstrated, respectively, that the blood vessels of these tumors were more mature and allowed for increased tumor infiltration of cytotoxic T cells.

Conclusions: TTFields application alongside docetaxel and an anti-VEGFR antibody increased treatment efficacy via normalization of tumor blood vessels, which allowed for increased tumor immune cell infiltration and presumably elevated tumor drug delivery.

Keywords: Tumor Treating Fields, NSCLC, anti-VEGFR

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.09 A New Treatment Approach for Non-Small Cell Lung Cancer

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Introduction: Lung cancer is the leading cause of cancer related deaths worldwide. Non-small cell lung cancers (NSCLC) account for 85-90% of all lung cancers. Despite recent advances in NSCLC therapies, the majority of patients with advanced disease ultimately relapse. Genomic instability is a hallmark of all cancers. To prevent cancer, cells possess a complex network of signalling pathways called the DNA damage response (DDR), which is involved in the detection, signalling, and repair of DNA. Failure of the DDR leads to cancer and tumorigenesis. Here we provide the first stages of development for a novel DDR-targeting therapeutic for the treatment of NSCLC.

Methods: Molecular dynamics, together with in vitro binding and site directed mutagenesis were used to identify the binding pose regulating chromatin remodelling, that is required for the efficient repair of DNA damage by the DDR. Based on the identified binding pose, we have developed a first-in-class small molecule inhibitor. On-target activity of this small molecule inhibitor was determined using cell viability, DNA repair and apoptosis assays. In vivo validation was additionally performed in a preclinical model of NSCLC.

Results: In-silico molecular dynamics, in vitro binding and site directed mutagenesis identified the binding pose regulating chromatin remodelling, that is required for the efficient repair of DNA damage. Using this data, a small molecule inhibitor was developed. Treatment with the inhibitor induced cell death and apoptosis of NSCLC cells in vitro and significantly reduced tumour growth in a preclinical model of NSCLC.

Conclusions: Our results demonstrate the early stages of development for a novel DDR-targeting therapeutic for the treatment of NSCLC, which would have applicability in the most aggressive and genetically unstable lung cancers.

Keywords: Non-small cell lung cancer, DNA damage response, Novel therapeutic

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.10 Evaluating the Role of the Blood-Brain Barrier in Intracranial Response Rates for Metastatic Lung Cancer

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Introduction: Lung cancer is the second most common cancer overall and the leading cause of cancer death worldwide, as well as the most common cause of brain metastases (BMs) with reported prevalences of 10-20%.Drug delivery to normal brain tissue is limited by the blood-brain barrier (BBB). For this reason, systemic therapies are thought to be less effective for BMs than other disease sites. Many clinical trials exclude patients with BMs or require them to be stable after localized therapy.There is evidence that the BBB is disrupted in the setting of BMs and substances normally minimally detectible in normal brain tissue can achieve significant concentrations in BMs. This raises the question of whether response rates in lung cancer BMs are significantly different from other sites of disease.

Methods: We conducted a literature search to determine reported intracranial response rates for drugs or combination regimens used to treat metastatic lung cancer, as well as extracranial or overall response rates where available. The predicted penetration of each drug through an intact BBB was evaluated based on its molecular size, chemical properties, affinity for efflux transporters, and testing of cerebrospinal fluid and brain tissue samples in animal models (and human samples, where available), then rated as none (zero), poor (<5% systemic concentrations), low (5-10%), moderate (10-50%), good (50-80%), or excellent (80%-100%+).

Results: We reviewed 31 prospective and retrospective studies from 1989-2025 reporting intracranial response rates to systemic therapies for small cell and non-small cell lung cancer, as well as 10 studies or reviews discussing drug penetration through the BBB. Predicted BBB penetration for different agents ranged from none for monoclonal antibodies to excellent for certain targeted therapies. Across drug classes and lines of therapy, intracranial response rates were generally comparable to, or higher than, extracranial or overall response rates, regardless of predicted brain penetration.

Conclusions: Regardless of predicted brain penetration, systemic agents demonstrated comparable intracranial response rates to extracranial or overall response rates. This has important implications in drug and clinical trial design, suggesting that research should aim for maximum overall response rates rather than increased brain penetration and that the exclusion of patients with asymptomatic, untreated brain metastases from clinical trials is unwarranted.

CHEMOTHERAPY					
REGIMEN (LUNG CANCER SUBTYPE, IF ANY)	Line of therapy	Intracranial response rate (%)	Extracranial response rate (%)	Overall response rate (%)	Trial
SCLC					
CYCLOPHOSPHAMIDE, VINCRISTINE, ETOPOSIDE	1[st]	53			Twelves et al. 1990[7]
ETOPOSIDE, CYCLOPHOSPHAMIDE, VINCRISTINE, DOXORUBICIN	1[st]	82	75		Lee et al. 1989[8]
CARBOPLATIN	2[nd]/3[rd]	40	25		Kouri et al. 1993[9]
TOPOTECAN	2[nd]+	33	57		Kortei et al. 2002[10]
TENIPOSIDE	1[st]	22	20		Postmus et al. 2000[11]
NSCLC					
CARBOPLATIN, PACLITAXEL, GEMCITABINE OR VINORELBINE	1[st]	38	50		Cortes et al 2003[6]
CISPLATIN, TENIPOSIDE	1[st]	35			Minotti et al. 1988[7]
CISPLATIN, IFOSFAMIDE, IRINOTECAN		50	62		Fujita et al. 2000[8]
CISPLATIN, VINORELBINE	1[st]	27	35		Lee et al. 2008[9]
CISPLATIN, PEMETREXED	1[st]	42	36		Barlesi et al. 2011[10]
CARBOPLATIN, PEMETREXED	1[st]	40	17		Bailon et al. 2012[11]
IMMUNOTHERAPY					
REGIMEN (LUNG CANCER SUBTYPE, IF ANY)	Line of therapy	Intracranial response rate (%)	Extracranial response rate (%)	Overall response rate (%)	Trial
PEMBROLIZUMAB (PD-L1 >1%)	Any*	30	30		Goldberg et al 2020[12]
PEMBROLIZUMAB +/- CHEMOTHERAPY	Any	36		28	Sun et al. 2021[13]
PEMBROLIZUMAB (PD-L1 ≥ 50%)	1[st]	62		37.5	Metro et al. 2020[14]
PEMBROLIZUMAB (PD-L1 ≥ 50%)	1[st]	60		57	Wakuda et al. 2020[15]
PEMBROLIZUMAB (PD-L1 ≥ 50%)	1[st]	35.5		47	Descourt et al. 2023[17]
NIVOLUMAB	2[nd]+	9	11		Gauvain et al. 2018[16]
ATEZOLIZUMAB, CARBOPLATIN, PEMETREXED	1[st]	43		45	Nadal et al. 2023[18]
PD-1/PD-L1 BLOCKADE AS MONOTHERAPY	Any	16.4			Teixeira 2021[19]
TARGETED THERAPY					
REGIMEN (LUNG CANCER SUBTYPE, IF ANY)	Line of therapy	Intracranial response rate (%)	Extracranial response rate (%)	Overall response rate (%)	Trial
OSIMERTINIB (EGFR MUTATED)	2[nd]+	32			Xie et al. 2019[21]
OSIMERTINIB (EGFR MUTATED)	1[st] 2[nd] T790M mutation 2[nd] no T790M mutation	84 67 50	74 67 20		Peled et al. 2022[22]
OSIMERTINIB (EGFR MUTATED, WITH BM)	1[st]			76	Soria et al. 2018[23]
(NO BM)				81	
GEFITINIB OR ERLOTINIB (EGFR MUTATED, WITH BM)				66	
(NO BM)				73	
LORLATINIB (ALK POSITIVE)	1[st]	66		76	Shaw et al. 2020[24]
CRIZOTINIB (ALK POSITIVE)		20		58	
ALECTINIB (ALK POSITIVE)	1[st]	50		83	Peters et al. 2017[25]
CRIZOTINIB (ALK POSITIVE)		50		76	
BRIGATINIB (ALK POSITIVE)	1[st]	79		97	Camidge et al. 2018[26]
CRIZOTINIB (ALK POSITIVE)		23		83	
CRIZOTINIB (ALK POSITIVE)	2[nd]	18	53		Costa et al. 2015[27]
CRIZOTINIB (ALK POSITIVE)	1[st]/2[nd]	20	66		Yoshida et al. 2016[28]
CRIZOTINIB (ROS1 POSITIVE, WITH BM)	1[st]			77.8	Zhang et al. 2021[29]
(NO BM)				87.8	
TEPOTINIB (MET EXON 14 SKIPPING)	2[nd]+	55		56	Paik et al. 2020[30]
ADAGRASIB (KRAS G12C)	2[nd]+	33		43	Jänne et al 2022[31]

*Immunotherapy naive

Keywords: brain metastases, Blood-brain barrier, intracranial response

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.11 Peritumoral B Lymphocyte Mediated Immune Response Is Associated With Survival in Patients With Non-Small Cell Lung Cancer

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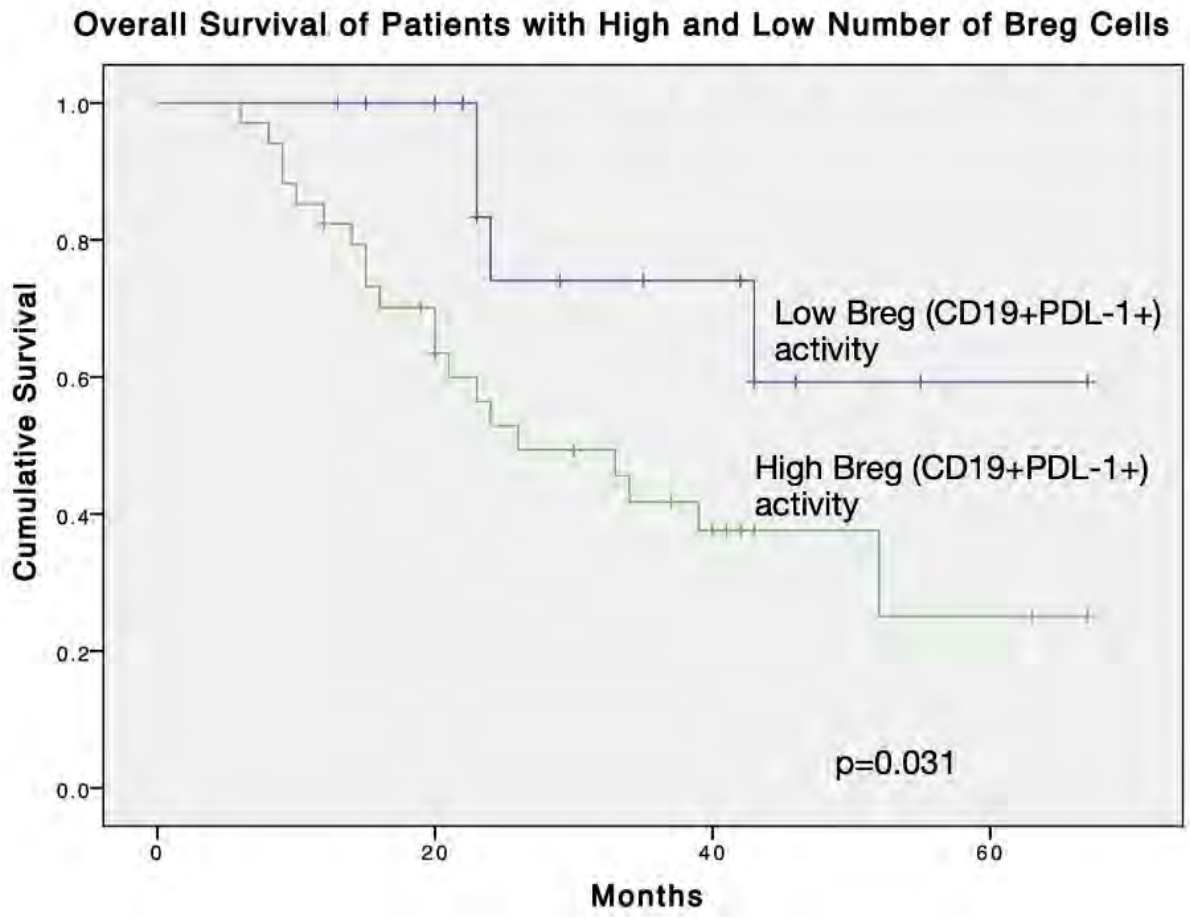
Introduction: Tumor-infiltrating immune cells play a significant role in the promotion or inhibition of tumor growth. As an integral component of the tumor microenvironment, tumor-infiltrating B lymphocytes and T lymphocytes exist and play important roles in shaping tumor development. We aimed to evaluate the T cell and B cell mediated immune microenvironment to find an association between survival and certain immune cell subpopulations.

Methods: : A total of 55 patients who underwent surgical resection from October 2018 to July 2023 with the diagnosis of stage IA to IIB non-small cell lung cancer (NSCLC) were enrolled. Samples from tumor, mediastinal lymph nodes, healthy lung tissue and peripheral blood were collected from all patients. Lymphocytes were isolated from the blood and the tumor mass. Different T and B lymphocyte phenotypes and functions were analyzed. Quantitative PCR was used to measure EBI3, IL-12p35 IL-10, LGALS1 and MAF mRNA expression.

Results: The mean age of all patients was 63.7 ± 7.8 years and 47 (85.5%) of them were male. The most common resection type was lobectomy (n=42, 76.3%) and histopathological diagnosis revealed adenocarcinoma in 17 (30.9%) cases. There was no significantly significant difference in terms of total T lymphocyte number and cytotoxicT lymphocytes between healthy tissue and tumor tissue. CD19+ B cells from the tumor tissue showed significantly higher PD-L1 expression(i.e. B regulatory cells) (14.5% ± 2.9%) compared to CD19+ B cells from healthy tissue (HT) and mediastinal lymph nodes (mLN), which exhibited PD-L1 expression levels of 7.0 ± 1.5% and 7.2 ± 1.7%, respectively($p<0.001$). Bregs cells were found to be significantly higher in mediastinal lymph nodes and peripheral blood of the patients with NSCLC. Higher activated T lymphocytes was associated with better survival ($p=0.011$) in mediastinal lymph nodes. In addition, CD3+ PD-L1+ T cells in the tumor($p=0.039$), lower number and activity of Breg cells in peripheral blood($p=0.031$)were significantly associated with better survival(Figure).

Conclusions: The anti-tumor immune response seemed to be closely associated with postoperative oncological outcomes. Particularly regulatory B lymphocytes, appear to play a role in anti-tumor immunity and survival. Future immunotherapeutic strategies may also target B lymphocytes to enhance treatment outcomes



Keywords: Lung cancer, B lymphocytes, Anti-tumor immunity

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.12 Sex-Specific Blood-Based Immune Signatures Predict Response to First-Line Immunotherapy in Advanced NSCLC: A Prospective Translational Study

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Introduction: Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have emerged as a cornerstone in the management of advanced non-small cell lung cancer (NSCLC) without identifiable actionable oncogenic drivers. Despite these advances, durable responses remain confined to a minority of patients, and PD-L1 expression alone is an insufficient predictive biomarker. Emerging evidence indicates that biological sex may influence antitumor immune responses and modulate the efficacy of ICIs, although the underlying biological mechanisms remain poorly understood.This study aims to investigate sex-specific circulating immune-inflammatory biomarkers associated with response to ICI-based therapy in NSCLC.

Methods: This is a prospective, single-center, observational translational study conducted in a real-world clinical setting. The study plans to enroll 100 patients (50 males, 50 females) with advanced or unresectable, EGFR/ALK-wildtype NSCLC, ECOG performance status 0-2, initiating first-line treatment with either ICI monotherapy or ICI combined with platinum-doublet chemotherapy. Peripheral blood samples are collected at three predefined timepoints: (1) baseline (prior to treatment), (2) first radiologic assessment (approximately 6-9 weeks post-treatment initiation), and (3) radiologically confirmed disease progression. Cytokine profiling is performed using the Q-Plex™ Human Cytokine Inflammation Panel, targeting nine cytokines (IFNγ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNFα). The primary endpoint is the association between baseline cytokine levels and objective response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), immune-related adverse events (irAEs), and longitudinal cytokine dynamics. All analyses will be stratified by sex to explore sex-specific immune correlates.

Results: As of the current reporting period, patient enrollment and biospecimen collection are ongoing. No clinical or biomarker analyses are available at this time. Cytokine and outcome analyses will be conducted upon completion of enrollment and sufficient follow-up. At this first interim analysis, 35 patients have been enrolled: 15 (43%) female, 28 (80%) with adenocarcinoma histology, 27 (77%) received pembrolizumab plus platinum-based chemotherapy, and 8 (23%) received ICI monotherapy.

Conclusions: This study aims to define sex-specific circulating immune-inflammatory profiles associated with response to first-line immune checkpoint inhibition in advanced NSCLC. By integrating cytokine profiling with longitudinal clinical outcomes in a sex-balanced cohort, the results are expected to contribute to the identification of predictive biomarkers that reflect differential immune dynamics by sex. These findings may ultimately support more refined, biomarker-driven treatment algorithms and promote sex-informed personalization of immunotherapy strategies in routine clinical practice.

Keywords: Non-small cell lung cancer, Sex-Based Immunobiology, immune check point inhibitors

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.13 LIF Is Associated With Poor Prognosis and Participates in Lung Cancer Growth and Implantation in Preclinical Models of NSCLC

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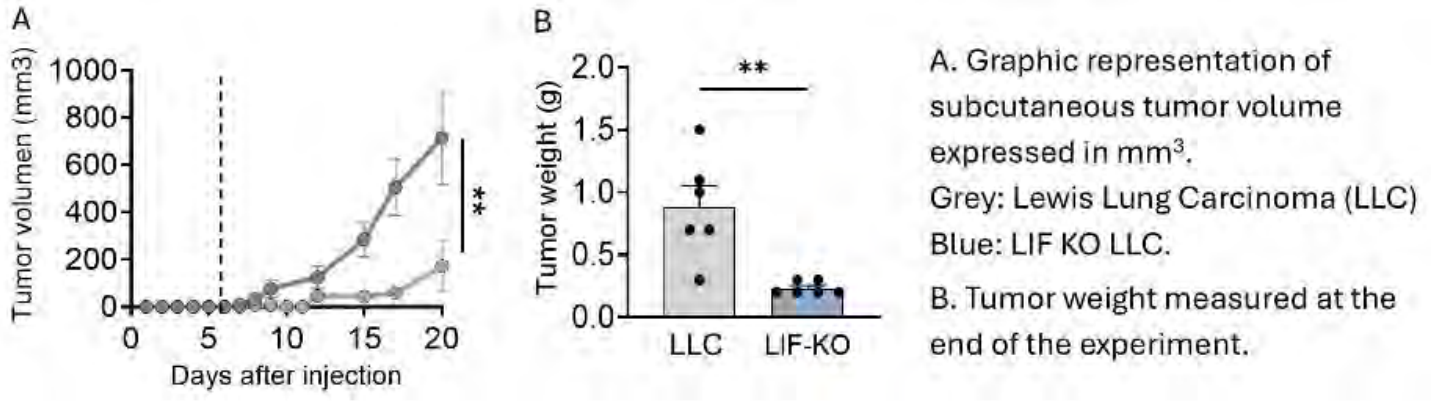
Introduction: LIF is a cytokine with multiple pro-tumorogenic roles. It maintains stemness, immune suppression and promotes cachexia. LIF expression is regulated by oncogenic pathways like KRAS, and it is involved in lung pathologies like fibrosis. We hypothesized that LIF may be a good target against NSCLC.

Methods: LIF mRNA expression was correlated with prognosis using the TCGA dataset and Cox proportional hazards models. A549, SW900, H460, H1299, H2126 cell lines were analyzed in culture. The murine Lewis Lung Carcinoma cell line (LLC) deficient in LIF was generated via CRISPR. LLC were injected subcutaneously or via tail vein in B6 mice. Expression of markers in murine tumors was analyzed by qPCR.

Results: LIF expression was significantly associated with worse overall survival (OS) in LUSC (HR = 1.25 (1.02-1.52)) after adjusting for disease stage. A similar association was observed in LUAD, although not statistically significant (HR = 1.17 (0.97-1.42). We analyzed expression and secretion of LIF in murine LLC and Human NSCLC cell lines. Secreted levels of this cytokine were heterogeneous in several cell lines in culture (25-700 pg/ml) and they were increased by placing cells under glucose starvation or hypoxia (125-1000 pg/ml). LIF-deficient LLC grew in culture at the same rate than the parental cells. However, cells injected subcutaneously in mice developed smaller tumors in the absence of LIF (0.88±0.41g versus 0.23±0.05g). In a subsequent experiment injecting cells through the tail vein, 15 of 20 mice injected with WT LLC developed tumors in the lung, while only 1 out of 20 mice developed tumors with LIF KO LLC cells. Analysis of cytokine and immune markers revealed significantly lower IL-6, neutrophils, E-selectin and CD163 in LIF-low tumors, consistent with less innate immune, pro-tumoral infiltration. Conversely, tumors with basal levels of LIF (WT LLC) displayed more Interferon gamma and CD8, suggesting a higher immune response when LIF is reduced.



Conclusions: LIF, which levels are increased by glucose deprivation and hypoxia, leads to larger tumors, immune suppression and more implantation of Lewis Lung Carcinoma in lungs of mice. Since several drugs targeting LIF or its receptor are being tested in clinical trials, we propose that LIF could potentially be a good target against NSCLC which could improve immune clearance and reduce tumor growth.

Keywords: LIF, Cytokines

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.14 Single-Cell Transcriptome Analysis Revealed an Activated Tumor Immune Microenvironment in KRAS Mutant NSCLC

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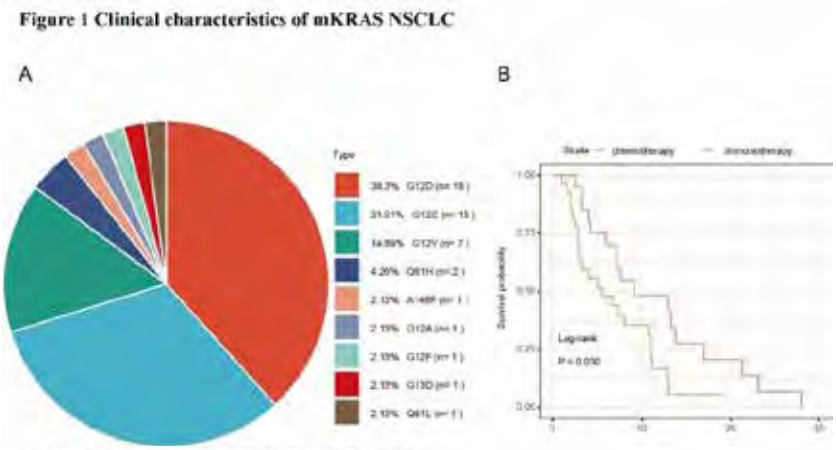
Introduction: Patients with KRAS-mutated(mKRAS) advanced non-small cell lung cancer (NSCLC) have a poor prognosis and immunotherapy is an effective treatment option. High expression of PD-L1 is an underlying mechanism, but the role of the tumor microenvironment(TME) related to immunotherapy has been little studied.

Methods: We enrolled a total of 47 NSCLC patients with KRAS mutations, 20 receiving first-line immunotherapy and 27 receiving first-line chemotherapy, and performed survival analysis. Single-cell RNA sequencing data from 10 mKRAS and 13 wild-type KRAS mutations(wtKRAS) were simultaneously integrated to explore differences in the immune microenvironment.

Results: Among 47 patients with mKRAS NSCLC, the most common KRAS mutation subtypes were G12D and G12C, with mutation rates of 38.30% and 31.91%, respectively(Figure 1A). The median PFS for patients receiving immunotherapy in the first-line setting was 9.10 (95% CI: 7.10-21.30) months, while the median PFS for patients receiving chemotherapy in the first-line setting was 5.63 (95% CI: 3.00-11.00) months, with a P-value of 0.030 and an HR value of 0.467 (95% CI: 0.235-0.928) (Figure 1B). Compared with wtKRAS NSCLC, tumor-infiltrating lymphocytes (B lymphocytes and T lymphocytes) were significantly increased in mKRAS NSCLC(Figure 2A-B). PDCD1, LAG3, and HAVCR2 were significantly enriched in mKRAS NSCLC(Figure 2C). The proportion of Tissue Resident Memory(TRM) CD8+T cell and Naïve CD8+T cell were prevalent in mKRAS NSCLC, while regulatory CD4+ T (Treg) cell was dominant in wtKRAS NSCLC(Figure 2D-E).

Conclusions: Our results offer a comprehension of the single-cell immunological landscape of mKRAS NSCLC. Enrich of CD8+ TRM and lack of CD4+ Treg might be key factors responsible for the active TME of mKRAS NSCLC.



Keywords: non-small cell lung cancer, immunotherapy, scRNA

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.15 Chemotherapy Upregulates PD-L1 Expression via cGAS-STING Pathway in Non-Small Cell Lung Cance

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Introduction: Expression of Programmed Cell Death Ligand 1 (PD-L1) is a key albeit incomplete predictive biomarker of response to anti-PD-1/PD-L1 inhibitors. Superior clinical efficacy of PD-1/PD-L1 inhibitors is mainly observed in patients with high PD-L1 tumour expression (KEYNOTE-024, KEYNOTE-042). We hypothesize that approaches modulating PD-L1 expression may prove useful in utility of anti-PD-1/PD-L1 inhibitors. Here we show that chemotherapy can upregulate the expression of PD-L1 through the activation of cGAS-STING pathway in NSCLC.

Methods: NSCLC cell lines including A549, MGH7, HCC4006, H226, H1944, and H2122 were treated with cisplatin at varying doses and time points. CRISPR-Cas9 mediated STING knock-out cell lines were generated and treated with cisplatin. MGH7 and A549 cells were treated with cGAMP (10ug) and poly (dA:dT = dsDNA); activators of STING and cGAS, respectively and ruxolitinib, a JAK1/2 inhibitor. Expression of PD-L1 and markers of cGAS-STING pathway were analyzed by western blot and flow cytometry.

Results: Treatment of NSCLC cell lines including A549, MGH7, HCC4006, H226, H1944, and H2122 with cisplatin showed upregulation in PD-L1 expression in a dose and time dependent manner. In addition to cisplatin, pemetrexed, docetaxel, and gemcitabine also led to PD-L1 upregulation in A549 and MGH7 cell lines. This upregulation in PD-L1 expression was sustained after a 72-hr drug holiday post-treatment. These findings were validated in-vivo in three NSCLC patient-derived xenograft (PDX) models, which also showed PD-L1 protein upregulation after 3, 10, and 17 days of cisplatin treatment. For the mechanistic studies, A549 and MGH7 cell lines were selected due to their diverse baseline expression of PD-L1 with A549 being ~1% positive and MGH7 being ~85% positive. After cisplatin treatment, MGH7 and A549 cells showed an upregulation of the cGAS-STING pathway markers including cGAS, p-STING, p-TBK, and p-H2AX, a marker of DNA damage. When STING knock-out A549 and MGH7 cells were treated with cisplatin, there was no increase in PD-L1 expression as compared to the wild-type cells confirming the role of this pathway in modulating PD-L1 expression. Untreated STING knock-out A549 and MGH7 cells also showed reduced PD-L1 expression as compared to the wild type cells indicating that cGAS-STING pathway regulates PD-L1 expression at baseline. Additionally, treatment of A549 and MGH7 cells with cGAS agonist poly (dA:dT) and STING agonist cGAMP also increased PD-L1 protein expression. When treated with a combination of ruxolitinib (JAK1/2 signalling inhibitor) and cGAMP/poly (dA:dT), PD-L1 upregulation was abrogated suggesting that JAK-STAT pathway works downstream of cGAS-STING signalling to regulate PD-L1 expression.

Conclusions: Cytotoxic chemotherapies used to treat NSCLC patients induce PD-L1 expression via the activation of cGAS-STING pathway in NSCLC. This study also indicates that the chemotherapy treatment alone can possibly contribute to drug resistance by upregulating PD-L1 and promoting immune evasion, emphasizing the need for subsequent anti-PD-1/PD-L1 treatment. Further research is necessary to validate this hypothesis.

Keywords: PD-L1, Chemotherapy, cGAS-STING

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.16 Cell-Specific Fluorescence Lifetime Values in Live Non-Small Cell Lung Cancer Cells

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Introduction: There is a need for early diagnosis in NSCLC. Fluorescence lifetime imaging (FLIM) is a translational technique that measures endogenous autofluorescent decay rates reflecting intrinsic metabolic activity. Fernandes et al1 have shown that fluorescence lifetime values are lower in NSCLC compared to adjacent non-tumour lung. However, the underlying source and heterogeneity of FLIM signals is not known at a cellular level. We utilise FLIM to understand the cell-specific FLIM signals within live tumour and non-tumour lung tissue.

Methods: Fresh NSCLC and adjacent non-tumour lung samples were obtained from consented patients undergoing surgical resection. Samples were digested to single-cell suspensions and used to establish 3D epithelial and tumour organoids as well as 2D cancer associated fibroblast (CAF) cultures. PBMCs were isolated from blood from consented patients. Label-free fluorescence lifetime imaging was performed using a laser scanning confocal microscope (STELLARIS FALCON, Leica Microsystems). Samples were excited at 488nm with an emission range of 498-596nm. FLIM images were analysed using cell-specific ROIs to quantify mean autofluorescence lifetimes.

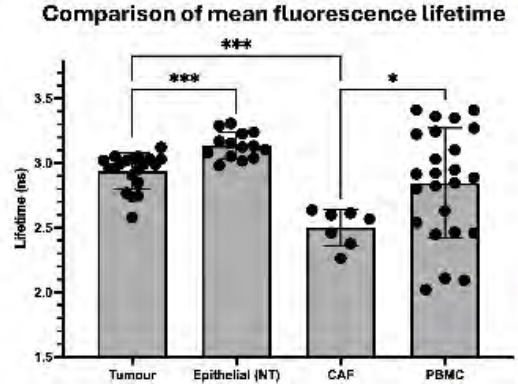
Results: 10 patient-derived samples were used, encompassing adenocarcinoma, squamous cell carcinoma and pleomorphic cell carcinoma, as well as one non-tumour tissue sample (Figure 1A). FLIM images revealed consistent morphology in CAFs and tumour cells, while PBMCs displayed more varied morphology (Figure 1B-D). Phasor analysis demonstrated similar vector plots across cell types, but greater variance in fluorescence lifetime of PBMCs compared to CAFs and tumour cells. All cell types showed a bi-exponential decay curve fit, with chi-squared values within an optimal range of 0.9-1.6. Following quantification across multiple ROIs and fields of view, tumour cells displayed significantly longer fluorescent lifetimes compared to CAFs, and similarly CAFs demonstrated significantly shorter fluorescence lifetimes compared to PBMCs (p=0.0002 and 0.0124, respectively). Fluorescent lifetimes of tumour cells and PBMCs showed no significant differences (Figure 1F). Interestingly, epithelial cells derived from non-tumour organoids from a single patient demonstrated a significantly higher FLIM signal than tumour cells derived from squamous cell carcinoma and pleomorphic cell carcinoma organoids (mean 3.137ns vs 2.940ns, p=0.0002).

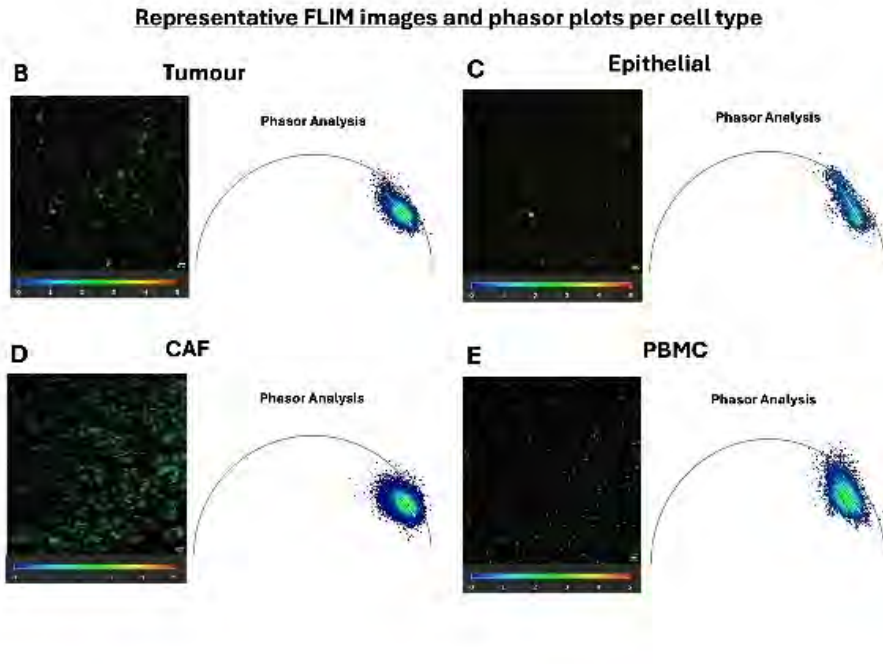
Conclusions: We demonstrate that primary human NSCLC displays cell-specific FLIM signals across patient samples. This forms the basis of enhancing our understanding of the constitutive makeup of FLIM signals in NSCLC. Further work will include increasing data across these cell types, subtyping immune cell populations and quantifying changes to FLIM according to targeted metabolic disruption using immunotherapeutic factors.

1. https://dx.doi.org/10.21037/tlcr-23-638

A **Patient cohort demographics**

Age	Sex	Tumour	Stage
68	F	Squamous Cell Carcinoma	pT2N0
64	F	Adenocarcinoma	pT2bN0
68	F	Adenocarcinoma	pT2aN0
55	M	Squamous Cell Carcinoma	pT4N2
61	F	Adenocarcinoma	pT2AN0
69	M	Adenocarcinoma	pT2aN0
46	M	Adenocarcinoma	pT2aN2
73	M	Giant Cell Pleomorphic Carcinoma	pT4 N1
56	M	Squamous Cell Carcinoma	pT2aN0
81	M	Squamous Cell Carcinoma	pT2aN0





Keywords: Fluorescence Lifetime Imaging, Patient-Derived Samples, Organoid Culture

EP.03 TUMOR BIOLOGY – TRANSLATIONAL BIOLOGY

EP.03.17 Altered Immune Profile in Lung Cancer Patients With Pneumonitis

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Introduction: Certain patients receiving immunotherapy experienced various degree of immune-related adverse events (irAEs), and pneumonitis is one of the most concerned irAEs. Clinical risk factors for pneumonitis include squamous cell carcinoma, preexisting interstitial lung disease, chronic obstructive lung disease and elder patients. Other immunological biomarkers of irAEs include elevated activated CD4+ and CD8+ T cells, lower regulatory T cells (Treg) and lower myeloid derived suppressor cells (MDSCs), and result in loss of self-tolerance and active T cells targeting healthy tissues. The real-world data of comprehensive immune profile of patients with pneumonitis irAE is few and we showed the immune profile of two lung cancer patients with pneumonitis.

Methods: We prospectively collected peripheral blood from advance lung cancer patients before receiving immunotherapy. PBMC were isolated and peripheral blood immune cell, including CD4, CD8, NK, NKT and MDSCs, were analyzed by flow cytometry thoroughly.

Results: From Jan 2024 to Dec 2024, seven lung cancer patients were enrolled before receiving immunotherapy. Three patients received adjuvant immunotherapy, and others were received chemotherapy with immunotherapy as advanced lung cancer treatment. Two of seven patients had grade 2 pneumonitis, one receiving adjuvant immunotherapy and another first line chemotherapy with immunotherapy. These two patients with pneumonitis, both had higher activated CD4 and CD8 T cells (CD4+TNF-α, CD4+IFN-γ, CD8+TNF-α+, CD8+IFN-γ+) and less MDSC (CD14+S100A9+). Besides these well-known immune cells, these two patients also had higher CD8+PD-1+ T cells but similar CD4+PD-1+/CD4+TIGIT+/CD8+TIGIT+ level. After using steroid and stop immunotherapy, pneumonitis of both patients was controlled. After stopping immunotherapy, these two patients eventually had disease progression.

Conclusions: Pneumonitis, a relative uncommon but important irAE, is difficult to predict. In this report, we showed that possible biomarker candidates with activated CD4 and CD8 T cells, MDSC, and CD8+PD-1+. Further study of validation is warranted.

Keywords: irAE, pneumonitis, immunotherapy

EP.04 SCREENING AND EARLY DETECTION

EP.04.01 Current Status of Lung Cancer Screening in Latin America

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Introduction: Lung cancer is one of the leading causes of cancer-related mortality in Latin America. The implementation of low-dose computed tomography (LDCT) screening programs has been shown to reduce mortality; however, their adoption in the region varies significantly.

Methods: A multicenter forum was organized with the participation of researchers from the included countries. Subsequently, information was updated through discussions with key opinion leaders and screening experts in countries where changes had occurred. Data were collected on centers with LDCT capabilities, diagnostic methods used, national regulations, public policies, structured reporting systems, and the existence of national screening campaigns.

Results: Brazil, Mexico, and Argentina have made the most progress in lung cancer screening, with the existence of both public and private programs. However, only Brazil has national regulations, and Mexico has an active screening campaign. Costa Rica, Colombia, Uruguay, Mexico, Argentina, and Peru use Lung-RADS for standardized reporting. Most countries lack national regulations or public policies supporting screening. Some, such as Chile, Brazil, and Argentina, have developed national consensus guidelines, while Guatemala remains in a preparatory phase. In countries like Nicaragua, Honduras, and El Salvador, screening is primarily based on chest radiography, whereas no documented initiatives exist in Venezuela.

Conclusions: Lung cancer screening in Latin America presents significant disparities. While some countries have made progress in implementing structured programs, most lack regulations and public policies. Strengthening regional cooperation and developing coordinated strategies are essential to improve early detection and reduce the burden of disease in the region.

Screening Priorities in Latin America

1. Education on implementing lung cancer screening programs in low-resource settings for pulmonologists, thoracic surgeons, and nurse navigators.
2. Training radiologists in structured reporting of low-dose chest CT scans.
3. Training leaders on quality indicators in lung cancer screening programs.

Country	Screening Availability	Diagnostic Methods	National screening regulations	Public policies	Structured LDCT reporting system	National screening campaigns
Costa Rica	1 private center	LDCT	No.	No.	LungRADS	No.
Dominican Republic	1 research center	Chest X-ray	No.	No.	No.	No.
Panama	indirect screening	LDCT	No.	No.	No.	No.
El Salvador	4 centers	LDCT	no	No.	No.	No.
Nicaragua	No – 2 private centers with capacity.	Chest X-ray	No.	No.	No.	No.
Honduras	No.	Chest X-ray	No.	No.	No.	No.
Colombia	4 centers (All private)	HR CT	No.	No.	LungRADS.	No.
Brazil	No.	Contrast CT	Yes.	Yes.	No.	No.
Uruguay	5 centers (All private)	LDCT	No.	No.	LungRADS	No.
Guatemala	Yes. Public and private system.	Spirometry	No.	Preparatory phase of a project.	No.	No.
Mexico	1 pilot project.	DLCO	No.	Yes.	LungRADS.	Yes.
Paraguay	No.	LDCT	No	No	No	No
Chile	2 public centers	LDCT	Chilean Screening Consensus.	No	No	No
Venezuela	2 private centers	Chest X-ray	No.	No.	No.	No.
Argentina	No.	LDCT	Argentine Screening Consensus.	No.	LungRADS.	No.
Peru	1 private center	LDCT	No.	National Comprehensive Cancer Care Plan	LungRADS	No.

Keywords: Lung Cancer, Screening, Latin American

EP.04.02 Fully-Automated Classification of Parenchymal Low Attenuation-Clusters as Indicators of Pulmonary Emphysema in Lung Cancer Screening

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Introduction: Emphysema, identified as a lung cancer risk factor, can be quantified on low dose CT(LDCT) in lung cancer screening(LCS) programs. Emphysema is commonly assessed by the percentage of Low Attenuation Area(LAA%), yet it lacks precise measurement of emphysema lesion size and number. Advanced LA-cluster analysis systematically distinguishes emphysema regions by size through iterative subtraction. In this study, we aim to optimize the early detection of emphysema by automatic quantification through LA-cluster analysis and compare it with LAA analysis, using a LDCT lung cancer screening dataset.

Methods: A random cohort of 352 consecutive LDCT examinations was selected from a LCS dataset. All scans were evaluated for emphysema by four readers according to the latest Fleischner criteria. Emphysema was automatically quantified by LAA analysis and LA-cluster analysis with thresholds from -940HU to -970HU. AI-based software Aview (Coreline soft, v.42) was used to automatically segment the lungs and for emphysema quantification. LA-clusters were calculated and classified by size below a set of HU thresholds. A range of cluster size from 5.0mm to 9.0mm with 0.5mm intervals were used as the cut-off value in discriminating normal/trace cases versus at least mild cases. Visual score was used as reference for comparison. Spearman's correlation coefficients assessed the correlation between the largest cluster and visual scores, as well as LAA% and visual scores.

Results: The highest agreement between cluster size and visual scores in discriminating normal/trace cases and at least mild cases was observed below -940 HU at 8.5mm, below -950 HU at 7.0m to 8.5mm, below -960 HU at 7.0mm and 7.5mm , and below -970HU at 6.0mm. The corresponding kappa values, ranging from 0.870 to 0.876, demonstrated a very good agreement. For LAA analysis, kappa values ranged from 0.497 to 0.601, indicating moderate agreement. Spearman's correlation coefficients indicated an association between cluster size and visual assessments, ranging from 0.664 to 0.674. Similarly, an association between LAA% and visual assessments was observed, with coefficients ranging from 0.522 to 0.619.

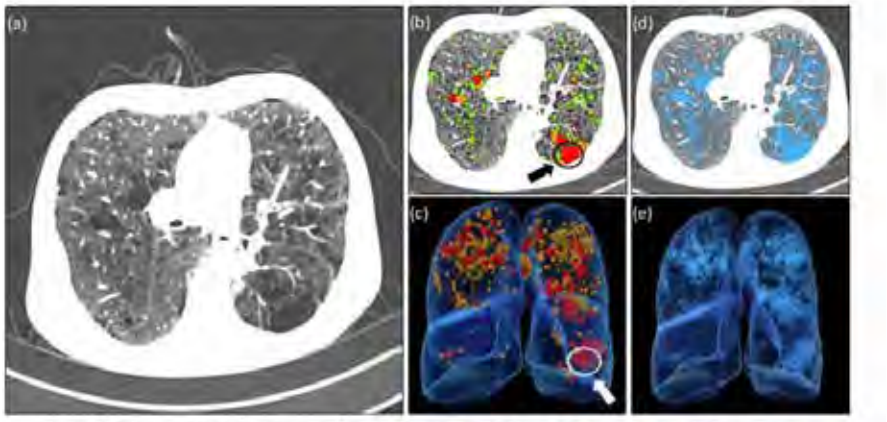

Figure 1 3D reconstructed images with axial CT and MPR views in a severe case with LA cluster analysis and LAA-analysis under -950HU. Figure 1(a) shows original MPR axial image, 1(b) shows the largest masked LA-clusters in an axial view, 1(c) shows 3D reconstructed image with LA-cluster, 1(d)shows masked LAA, and 1(e)shows 3D reconstructed image with LAA. The LA-clusters were masked in different colors based on the cluster diameters: clusters with diameters smaller than 3 mm were colored purple; those with diameters between 3 and 7 mm were colored green; clusters with diameters between 7 and 10 mm were colored orange; and clusters with diameters larger than 10 mm were colored red. The largest LA cluster is indicated by black circles and arrows in the axial images, while the same cluster in the 3D reconstructed images are highlighted with white circles and arrows. The LAA was colored in blue.

Conclusions: Optimal cluster size cut-off varied at different HU thresholds. Higher agreements between visual severity scores and fully-automated LA-cluster size compared to LAA analysis for CT-based emphysema detection suggests the application of LA-cluster analysis has more potential for early emphysema detection in LDCT lung cancer screening.

Keywords: Lung cancer screening, Chronic obstructive pulmonary disease, Quantitative image analysis

EP.04 SCREENING AND EARLY DETECTION

EP.04.03 Uptake and Impact of a Framework to Support Implementation of Low-Dose Computed Tomography (LDCT) Screening for Lung Cancer

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Introduction: The Lung Cancer Policy Network is a global network of multidisciplinary experts from the lung cancer and oncology community. In 2023, the Network developed a framework to support the implementation of low-dose computed tomography (LDCT) screening for lung cancer. Since then, the framework and associated online toolkit have supported those involved in the planning and delivery of LDCT screening programmes around the world.

Methods: Development of the framework was informed by a review of peer-reviewed and grey literature from 2010-22, expert interviews and insights from Network members. To further refine the framework, it was applied to five countries where screening implementation is underway: Canada, Poland, South Korea, the UK and the US. To support those applying the framework, the Network has developed an online toolkit that includes policy briefs, videos and a suite of useful materials. These resources are applicable to a wide variety of contexts in recognition of the fact that, whilst not all health systems will be fully 'ready' for lung cancer screening implementation, this should not delay planning for a screening programme. Over the past year, the toolkit has been expanded to include new resources focused on engaging traditionally underserved communities, and a summary guide to support those applying the framework to their regional context. Later this year, the Network will publish case studies and reference documents to support financial planning for screening programmes.

Results: To date, the framework has been downloaded nearly 3,000 times and the toolkit has been used by almost 7,400 people. Application of the framework is already having an impact on the implementation of lung cancer screening programmes: • Initial assessment in Kazakhstan • Progress in Australia • Collaboration with the Asia Pacific Coalition Against Lung Cancer, including a webinar and workshop that used the framework to structure discussions • The launch of a policy brief on screening priorities in the Middle East and Africa that was informed by the framework and supported by a policy call for screening in the region.

Conclusions: To our knowledge, this is the first framework to support the implementation of LDCT screening programmes globally . Since the framework was developed, the Network has been delighted to witness its application to drive policy commitments and support screening implementation in a variety of settings. By expanding application of the framework to more health systems, comprehensive evidence can be generated to inform considerations for implementation and facilitate high-quality, equitable and cost-effective screening around the world.

Keywords: Screening, Implementation research, Framework

EP.04.04 A Relative Perspective on Whether Risk-Based Lung Screening Eligibility Prioritize People With Higher Competing Mortality

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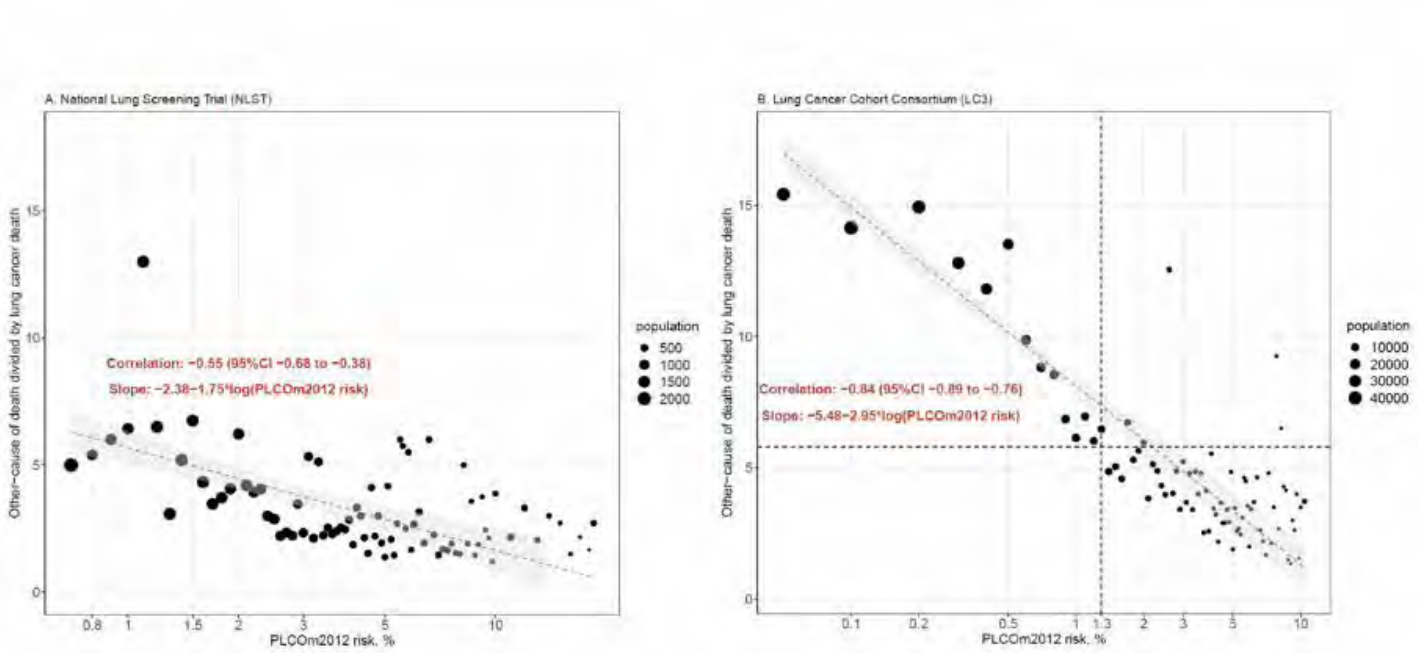
Introduction: Risk-based lung cancer screening is more efficient than categorical eligibility criteria, but concerns have been raised that risk models prioritize individuals with high competing mortality and lower screening benefit. We addressed this question by evaluating the ratio between competing causes of death and lung cancer death as a function of lung cancer risk.

Methods: We analyzed 53,152 participants from the National Lung Screening Trial (NLST) and 400,935 individuals aged 50-80 with a smoking history from 3 cohorts in the Lung Cancer Cohort Consortium (LC3). Within categories of 6-year lung cancer risk by the PLCOm2012 model, we calculated the ratio of other-cause deaths to lung cancer deaths.

Results: Among NLST participants, both lung cancer and other-cause mortality increased with increasing lung cancer risk. The ratio of other-cause to lung cancer deaths was inversely correlated with lung cancer risk (Pearson ρ=-0.55 [95%CI -0.68, -0.38], Figure 1A). The ratios across risk quintiles (lowest to highest) were 5.8, 4.5, 3.1, 2.6, and 2.3. In LC3, the ratio was also inversely correlated with lung cancer risk (Pearson ρ=-0.84 [95%CI 0.89, 0.76], Figure 1B).

Conclusions: We confirm that other-cause mortality increases among people with higher lung cancer risk. However, the ratio between competing and lung cancer death decreases with lung cancer risk. This is in line with the hypothesis that individuals at high lung cancer risk are more likely to benefit from screening, including when considering their risk of death from competing causes. We will extend this analysis to all cohorts from LC3.



Keywords: Screening, Risk-based strategy, Competing mortality

EP.04 SCREENING AND EARLY DETECTION

EP.04.05 Lung Cancer Diagnosis Among Screening Participants in the Multi-Health-System Philadelphia Lung Cancer Learning Community

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Introduction: Uptake of lung cancer screening (LCS) is reported to be 18-20% among eligible individuals but varies at the national level, state level, and by other geographic measures. Our group has previously demonstrated the feasibility of a citywide, multi-health-system analysis of LCS through a novel research collaboration, the Philadelphia Lung Cancer Learning Community (PLC2). The objective of this follow-up analysis is to examine lung cancer diagnosis among individuals receiving LCS in Philadelphia.

Methods: Individuals eligible for LCS by USPSTF 2021 criteria and who received a low-dose CT (LDCT) chest scan between January 1, 2014 and December 31, 2023 were identified at two PLC2 healthcare systems. The analysis was restricted to Philadelphia residents by geocoding street addresses obtained from the electronic health record (EHR) using ArcGIS. At Jefferson Health patient data were extracted from the prospectively accruing Jefferson LCS Registry, a data repository that includes USPSTF-eligible individuals receiving centralized LCS at multiple health system locations. At Penn Medicine patient data, from the hybrid LCS Program were identified and extracted retrospectively from the EHR using LCS-specific Current Procedural Terminology or Healthcare Common Procedure Coding System codes (71271 or G0297, respectively). At both sites, the first completed LCS was categorized as the baseline LDCT for each screened patient, and baseline characteristics were extracted before or on the baseline LCS date. Background characteristics and lung cancer diagnoses were aggregated among PLC2 sites for descriptive statistical analysis.

Results: During the 10-year study period 10,418 USPSTF 2021-eligible individuals residing in Philadelphia completed LCS, and more than half (54.8%) of baseline LDCTs were completed in 2021, 2022, or 2023. The study cohort was comprised of 52.6% women, as well as 62.8% Non-Hispanic Whites, 25.3% Non-Hispanic Blacks, 3.2% Hispanics, and 4.1% Multiple/Other race and ethnicity. More than half of screened individuals (60.4%) reported a current smoking status, and 87.9% had a smoking history of at least 30 pack-years. The prevalence of additional lung cancer risk factors including diagnosis of chronic obstructive pulmonary disease (31.0%), personal history of cancer (9.0%), and family history of lung cancer (15.5%) was also ascertained. Despite significant differences in prevalence and distribution of lung cancer risk factors among participants at each study site, there was no difference in cancer detection rate between sites (3.5% vs. 3.6%, p=0.75). All individuals were classified by USPSTF-2013 and -2021 eligibility and were assigned a 6-year lung cancer risk using the Prostate, Lung, Colorectal, and Ovarian (PLCOm2012) risk model. All 10,418 individuals were geocoded to one of 374 residential census tracts in Philadelphia.

Conclusions: LCS at PLC2 institutions in Philadelphia can be systematically characterized using a common data model among multiple health systems to examine individual- and neighborhood-level factors. Ascertainment of lung cancer risk and lung cancer diagnosis can help to identify areas for future research and implementation of strategies to guide lung cancer prevention and control across the city.

EP.04 SCREENING AND EARLY DETECTION

EP.04.06 Health Beliefs and Adherence to Lung Cancer Screening in a Diverse, Real-World Population

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Introduction: Lung cancer screening (LCS) with low-dose CT (LDCT) remains markedly underutilized. Prior studies suggest that perceptions and attitudes regarding LCS may influence intention to undergo LDCT; however, little is known about these beliefs affect real-world LDCT adherence, especially among vulnerable populations. We examined LCS-related health beliefs and LDCT completion in an urban safety-net healthcare system (Parkland Health, Dallas, Texas).

Methods: English- and Spanish-speaking patients eligible for LCS based on 2013 United States Preventative Services Task Force criteria for whom LDCT had been ordered (but not yet performed) were invited to participate in a survey assessing demographic information, smoking history, and perceptions of lung cancer risk and lung cancer screening. Survey items were adapted from validated measures, including the Lung Cancer Screening Health Belief Scales and the Lerman Breast Cancer Worry Scales, to assess LCS-related beliefs (i.e., perceived risk, benefits, barriers, and self-efficacy) and worry about lung cancer. We evaluated the association between these parameters and LDCT completion using the two-sample T test and Chi-square test.

Results: Among 447 eligible individuals, 411 participated in the survey (including 71% from racial/ethnic minoritized groups), of whom 339 (82%) completed the initial LDCT. Almost half believed that they were at risk for lung cancer in their lifetime, and over 90% believed that LCS would help find lung cancer early. Higher self-efficacy scores and lower perceived barriers scores were associated with LDCT completion (P=0.002 and P=0.004, respectively; Figure 1). Perceived risk and benefit scores were not associated with LDCT completion. Individuals who did not complete the first LDCT were more likely to note fear of lung cancer (33% vs. 17%; P=0.008), stigma related to lung cancer (33% vs. 18%; P<0.001), and worry affecting mood (82% vs. 67%; P=0.02).

Conclusions: In a diverse, real-world lung cancer screening population, most patients believed that LCS helps find lung cancer early, yet approximately 20% of patients did not complete the initial LDCT. Perceived fear, stigma, and worry affecting mood were associated with reduced LDCT completion. These findings offer insight into potentially modifiable factors and future interventions to improve LCS uptake among eligible individuals.

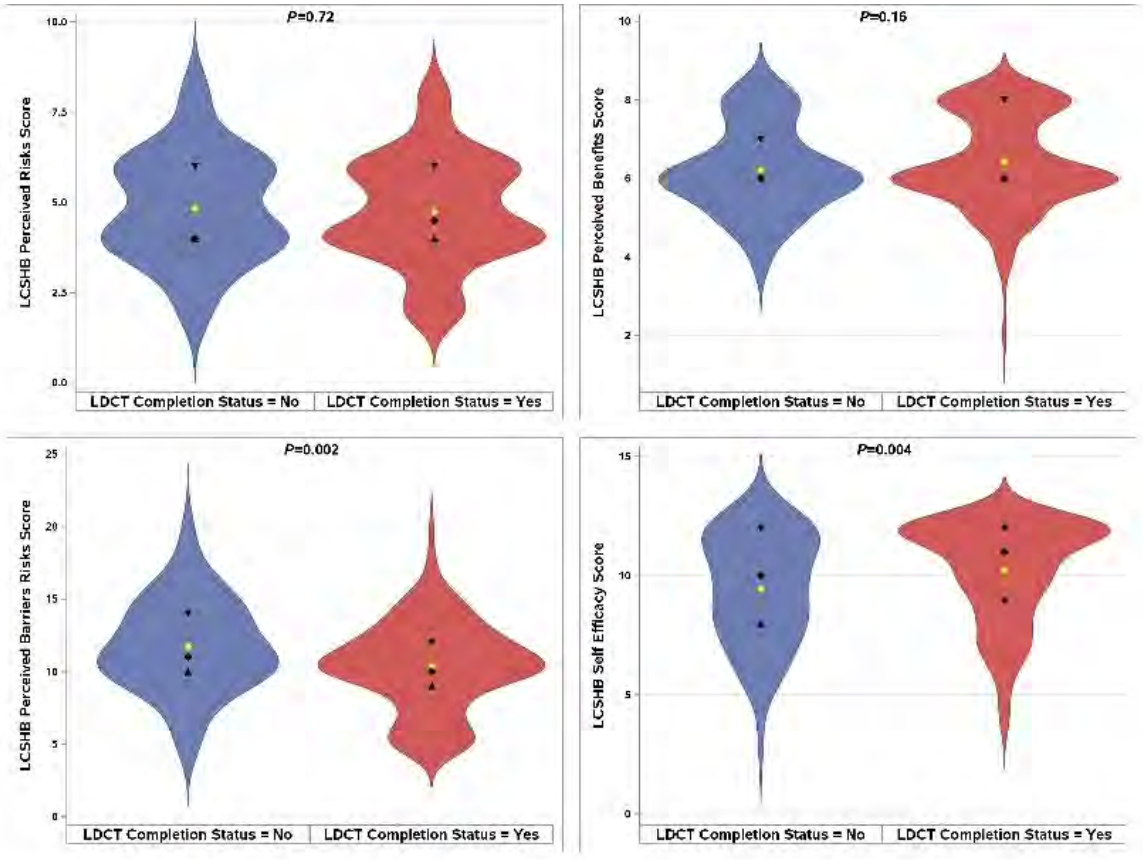

Figure 1: Distribution of Lung Cancer Screening Health Belief (LCSHB) Scale scores based on low-dose CT scan completion status among survey respondents. Violin plots reveal mean (yellow diamond), median (black diamond), and interquartile range (triangles)

Keywords: Lung Cancer Screening, Lung Cancer Stigma, Health Beliefs

EP.04 SCREENING AND EARLY DETECTION

EP.04.07 Participant and Provider Experiences in an Indigenous Focused Trial of Lung Cancer Screening in Aotearoa New Zealan

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Introduction: We examined the views of participants, their whānau (family / support people), and primary care staff in a lung cancer screening study that compared primary care versus central hub invitations for Māori individuals aged 55-74 in the Auckland and Waitemata districts of Aotearoa, New Zealand. Our study aimed to explore the acceptability of the screening process, participant burden, and experiences at various stages of the programme.

Methods: Surveys were administered to all participants who completed a risk assessment, including those not eligible for a CT scan (n=467), those who were eligible and underwent a CT scan (n=505), and those who declined a CT scan (n=40). Interviews were conducted with a selected group of participants who underwent a CT scan (n=25). Additionally, surveys were provided to whānau members who accompanied participants to the CT scan and to staff at primary care clinics involved in the study. Data collection was carried out through a mix of online, in-person, phone, or mailed surveys, while interviews with selected participants were conducted over the phone. Quantitative data were analysed using descriptive statistics and inferential analysis (chi-square tests), while interviews and open-ended survey responses were analysed thematically.

Results: Of those who completed the risk assessment but were not eligible for a CT scan, 32% (n=149) completed a survey. Participants expressed overwhelmingly positive experiences regarding the study and the information provided. Reactions to eligibility varied, with some participants feeling relieved and pleased that their risk level was too low to require a CT scan, while others were surprised or anxious. For those who were eligible and completed a CT scan, there was a 50% response rate (n=253). These participants were largely satisfied with the process and would recommend it to others. A minor concern raised (by a small number of participants) was the waiting time for results. Sixteen whānau members completed a survey and reported feeling welcomed and valued throughout the process. For the participants who declined a CT scan, the response rate was only 10%. Reasons for decline included low perceived risk, anxiety, and concerns about transport. Fifteen clinic staff from participating practices also completed a survey, expressing overall satisfaction with being involved in the study and increased knowledge, though some noted that the study was more time-consuming than anticipated.

Conclusions: The lung cancer screening programme was generally well-received by participants, whānau, and providers, with high satisfaction regarding the information and support provided throughout the process. While most participants were satisfied with the screening process, some concerns were raised, particularly regarding waiting times for results. Overall, the programme was viewed positively, with a high level of acceptance and a willingness to recommend participation to others.

Keywords: Screening, Indigenous, Equity

EP.04 SCREENING AND EARLY DETECTION

EP.04.08 Building Policy Recommendations Using an Implementation Framework for Low-Dose Computed Tomography Screening

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Introduction: Lung cancer screening can reduce mortality by up to 25%, and it shifts diagnosis to an earlier stage, where lung cancer is more treatable and thus more survivable. However, many countries face challenges to implementation. In 2023, the Lung Cancer Policy Network developed a framework to support the implementation of low-dose computed tomography screening. An online toolkit was also created to assist in applying the framework. Using this framework, the Network and the Asia Pacific Coalition Against Lung Cancer held a collaborative workshop in October 2024. The workshop, part of the Asia Conference on Lung Cancer, brought together stakeholders including clinicians, screening leads and implementation researchers to develop a set of tailored policy recommendations for implementing screening in the Asia-Pacific region.

Methods: The workshop followed a webinar that showcased screening activities in the region and featured case studies from Australia, India, Singapore and South Korea. Registrants for the webinar indicated the key challenges they faced in implementing lung cancer screening, and the four most popular responses were selected for discussion at the workshop. Throughout the workshop, the Network's framework was used as a tool to discuss how to facilitate and optimise the implementation of lung cancer screening.

Results: The workshop brought together more than 40 delegates from over 10 countries. The discussion topics were: • Building awareness of screening and its benefits • Making lung cancer a policy priority • Gaining financial investment for lung cancer screening • Optimising workforce capacity for screening. In each group, delegates discussed challenges and actionable solutions, leading to the development of overarching policy recommendations.

Conclusions: The use of the implementation framework in a workshop format led to the development of tailored policy recommendations. The framework is a globally applicable tool, so this approach can be replicated to highlight the key challenges to implementation and develop tailored local and regional recommendations to meet these challenges.

Keywords: Screening, Early detection, Policy

EP.04 SCREENING AND EARLY DETECTION

EP.04.10 Evaluating Primary Care Practice's LCS Smoking History Accuracy for Maori Patients - Implications for a Future Lung Cancer Screening Programme

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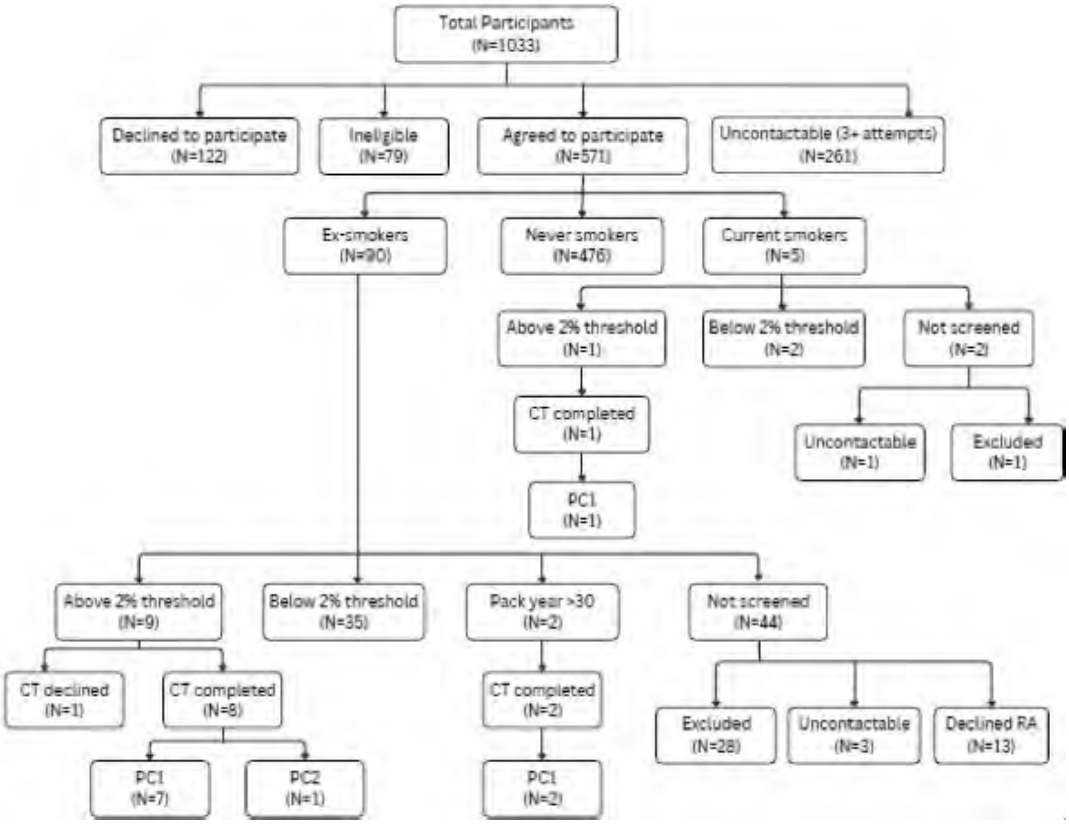
Introduction: Lung cancer is a common cause of cancer death for Māori (Indigenous) and non-Māori, with significant ethnic inequities in incidence and mortality in Aotearoa New Zealand. Lung cancer is the single largest contributor to the difference in life expectancy between Māori and non-Māori, hence, a key issue is developing a screening strategy that will ensure benefit for Māori. Accurate smoking history is essential for identifying individuals eligible for lung cancer screening. We evaluated records in primary care settings to determine the extent of misclassification of smokers and former smokers as 'never smoker'. This work was conducted as part of a broader lung cancer screening research programme in the Waitematā and Auckland districts of Aotearoa, New Zealand.

Methods: 1033 Māori participants from participating clinics with a recorded status of 'never smoker' were identified. Of these, 79 were excluded as they were ineligible to take part in lung cancer screening, 122 declined to participate, and 261 were uncontactable after three attempts. The remaining 571 participants agreed to complete a verification audit via a phone call. Those who reported a history of smoking were invited to participate in the lung cancer screening study.

Results: Of the 571 verification participants, 476 (83.4%) were confirmed as never smokers, 90 (15.8%) were ex-smokers, and 5 (0.9%) were current smokers. A total of 49 participants (60% of current smokers and 51% of ex-smokers) agreed to participate in the lung cancer screening study and proceeded to a lung cancer screening risk assessment. Twelve (12.6%) of these participants (11 ex-smokers and 1 current smoker) were eligible for a CT scan, with 11 completing the scan. Of those that completed the scan, ten had no significant nodules (PC1) and one participant had a low-risk nodule (PC2) (Figure 1).

Conclusions: This study continues our work as part of the first organised programme for Lung Cancer Screening. Our findings highlight inaccuracies in primary care smoking records, with 16.7% of individuals recorded as never smokers self-reporting a history of smoking. Misclassification led to missed screening opportunities for some of the misclassified in this group. Addressing this misclassification is important as a future screening programme will rely on primary care smoking records to ascertain eligibility for screening.



Keywords: Lung cancer screening, Smoking history accuracy, Indigenous health

EP.04 SCREENING AND EARLY DETECTION

EP.04.11 Feasibility of AI-Assisted Mobile Low-Dose CT Screening in Underserved Communities in China

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Introduction: Low-dose computed tomography (LDCT) has been shown to enhance early lung cancer detection rate and reduce associated mortality by 20%. Despite the recommendations of lung cancer screening (LCS) guidelines and the evidence supporting the effectiveness of population-based LDCT screening, many significant screening barriers remain. There are limited data from clinical practice regarding whether community-based mobile LDCT screening is associated with reduced lung-cancer mortality in China. This study aims to evaluate whether community-based mobile LDCT screening program is associated with improved prognosis among adults with lung cancer in mainland China and examines the operational challenges encountered during implementation.

Methods: This study was carried out in rural area in Fujian Province, China, between July 2022 and December 2024. This study included participants comprised socioeconomically disadvantaged individuals aged ≥40 years without prior LDCT exposure. Participants underwent LDCT screening conducted by a multidisciplinary research team. With the aid of the AI-based "InferRead CT Lung Research" system, physicians conducted radiological interpretations and finalized standardized diagnostic reports. The primary efficacy endpoints were lung cancer detection and diagnosis rates. The operational challenges encountered during implementation were collected by think-aloud method.

Results: A total of 13,018 individuals (mean [SD] baseline age, 59.3 [3.8] years; 6768 [51.99%] female) participated in this study. The detection rates of suspected lung cancer cases and confirmed cases were 1.35% (n = 176) and 0.7% (n = 86), respectively. Despite the effectiveness of the lung cancer screening program, several operational challenges were identified, including securing independent and stable funding, insufficient human resources, insufficient of the project's publicity, unstandardized resident health records and unability to providing logistics and sourcing services.

Conclusions: This AI-assisted LDCT model for lung cancer screening demonstrates significant potential to reduce healthcare disparities in underserved regions and could be extended to broader populations in similar low-resource settings.

Keywords: Lung cancer screening, AI, underserved communities

EP.04.12 Outcome of Lung RADS Category 4 in Lung Cancer Screening Population at Tertiary Hospital, Single Center Study

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Introduction: Lung cancer remains a major challenge in oncology, characterized by its increasing incidence and high mortality rate. Despite diagnostic advances and novel therapeutic strategies, the importance of early detection and prediction of lung cancer is still decisive. To evaluate significance and the role of screening chest CT, Lung RADs category 4 group was analyzed and matching with follow ups.

Methods: For recent 13 months, we reviewed the medical record and chest CT scans of whom received lung cancer screening low dose CT scans, Total 2,175 (male 1,798, female 377) were included, The distribution of category was 1(785) 2(1,191) 3(65) 4A(89), 4B(50), 4X(5).

Results: Total 145 patients were included. Age was ranging from 55 to 79 years old, the radio of M;F was 134:11. The evaluation by follow up CT scan result was 76(stable) 37(resolved) 11(benign(inflammation), 9(malignancy), 12(loss of follow up). The character of nodule is solid(129), part solid (15) and GGN(1). The location of nodules was RUL(48), LUL(35) RLL(28), RML(17), LLL(15), endobronchial(2). Histopathology were adeno(5) squamous(2), small cell(1), adenosqamous(1). The associated significant findings were ILA(47), emphysema(24), coronary calcification (67 mild-41, moderate-18, severe-9) were shown. Previous tuberculosis infection was shown in 89/145 and active pulmonary tuberculosis was shown in 7. Among C3 lesions, lung cancer diagnosis for two more follow up was 9/155(5.8%).

Conclusions: In conclusion, the rate of lung cancer in C4 was 9/145, (6.2%), 4A(3), 4B(5), 4X(1) each. The fuzzy margin with banishing perilesional GGO has the transient lesion especially 4A nodule. The density and size determinant require additional variable such as the shape of nodule.

Tab. 1 The Distribution of Category

	No		%
1	785		36.1
2	1091	(2b 36)	50.2
3	155		7.1
4A	89		4.1
4B	50		2.3
4x	5		0.2
	2175		100

Keywords: Lung RADS, Screening, Low dose CT

EP.04 SCREENING AND EARLY DETECTION

EP.04.13 Emphysema on Baseline CT Predicts Copd and Cardiovascular Death After 25 Years in Lung Cancer Screening

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Introduction: The usefulness of assessing baseline visual emphysema in lung cancer screening (LCS) cohorts is unknown. Purpose: To determine whether assessment of emphysema on low-dose chest CT (LDCT) is a predictor of death up to 25 years later from all-causes, chronic obstructive pulmonary disease (COPD), and cardiovascular (CVD).

Methods: Prospective cohort of smokers aged 40-85 years underwent baseline LDCT screening for LC between June 2000 and December 2008 and were followed until December 31, 2024.Visual emphysema was classified as none(0), mild(1), moderate(2), or severe(3). Self-reported smoking history and comorbidities were documented at baseline. Date and cause of death (ICD-10) were obtained from the National Death Index, physicians, and family. Adjusted Cox proportional hazards regression models and Fine-Gray subdistribution hazard model analyzed emphysema and mortality outcomes.

Results: Among 9047 participants (51.2%women, 48.8%men; median age:65 years[IQR:61-69]; median pack-years: 43[IQR:28-64]), 2637(29.1%) had emphysema. It was mild(1908;21.1%), moderate(512;5.7%), and severe(217;2.4%). After adjusting for sex, age, pack-years, and years since quitting, emphysema remained a significant predictor of all-cause mortality (HR1.29;95%CI,1.21-1.38), COPD mortality (HR3.28;95%CI,2.58-4.17), and CVD mortality(HR1.14;95%CI,1.01-1.30). A dose-response relationship was observed between emphysema severity and both all-cause and COPD mortality, but not CVD mortality, with greater emphysema severity associated with higher risk. Adjusted Fine-Gray subdistribution hazard model, which accounts for competing risks, the association between emphysema and COPD mortality remained significant but was attenuated(HR3.01; 95%CI,2.36-3.84), while the association with CVD mortality was no longer significant (HR1.02;95%CI,0.89-1.16).

Conclusions: Baseline emphysema on LDCT in asymptomatic participants of a LCS cohort predicts all-cause, COPD, and CVD mortality up to 25 years later, underscoring the importance of emphysema diagnosis in comprehensive LCS programs.

Keywords: Lung cancer screening, Emphysema, Mortality

EP.04 SCREENING AND EARLY DETECTION

EP.04.14 Pilot Lung Cancer Screening Program and "Lung Health Check" in Lleida: Preliminary Results

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Introduction: Lung cancer (LC) screening facilitates early detection, and leads to the diagnosis of other smoking-related conditions.

Methods: Descriptive study of the lung LC screening program initiated in May 2023 in Lleida, following the protocol of the International Early Lung Cancer Action Program (I-ELCAP). Includes smokers or former smokers of ≤15 years, with an exposure of ≥20 pack-years and aged 50-80. Participants undergo low-dose chest CT scans, pulmonary function tests, alpha-1 antitrypsin deficiency (AATD) screening and blood tests.

Results: A total of 276 subjects were evaluated, primarily men (63%) and former smokers (53.1%) with COPD (41.3%). Spirometry values were generally preserved (FEV1: 85% and FVC: 91% on average), however, 100(36.6%) exhibited an FEV1/FVC ratio <70%, 121(45%) had abnormalities in DLCO, and 202(76.2%)exhibited higher RV. Radiological emphysema was diagnosed in 128(46.4%) and AATD-related mutations were detected in 60 participants (23%). Eleven cases of LC (4%) were identified; ten (90.9%) were in stage I and one (9.1%) in stage IV. Six patients underwent surgery, three received radiotherapy, one chemotherapy and immunotherapy, and one refused treatment. Cases eligible for anatomopathological confirmation showed six adenocarcinomas and three squamous cell carcinomas.

Conclusions: Our LC screening pilot has proven effective in early LC detection and in potentially identifying other smoking-related diseases.

Keywords: Lung cancer screening, Low-dose chest CT scan

EP.04 SCREENING AND EARLY DETECTION

EP.04.15 Determinants of Lung Cancer Screening Intention Among Adults Eligible for Lung Cancer Screening

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Introduction: Lung cancer screening (LCS) with low-dose computed tomography is a proven effective approach to reducing lung cancer mortality. Yet, this life-saving screening is underutilized. To participate in LCS, an individual must first have the intention and then take appropriate actions. Yet, little is known about the LCS intention among high-risk individuals. This study investigated LCS awareness and intention and identified individual-level determinants associated with LCS intention among screening-eligible adults who never had LCS.

Methods: From December 2023 to February 2024, we conducted a cross-sectional online survey using the Qualtrics Research Panel to recruit individuals eligible for LCS—those aged 50-80 years old without a history of lung cancer who currently use cigarettes or had quit within the past 15 years with ≥20 pack-years tobacco exposure history. This study included LCS-eligible adults who never had LCS (n=521). The self-reported survey assessed participant socio-demographics, health-risk behaviors, cancer beliefs, chronic health conditions, and awareness, use, and intention of LCS guided by the LCS participation conceptual model. The outcome variable was the self-reported intention to undergo LCS within the next 3 months if recommended by healthcare providers. We conducted descriptive statistics and multivariable logistic regression.

Results: Most participants were female (63.3%), White (83.7%), insured (91.0%) with a mean age of 60.5 (SD 7.3) years, and the majority had an annual household income of ≤$34,000 (52.6%). Most participants reported current cigarette use (83.4%). The mean cigarette-pack years of use was 38.2 (SD 15.9) and ranged from 20-120 smoking-pack years. Approximately 9.0% had a history of skin and other than lung cancer history, 19.4% reported having first-degree and 23.8% second-degree family history of lung cancer. Close to half of the participants, 43.7%, had heard about LCS, yet 93.5% reported that their healthcare provider had not discussed having LCS in the past year. About one-third (33.4%) reported intention to undergo LCS within the next 3 months if recommended by healthcare providers. In terms of cancer beliefs, 76.0% believe everything causes cancer, 27.2% believe there is little that can be done to reduce cancer risk, 75.0% agree that multiple cancer prevention recommendations are confusing, and 67.4% automatically associate cancer with death. In the regression model, participants who attended some college, retired, self-identify as Black, have a healthcare provider whom they usually visit, have a second-degree family history of lung cancer, and believe that there are too many recommendations about preventing cancer were more likely to report an intention to undergo LCS within the next 3 months if recommended compared to their counterparts.

Conclusions: Our study results showed that many LCS-eligible adults are unaware of LCS, but they are willing to undergo LCS if recommended by providers. However, most participants have not discussed LCS with their providers in the past year, indicating critical gaps in shared decision-making between the patient and the provider to discuss the benefits and risks of LCS. Effective interventions are needed to improve LCS awareness and shared decision-making in clinical settings, which will lead to patient-centered, informed decision-making in LCS and, ultimately, increase LCS uptake.

Keywords: Lung cancer screening, Intention to screen, high-risk individuals

EP.04.16 Piloting Lung Cancer Screening: Tumor Detection Rate, Psychological Distress and Incidental Findings

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Introduction: Lung cancer constitutes the leading cause of cancer-related deaths in Switzerland. Since 2019, a pilot study evaluating the feasibility and efficacy of low-dose CT lung cancer screening (LCS) program in Switzerland is ongoing. This analysis summarizes the findings and obstacles of a screening program.

Methods: 307 participants (178 males, median age: 62 years) smokers (200 active) or ex-smokers were included in the lung cancer screening consisting of an interview and a low-dose CT. In a subset of 140 participants (62 females) psychological distress was assessed using a visual analog scale (Range: 0-10). Furthermore, to assess coronary artery calcification (CAC) as incidental finding, the SHEMESH score was utilized. Imaging was scored by two experienced radiologists using a score ranging from 0 to 12.

Results: 11 cancers have been detected (3.58%), 9 lung cancers (2.93%) in stage AIS (1), stage I (3), stage IIIA (3, all incidental N2), stage IV (2), 1 thymoma, 1 thyroid cancer. Most of the participants experienced only minor psychological distress, however some instances of significant stress were reported (Figure 1A). There was a trend for higher reports of psychological distress in females compared to males ($p = 0.053$). 22.8% participants had a SHEMESH score between 4 and 12 (Figure 1B), of which 28.6% (20 participants) described symptoms potentially indicating CAC. Participants with a SHEMESH scores above 4 were advised to consult a specialist.

Conclusions: Employing low-dose CT scans as a screening modality led not only to detection of multiple malignancies; it was also seen that careful consideration of incidental finding and their implication is important within screening programs. Overall, only minimal psychological distress was reported.

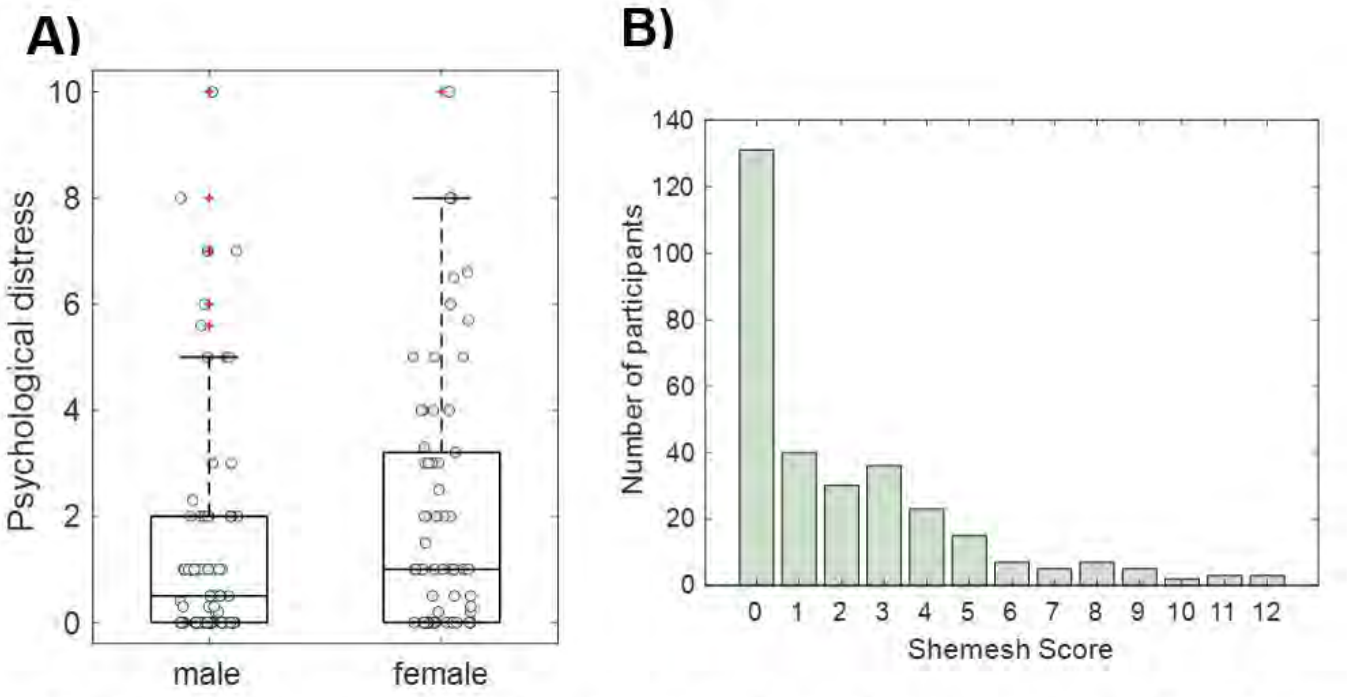

Figure 1: A: Psychological distress reports using a visual analogue scale in males and females, **B**: Number of participants per SHEMESH score

Keywords: Early detection, Incidental findings, Psychological distress

EP.04 SCREENING AND EARLY DETECTION

EP.04.17 Radiomics Predicts IASLC Grades of Invasive Pulmonary Adenocarcinoma by Distinguishing High-Grade Patterns and Predominant Subtypes

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Introduction: Accurate grading of invasive adenocarcinoma (ADC) according to the IASLC system is crucial for prognosis assessment and treatment planning. In the IASLC grading system, it incorporates both high-grade patterns and predominant ADC subtypes for grade classification. This study aimed to construct a radiomics model for IASLC grading by differentiating high-grade patterns and predominant subtypes.

Methods: We retrospectively collected 529 ADC cases from patients who underwent radical surgical resection. The dataset was randomly split into training and validation cohorts at a 7:3 ratio, and radiomics features were extracted from annotated CT images. A radiomics model was developed, comprising two submodels tailored for IASLC grading. One submodel identified whether high-grade patterns exceeded 20% within an ADC, while the other distinguished between lepidic and acinar/papillary predominant subtypes. The final IASLC grade was determined by integrating predictions from both submodels. Feature selection was performed using the minimum redundancy maximum relevance method and the least absolute shrinkage and selection operator. Logistic regression was applied for submodel construction, and model performance was evaluated using the area under the curve (AUC). Decision curve analysis was performed to assess clinical applicability.

Results: The radiomics submodel predicting high-grade patterns achieved AUCs of 0.95 and 0.96 in the training and validation sets, respectively, while the submodel distinguishing predominant subtypes attained AUCs of 0.83 and 0.78. By combining results of both submodels, the overall radiomics model achieved AUCs of 0.95, 0.85, and 0.96 for IASLC grades 1, 2, and 3 in the validation dataset. Decision curves showed the potential of the mdoel for clinical implementation.

Conclusions: Radiomics enables accurate IASLC grading of ADCs by differentiating high-grade patterns and predominant subtypes. The proposed radiomics model may provide precise preoperative diagnosis, potentially enhancing treatment planning.

Keywords: IASLC grading, Radiomics, Invasive Pulmonary Adenocarcinoma

EP.04 SCREENING AND EARLY DETECTION

EP.04.18 Preoperative Prediction of Grade 3 Invasive Non-Mucinous Adenocarcinoma Using Semiconductor 18F-FDG-PET/CT: A Diagnostic Accuracy Study

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Introduction: Invasive non-mucinous adenocarcinoma (INMA) is a major subtype of non-small cell lung cancer (NSCLC). A three-tier pathological grading system of INMA has been introduced by the 2021 WHO classification and patients with Grade 3 INMA are known to have a poor prognosis after resection. Accurate preoperative prediction of grade 3 INMA may offer optimal treatment strategies. Conventional imaging methods, such as CT and conventional ^{18}F-FDG-PET/CT (cPET/CT), may be useful for this but the diagnostic ability seems limited. Semiconductor ^{18}F-FDG-PET/CT (sPET/CT) recently emerged as a tool to offer a higher spatial resolution and may improve diagnostic accuracy to predict grade 3 INMA.

Methods: We retrospectively reviewed 550 INMA patients who underwent surgical resection at Tohoku University Hospital between 2010 and 2022. Patients were divided into two cohorts based on the PET which they preoperatively underwent: cPET/CT (n=328) and sPET/CT (n=222). The resected INMA was pathologically classified according to WHO 2021 criteria. Diagnostic performance for predicting grade 3 INMA was assessed via receiver operating characteristic (ROC) curve analysis. Survival analyses were performed using Kaplan-Meier methods.

Results: n the cPET/CT cohort, the sensitivity and specificity for predicting grade 3 tumors were 84% and 59%, respectively, with an area under the curve (AUC) of 0.769. In contrast, sPET/CT showed improved diagnostic performance with a sensitivity of 74.5%, a specificity of 78.4%, and an AUC of 0.811, using a SUVmax cutoff of 6.8. The superiority of sPET/CT was especially notable in clinical stage II or higher, or smaller tumors (≤2 cm).

Conclusions: sPET/CT is a valuable non-invasive modality for the preoperative identification of grade 3 INMAs, offering superior diagnostic accuracy compared to cPET/CT. Its use may enhance treatment planning, including decisions regarding neoadjuvant therapy or the types of lung resection procedures, thereby contributing to improved personalized care in NSCLC.

This abstract was prepared with the assistance of ChatGPT, a language model developed by OpenAI, used for language refinement and formatting.

Keywords: Non-Small Cell Lung Cancer (NSCLC), Semiconductor PET/CT, Tumor Grading / WHO Classification

EP.04 SCREENING AND EARLY DETECTION

EP.04.19 Radiologic Characteristicsof Solitary Pulmonary Capillary Hemangioma

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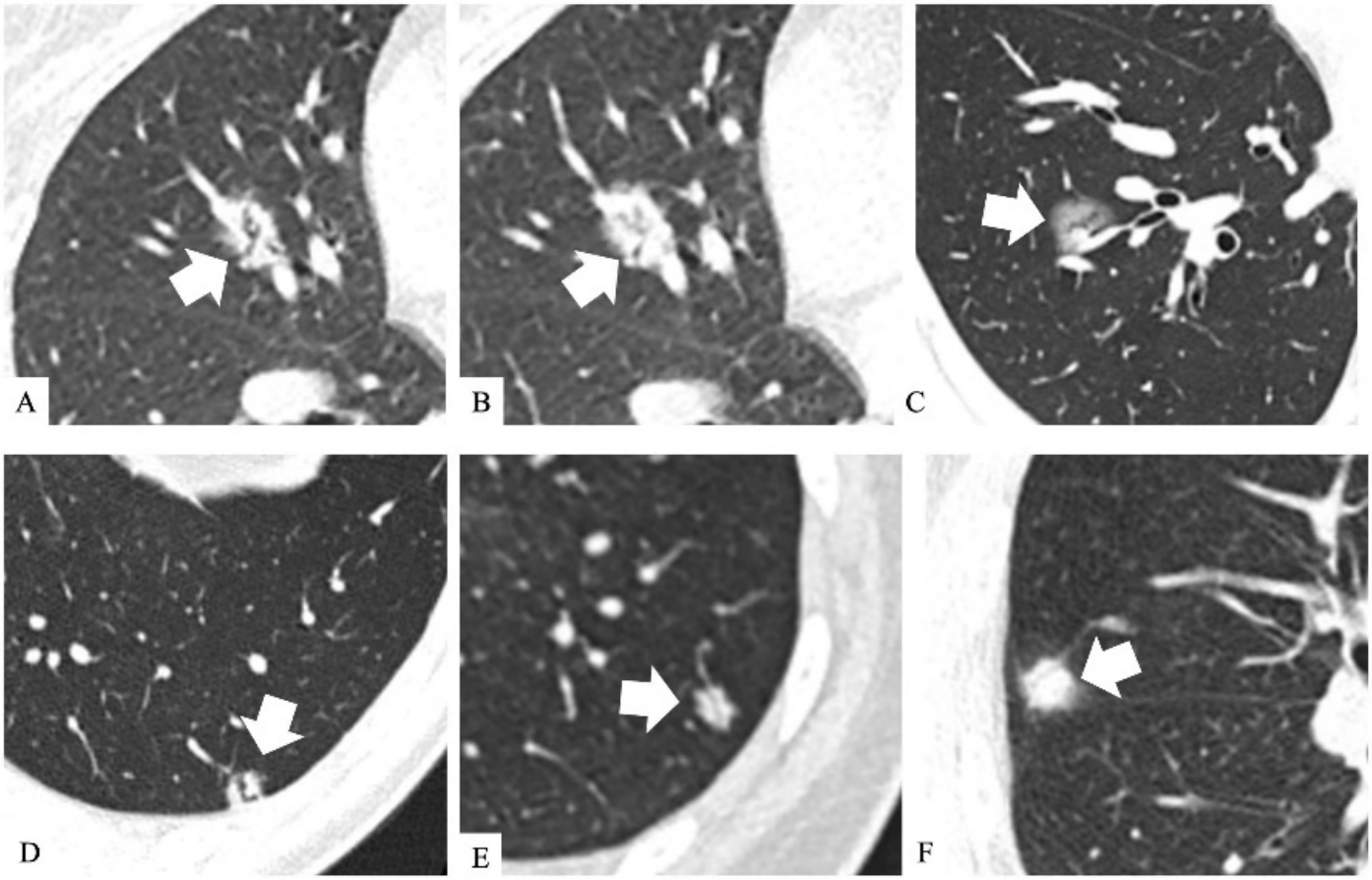
Introduction: Solitary pulmonary capillary hemangioma (SPCH) is a rare benign disease that is often radiologically underrecognized and may mimic malignant nodules such as lung adenocarcinoma. The purpose of this study is to demonstrate radiologic features of SPCH and compare characteristics between SPCH and adenocarcinoma.

Methods: This retrospective study included all histologically confirmed SPCH cases at our institution between July 2015 and December 2024. For comparison, propensity score matching lung adenocarcinoma cases in our hospital in the same period were selected. Each nodule's consistency, size, location, spiculation, pleural retraction, air bronchogram and perivascular lucency were evaluated by two chest radiologists independently, blinded to clinical and pathology information. The chi-square or Fisher's exact tests were used for categorical data and Mann-Whitney U tests for continuous data.

Results: The study comprised 44 SPCH patients (28 females [63.6%], 16 males [36.4%]; median age, 46 years [range, 27-70 years]). SPCH were predominantly located in both lower lobes (77.3%) and peripheral lung zone (79.5%), shown as solid nodules (54.5%). On CT, 54.5% were solid nodules, 27.3% nonsolid, and 18.2% part-solid. Most SPCH lacked spiculation (95.5%, 42/44) and pleural retraction (81.4%, 35/44). Air bronchograms were present in 56.8% (25/44) of SPCH, in which most of case had patent bronchiole with or without dilation passing through the nodule (N=12). There were 7 cases had dilated bronchiole obstructed abruptly by the nodule or with disruption in the peripheral area of the nodule, while the rest of the 5 cases had area of branching or tubular lucency within the central of the nodule. Perivascular lucency was observed in 9.1% (4/44) of SPCH. Comparing with the 344 matched adenocarcinomas, SPCH were more likely in both lower lobes (33/44, 75%), while adenocarcinomas were more in upper lobes (209/233, 60.8%). SPCH more liekly have air bronchogram and less likely present with lobulation, spiculation and pleural retraction (all $P<0.05$).

Conclusions: SPCH were more likely to be located in both lower lobes and peripheral lung zone, typically lacking spiculation, lobulation and pleural retraction but often exhibiting air bronchograms. Central branching and tubular lucency and perivascular lucency are more specifically seen in SPCH.



Example chest CT images showing air bronchogram in solitary pulmonary capillary hemangioma.

EP.04 SCREENING AND EARLY DETECTION

EP.04.20 Exploring Diffusion-Weighted Magnetic Resonance Imaging in Lung Cancer Screening

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Introduction: There is evidence that magnetic resonance imaging (MRI) offers sensitivity comparable to computed tomography (CT) in evaluating pulmonary nodules.[1] Specifically, diffusion-weighted imaging (DWI) sequences generate images based on water molecule diffusion through tissue, quantified as the apparent diffusion coefficient (ADC). ADC is typically lower in malignant tumors than in benign nodules[2],[3] and has been used in other tissues, such as thyroid nodules, as a noninvasive risk stratification tool.[4] This study examines the role of DWI in lung nodules found in lung cancer screening (LCS).

Methods: This ongoing prospective study includes participants eligible for LCS with at least one lung nodule ≥6 mm on LDCT, who then underwent MRI. Diffusion-weighted imaging (DWI) was performed using a 3T MRI scanner, and ADC maps were reconstructed. ADC values of pulmonary nodules were analyzed and compared to background lung parenchyma. Statistical analysis was conducted using a paired t-test.

Results: A total of 21 nodules were evaluated, 18 (86%) of which were solid. All solid nodules appeared on at least one MRI sequence, with 16/18 (89%) visualized on DWI, allowing for ADC calculation. The mean ADC of lung nodules was 1.094 × 10^{-3} mm^2/s, significantly higher than background lung parenchyma (0.116 × 10^{-3} mm^2/s, p<.001). All nodules remain under serial imaging, with no diagnostic procedures performed to confirm malignancy.

Conclusions: Most solid nodules larger than 6 mm were visible on MRI, particularly DWI, where ADC may aid in future risk stratification. As our study is ongoing, none of the nodules have yet undergone diagnostic confirmation of malignancy, with findings to be reported later.

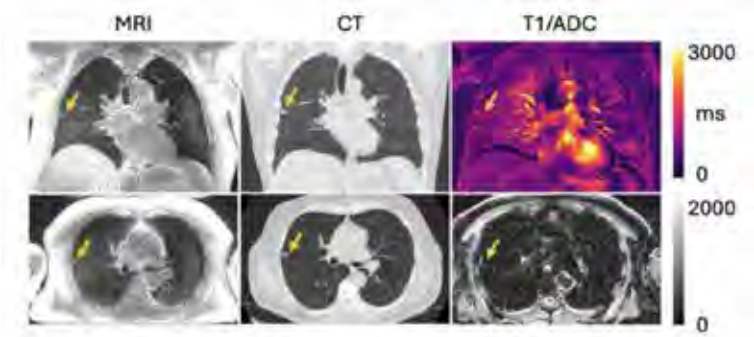
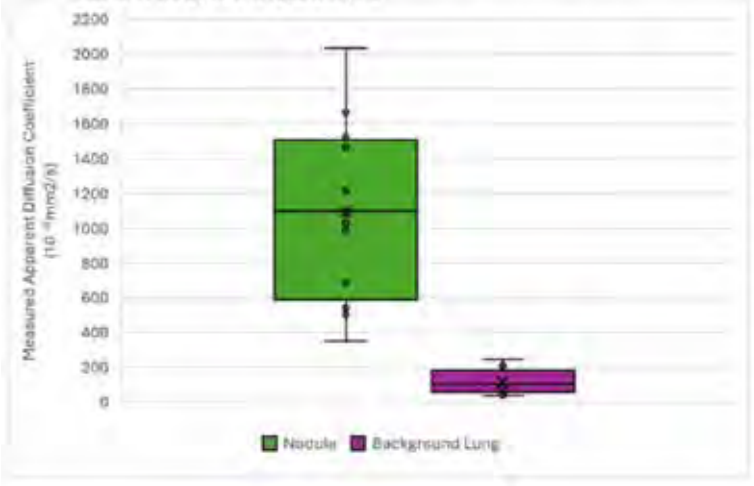


Figure 1: MR images and CT images (top: coronal cut, bottom: axial cut) showing 11x5 mm solid nodule (yellow arrow) in the peripheral right upper lobe. Last column showing T1 mapping in the top row and ADC mapping from the DWI sequence in the bottom row with signal intensity scale located on the right side.

Figure 2: Measurement of ADC using diffusion weighted imaging sequence of MRI: nodule vs background lung parenchyma



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Keywords: lung cancer screening, diffusion weighted imaging, apparent diffusion coefficient

EP.04 SCREENING AND EARLY DETECTION

EP.04.21 Imaging Manifestations in 4 Cases of Invasive Pulmonary Adenocarcinoma With Indolent Growth

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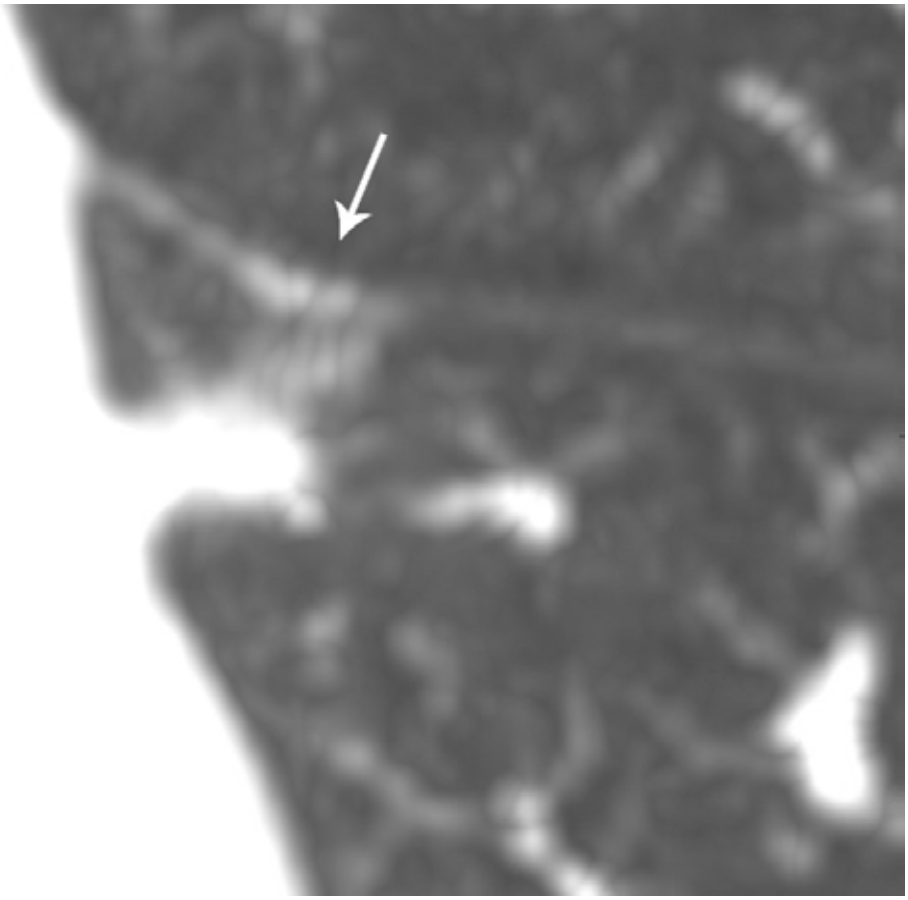
Introduction: Pathologically, the invasive component within the pulmonary tumor, particular adenocarcinoma, appears as a solid opacity on thoracic CT image [1,2]. The average doubling time of solid lung cancer is 207 days (range 39-400 days) [3-7], and key factors of growth rate include histological type, size, solidity, thick coarse spiculation, smoking history [7-9]. Slow growing solid adenocarcinoma on imaging shows signs of vacuoles, air-bronchogram in tumor [10, 11]. The authors encountered 4 cases of slow growing lung invasive adenocarcinoma, and their clinical, imaging manifestations are reported as follows.

Methods: All four patients were diagnosed with peripheral lung carcinoma, comprising 3 females and 1 male, with a mean age of 57 years (range: 49-61 years). The long diameter was measured on image showing the maximal nodule section, the wide diameter was the longest perpendicular to the length. Tumor volume doubling time (VDT) at two intervals in days between the first and last imaging was calculated using the modified Schwartz equation. A standard reconstruction algorithm was used, lung window, window width, 1000 HU; window level, −700 HU. Reconstruction thicknesses were 1.25 or 1.0 mm, and the intervals were equal to each corresponding thickness. Maximum intensity projection (MIP) slab thickness was five times the original slice thickness resulting in 5 line opacities of interlobar fissure or pleural tail-sign on lung window of unsharpened image, which was known as 5-line sign. 5-line sign clear defined as smooth contour lines and clear line intervals, otherwise, it is unclear.

Results: The pathological diagnosis of pulmonary nodules in all 4 cases was invasive adenocarcinoma, including 2 cases of solid nodules and 2 cases of solid-dominant nodules with a solid component greater than 90%. All 4 cases on CT images showed pleural tail sign, and MIP reconstruction image revealed a clear 5-line sign (Figure). The average VDT of tumor is 1994 days, ranging from 1593 to 2485 days. One case showed air-bronchogram within the tumor. Follow up for 4-10 years after surgery showed no recurrence or metastasis. Figure legend: MIP reconstruction shows a clear 5-line sign (arrow). A left lung nodule with a tail sign was discovered in 2010 and surgically removed in 2018 due to accelerated growth.

Conclusions: A clear 5-line sign displayed on MIP reconstruction of a nodule with a pleural tail sign may be a meaningful sign of indolent growth in invasive adenocarcinoma of the lung in addition to the vacuole and air-bronchogram in tumor.



Keywords: lung adenocarcinoma, growth, tomography, x-ray computed

EP.04.22 Internal Validation of the IASTO-PDPI Lung Cancer Risk Level at Indonesia's National Respiratory Center, Persahabatan Hospital

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Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide, often diagnosed at an advanced stage when curative surgical intervention is no longer an option, limiting treatment and prognosis. Assessing lung cancer risk is essential for guiding treatment decisions, as early detection improves survival. The IASTO-PDPI form (Indonesian Association for the Study of Thoracic Oncology-Indonesian Society of Respirology) was developed as a screening tool for high-risk individuals. Lung cancer risk factors vary across populations due to demographic and environmental differences. In Indonesia, it develops at a younger age due to earlier tobacco exposure. This study evaluates the internal validity and reliability of the IASTO-PDPI form to determine its clinical applicability for nationwide implementation.

Methods: A cross-sectional study was conducted at the outpatient clinic of Persahabatan Hospital from May 2024 to January 2025, involving 200 participants: lung cancer patients (n=150) and chronic obstructive pulmonary disease (COPD) patients (n=50). Validity was assessed using Pearson's correlation test, while reliability was evaluated using Cronbach's alpha coefficient. A p-value of <0.05 was considered statistically significant.

Results: The lung cancer group had a younger median diagnosis age of 59 years, with 61.4% of cases occurring in the 45-65 age group. In contrast, the COPD group had a median age of 65 years. COPD patients were included as a comparison group due to shared pathophysiological pathways with lung cancer, enabling a more precise risk evaluation. Validity analysis showed that 8 of 9 form items significantly correlated with the total score. Seven items demonstrated strong statistical significance (p<0.001), while family history of lung cancer (r=0.163, p=0.021) remained valid. The strongest correlations were observed for cigarette smoke exposure (r=0.664) and occupational carcinogen exposure (r=0.625), highlighting their substantial impact on lung cancer risk. Conversely, the prior cancer history item had a negative correlation (-0.113) and was not statistically significant (p=0.111), indicating invalidity. Reliability testing yielded a Cronbach's alpha of 0.420, suggesting suboptimal internal consistency.

Conclusions: The IASTO-PDPI form demonstrated good validity in identifying lung cancer risk factors but requires refinement to improve reliability. Personal history of cancer remains a recognized risk factor and may be considered in future screening eligibility criteria. In Indonesia, the likelihood of diagnosing lung cancer in individuals with prior malignancies is low, primarily due to lower life expectancy, high cancer mortality, and late-stage detection. Refining the invalid form item and enhancing reliability are essential before the clinical implementation of lung cancer screening across Indonesia.

Form Item	Correlation Coefficient (r)	p-value	Validity
Gender	0.572	<0.001	Valid
Age	0.284	<0.001	Valid
History of Cancer	-0.113	0.111	Invalid
Family History of Lung Cancer	0.163	0.021	Valid
Cigarette Smoke Exposure	0.664	<0.001	Valid
Occupational Carcinogen Exposure	0.625	<0.001	Valid
High Pollution Residence	0.356	<0.001	Valid
Unhealthy Indoor Environment	0.373	<0.001	Valid
Chronic Lung Disease History	0.329	<0.001	Valid

Keywords: Lung cancer screening, Validity and reliability, IASTO-PDPI form

EP.04 SCREENING AND EARLY DETECTION

EP.04.23 Prediction of STAS Positivity in Non-Small Cell Lung Cancer

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Introduction: Spread through air spaces (STAS), a histopathological hallmark of tumor cell dissemination into lung air spaces beyond the primary lesion, is increasingly being recognized as a critical prognostic factor in non-small cell lung cancer (NSCLC). Its presence is correlated with aggressive tumor behavior, higher recurrence rates, and diminished survival, particularly in adenocarcinoma subtypes. Accurate preoperative prediction of STAS is essential to optimize surgical strategies, adjuvant therapies, and patient outcomes. This study aimed to identify robust clinical, pathological, and imaging predictors of STAS positivity to refine the risk stratification and inform personalized therapeutic approaches.

Methods: A retrospective cohort analysis was conducted on 380 patients with resected primary NSCLC (selected from an initial cohort of 1,166 individuals treated between September 2001 and November 2024). The inclusion criteria required comprehensive STAS data from histopathological reports. Demographic variables (age, sex, and smoking history), clinical parameters (preoperative blood cell counts and comorbidities), pathological features (tumor stage and histopathology), and imaging biomarkers (lymph node SUVmax from PET/CT) were analyzed. Statistical methods included univariate analyses (chi-square test, t-test, and Mann-Whitney U test) and multivariate logistic regression to identify independent predictors. Receiver operating characteristic (ROC) curves assessed the discriminative power of significant variables.

Results: STAS positivity was identified in 188 patients (49.5%), with a significantly higher prevalence of adenocarcinoma (62.2% vs. 34.5% in non-adenocarcinoma subtypes; p<0.0001). Elevated preoperative monocyte counts (>0.73 × 10^3/mL) emerged as a strong independent predictor (OR 15.12, 95% CI 3.14-72.76, p=0.001), alongside adenocarcinoma histopathology (OR 2.71, 95% CI 1.34-5.46, p=0.005). Pathological nodal involvement (N1/N2 stages) and higher lymph node SUVmax were associated with STAS in univariate analysis (p<0.05), but were not significant in multivariate models. ROC analysis demonstrated a moderate predictive accuracy for SUVmax (AUC=0.592), suggesting limited standalone utility. Notably, STAS-positive patients reported lower rates of excessive phlegm (6.9% vs. 16.7%, p=0.003), a novel finding that warrants further exploration.

Conclusions: This study highlights adenocarcinoma histopathology and elevated preoperative monocyte counts as robust independent predictors of STAS in NSCLC. The association between systemic inflammation (reflected by monocytosis) and STAS underscores the interplay between tumor biology and host immune responses. Although PET/CT-derived SUVmax showed univariate correlations, its limited discriminative power in multivariate analysis emphasizes the need for complementary biomarkers. These findings support the integration of inflammatory markers and histopathological data into preoperative risk models to guide surgical planning (e.g., favoring lobectomy over sublobar resection in high-risk cases) and adjuvant therapy decisions. The limitations include the retrospective design and potential interobserver variability in the STAS assessment. Future multicenter studies should validate these predictors in larger cohorts, explore the molecular mechanisms linking monocytes to STAS, and investigate advanced imaging modalities (e.g., AI-enhanced radiomics) to improve predictive accuracy.

Keywords: Adenocarcinoma, Lung Neoplasms, Spread Through Air Spaces

EP.04.24 Initial Experience With Cancer Screening Center: Model to Improve Lung Cancer Screening Uptake

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Introduction: Lung cancer screening (LCS) is an essential step for early detection and improving survival rates for patients with lung cancer. In 2022, LCS uptake in the United States remained low at 16.0%, highlighting an important area of improvement. In 2022, our hospital established an all-encompassing screening center to provide integrated, multi-cancer screening services. We sought to describe our initial experience and determine whether a cancer screening center is associated with improved LCS uptake.

Methods: A retrospective review of 1,085 medical records was conducted. Patients aged 18 and older who visited the screening center between January 1, 2022, and December 31, 2022, were included. Eligibility for lung, breast, cervical, and colorectal cancer screening was determined using the United States Preventive Services Task Force criteria at the time of the office visit. Electronic medical records were reviewed through December 31, 2023, to assess screening completion. We collected demographics, primary diagnosis, procedures ordered, insurance status, personal and family cancer history, and smoking history. LCS uptake was calculated by determining the proportion of eligible patients who completed screening with low-dose CT scans out of the total due for screening.

Results: 1,085 patients were included in the study, with a mean age of 54.8 years (Table). Among them, 65 (6.0%) were current smokers, 284 (26.2%) were former smokers, and 734 (67.6%) had never smoked. The most common cancer screening for which patients were eligible included colorectal (n=368, 33.9%), breast (n=299, 27.6%), cervical (n=241, 22.2%), and lung cancer (n=76, 7.0%). Within the 76 patients eligible for LCS, 38 qualified for both colorectal and lung (50.0%), 19 for lung alone (25.0%), 7 for breast and lung (9.2%), 3 for all four cancers (3.9%), 2 for colorectal, cervical, and lung (2.6%), 4 for breast, colorectal, and lung (5.3%), and 3 for cervical, lung, and breast (3.9%). The mean age of those eligible for LCS was 62.5 years. Of the LCS-eligible cohort, 29 (38.2%) were female, 28 (36.8%) had a personal history of cancer, 44 (57.9%) had a family history of cancer, 23 (30.3%) were current smokers, and 53 (69.7%) were former smokers. Within this LCS-eligible cohort of 76 patients due for lung screening, 67 underwent the screening test, yielding an LCS uptake rate of 88.2% (67/76).

Conclusions: Our all-encompassing cancer screening center yielded a remarkable LCS uptake and provides a possible model to improve screening uptake. We will continue to investigate our experience and explore areas of improvement.

Table: Patient Characteristics

	All Patients (n=1085)	Lung Cancer Screening Eligible Patients (n=76)
Age, mean (standard deviation)	54.8 (15.0)	62.5 (7.3)
Gender, n (%)		
Female	758 (69.9%)	29 (38.2%)
Male	327 (30.1%)	47 (61.8%)
Personal history of cancer, n (%)		
Yes	381 (35.1%)	28 (36.8%)
No	704 (64.9%)	48 (63.2%)
Family history of cancer, n (%)		
Yes	864 (79.6%)	44 (57.9%)
No	221 (20.4%)	32 (42.1%)
Smoking history, n (%)		
Current	65 (6.0%)	23 (30.3%)
Former	284 (26.2%)	53 (69.7%)
Never	734 (67.6%)	0 (0%)
Unknown	2 (0.2%)	0 (0%)
Lung cancer screening-eligible patients (n=76)		
Colorectal/Lung		38 (50.0%)
Lung		19 (25.0%)
Breast/Lung		7 (9.2%)
Breast/Cervical/Colorectal/Lung		3 (3.9%)
Cervical/Colorectal/Lung		2 (2.6%)
Breast/Colorectal/Lung		4 (5.3%)
Cervical/Lung		0 (0.0%)
Cervical/Lung/Breast		3 (3.9%)
Lung cancer screening uptake		67/76 (88.2%)

Keywords: lung cancer screening uptake, cancer screening center

EP.04 SCREENING AND EARLY DETECTION

EP.04.25 Integrated Biological and Imaging Assessment for Pulmonary Nodule Malignancy: A Real-World Study With Large Cohort Modeling and Validationes

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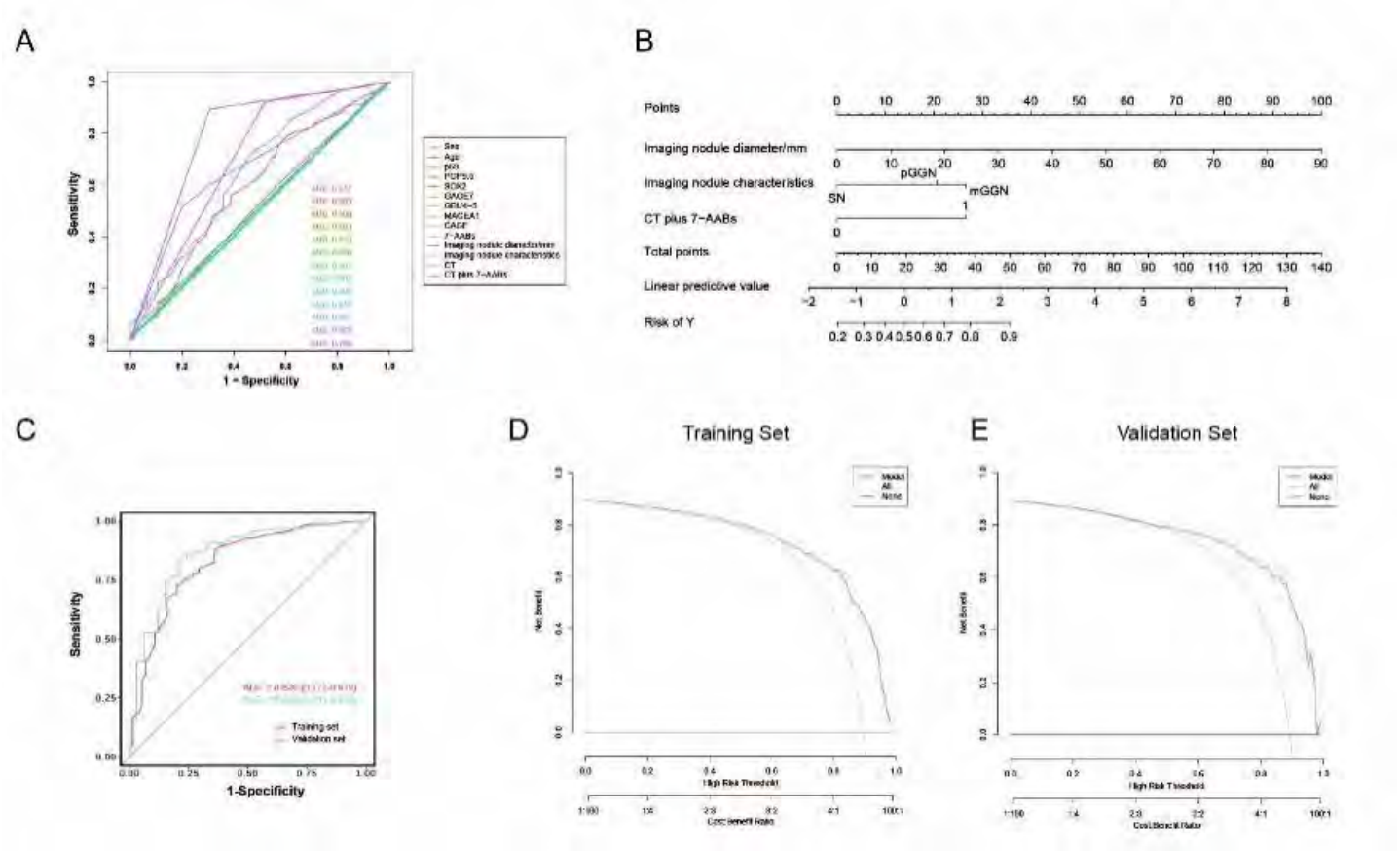
Introduction: Accurate early diagnosis of lung cancer is critical for prognosis improvement. Current imaging-based differentiation of pulmonary nodules faces limitations in specificity and sensitivity. Tumor-associated autoantibodies (e.g., 7-AABs) have emerged as promising biomarkers for early detection. Leveraging a large real-world cohort, this study innovatively integrates CT imaging features with seven lung cancer-related serum autoantibodies (7-AABs) to develop a multidimensional prediction model, aiming to optimize diagnostic accuracy and support clinical decision-making for pulmonary nodule management.

Methods: A retrospective cohort of 1,017 pathologically confirmed pulmonary nodule patients (training set: 712; validation set: 305) from the First Affiliated Hospital of Zhejiang University (January 2020-April 2024) was analyzed. Independent predictors were identified via univariate and multivariate logistic regression, followed by nomogram construction. Model performance was assessed using ROC curves, calibration plots, and decision curve analysis (DCA).

Results: Univariate analysis revealed that the combination of CT and 7-AABs achieved a higher AUC (0.794) compared to CT alone (0.667) or 7-AABs alone (0.514) (Fig1.A). Multivariate analysis identified nodule diameter (OR=1.075), nodule nature (solid vs. mixed ground-glass nodule, OR=0.134), and CT combined with 7-AABs (OR=6.581) as independent predictors. The nomogram model demonstrated excellent discrimination (Fig1.B), with AUCs of 0.826 (training set) and 0.862 (validation set) (Fig1.C). DCA confirmed its superior net clinical benefit over single-modality approaches (Fig1.D, E).

Conclusions: The integration of 7-AABs and CT significantly enhances the accuracy of distinguishing benign and malignant pulmonary nodules. The validated prediction model provides a robust tool for clinical decision-making, facilitating personalized diagnostic and therapeutic strategies.



Keywords: Pulmonary Nodules, Autoantibody, Early Diagnosis

EP.04 SCREENING AND EARLY DETECTION

EP.04.26 A Case Series on Video Fiber Optic Bronchoscopy in the Diagnosis of Non Small Cell Lung Cancer (NSCLC) Subtype: Squamous Cell

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Introduction: Squamous cell lung cancer is a frequently occurring carcinoma in frequent smokers1. Around 80% of lung cancers can be accounted to Non small cell lung cancer (NSCLC) out of which 20 to 30% are squamous subtype2. The symptoms include chest pains, cough, shortness of breath, loss of weight an appetite, fatigue etc. Other factors such as second hand smoke, pollution, exposure to metals or asbestos can also lead to development of carcinoma3. The diagnosis can be done using a combination of imaging, biopsy or molecular characterization

Methods: In the present study, patients with symptoms of NSCLC were diagnosed using endobronchial biopsy assisted through fiber optic bronchoscopy. Absence of pleural effusion necessitated the need for a biopsy. All the patients had a history of smoking. Washing and brushing of bronchoscope was carried out after each procedure. The biopsied samples were sent for BAL -cytology, HPE, GeneXpert NTEP (NS) and AFB culture.Case series: Patient 1: A 50 year old patient presented with the symptoms of trouble in breathing, wheezing and weight loss. With video bronchoscopy a mass lesion protruding from right upper lobe, occluding >50% of Lumen of RMB, highly vascular was observed while the left lung and trachea were normal. Two Grey white/ dark brown soft tissues measuring 0.5 x 0.2 x 0.1 cm was biopsied and sent for analysis. Non small cell carcinoma, favoring squamous cell carcinoma was diagnosed with clinical correlation. Patient 2: A 53 year old patient presented with the symptoms of coughing up blood, hoarseness, fatigue and weight loss. With fiber optic bronchoscope an endobronchial mass was seen in right main bronchus (RMB) obstructing the opening while the left bronchial tree and trachea were normal. Multiple Grey white/ dark brown soft tissues measuring 2 x 1 x 0.5 cm was biopsied and sent for analysis. Non small cell carcinoma, favoring squamous cell carcinoma was diagnosed with clinical correlation. Patient 3: A 61 year old patient presented with the symptoms of shortness of breath, weight loss, recurring lung infections such as pneumonia and bronchitis. With video bronchoscopy an endobronchial mass was seen in right main bronchus (RMB) obstructing the opening while the left bronchial tree was normal. Multiple Grey white soft tissues, completely embedded measuring 1x 0.7x 0.4 cm was biopsied and sent for analysis. Keratinizing squamous cell carcinoma, moderately differentiated was diagnosed with clinical correlation.

Results: It was observed that malignant epithelial cells arranged in sheets and clusters with high N:C round to oval nuclei with vesicular chromatin and moderate amount of pink eosinophilia. Through the biopsy the diagnosis of Non small cell lung cancer, squamous sub type was concluded.

Conclusions: In the absence of pleural effusion, biopsy using a bronchoscopy can be very effective in diagnosis. This case series demonstrates the effectiveness of Fiber optic bronchoscopy and endobronchial biopsy in diagnosing squamous cell lung carcinoma in patients presenting with various respiratory symptoms. The procedure allowed for direct visualization of endobronchial masses and provided tissue samples for pathological and microbiological analysis, leading to accurate diagnoses.

Keywords: Fibre optic bronchoscopy, Non small cell lung cancer (NSCLC), Endobronchial biopsy

EP.04 SCREENING AND EARLY DETECTION

EP.04.27 Enhancing Lung Cancer Screening: A Comparative Evaluation of Predictive Models for Malignancy in Pulmonary Nodules

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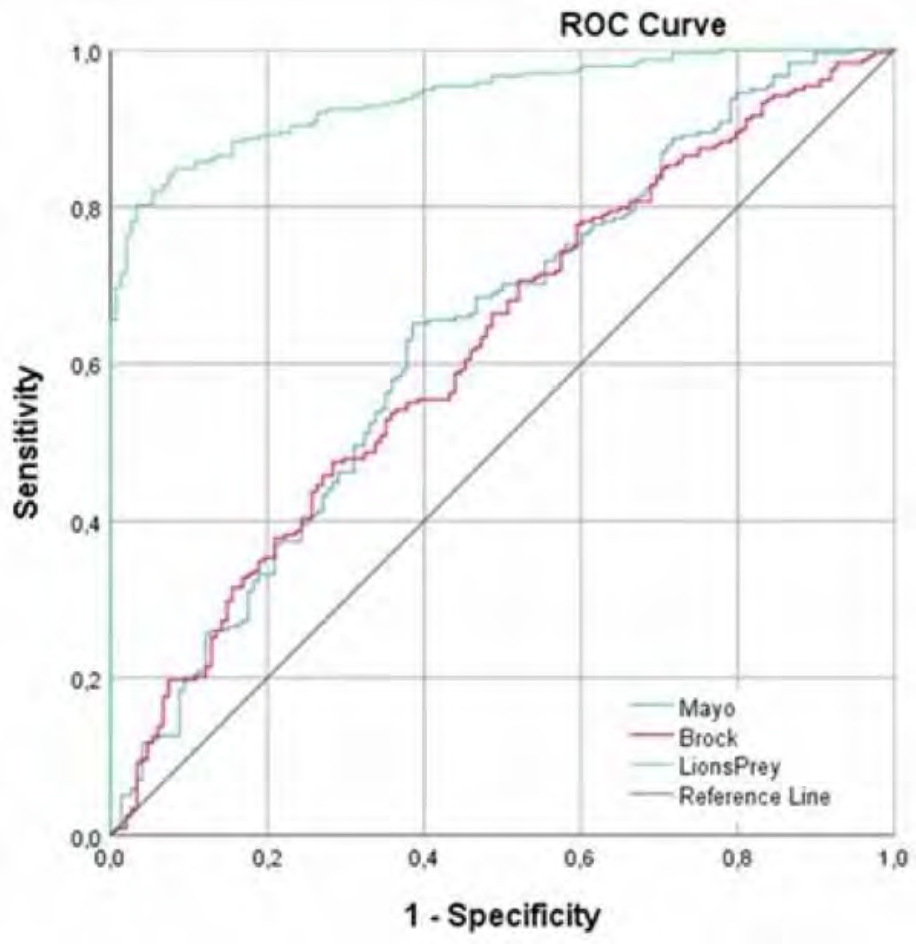
Introduction: Lung cancer screening is becoming increasingly widespread, resulting in more incidental detections of pulmonary lesions. Consequently, accurate malignancy classification is crucial. The Brock and Mayo models are well-established risk tools. This study evaluates the predictive accuracy of these models in comparison to the new LIONS PREY (Lung lesION Score PREdicts malignancY). Unlike the established models, LIONS PREY includes lesion progression as an optional parameter and assigns greater weight to smoking as a risk factor.

Methods: We retrospectively included all patients who underwent resection of a pulmonary lesion (≤30mm) at our lung cancer center between 08/2022 and 08/2024, excluding those with incomplete clinical parameters for model calculation. Two study groups were formed based on histopathological results (group M: malignant, group B: benign). The threshold for benign versus malignant nodules was defined at a predicted malignancy probability of ≥80%. We evaluated the predictive accuracy of the Brock, Mayo, and LIONS PREY models based on calibration (observed/expected ratio), discrimination (AUC), and the total number of correctly classified patients (OCC).

Results: During the treatment period, 776 patients underwent resection at our center. LIONS PREY showed a significantly higher precision according to OCC (95.4%, p=0.008) compared to the Brock (64.1%) and Mayo (69.8%) models. The calibration of LIONS PREY (O/E-ratio: 1.1) was significantly superior (p=0.036) to the Brock (1.4) and Mayo (1.3) models, indicating that both established models underestimated malignancy in pulmonary lesions. In terms of discriminatory power, LIONS PREY (AUC: 0.94; 95%-CI: 0.92-0.96) outperformed both the Brock (AUC: 0.62; 95%-CI: 0.56-0.68) and Mayo (AUC: 0.64; 95%-CI: 0.58-0.69) models (p=0.003, DeLong analysis).

Conclusions: The success of a lung cancer screening program depends on an effective model for assessing malignancy. The newly developed LIONS PREY demonstrates superior accuracy compared to the established Brock and Mayo models and should be prioritized in lung cancer screening initiatives.

Parameter	LIONS PREY	Brock model	Mayo model
Patient related parameters			
Age	+	+	+
Sex	-	+	-
Family history of lung cancer	-	+	-
Emphysema	-	+	-
Extra-thoracic cancer	-	-	+
History of any cancer	+	-	-
Nodule related parameters			
Size	+	+	+
Solidity	+	+	-
Location (upper lung)	-	+	+
Count	-	+	-
Spiculation	+	+	+
Size progression	+ (optional)	-	-
Risk factor related parameters			
Smoking history	+	-	+
Pack Years	+	-	-



Keywords: lung cancer screening, prediction of malignancy, Brock, Mayo, LIONS PREY models

EP.04 SCREENING AND EARLY DETECTION

EP.04.28 TD-GC-MS-Based Breath Analysis for Early Diagnosis of Lung Cancer

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Introduction: Lung cancer (LC) is the most common type of cancer worldwide and the leading cause of cancer-related deaths. Most LC patients are diagnosed at an advanced stage, as the disease is often asymptomatic in its early phases. The poor prognosis associated with advanced stages underscores the urgent need for screening and early diagnosis, when patients may benefit from potentially curative treatments. An ideal screening test should detect the disease at an early stage, have a low false-positive rate, minimize unnecessary invasive procedures, cause no harm to healthy individuals, be cost-effective, and ultimately reduce mortality. In recent years, breath analysis has emerged as a promising non-invasive diagnostic method for early LC detection.

Methods: The study analyzed breath samples from 73 (63 males/ 10 females; mean age: 62.7 years) LC patients (Stage I: 13, Stage II: 16, Stage III: 35, Stage IV: 30) and 68 healthy controls (38 males/ 30 females; mean age: 39.6 years). All LC patients were newly diagnosed, treatment-naïve individuals with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. The samples were analyzed using thermal desorption-gas chromatography-mass spectrometry (TD-GC-MS) to identify volatile organic compounds (VOCs). Peak area related to amount of each compound was calculated by automated integration using a software which was available onto the GC-MS system, otherwise targeted low intensity signals were integrated manually for the correlation of increasing or decreasing compound concentrations in breath. Additionally, demographic and pathological data were analyzed.

Results: 23 of 105 VOCs detected in breath were identified as potential biomarkers for LC. Compared to the control group, n-butane (p=0.039), isobutane (p=0.048), and 2,4-dimethylhexane (p=0.025) were significantly higher in LC patients, while dodecane (p=0.046) was significantly lower. Biochemical parameters did not show significant differences between age groups or genders. Smokers had elevated levels of 2-methylpentane and benzene compared to non-smokers and former smokers. Stage III and IV patients had higher median n-butane levels than earlier stages. Stage I and III patients had higher isobutane, isoprene, ethanol, 2-methylpentane, 4-methylheptane, 4-methyloctane, and ethylbenzene levels than stage II and IV patients. Stage I patients had the highest levels of acetone, benzene, toluene, isoprene, and 1,2-pentadiene, whereas stage IV patients had the lowest 1,4-dichlorobenzene levels. Other biochemical markers did not show significant differences across stages.

Conclusions: TD-GC-MS data demonstrated significant differences in VOCs between LC patients and healthy controls. Establishing a standardized protocol for breath sample collection and analysis may enable the use of these compounds as biomarkers for early LC detection in clinical settings. Such an approach may substantially improve diagnostic accuracy and promote timely interventions for patients at risk.

Keywords: Volatile organic compounds, breath analysis, gas chromatography-mass spectrometry

EP.04 SCREENING AND EARLY DETECTION

EP.04.29 Tobacco-Related Atheromatous Disease as Eligibility Criteria for Lung Cancer Screening: A Prospective Evaluation

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Introduction: Criteria for lung cancer screening (LCS) eligibility are usually based on age, amount of tobacco consumption in pack-years or number of cigarettes smoked per day and duration, and delay from smoking cessation. We hypothesized that age (>45 years old), daily cigarette smoking for 10 years and history of tobacco related atheromatous diseases were relevant criteria for LCS eligibility.The primary objective was to report lung cancer prevalence after a first round of LCS among patients with history of cardiovascular atheromatous related diseases in two prospective cohorts (PREVALUNG, NCT 03976804 and PREVALUNG ETOILE, NCT 05649046). We also compared eligibility to NLST (NCT 00047385) and NELSON (NL580) trials as well as lung cancer prevalence at first LCS round and rate stage I and II LC. We finally reported outcomes after lung cancer diagnosis.

Methods: We analyzed the results of 502 patients who were prospectively enrolled in PREVALUNG and PREVALUNG ETOILE cohorts and underwent a first LCS round in two academic centers from November 2019 to May 2024. Inclusion criteria were 45-75 years old, history of a tobacco related atheromatous disease and history of tobacco consumption for 10 years. Main exclusion criteria were symptoms of LC, existing follow-up for pulmonary nodule, pulmonary fibrosis or hypertension, dyspnea at rest, active pulmonary infectious disease.Lung cancer prevalence was reported as % and 95% confidence interval. Comparison between proportions were performed using Chi squared test of Fischer's exact test when appropriate. Analyses were performed using STATA 18.

Results: Among the 502 patients, lung cancer prevalence was 2.99% [1.81 - 4.90]. 58.8% met the NELSON eligibility criteria and 50.4% met the NLST criteria. Among diagnosed lung cancer (n=15), 11 (73.3%) were detected at stage I, one (6.7%) at stage II (i.e 80% at stage I or II), one (6.7%) at stage III, and two (3.3%) at stage IV. Lung cancer prevalence at first round of LCS was significantly higher among patients with atheromatous cardiovascular diseases compared with participants of NLST and NELSON trials (risk ratio 2.91 [1.74 - 4.86] and 3.37 [1.92 - 51], respectively). Among patients with lung cancer, proportion with stage I or II lung cancer at diagnostic (80.0%) were not significantly different compared with NLST at first round (61.3%), p=NS. All patients diagnosed with lung cancer underwent lung cancer specific treatment according to the recommandations including 12 patients who underwent anatomic resection with lymph node dissection, 1 radio-chemotherapy and 2 systemic treatments. After surgery, in-hospital mortality was null and there was no serious adverse event (i.e. Clavien-Dindo > 3).

Conclusions: Among patients with history of tobacco-related atheromatous diseases, lung cancer prevalence is higher compared with NLST and NELSON populations. Lung cancer were diagnosed at a curative early stage in 80% and outcomes after curative surgical resection proved feasibility and safety. We conclude that history of tobacco-related atheromatous diseases is a relevant criteria for lung cancer eligibility.

Keywords: lung, cancer, screening

EP.04 SCREENING AND EARLY DETECTION

EP.04.30 Second Primary Lung Cancer in Surgically Treated Breast Cancer Patients: Association or Incidental Finding?

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Introduction: Breast cancer survivors face a 40% higher likelihood of developing a second cancer, with lung cancer being the most common. Related to this risk, follow-up chest CT scans in breast cancer patients, especially those with lymph node involvement, lead to a higher detection rate of lung nodules.

Methods: Prospective study on breast cancer patients (BCPs) surgically treated in a single center between 01.2019-01.2024 was conducted. BCPs who developed pulmonary nodules after surgery were analysed. The primary aim was to estimate the frequency of lung cancer in a population of patients undergoing oncologic surgery for primary breast cancer. Secondary aim was comparing the diagnostic and therapeutic recommendations between the oncologist and the thoracic surgeon during CT evaluation of pulmonary nodule

Results: Out of 598 BCPs, 16 second primary NSCLC were identified (2.7%). A total of 136 patients showed a pulmonary nodule on CT scan, 35 of them (25.7%) were surgically resected or biopsied while 101 (74.3%) were kept in radiological follow-up. Among NSCLC, 14 (87.5%) were early stages. Retrospectively analysing all CT scan of patients with lung nodules, a different evaluation between oncologist and thoracic surgeon was noticed: the oncologist identified a suspicious lung cancer in a small percentage of patients (table 1)

Conclusions: Our analysis reported a 2.7% of secondary primary NSCLC among 598 BCPs. Due to the high risk to develop a second primary NSCLC, CT-scan during follow-up of high-risk BC patients should be considered. Moreover, a combined evaluation of CT scan between oncologist and thoracic surgeon is recommended to promptly identify second primary NSCLC

Table1. differences in evaluation of pulmonary nodules (second primary NSCLC) between surgeon and oncologist

		Thoracic Surgeon Evaluation				
		No indication	Control CT	Biopsy	^{18}FDG/PET	surgery
Oncologist Evaluation	No indication	2	1	3	1	7
	Control CT	0	1	1	3	6
	Surgical evaluation	1	0	0	0	1
	Biopsy	0	0	0	2	1
	^{18}FDG/PET	0	0	1	0	1
Total of patients		3	2	5	6	**16**

Keywords: lung cancer, breast cancer, early detection

EP.04 SCREENING AND EARLY DETECTION

EP.04.31 Nomogram for Predicting Lung Cancer-Free Survival in Patients With Persistent Pulmonary Nodules

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Introduction: Early detection of lung cancer is essential for improving prognosis. This study aimed to identify key predictors of lung cancer-free survival (LCFS) in patients with persistent pulmonary nodules and to develop a predictive nomogram model.

Methods: We retrospectively analyzed data from patients with persistent pulmonary nodules evaluated at MD Anderson Cancer Center between November 2003 and December 2022. Persistent pulmonary nodules were defined as nodules visible on at least two CT scans, three months apart without evidence of shrinkage. Thoracic radiologists reviewed radiologic features. LCFS was calculated from the detection of persistent pulmonary nodules to lung cancer diagnosis or last follow-up. Multivariable Cox regression was used to identify independent predictors of LCFS, and a nomogram was constructed to estimate 6-, 12-, and 24-month cancer-free survival probabilities. Discriminative ability was evaluated using the concordance index (C-index) and time-dependent receiver operating characteristic (ROC) curves. Calibration plots assessed model agreement, and Kaplan-Meier (KM) curves compared survival across risk groups. Decision curve analysis (DCA) evaluated clinical utility against nodule size alone.

Results: A total of 392 persistent pulmonary nodules were included. The median follow-up from the second CT scan (used to define persistence) was 592 days. Nodules were randomly divided into training (n = 274) and validation (n = 118) cohorts. Multivariate analysis identified smaller nodule size, ground-glass opacity (GGO) type, and absence of spiculation as independent predictors of prolonged lung cancer-free survival (LCFS). The final nomogram, incorporating age, gender, smoking history, family history of lung cancer, emphysema, nodule size, type, location, count, and spiculation, demonstrated strong discriminatory performance, with a C-index of 0.771 in the training cohort and 0.727 in the validation cohort. The area under the ROC curve (AUC) at 6, 12, and 24 months was 0.874, 0.827, and 0.787 in the training cohort, and 0.893, 0.866, and 0.681 in the validation cohort, respectively. Calibration plots showed excellent agreement between predicted and observed outcomes. Risk stratification based on the nomogram effectively separated patients into high- and low-risk groups ($p < 0.001$). DCA demonstrated that the nomogram offered greater clinical benefit than using nodule size alone.

Conclusions: We developed and validated a nomogram for predicting cancer-free survival in patients with persistent pulmonary nodules. This tool may support clinicians in making personalized decisions regarding early detection of lung cancer.

EP.04 SCREENING AND EARLY DETECTION

EP.04.32 The Impact of Symptom Monitoring on Survival Among Patients With Lung Cancer. a 4-Year Follow-Up of the SYMPRO-Lung Study

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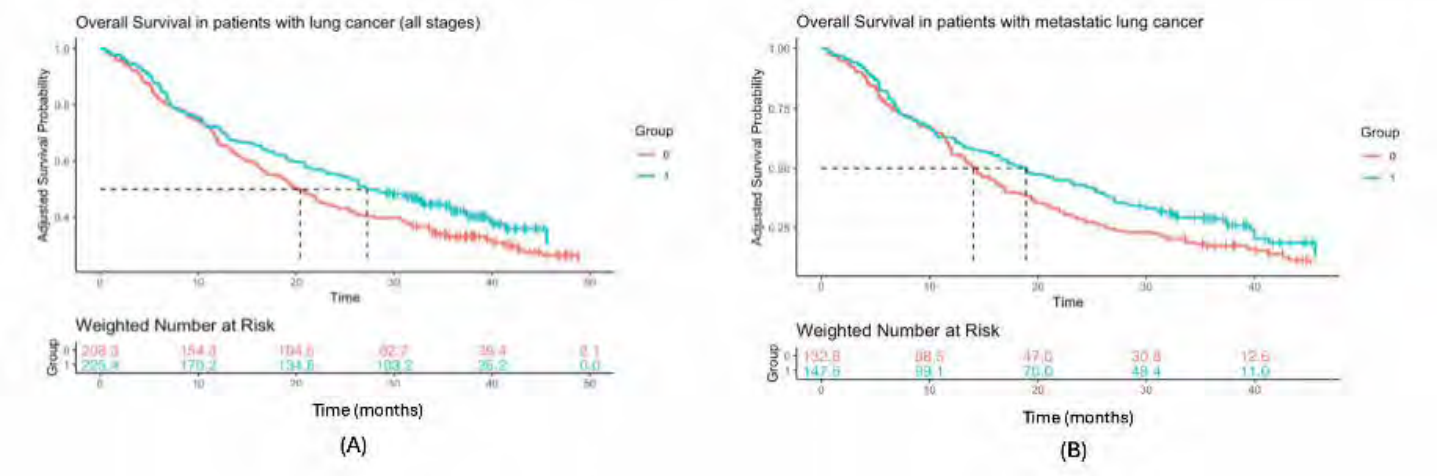
Introduction: The SYMPRO-Lung study assessed the effect of patient-reported outcome (PRO) symptom monitoring on health-related quality of life (HRQoL) and Overall Survival (OS) in lung cancer patients. Within this study, a significant improvement in 1-year HRQoL and even a trend towards a survival benefit following PRO symptom monitoring was observed1. A study in metastatic cancer patients found no survival benefit within 2 years of follow-up2. Nonetheless, this effect may be more pronounced in earlier stages of the disease or with prolonged follow-up. Therefore, this study aims to assess the long-term effect of PRO symptom monitoring on OS in early- and advanced-stage lung cancer up to 4 years follow-up.

Methods: The SYMPRO-Lung study included patients with stage I to IV lung cancer. Patients in the intervention group completed weekly PRO symptom assessments. The control group received usual care. Data collection started between 2019 and 2021 and was extended with information from the national cancer registry up to 2024. Cox proportional hazards analysis was used to assess the association between PRO symptom monitoring and OS in patients with stage I to IV lung cancer, while adjusting for potential confounders (months since initial diagnosis to development of first metastasis, months since initial diagnosis to first systemic treatment, line of systemic treatment, and a random effect for site clustering). A sensitivity analysis was conducted including only patients with metastatic (M1) lung cancer.

Results: A total of 446 patients were included in the analysis. Baseline characteristics were similar across the intervention (n=235) and control group (n=211). In the total study population, PRO symptom monitoring was significantly associated with improved OS (HR 0.73, 95% CI 0.57-0.92, Figure 1A). In patients with M1 lung cancer, a tendency but non-significant association towards an OS benefit was observed in the PRO symptom monitoring group (HR 0.79, 95% CI 0.61: 1.04) (Figure 1B).

Conclusions: PRO symptom monitoring was significantly associated with improved OS over a 4-year follow-up period in patients with lung cancer. Although non-significant, a similar tendency towards a survival benefit of PRO symptom monitoring in patients with M1 disease was observed. Although the impact of PRO symptom monitoring on OS might be more pronounced in patients with early-stage lung cancer, the clearly demonstrated benefits of PRO symptom monitoring on both HRQoL as well as survival in the total lung cancer population could pave the path towards successful implementation.



Keywords: Lung cancer, Symptom monitoring

EP.04 SCREENING AND EARLY DETECTION

EP.04.33 Exhaled Breath Analysis Using Infrared Spectroscopy Combined With Machine Learning Algorithms for Lung Cancer Diagnosis

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Introduction: Lung cancer (LC) is the leading cause of cancer-related mortality worldwide, with an overall 5-year survival rate of 19% and a median survival of 12-months. Early diagnosis is crucial, and breath analysis using Fourier transform infrared (FTIR) spectroscopy is a promising non-invasive method for the early detection of LC. This study utilized FTIR spectroscopy combined with machine learning algorithms to develop a unique breath analysis method, enabling the identification of lung cancer and its discrimination from healthy individuals.

Methods: The study analyzed breath samples from 64 LC patients and 47 healthy controls. All LC patients were newly diagnosed, treatment-naïve individuals with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. Spectra of breath samples were obtained using a PerkinElmer Frontier FTIR spectrometer equipped with a gas cell featuring a 16-meter optical path length and a 2.3-liter internal volume. The breath samples were categorized and classified using unsupervised multivariate analysis (principal component analysis (PCA)) and machine learning techniques. The identification of LC from infrared spectra of breath samples was examined using probabilistic neural network (PNN), support vector machine (SVM), and linear discriminant analysis (LDA) classifiers.

Results: The IR gas-phase spectra from the breath samples of both LC patients and healthy controls revealed distinct spectral bands, particularly in the 1300-800 cm-1 region. Two peaks at 879 and 882 cm-1, which belongs to out-of-plane C-H bending bands of aromatic compounds, were found to be more intense in the breath samples of healthy controls compared to those of LC patients. PCA results demonstrated the most distinct separation between the breath spectra of LC patients and healthy controls in the 915-850 cm-1 region, where out-of-plane C-H bending vibrations of substituted aromatic compounds were observed. SVM and PNN techniques were effectively applied to diagnose LC from breath IR data, achieving an accuracy of slightly over 70%. The breath diagnostic approach could potentially be used as a decision support system, as 5-fold test performances for both classifiers exceed 70%. However, the 885-870 cm-1 spectral region yielded the best results in LDA classification, with an accuracy of 83.8%, while the 915-850 cm-1 region also provided comparable predictions, with an accuracy of 81.1%.

Conclusions: FTIR spectroscopy combined with machine learning techniques, emerges a potential non-invasive tool for the diagnosis of LC through exhaled breath analysis.

Keywords: exhaled breath, FTIR spectroscopy, machine learning

EP.04.34 Preliminary Results of Added Benefit of Blood-Based Biomarkers in a Lung Cancer Screening Program

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Introduction: Screening for lung cancer using low-dose computed tomography (LDCT) has been proven effective in detecting early-stage lung cancers. However indetermined results are frequent, making the best follow-up strategy difficult to determine. Researchers have identified a signature consisting of 24 microRNAs with high prognostic value [1]. Here we combine microRNAs measurements with the results obtained from LDCT, to determine and confirm the added value of circulating microRNA biomarker measurements in an independent cohort.

Methods: Blood samples from four participants of our ongoing lung cancer screening were analyzed. All participants were later on diagnosed with a malignancy. Three were diagnosed with a lung cancer, while one participant had a thyroid cancer. Two negative controls of patients with a negative biopsy were used. microRNAs were analyzed by blinded personnel. The ratios for the presence of disease (PD) and presence of an aggressive (PAD) disease were then assessed.

Results: All four malignancies showed a positive profile for PD, and a negative profile for PAD. In the controls the thresholds for PD and PAD were not crossed. The results per each participant with the correlating details of the malignancy can be found in Figure 1.

Conclusions: In our pilot, all malignancies were labeled as presences of disease, while in the negative control samples no presence was observed. In our sample, a delineation between different lung cancer stages was not yet observed, a different picture might emerge with additional samples. As the blood collection was well tolerated and the analysis of the biomarkers is well defined, there is an added benefit to guide a risk-based approach consisting of CTs and blood-based biomarker monitoring in lung cancer screenings.

References [1] Boeri, M., et al., MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. Proc Natl Acad Sci U S A, 2011. 108(9): p. 3713-8.

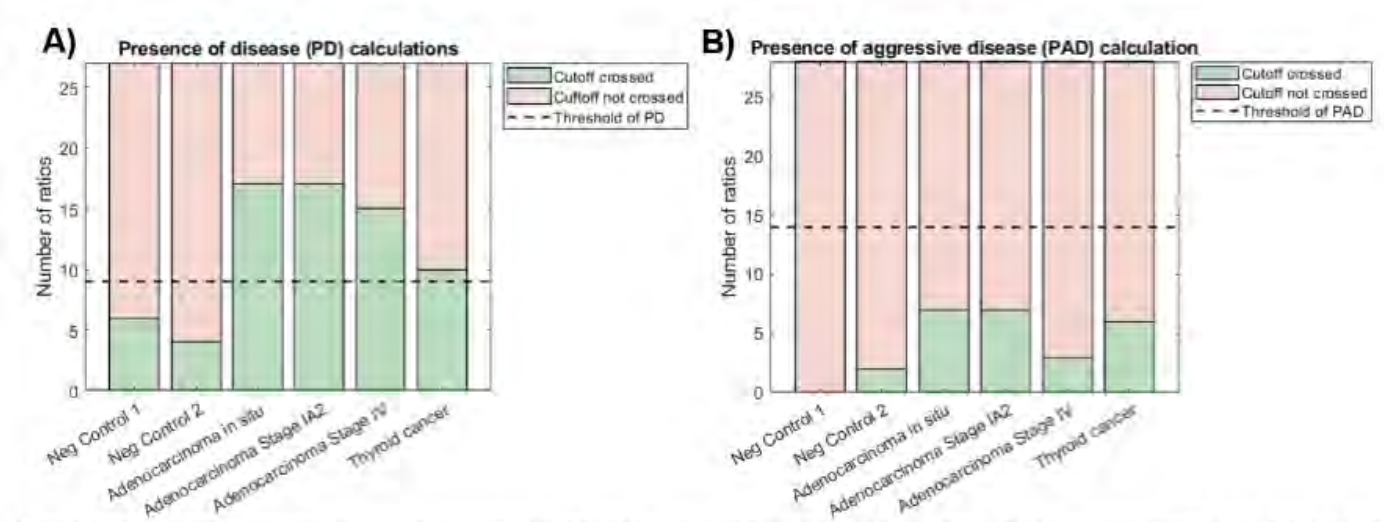

Figure 1. Numbers of miRNAs ratios which crossed or did not cross the predefined cutoffs. A) shows the results for the PD calculation with the threshold for a positive result. B) Results for the PAD with the respective threshold

Keywords: microRNA, Lung Cancer Screening, Indetermined results

EP.04 SCREENING AND EARLY DETECTION

EP.04.35 Innovative Intraoperative Technique for Rapid Tumor Identification in Lung Cancer Through Spectral Characterization: A Promising Exploration

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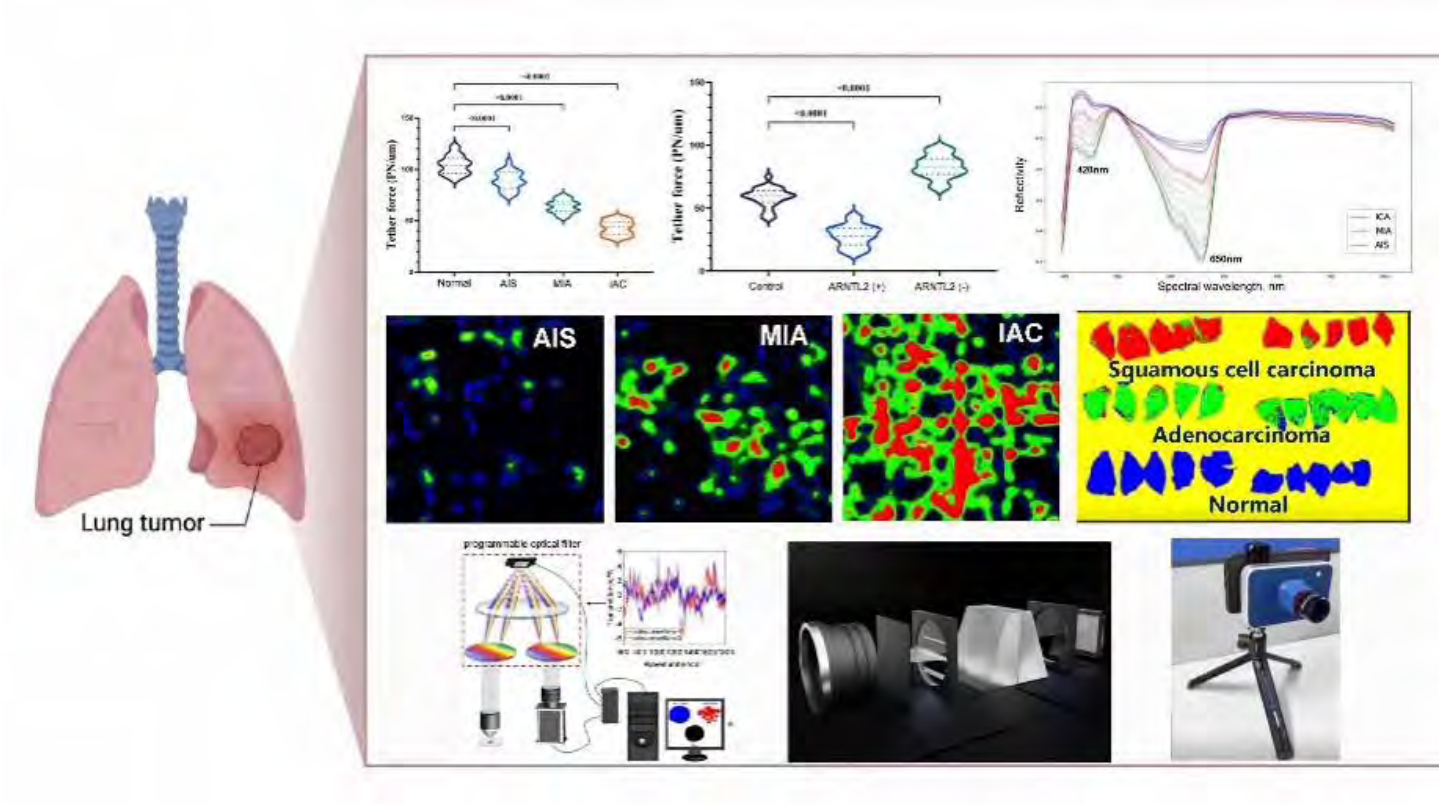
Introduction: To investigate a novel approach for the rapid identification of lung cancer tumor location and type using distinct spectral characteristics, aiming to improve intraoperative decision-making and reduce dependence on time-consuming frozen section pathology.

Methods: This study builds upon our previous findings, which characterized the mechanical rigidity of lung cancer tumor cells using spectral features and simulated mechanical signals. The optical properties of tumor tissues were evaluated using a CMOS-based spectrophotometric camera with a resolution of less than 10 nanometers. The camera is integrated with an on-chip operating system, and we developed a corresponding interface and software platform to enable portable, handheld spectral imaging analysis.

Results: During the progression of lung adenocarcinoma from adenocarcinoma in situ (AIS) to minimally invasive adenocarcinoma (MIA) and ultimately to invasive adenocarcinoma (IAC), significant spectral differences were observed between the wavelengths of 420 nm and 650 nm. These differences reflect substantial alterations in the average cellular mechanical stiffness, which are associated with changes in cytoskeletal protein characteristics per unit area of tumor tissue. We investigated the spectral characteristics of various pathological types of lung cancer tissues. Notably, distinct spectral features were observed for normal alveolar epithelial cells, lung squamous cell carcinoma, and lung adenocarcinoma across different wavelengths. Leveraging the spectrophotometric camera, we further explored the feasibility of rapid intraoperative identification of different pathological lung cancer subtypes. In a study of 30 samples (10 normal controls, 10 lung adenocarcinomas, and 10 lung squamous cell carcinomas), spectral analysis results were in complete agreement with intraoperative frozen sections and postoperative paraffin pathology findings.

Conclusions: The distinct spectral characteristics of lung cancer, resulting from differences in membrane tension compared to normal alveolar epithelial cells, suggest a viable approach for intraoperative rapid identification. Various pathological types and developmental stages of lung cancer, such as ranging from AIS to MIA and IAC, correspond to specific spectral ranges. Further research and validation are essential to confirm the effectiveness of this technique in clinical practice.



Keywords: spectral characteristics, intraoperative identification, innovative technique

EP.04 SCREENING AND EARLY DETECTION

EP.04.36 Evaluation of the Utility of msignal® for Lung Cancer Screening in a Rural Region of Northern Japan (Hokkaido Region)

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Introduction: Advances in minimally invasive surgery, immunotherapy, and molecular targeted therapies have significantly improved the prognosis of patients with advanced lung cancer. However, further reducing lung cancer mortality requires early diagnosis, making widespread screening essential. In particular, Hokkaido, the northernmost and second-largest island of Japan, has one of the highest cancer mortality rates nationwide. Due to its geographically vast area and limited medical access, the cancer screening participation rate in Hokkaido remains among the lowest in Japan. Recent advances in liquid biopsy technologies have made non-invasive, repeatable cancer diagnostics increasingly feasible. Among these, microRNAs (miRNAs) are gaining attention as key biomarkers involved in tumor growth, metastasis, and the tumor microenvironment, making them useful tools for early diagnosis and understanding cancer biology. Craif Inc. has developed miSignal® Scan, a testing service that analyzes urinary miRNA profiles obtained through next-generation sequencing and applies a machine learning model to distinguish between healthy individuals and those at risk of various cancer types. This service provides a risk assessment for seven types of cancer, including lung cancer, based on a predictive model. A predictive model was developed using 278 lung cancer patients and 125 healthy controls. The data were split into training and validation cohorts in a 3:1 ratio. In the study, 37 miRNAs were upregulated and 2 miRNAs were downregulated in lung cancer. A predictive model utilizing 40 selected miRNAs achieved an area under the ROC curve (AUC) of 0.951 in a validation cohort, indicating a high potential for early lung cancer detection. In this study, this service was offered to 100 elderly residents of Iwanai Town, Hokkaido, as part of a prospective observational study. High-risk individuals were referred for further diagnostic examinations at Iwanai Kyokai Hospital or affiliated institutions.This study aims to evaluate the utility of miSignal® Scan as a lung cancer screening method in a rural region with low screening participation rates.

Methods: A model case study was conducted in a rural region of Hokkaido, Northern Japan. A total of 100 individuals (male-to-female ratio of 46:54, mean age 67.2 years) aged 60 or older who had not undergone lung cancer screening in five years were screened using the miSignal® Scan technology provided by Craif Inc. Participants classified as moderate or high risk were referred for further examination with chest CT scans.

Results: Out of 100 participants, five were classified as moderate risk. Among the three individuals who underwent CT scans, one case of suspected lung cancer was identified and subsequently diagnosed as adenocarcinoma in situ (AIS) through pathological examination.

Conclusions: Urinary miRNA-based screening is a non-invasive and convenient method that can be performed at home, making it a potentially effective screening tool for regions with geographical constraints and limited medical resources. This study highlights the potential of such methods to address existing barriers to cancer screening in underserved areas. Further large-scale prospective studies are warranted to validate its utility as a novel lung cancer screening method and to explore its role in encouraging cancer screening participation in regions with low screening rates.

Keywords: Minimally invasive screening, Liquid biopsy, Cancer screening in underserved areas

EP.04 SCREENING AND EARLY DETECTION

EP.04.37 An Observational Study Evaluating the Benefits of AI-Assisted Lung Cancer Screening Using Chest X-Rays in Bangkok, Thailand

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Introduction: Lung Cancer (LC) is the most common cancer and the leading cause of cancer deaths in Thailand. Low Dose CT has been shown to improve survival; however, reimbursement is not currently available. The aim of this observational study is to evaluate the performance of Artificial Intelligence (AI) to assess LC risk in Chest X-Rays (CXRs) in the Bangkok area.

Methods: qXR-Lung Nodule (LN) and qXR-Lung Nodule Malignancy Score (LNMS) algorithm was deployed across six hospitals in Bangkok. Patients with prior LC were excluded. Images flagged for nodules by AI were read by radiologists who categorized them as having nodules/normal/inconclusive and rated the risk of malignancy for those categorized as nodules into high/low/inconclusive. Images rated as inconclusive were read by a pulmonologist who suggested follow-up investigations- CT/no action/follow-up required. The Positive Predictive Value (PPV) of LN, the PPV and Negative Predictive Value (NPV) of LNMS algorithms are reported with radiologist and pulmonologist as reference standard. Patients who were referred to CT were considered as having high-risk nodules. The predictive values of LNMS were calculated using only those patients confirmed as having nodule by either radiologist or pulmonologist. The 95% CI of the predictive values were constructed using the modified Wilson's score method.

Results: Overall, 7,784 patients were screened and the AI flagged nodule in 988 (946 low-risk and 42 high-risk) patients (12.7%). Mean age was 51.7 and 62.6% were females. 79 patients were excluded from analysis due incomplete radiologist assessment. The PPV of LN was 66.4% (63.3-69.4). The PPV of LN was higher when the nodules malignancy risk was high 96.77% (83.81 - 99.43) when compared to low risk 64.92% (61.70 - 68.01). The PPV of high-LNMS was 50.0% (33.2-66.8), and the NPV of low-LNMS was 92.8% (90.4-94.7). The incidence of suspected and confirmed lung cancer was 7.79 and 1.30 per 1000 person years respectively. Increasing age and active smoking was associated with LC in this cohort.

Conclusions: AI achieved a reasonable PPV of 66.4% in flagging nodule. This could be considered clinically useful as predictive values depends on prevalence and the reference standard for this study was radiologists and a high inter-reader variability is known among radiologists. The PPV was higher when the nodule was flagged as high-risk by LNMS. A limitation of this study is there was no comparator arm to test whether AI assisted workflow had a higher incidence compared to standard workflow.

Keywords: AI-assisted, Lung cancer screening, Chest X-rays

EP.04 SCREENING AND EARLY DETECTION

EP.04.38 A Computational Framework for Estimating Transportability in Cancer Screening Trials

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Introduction: Lung cancer screening has been shown in trials such as NLST and NELSON to reduce mortality, while trials such as PLCO and ITALUNG have reported null results. Although researchers have speculated that this variation may stem from differences in baseline demographics or trial implementation, such explanations remain largely qualitative and speculative. Despite extensive critiques of screening trials and their inconsistent results, no prior work has explicitly modeled the full probabilistic pathway from screening to mortality. In particular, the pathway from screening to subsequent treatment is typically left implicit, limiting our ability to generalize trial findings to new populations. We formalize this pathway to provide a framework for policymakers to assess whether trial results are likely to transport to novel target populations.

Methods: We started with a simple model and expanded the full expression from screening S to mortality Y by incorporating disease severity D, symptom level X, and treatment T.

Results: Under randomization of screening, the naive mortality difference of the screened groups,

$E[Y=1 |S=1] - E[Y=1 | S=0]$,

identifies the average treatment effect of a screening protocol in a target population. We demonstrate an alternate decomposition of the average treatment effect that includes nontrivial terms for the difference in treatment probability

$P(T=i|(S,X,D) = (1,x,d)) - P(T=i|(S,X,D) = (0,x,d))$,

the prevalence $P(D=d)$ of disease severity, and combinations of terms of the expected outcome difference conditioned on choice of treatment and screening

$E[Y|(T,S,X,D) = (t,s,x,d)]$.

The presence of these terms even after randomization of screening indicate how the average treatment effect of screening is sensitive to both demographic factors as well as the post-screening treatment regime, both of which may vary across populations and medical contexts. Transporting trial results may therefore fail, as differences in any of these terms in a novel demographic or medical context can result in discrepant estimates of the average treatment effect of screening.

Conclusions: Randomization of screening alone does not guarantee transportable estimates of outcome differences across medical contexts. Our framework provides an avenue to explain why some trials show significant benefits while others do not: differences in post-screening treatment regimes, symptom presentations, and disease severity distributions all influence the observed mortality effects. The original publications for NLST, NELSON, PLCO, and ITALUNG did not report the joint distributions of screening, treatment, cancer staging, and outcome needed to estimate transportability to new contexts. Modeling these components allows researchers to predict whether a screening protocol will succeed in a new setting.

To improve transportability, screening trials must move beyond reporting average effects. Instead, they should publish outcomes stratified by all causal factors linking screening to mortality, especially treatment, which is often unreported or inconsistently applied across trials. These details enable decomposition of the screening effect and estimation of how well it transfers to new populations.

Ultimately, current screening trials designs are insufficient for transportable insights. By modeling the full causal pathway and requiring detailed outcome reporting, we can move from speculative interpretation to evidence-based prediction of screening efficacy across new populations.

Keywords: Screening, Computational Methods

EP.04 SCREENING AND EARLY DETECTION

EP.04.39 Lung Cancer Early Screening via cfDNA Fragmentome Profiling

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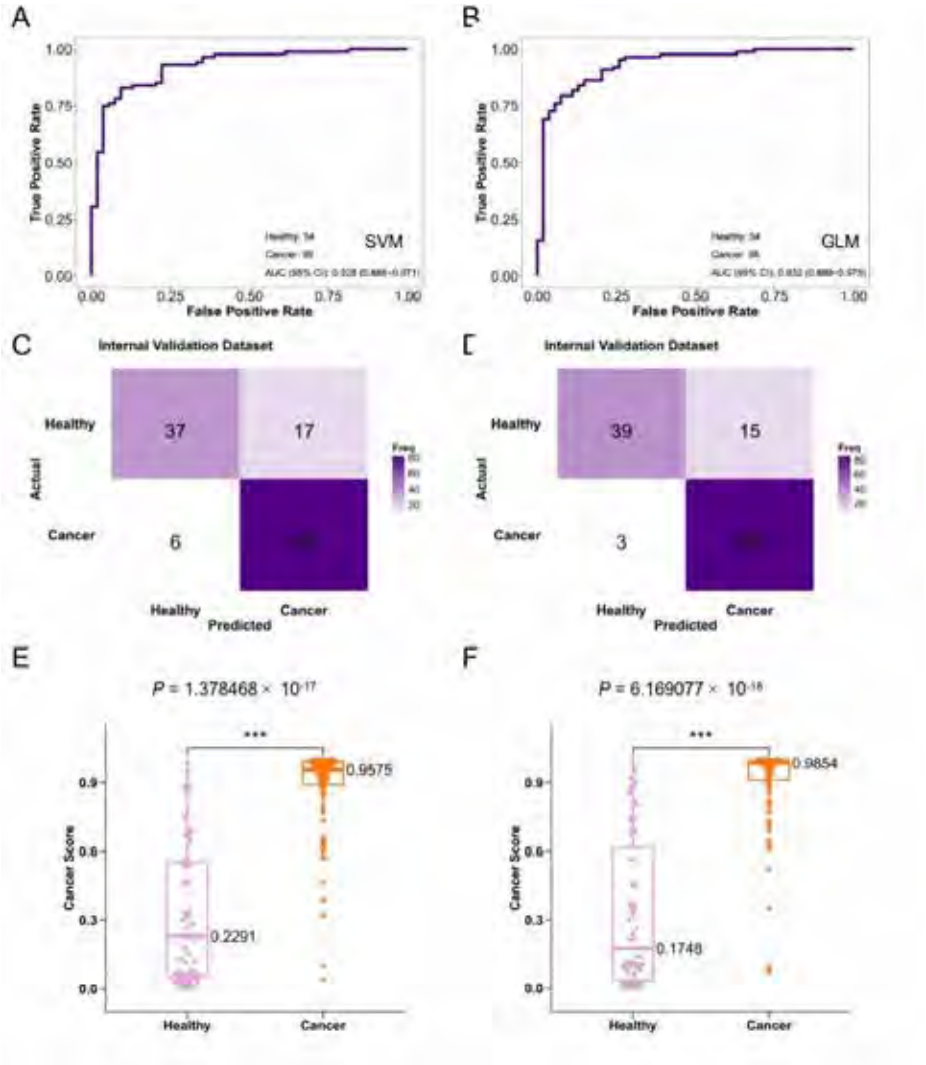
Introduction: Lung cancer is a leading cause of cancer-related deaths worldwide, and early screening is crucial for improving patient survival rates. cfDNA has demonstrated superior sensitivity and specificity in early screening for lung cancer. This study combines cfDNA sequencing technology with various machine learning models to explore the differentiation of benign and malignant lung nodules.

Methods: We enrolled 175 lung cancer patients and 107 healthy controls, and analyzed their plasma cfDNA samples using whole-genome sequencing (WGS). In the training cohort, multiple features were extracted, including fragment length, 3' end motif, methylation motif, N-index, E-index, and CNV, which were used as input features for analysis. We performed lung cancer malignancy prediction using generalized linear models (GLM) and support vector machines (SVM). We conducted extensive evaluation on the validation dataset. By comparing the predictions of different models, we were able to validate the accuracy, sensitivity, specificity, and generalizability of these models in lung cancer screening.

Results: This study employs deep learning algorithms to conduct multimodal integrated analysis of cfDNA molecular omics, copy number variations, and epigenetic characteristics, aiming to simultaneously achieve the differentiation of benign and malignant lung nodules. Based on the training dataset (n = 140), we constructed a multimodal deep learning classification model. The 10-fold cross-validation results showed its performance in distinguishing benign from malignant as 71.7% specificity and 92.0% sensitivity (AUC: 0.925). The model performed stably in the independent validation cohort (n = 142), with specificity and sensitivity of 72.2% and 96.6% (AUC: 0.932), respectively.

Conclusions: This study developed a deep learning model based on cfDNA multi-dimensional omics features, focusing on the precise analysis of lung cancer malignancy prediction. This approach provides a highly sensitive, non-invasive solution for lung cancer screening. Future research will involve large-scale validation and further explore the clinical potential of staging prediction and therapeutic monitoring.



Keywords: blood omics, lung cancer screening

EP.04 SCREENING AND EARLY DETECTION

EP.04.40 Preoperative Prediction of Occult Lymph Node Metastasis in Clinical Stage I NSCLC Using CT Radiomics, PET, and ctDNA

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Introduction: Accurate preoperative prediction of occult lymph node metastasis (OLNM) is essential for optimizing treatment strategy in early-stage non-small cell lung cancer (NSCLC). This study aimed to develop a multimodal predictive model combining CT radiomics, PET quantification, and ctDNA.

Methods: Patients with clinical stage I NSCLC were selected from a thoracic surgery database. Clinical data, circulating tumor DNA (ctDNA), and PET-CT quantification data were accessible for all patients. Using the preoperative contrast-enhanced CT scans, 20 radiomics features were derived from the whole tumor region of interest. All patients were divided into groups according to the pathological status of their lymph nodes, either positive (pN+) or negative (pN-) for cancer.

Results: We evaluated CT radiomics, PET, and ctDNA for OLNM prediction in 554 patients. Two predictive models were developed: Model 1 (clinical variables, CT radiomics, and ctDNA, n=554) and Model 2 (clinical variables, CT radiomics, ctDNA, and PET, n=372). LASSO regression identified key features. In Model 1, body mass index (BMI), tumor solidity, ctDNA positivity, and CT radiomics features such as kurtosis and density were selected. In Model 2, features included tumor solidity, SUVmax at the tumor edge (SUVmax_edge), and CT radiomics features, including small area low gray level emphasis, density, and mass. Model 1 achieved an AUC of 0.80 (accuracy: 0.85), and Model 2 achieved an AUC of 0.81 (accuracy: 0.87). Both models had high specificity (>0.99) but lower sensitivity. The combination of clinical, imaging, and ctDNA data enabled effective OLNM prediction across both models, supporting better risk stratification and treatment decisions.

Conclusions: Integration of CT radiomics, PET quantification, and ctDNA testing along with routine clinical variables improves OLNM prediction.

Table 1. Characteristics of 554 patients

Characteristics	Total	pN positive		P value
		Negative (n=465)	Positive(n=89)	
Gender (%)				.305
Male	366 (66.06)	303 (65.16)	63 (70.79)	
Female	188 (33.94)	162 (34.84)	26 (29.21)	
Age (mean±SD)	64.83±9.47	65.01±9.55	63.92±9.06	.322
BMI (mean±SD)	24.38±3.10	24.27±3.12	25.08±2.91	.024
Smoking status (%)				.079
Never	225 (40.61)	198 (42.58)	27 (30.34)	
Current	155 (27.98)	128 (27.53)	27 (30.34)	
Ex	174 (31.41)	139 (29.89)	35 (39.33)	
Lung adenocarcinoma (%)				.002
Adenocarcinoma	372 (67.15)	325 (69.89)	47 (52.81)	
Non adenocarinoma	182 (32.85)	140 (30.11)	42 (47.19)	
Tumor solidity (%)				< .0001
Non-solid	11 (1.99)	11 (2.37)	0 (0.00)	
Part-solid	201 (36.28)	193 (41.51)	8 (8.99)	
Solid	342 (61.73)	261 (56.13)	81 (91.01)	
Tumor size (mm, mean±SD)	28.71±7.20	28.40±7.28	30.34±6.59	.020
Tumor solid size (mm, mean±SD)	25.12±9.02	24.24±9.19	29.67±6.45	< .0001
CTR (mean±SD)	0.87±0.22	0.85±0.23	0.98±0.07	< .0001
Tumor volume (mm^3, mean±SD)	7978.07±6367.52	7527.37±6037.16	10327.77±7477.46	.000
PET-CT variables[3)]				
SUVmax_edge (mean±SD)	6.03±5.19	5.43±5.00	9.69±4.81	< .0001
SUVavg_edge (mean±SD)	2.78±2.02	2.52±1.93	4.36±1.85	< .0001
MTV_edge (mean±SD)	13.00±32.28	12.63±34.11	15.31±17.19	.058
TLG_edge (mean±SD)	46.27±174.09	43.02±185.45	66.28±69.86	.372
ctDNA (%)				< .0001
Negative	373 (67.33)	339 (72.90)	34 (38.20)	
Positive	181 (32.67)	126 (27.10)	55 (61.80)	
cT category (%)				.000
cT1	347 (62.64)	307 (66.02)	40 (44.94)	
cT2	207 (37.36)	158 (33.98)	49 (55.06)	
pT category (%)				.008
pT1	314 (56.68)	275 (59.14)	38 (42.70)	
pT2	227 (40.97)	182 (39.14)	46 (51.69)	
pT3	9 (1.63)	6 (1.29)	3 (3.37)	
pT4	4 (0.72)	2 (0.43)	2 (2.25)	
pN category (%)				< .0001
pN0	465 (83.94)	465 (100.00)	0 (0.00)	
pN1	46 (8.30)	0 (0.00)	46 (51.69)	
pN2	43 (7.76)	0 (0.00)	43 (48.31)	

1) Chi-squared test for categorical variables

2) Independent t-test for continuous variables

3) n=372 : Negative (n=320), Positive (n=52)

Table 2. LASSO Model variables, performance and validation (Model 1 and Model 2)

Selected variables (OR, 95% CI, p-value)	**Model 1 (Clinical + CT Radiomics + ctDNA, n=554)**	**Model 2 (Clinical + CT Radiomics + ctDNA + PET, n=372)**
BMI	1.17 (1.14–1.20), p < 0.001	–
Tumor solidity (ref. not solid)	1.31 (1.16–1.47), p < 0.001	–
ctDNA Positivity	1.44 (1.33–1.56), p < 0.001	–
SUVmax_edge	–	1.20 (1.16–1.25), p < 0.001
Kurtosis	1.29 (1.24-1.34) p < 0.001	–
Small Area Low Gray Level Emphasis	0.91 (0.87-0.95) p = 0.010	0.93 (0.90-0.96) p < 0.001
Percentile_2.5	–	1.36 (1.24–1.49), p < 0.001
Density	1.59 (1.48–1.72), p < 0.001	1.45 (1.27–1.66), p < 0.001
Mass	–	1.14 (1.11–1.17), p < 0.001
Lacunarity_b0	0.91 (0.86-0.96) p = 0.015	
SUVmax_edge	–	1.20 (1.16–1.25), p < 0.001
Validation Results (Training/Test)	**Model 1 (Clinical + CT Radiomics + ctDNA, n=554)**	**Model 2 (Clinical + CT Radiomics + ctDNA + PET, n=372)**
Accuracy	0.85 / 0.85	0.87 / 0.86
AUC	0.80 / 0.80	0.80 / 0.81
Sensitivity	0.16 / 0.28	0.12 / 0.21
Specificity	0.99 / 0.99	0.99 / 0.99

Keywords: Occult lymph node metastasis (OLNM), Radiomics, Multimodal prediction

EP.04 SCREENING AND EARLY DETECTION

EP.04.41 Detecting Minimal Residual Disease (MRD) in Lung Cancer Using an Epigenetic-Based Liquid Biopsy Approach

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Introduction: Detecting minimal residual disease (MRD) in lung cancer is critical, as many patients relapse after curative surgery. Despite therapeutic advancements, a widely accessible, precise MRD detection method remains unavailable. Liquid biopsy, particularly analysis of cell-free DNA (cfDNA) and its epigenetic signatures, offers a promising non-invasive solution.

Methods: We developed a novel, ultra-sensitive, and cost-effective blood-based assay for lung cancer detection and monitoring.

- Sample Collection: Blood samples were collected from 47 early-stage NSCLC patients and 64 healthy individuals.
- cfDNA Isolation & Epigenetic Profiling: cfDNA was extracted, fluorescently labeled, and hybridized to a custom microarray targeting lung cancer-specific methylation regions.
- Data Analysis: An AI-based pipeline was used for biomarker selection. Epigenetic patterns were evaluated using heatmap clustering, principal component analysis (PCA), and ROC curves. Sensitivity and specificity were optimized using the Youden Index.

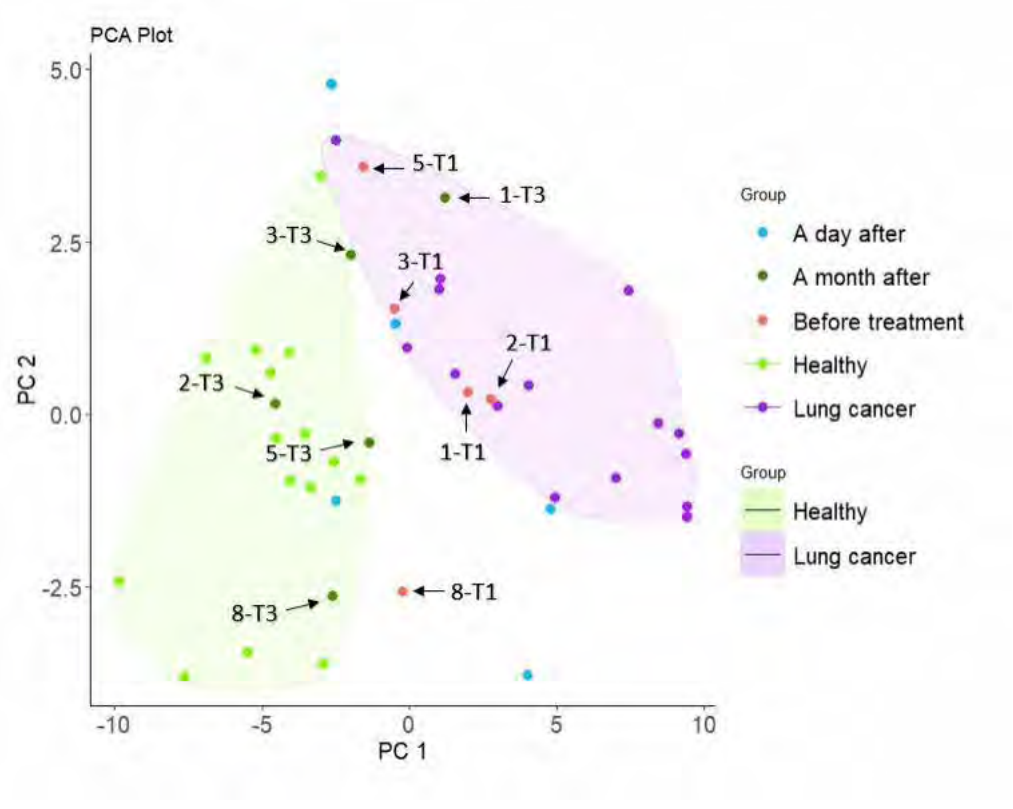
Results:

· Early Detection: The assay distinguished NSCLC patients from healthy controls with 91% sensitivity and 94% specificity.

· MRD Detection: In five NSCLC patients tested pre-operatively, one day post-op, and one month post-op, four showed a marked shift in their epigenetic profile post-surgery, clustering with healthy controls in PCA, suggesting significant tumor DNA clearance.

· Limitations: Small sample size, tumor heterogeneity, and potential confounding from benign lung conditions.

Conclusions: This novel epigenetic-based liquid biopsy shows strong potential for detecting MRD and monitoring recurrence in early-stage NSCLC. The observed epigenetic shifts post-surgery support its utility in real-time tumor monitoring and early intervention. Ongoing studies aim to validate these findings in larger cohorts and assess integration into personalized lung cancer management.



Keywords: Minimal Residual Disease (MRD), Epigenetic Liquid Biopsy, NSCLC Early Detection

EP.04 SCREENING AND EARLY DETECTION

EP.04.42 Alunghive: Autonomous Registry and Analytics System to Transform Clinical Workflow and Enable Multicenter Lung Cancer Screening Research

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Introduction: The expansion of low-dose CT (LDCT) lung cancer screening programs has introduced significant operational complexity across health systems, particularly in managing longitudinal workflows, follow-up adherence, and multicenter research participation. Despite growing adoption of AI tools for nodule detection and Lung-RADS classification, integration into real-world workflows remains disjointed, often reliant on manual data abstraction, unscalable registries, and fragmented communication between clinical and research teams. There is a critical need for a system-level solution that unifies imaging, clinical data, and research workflows into a single autonomous platform.

Methods: We developed LungHive, an autonomous clincial patient registry, a digital health infrastructure designed to autonomously ingest imaging and clinical data, apply validated AI pipelines, and output structured insights for both care delivery and research purposes. Within AURA, the LungHive vertical provides a turnkey solution for lung cancer screening and trial support. The system integrates with PACS, EHR, and research databases, enabling real-time AI analysis (Lung-RADS scoring, temporal nodule tracking), patient-specific registry building, and dynamic eligibility screening. We deployed AURA-LungHive at Vanderbilt University Medical Center, embedding it into the clinical screening flow and configuring it to support prospective research trials across multiple sites.

Results: AURA-LungHive processed LDCT imaging and clinical context from over 2,000 patients, producing structured outputs including Lung-RADS scores, growth metrics, risk of developing lung cancer, probability of malignancy of pulmonary nodules based upon several radiomic models, and care recommendations. Integration with Vanderbilt's workflows enabled: (1) Autonomous registry generation and real-time tracking of follow-up compliance (2) Pre-filled radiology reports and dashboards for care teams, reducing time-to-read and improving standardization (3) AI-driven eligibility algorithms that combined structured imaging and unstructured clinical data (e.g., smoking history, comorbidities) to support real-time cohort discovery for research protocols. (4) A single unified data pipeline serving both clinical care and research data capture, reducing duplication and manual effort. The system also supports federated deployments across multiple centers, allowing external institutions to join shared trials while maintaining local workflows. AURA was configured to be compliant with HIPAA, 21 CFR Part 11, and institutional IRB requirements, ensuring interoperability and auditability.

Conclusions: LungHive demonstrates a scalable, autonomous framework to support both clinical lung cancer screening and multicenter research trial infrastructure. By bridging imaging, clinical, and research systems through an AI-powered registry, the platform enables a new model of screening that is intelligent, efficient, and trial-ready. Unlike point AI tools, AURA represents a full-stack transformation of lung cancer workflow—from detection to intervention to discovery. Integration within the Vanderbilt and ongoing expansion to additional sites highlights its potential as a foundational layer for learning health systems in thoracic oncology.

Keywords: Computed Tomography, Early Detection, Radiomics

EP.04 SCREENING AND EARLY DETECTION

EP.04.43 Chest X-Ray Analysis With Artificial Intelligence Software Aids in the Early Diagnosis of Lung Cancer- a Case Series

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Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide. Though screening with low dose computed tomography (LDCT) is effective in reducing mortality, widespread adoption is limited. Chest X-ray is a frequently used imaging modality. Pulmonary nodules are often missed or underreported on routine chest X-rays, contributing to missed lung cancer diagnosis. Artificial intelligence (AI)-based software has shown potential in identifying high-risk nodules. But prospective reports on the real-world impact of these tools on patient outcomes are limited.

Methods: qXR software (Qure.ai, Mumbai India) is a deep learning based algorithm that can detect lung nodules on posteroanterior (PA) chest X-rays. qXR also categorizes the nodules as low or high risk. qXR automated interpretation tool was routinely used on all chest X-rays obtained in our center from February 2024 till November 2024. Patients flagged with a high-risk nodule by qXR were reviewed by radiologists and chest physicians, and in case of suspicion were evaluated further with a thoracic CT scan.

Results: We present case series of three patients in whom AI software (qXR, Qure.ai) flagged suspicious pulmonary nodules on chest X-rays obtained for non-respiratory conditions (Table 1: case 1- screening prior to anti-TNF therapy, case 2- fever evaluation, case 3- smoking cessation counseling). Subsequent imaging and biopsy confirmed early-stage lung cancer in all cases. Each patient underwent curative surgical intervention with favourable outcomes.

Conclusions: AI-powered chest X-ray analysis can act as a safety net, particularly in settings with limited radiologist availability or high workloads. It also offers a screening opportunity independent of specific criteria such as age, smoking history, or family history of cancer diagnoses. In countries without lung cancer screening programs or where radiologists do not evaluate all chest X-rays, the use of AI software for chest X-ray analysis can enable early detection of high-risk nodules.

Table 1: Summary of patients diagnosed with early stage lung cancer through nodules detected by AI chest X-ray

Age/ Gender	Primary presentation	Admission clinic	Nodule diameter on chest X ray	Nodule diameter on CT	Diagnosis	pTNM stage
57/ Male	Evaluation for anti-TNF treatment in a patient with ulcerative colitis	Gastroenterology	9 mm	9 mm	Adenocarcinoma	T2a (vpi) N0 M0
64/ Male	Hyperglicemia and fever, diagnosed as urinary tract infection	Emergency	23 mm	19 mm	Adenocarcinoma	T1b N0 M0
65/ Female	Cessation of smoking therapy	Family medicine	18 mm	24x37 mm	Squamous cell carcinoma	T3 (satellite nodule) N0 M0

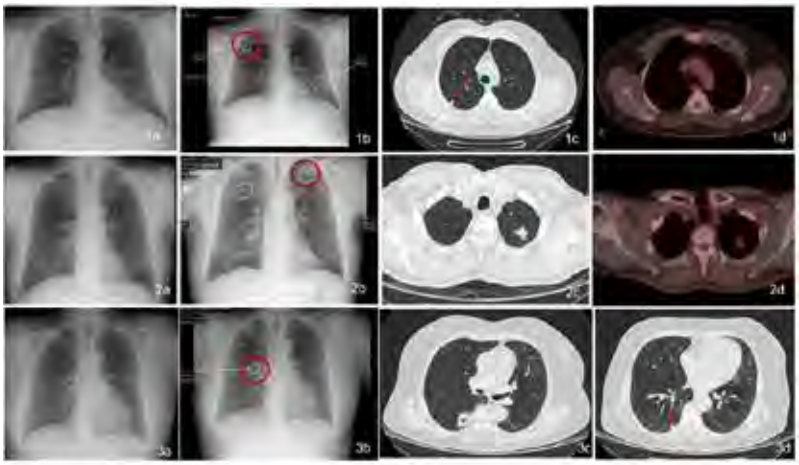

Figure. 1,2,3a: Chest X-ray image of the patients without AI, 1,2,3b: AI interpretation of chest X-ray. Suspicious nodules are marked by red circles, 1,2,3c and 3d: Computed tomography (CT) sections (Arrows show nodules), 1,2d: PET/CT sections

Keywords: Lung Cancer, Artificial Intelligence, Early Diagnosis and Screening

EP.05 PULMONOLOGY AND STAGING

EP.05.01 Use of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Molecular Characterization of Non-Small Cell Lung Cancer

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Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) represents the gold-standard technique for the assessment of hilar and mediastinal lesions. The molecular characterization of non-small cell lung cancer (NSCLC) aims to identify genetic and molecular alterations that drive tumorigenesis, disease progression and therapeutic resistance. This approach has elucidated key oncogenic mutations in genes such as EGFR and KRAS, as well as the expression of predictive biomarkers such as PD-L1 (Programmed Death-Ligand 1), which play a crucial role in guiding targeted therapies. Advances in high-throughput sequencing technologies, including Next-Generation Sequencing (NGS), have revolutionized molecular profiling, enabling the refinement of personalized treatment strategies

Methods: A retrospective cohort study was conducted, analysing 836 patients who underwent linear EBUS between 2021 and 2024 at Hospital Clínic de Barcelona.

Results: A total of 147 NSCLC patients who underwent EBUS-TBNA for molecular testing were included in the study. The cohort predominantly comprised male patients (61%) with a mean age of 66.57 years. Active smokers accounted for 39% of cases, while 51% were former smokers. Pulmonary adenocarcinoma was the most common histological subtype (56%), with the primary tumour localized in the right upper lobe in 40.1% of cases. NGS analysis was unfeasible due to insufficient sample material in 2% (3/147) of cases. The subcarinal lymph node was the most frequently sampled site (41.5%). The mean tumour cell count was 55.25. In 83% (119/144) of cases, molecular analysis was positive, with TP53, KRAS, and EGFR mutations detected in 16.6%, 26.9%, and 13.1% of cases, respectively. Regarding PD-L1, in 82% of cases (120/147), the sample was adequate for analysis, with a positivity rate of 39%.

Conclusions: EBUS-TBNA-derived cytological specimens serve as a critical resource for the comprehensive molecular characterization of NSCLC, reinforcing their pivotal role in precision oncology and the implementation of targeted therapeutic strategies.

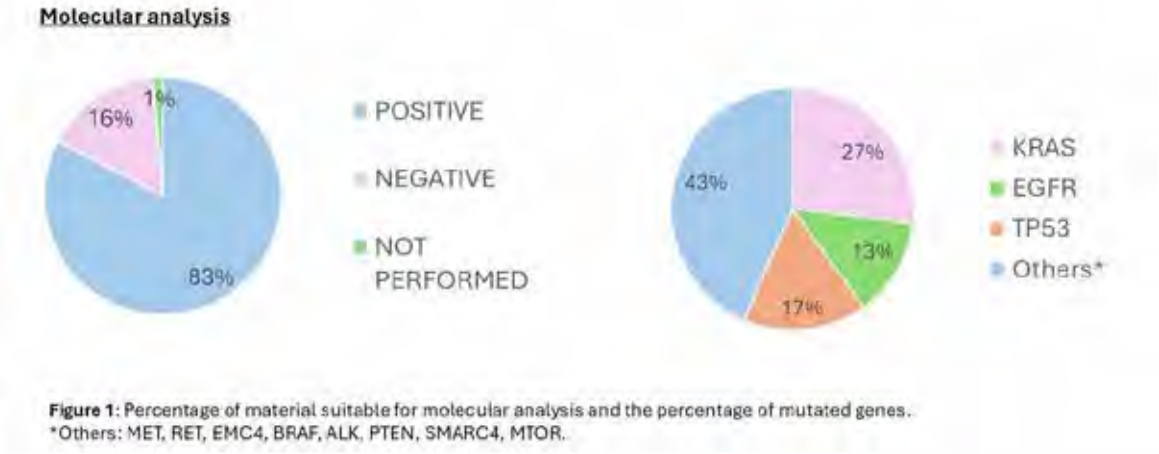

Figure 1: Percentage of material suitable for molecular analysis and the percentage of mutated genes. *Others: MET, RET, EMC4, BRAF, ALK, PTEN, SMARC4, MTOR.

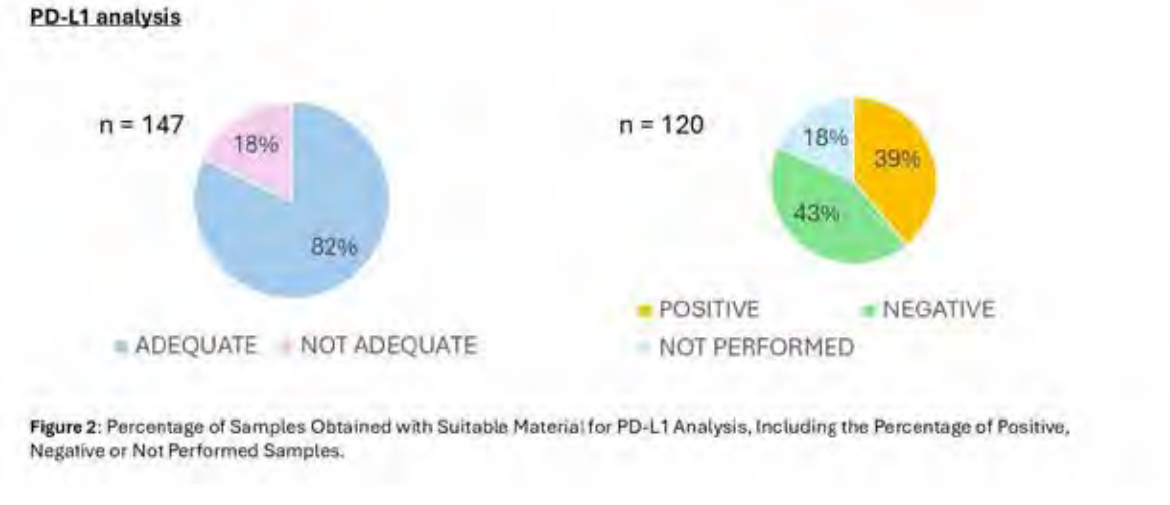

Figure 2: Percentage of Samples Obtained with Suitable Material for PD-L1 Analysis, Including the Percentage of Positive, Negative or Not Performed Samples.

Keywords: EBUS-TBNA, NSCLC, NGS

EP.05.02 Evaluation of ROSE Utility in Multiplex Gene-Panel Testing Using Samples From EBUS-GS for Lung Cancer

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Introduction: The genomic diagnostic yield remains a significant challenge in the era of targeted therapy. Endobronchial ultrasound-guided sheath (EBUS-GS) transbronchial lung biopsy is a widely utilized procedure for the evaluation of peripheral pulmonary lesions (PPLs). Additionally, Rapid On-Site Evaluation (ROSE) serves as a supplementary method for real-time decision-making. While both EBUS-GS and ROSE are well-established techniques for PPLs biopsy, the utility of ROSE in assessing EBUS-GS obtained samples for multiplex gene-panel testing (MGPT), including next-generation sequencing, has yet to be fully elucidated.

Methods: We retrospectively analyzed consecutive cases of patients who underwent MGPT using specimens obtained via EBUS-GS at Ehime University Hospital and Saiseikai Imabari Hospital between Spring 2020 and Spring 2024. Patients were categorized into two groups: the ROSE group (undergoing ROSE during bronchoscopy) and the non-ROSE group (without ROSE). The primary objective of this study was to determine the MGPT success rate. Statistical analysis was performed using logistic regression with inverse probability weighting (IPW) to adjust for multiple covariates.

Results: A total of 89 patients were included, of whom 60 (67.4%) were male. The median age was 72.0 years (interquartile range: 67.0-77.0 years). ROSE was performed in 33 patients (37.1%). Successful MGPT results were obtained in 31 of 33 patients (93.9%) in the ROSE group and in 42 of 56 patients (75.0%) in the non-ROSE group, demonstrating statistical significance (p = 0.043). After IPW adjustment, the ROSE group exhibited a significantly higher MGPT success rate, with an odds ratio of 5.37 (95% confidence interval: 1.09-26.4; p = 0.042).

Conclusions: Although this study could not directly assess whether ROSE improves the adequacy of gene products, it demonstrated for the first time a significant improvement in MGPT success rates when ROSE was utilized during EBUS-GS. We consider that ROSE enhances the precision of biopsies, thereby increasing MGPT success.

Table 1. Logistic regression analysis of MGPT success before and after IPW

Before IPW adjusted (mono-variate)	OR (95%CI)	p-value
Age > 70	0.51 (0.15-1.72)	0.275
Male	0.93 (0.29-2.97)	0.900
Smoking history	0.95 (0.270-3.30)	0.932
Solid tumor	0 (0-infinite)	0.994
Upper lobe	0.82 (0.28-2.44)	0.728
Outer location	1.13 (0.35-3.63)	0.843
Target legion size > 20mm	3.14 (0.67-14.78)	0.148
Distance from pleura > 10mm	0.74 (0.25-2.18)	0.583
CT-BS positive	0.74 (0.08-6.65)	0.792
Interstitial lung disease	0.32 (0.07-1.50)	0.148
"within" image of EBUS	9.14 (2.73-30.64)	0.0003
ROSE	5.17 (1.09-24.41)	0.038
After IPW adjusted	**OR (95% CI)**	**p-value**
ROSE	5.37 (1.09-26.40)	0.042

Keywords: ROSE, EBUS-GS, MGPT

EP.05 PULMONOLOGY AND STAGING

EP.05.03 Analysis of Left Upper Pulmonary Arterial Bronchial Concomitant Consistency Based on Three-Dimensional Reconstructio

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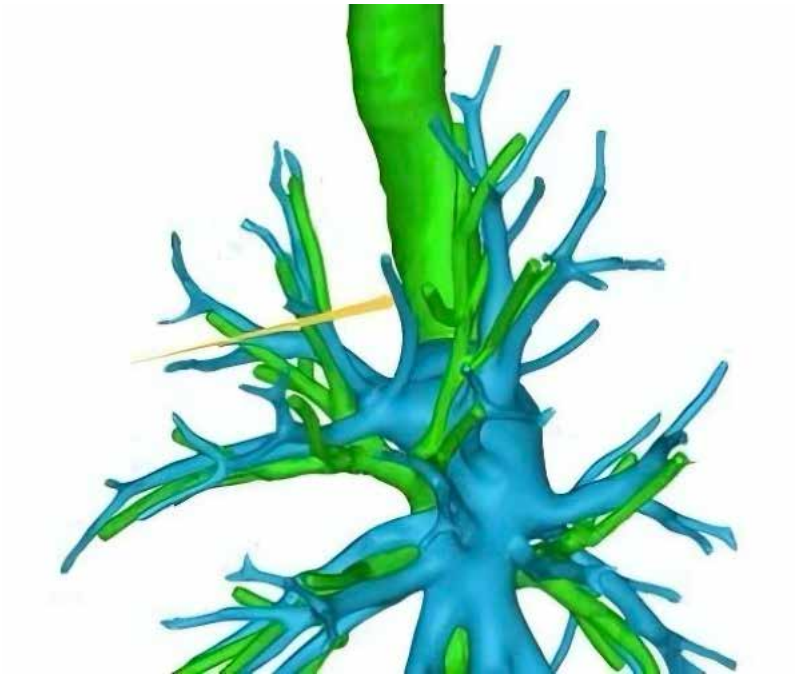
Introduction: Variations in blood vessels and bronchi in the upper lobe of the left lung are very common. The aim of this study is to summarize the accompanying conditions of arterial and bronchial variability in the left upper under three-dimensional(3D) reconstruction.

Methods: From September 2019 to December 2023, 300 patients with early-stage non-small cell lung cancer in the upper left lung who underwent preoperative lung 3D reconstruction planning were included in this study and the the accompanying pulmonary artery bronchus was analyzed.

Results: The most common type of cross lobar distribution is the variant distribution of A8 branch to the lingular region, with a total of 67 cases: A8 branch entering S5(57/300, 19%); A8 branch enters S4(9/300, 3%); A8 branch enters S4+5 (1/300,0.3%). The proportion of A8 branches with cross lobe distribution and fused fissure was 29/67(43.2%). The incidence of A8 variant distribution and fused fissure was statistically significant (P=0.001). The incidence of bronchial and arterial concomitant variation was higher in S1+2c and S3a. There was a significant statistical difference in the correlation analysis between the distribution of A1+2 branches and the accompanying variation of S1+2c arteries and bronchi (P=0.045). There was a significant statistical difference in the correlation between the common trunk types of A3a, b, and c branches and the accompanying variation of A3a arteries and bronchi (P=0.000). The most common accompanying variations of arteries and bronchi in the lingular segment were two types of mediastinal lingual artery.

Conclusions: Preoperative 3D reconstruction is helpful for in-depth analysis of the distribution of left upper lobe arteries and accompanying variations in arterial bronchi, which may facilitate surgeon to perform segementectomy for early-stage lung cancer.



Keywords: three-dimensional, left upper lobe, accompanying variation

EP.05.04 SUVmax Predicts Pathologic Complete Response and Survival in Lung Cancer Patients Undergoing Neaodjuvant Treatment

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Introduction: Pathologic complete response (PCR) is linked to improved overall and recurrence-free survival in patients with non-small cell lung cancer (NSCLC) treated with neoadjuvant chemoradiotherapy. While several clinical factors have been identified as predictors of PCR, the role of positron emission tomography/computed tomography (PET/CT) in this context remains under investigation.

Methods: We retrospectively analyzed 115 consecutive patients who underwent pulmonary resection following neoadjuvant chemotherapy or chemoradiotherapy at our institution between June 2006 and October 2024. Major pathologic response (MPR) was defined as the presence of less than 10% viable tumor cells, and pathologic complete response (PCR) was defined as the complete absence of viable tumor cells in the postoperative pathological examination

Results: Demographic and clinical features of the cohort is summarized in Table 1. Lower SUVmax on PET/CT performed after neoadjuvant treatment was associated with higher likelihood of PCR (p=0.008, Odds Ratio 0.85 [95% Confidence Interval 0.75-0.95]). The area under ROC curve (AUC) was 0.77 (Figure 1), and the optimal threshold of SUVmax was found to be 6.45. PCR rate was significantly lower in the higher SUVmax group (6.4% vs. 42.1%, p<0.0001). Patients who achieved a major pathologic response and complete pathologic response had median survival times of 117.6 ± 20.6 months and 56.5 ± 9.9 months, respectively (p = 0.034)(Figure)

Conclusions: Low SUVmax on PET/CT performed after neoadjuvant chemoradiotherapy is a strong predictor of pathologic complete response (PCR) and overall survival in patients with NSCLC, with a threshold of 6.45. Further research may elucidate whether select patients in this group could benefit from close follow-up rather than surgical resection.

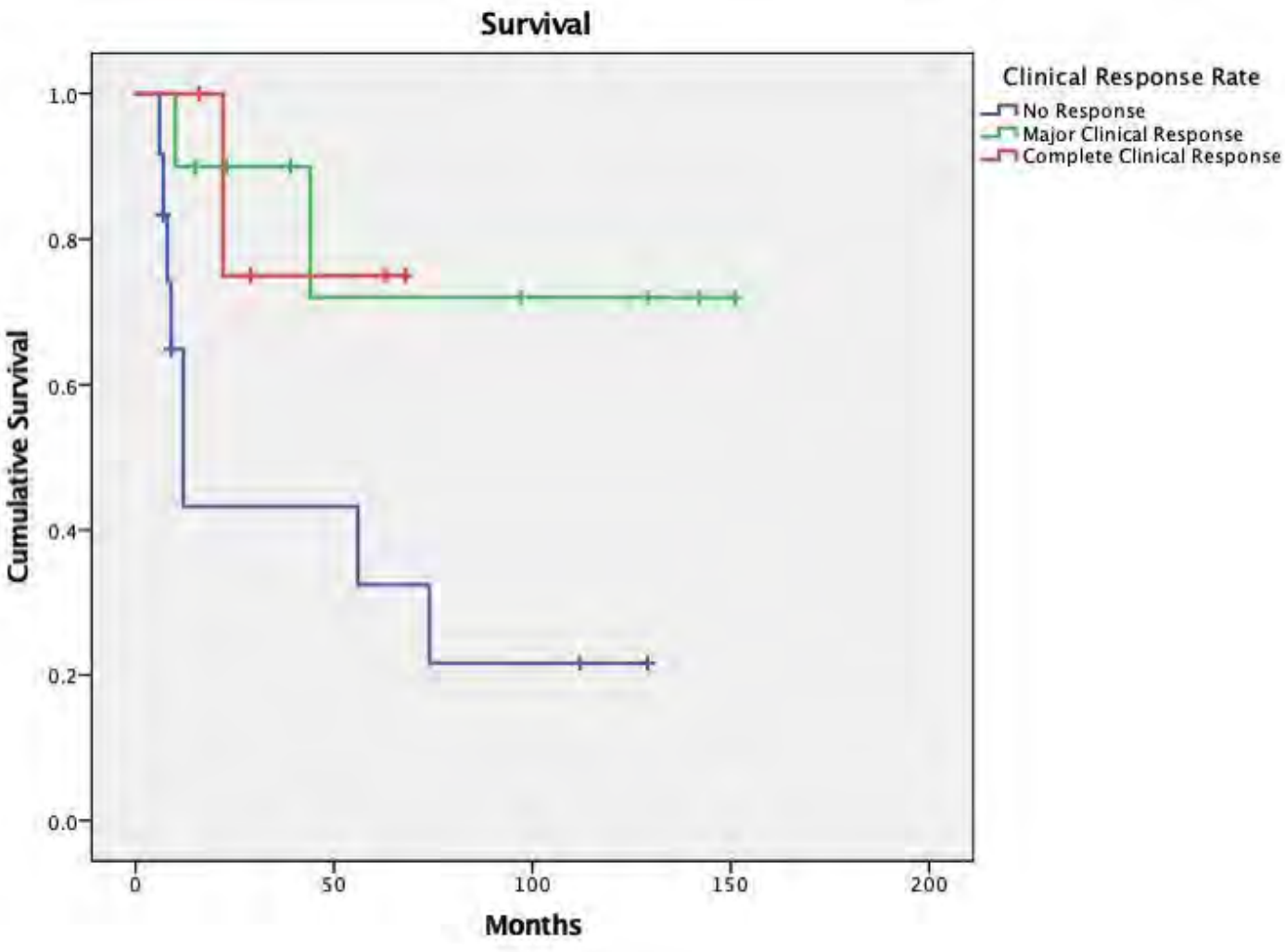

Table 1. Demographic Parameters of Patients

	n (%)
Age (Mean ± SD)	58.5 ± 8.3
Gender	
Female	17 (14.8%)
Male	98 (85.2%)
Pretreatment Pathological Diagnosis	
Adenocarcinoma	58 (50.4%)
Squamous Cell Carcinoma	45 (39.1%)
Neuroendocrine Carcinoma	7 (6.1%)
Other	5 (4.3%)
Neoadjuvant Treatment Indication	
N1/N2/N3	39 (33.9%)
T2/T3/T4	40 (34.7%)
M1	10 (8.7%)
Other	26 (22.6%)
Neoadjuvant Treatment	
Chemotherapy	45 (39.2%)
Chemoradiotherapy	70 (60.8%)
Pathologic Response	
No Response	72 (62.6%)
Major Pathologic Response	16 (13.9%)
Pathologic Complete Response	27 (23.5%)
ypT Stage	
ypT0	28 (24.3%)
ypT1	40 (34.8%)
ypT2	28 (24.3%)
ypT3	11 (9.6%)
ypT4	8 (7.0%)

SD, standard deviation.

Keywords: Neoadjuvant therapy, Complete pathologic response, SUVmax

EP.05 PULMONOLOGY AND STAGING

EP.05.05 Invasive Mediastinal Staging of NSCLC Using Vamla: Results and Perspectives

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Introduction: Invasive mediastinal staging of resectable NSCLC is still discussible field of thoracic oncology especially in the era of novel therapeutic opportunities of combined treatment. Hereby we present immediate results and impact to the treatment decisions of video-assisted mediastinal lymphadenectomy (VAMLA) and video-mediastinoscopy in routine using.

Methods: In period from August 2020 to December 2024 we retrospectively reviewed diagnostic results of 1110 patients after VAMLA. Median age was 65 (58; 69) years with male predominance 90/20. Centrally located NSCLC was diagnosed in 33 (32,4%) cases. The indications for invasive mediastinal staging were as follows: central tumor, tumor size > 30 mm, lymph node size > 10 mm, lymph node SUV > 2,5.

Results: The clinical stage (TNM 8) after invasive staging was changed in 58 (52,7%) of 110 patients (95%CI:40.3-62.3), with an up- and downstaging rates in 12 (10.9%;95%CI:5.8-18.3) and 46 (41%;95%CI:32.5-51.6) cases respectively. Firstline therapy was surgery, chemoimmunotherapy in 63 (57,2%) and 43(39,1%) cases. Complication rate following mediastinal staging was 7,2% (n=8) including recurrent nerve palsy, azygous vein injury, seroma and hemothorax in 4 (3,6%), 2 (1,8%), 1 (0,9%) and 1 (0,9%) case respectively.

Conclusions: Invasive mediastinal staging using VAMLA is important investigation for patients with clinically locally advanced NSCLC, especially to establish patients with pathomorphological N0-N1 disease to ensure the best first step in multimodality treatment.

Keywords: tumor, nodus, metastasis

EP.05.06 Should We Screen Patients With Stage IV Non-Small Cell Lung Cancer for Brain Metastases at Diagnosis?r

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Introduction: Brain metastases (BM) significantly impact morbidity and mortality in NSCLC patients, with approximately one-third developing BM during the course of their disease. According to the 2025 NCCN guidelines, every NSCLC patient should be screened for brain metastasis except stage I. However, we did not found in the literature characteristics to better select those patients who would really benefit of brain MRI screening. Regarding the treatments of BM, indications for SBRT are increasing and systemic treatments such as brain penetrating targeted therapies and immune checkpoint inhibitors are substantially modifying frontline brain therapeutic algorithm. Although prior studies suggested that brain MRI screening is associated with longer survival, it remains unclear whether early BM detection reduces the use of WBRT and related potential neurotoxicity. These advances in oncology alter the incidence and prognosis of BM, highlighting the need for a deeper understanding of BM epidemiology to optimize management strategies.

Methods: We retrospectively analyzed clinical data from patients diagnosed with NSCLC between 2010 and 2020 at Institut Jules Bordet, Belgium. All patients underwent brain MRI at diagnosis. The objective was to assess the added value of brain MRI in patients with newly diagnosed stage IV NSCLC with extracranial metastases and without neurological symptoms.

Results: Of 381 stage IV NSCLC patients initially included, 326 met the inclusion criteria; 45 patients were excluded due to symptomatic BM at baseline, and 10 due to the absence of extracranial metastases. Asymptomatic BM was detected in 53 patients (16%). Demographic characteristics are detailed in Table 1. Patients with baseline BM had a significantly worse performance status (PS) and more lung, bone, adrenal and/or soft tissue metastases at baseline. The other demographic variables showed no significant differences. First-line treatments for patients with baseline BM included best supportive care (BSC) (N=4), local brain treatment alone followed by BSC (N=6), combined local and systemic treatment (N=13), and systemic treatment alone (N=30). Among patients receiving local brain treatment (n=19), 16 underwent upfront whole-brain radiotherapy (WBRT). In the cohort without BM at baseline, 91 patients (33%) subsequently developed BM, of whom 55 received WBRT.

Conclusions: Our study confirms the high incidence of asymptomatic BM in stage IV NSCLC (1 in 6 patients), supporting systematic brain MRI in the initial diagnostic work up. Only a worse PS and some metastatic sites showed a predictive value for baseline BM. These results should be validated in prospective studies such as BrainStorm (NCT04109131), a multicentric prospective cohort.

Characteristics at baseline	Baseline BM N=53	No baseline BM N =273	p-value
Age, median (SD)	60 (11,1)	63,5 (10,8)	p=0.940
Smoking history			p=0.907
Current smoker, n (%)	29 (56%)	139 (51%)	
Former smoker, n (%)	15 (28%)	88 (32%)	
Non smoker, n (%)	9 (17%)	44 (16%)	
PS			**p=0.004**
PS 0-1	35 (66%)	228 (83%)	
PS 2	12 (23%)	35 (13%)	
PS 3-4	6 (11%)	9 (3%)	
Gender, n (%)			**p=0.579**
Male	29 (55%)	160 (59%)	
Woman	24 (45%)	112 (41%)	
Histology sub-types, n (%)			p=0.279
Adenocarcinoma	44 (83%)	192 (71%)	
Squamous	5 (9%)	38 (14%)	
Other	4 (7%)	42 (15%)	
T stage*, n (%)			p=0.256
T1-T2	15 (28%)	95 (35%)	
T3-T4	31 (58%)	158 (58%)	

Characteristics at baseline	Baseline BM N=53	No baseline BM N =273	p-value
N stage*, n (%)			p=0.271
N0-N1	7 (13%)	60 (22%)	
N2	18 (34%)	101 (37%)	
N3	28 (53%)	109 (40%)	
Metastatic sites, n (%)			
Lung	30 (57%)	113 (41%)	**p=0.043**
Pleura	39 (74%)	217 (79%)	p=0.313
Liver	39 (74%)	51 (19%)	p=0.202
Bone	37 (70%)	148 (54%)	**p=0.038**
Lymph nodes	48 (91%)	53 (19%)	p=0.080
Adrenal	34 (64%)	64 (23%)	**p=0.001**
Soft tissue	40 (75%)	25 (9%)	**p=0.043**
EGFR mutation, N (%)			p=0.240
Presence	7 (13%)	24 (9%)	
Absence	25 (47%)	150 (55%)	
Not done	21 (40%)	99 (36%)	
ALK fusion, N (%)			p=0.817
Presence	1 (2%)	7 (2%)	
Absence	25 (47%)	136 (50%)	
Not done	27 (51%)	130 (48%)	

**8th TNM classification* *Legend: BM: brain metastases, SD: standard deviation, NSCLC: non-small cell lung cancer*

Keywords: NSCLC, Brain metastases, Epidemiology

EP.05.07 Prognostic Impact of Double Positive in EGFR Mutation and PD-L1 Expression in Resected pN0M0 G2-3 Adenocarcinoma

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Introduction: Actionable EGFR mutation and expression of PD-L1 guide the treatment strategy in resected lung adenocarcinoma postoperatively or after recurrence. We have reported positive EGFR mutation status is a risk of recurrence in pathological intermediate or high-grade cases, and PD-L1 expression status is known to be positive in high-malignant cases with solid component. The prognostic impact of EGFR mutation accompanied by positive PD-L1 expression is little known. We evaluate the prognostic impact of concomitant expression of EGFR mutation and PD-L1 expression in completely resected adenocarcinoma.

Methods: We retrospectively reviewed consecutive completely resected pN0M0 adenocarcinoma cases with moderate or high risk of recurrence (IASLC histological Grade 2-3). EGFR mutation status and PD-L1 expression were evaluated in all reviewed cases. We excluded cases with no or little risk of recurrence (AIS, MIA, or IASLC histological Grade 1), treated with adjuvant EGFR-TKI, lack in data, or histological variant types.To evaluate the prognostic impact, recurrence-free survival (RFS) was calculated using Kaplan-Meier method and compared using the log-rank test. Significance was defined as a two-tailed P-value < 0.05.

Results: We reviewed 190 cases. EGFR mutation was detected in 81 cases and PD-L1 expression was positive (TPS >1%) in 119 cases. Forty-four cases harbored EGFR mutation accompanied by positive PD-L1 expression, and 37 cases harbored EGFR mutation without PD-L1 expression.Five-year RFS of EGFR+/PD-L1+ and EGFR+/PD-L1- were 73.1 % and 84.5 %, respectively (HR 2.77, 95%CI 1.04-6.30, p value = 0.041). There was no significant difference between two cohort regarding sex, age, surgical procedure, tumor invasive size, histological grade, pleural invasion, and lymphovascular invasion status. Multivariate analysis revealed positive PD-L1 expression (TPS >1%), tumor invasive size, and lymphovascular invasion were significantly related to worse RFS (positive PD-L1 expression: HR 2.09, 95% CI 1.040-4.206, p value = 0.039).

Conclusions: Double positive status of EGFR mutation and PD-L1 expression is related to worse RFS in resected pN0M0 histological Grade 2-3 adenocarcinoma compared to EGFR-mutant but PD-L1 negative cases. Evaluating EGFR mutation and PD-L1 expression might be useful to classify the resected cases by risk of recurrence.

Keywords: EGFR, PD-L1, staging

EP.05.08 Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) for Staging cN0-N1 Non-Small Cell Lung Cancer

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Introduction: The diagnostic performance of EBUS-TBNA for staging clinical (c) N0-1 NSCLC is low. We aimed to assess: 1) the accuracy of EBUS-TBNA; 2) the rate and associated risk factors for unsuspected (u) N2 rates in patients with NSCLC and normal mediastinum by integrated positron emission tomography (PET) - computed tomography (CT).

Methods: Retrospective observational single-centre study of all consecutive systematic EBUS-TBNA for staging cN0-1 NSCLC from 2017 to 2024. All patients with negative EBUS-TBNA underwent VAMLA as confirmatory test. Systematic nodal dissection (SND) performed during lung resection was considered the reference standard test to validate negative VAMLAs. Pathologic findings were reviewed, and staging values were calculated (including 95% confidence interval [CI]) using the standard formulas. uN2 rates were analysed in the global series and in the subgroups of tumours according to their clinical tumour and nodal categories by PET-CT. Clinical and histological variables were analysed using univariable (Chi-square or Fisher's exact test) and multivariable logistic regression to identify predictors for uN2.

Results: 112 patients (83 men; median age 67, range 46-84) underwent EBUS-TBNA. A mean of 4.7 nodal stations and a mean of 10.4 lymph nodes were sampled. 7 EBUS were positive; 105 patients underwent VAMLA and 15 were positive; 90 patients underwent resection and SND identified 1 N2 at #9 lymph node station. Table 1 shows staging values of EBUS-TBNA according to cN category. The uN2 rate for the whole series was 20.5%. The uN2 rates according to presurgical cT and cN categories by PET-CT were: 5.71% (2/35) in cT1N0; 13.3% (4/30) in cT2N0; 26.6% (4/15) in cT3N0; 33.3% (2/6) in cT4N0; 42.3% (11/26) in cN1. Multivariate logistic regression analysis revealed that cT3-4N0 (odds ratio (OR)= 3.47 [95% confidence interval (CI) 1.21-9.96], p=0.02) and cN1 (OR 3.50, 95% [CI 1.22-10.05], p= 0.02) were independently risk factors for uN2.

Conclusions: The diagnostic performance of EBUS-TBNA alone for staging this specific setting of tumours was unsatisfactory. The rate of uN2 of this cohort of patients with cN0-1 NSCLC was high. The addition of confirmatory VAMLA adds value and could be considered the reference staging procedure for staging NSCLC and normal mediastinum especially for cT3-4N0 and cN1 tumours.

Table 1. Staging values of EBUS-TBNA according to cN category

	n	Preval. (%)	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	Accuracy 95% CI
cN0	86	13.9	0.36 (0.15-0.64)	1 (0.95-1)	1 (0.51-1)	0.91 (0.83-0.95)	0.91 (0.84-0.96)
cN1	26	42.3	0.27 (0.09-0.56)	1 (0.79-1)	0 (0-0.20)	0.72 (0.43-0.90)	0.69 (0.5-0.83)

n: number of patients; Preval: prevalence; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval

Keywords: EBUS-TBNA, VAMLA, NON-SMALL CELL LUNG CANCER

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.01 Tumor-Infiltrating Lymphocytes as Predictors of Chemotherapy Response in Non-Small Cell Lung Cancer: A Retrospective Cross-Sectional Stud

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Introduction: Tumor-infiltrating lymphocytes (TILs) have emerged as potential biomarkers of prognosis and response to therapy in non-small cell lung cancer (NSCLC). While high TIL density has been associated with better outcomes, their predictive value for chemotherapy response remains underexplored. This study evaluates the correlation between TIL density and tumor size reduction after exclusively chemotherapy treatment in NSCLC patients.

Methods: This retrospective cross-sectional study included 51 NSCLC patients (stage III-IV) treated exclusively with chemotherapy. TIL density was assessed in hematoxylin-eosin (H&E)-stained biopsy specimens obtained post-chemotherapy and categorized as low (0-25%), moderate (25-50%), or high (>50%). Tumor size before and after treatment was measured via imaging. ANCOVA was performed to determine the association between TIL density and tumor reduction, adjusting for confounders (age, sex, and clinical stage). Interobserver agreement for TIL quantification was evaluated using Cohen's kappa, Fleiss' kappa, and Krippendorff's alpha.

Results: Higher TIL density was significantly associated with greater tumor shrinkage ($F = 83.109$, $p < 0.001$, $\eta^2 = 0.551$). Patients with high TIL levels showed a mean tumor reduction of -3.18 cm (SD = 1.52), while those with low TILs exhibited a reduction of 0.52 cm (SD = 2.28). TIL density also correlated positively with overall survival, with high-density patients demonstrating the longest survival (mean 22.75 months, SD = 21.90). Interobserver agreement for TIL categorization was substantial (mean Cohen's kappa = 0.673).

Conclusions: TILs are promising biomarkers for predicting chemotherapy response in NSCLC. Standardized TIL assessment may improve patient stratification and treatment planning, with potential implications for immunotherapy escalation or, conversely, identifying patients who may not require immunotherapy. Further prospective studies integrating immunohistochemistry and molecular profiling are needed to refine TIL-based therapeutic strategies.

Keywords: Tumor-infiltrating lymphocytes, NSCLC, prognostic biomarkers

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.02 Clinical Significance and Preoperative Prediction of High-Grade Subtypes in Early-Stage Lung Adenocarcinoma

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Introduction: The indication for sublober resection for early-staged lung cancer is determined based on radiographic findings including tumor size and consolidation tumor ratio (CTR) according to the JCOG study. However, some cases exhibit discrepancies between the results of preoperative imaging and postoperative histopathological examination and poor patient outcomes. The biological backgrounds of these cases remain unclear.

Methods: We reviewed 585 patients who underwent complete resection for lung adenocarcinoma with tumor size ≤3cm and cN0 between January 2011 and December 2019. We examined the relationship between clinical outcomes and histologic characteristics, especially focusing on high-grade components: solid (SOL) or micropapillary (MIP). Furthermore, the predictive ability of radiologic or cytopathologic examinations for those subtypes was evaluated.

Results: The SOL and MIP components were identified in 98 (16.8%) and 90 (15.4%) patients, respectively. Radiology-pathology discordance was found in 148 (25.2%) patients and significantly associated with the presence of histologic high-grade components, with 71.9% and 70.4% of patients with upstaged lymph node and pleural invasion statuses having high-grade components, respectively. The overall and recurrence free survival of patients with high-grade components were significantly worse than those of patients without them. In multivariate analysis, SOL and MIP components were independent prognostic factors (hazard ratio, 2.01 and 1.96; p = .02 and .02, respectively). The distribution of high-grade components was distinctly associated with tumor size and CTR. Logistic regression analyses for preoperative prediction of high-grade component demonstrated that radiographically pure-solid appearance and higher high maximum standardized uptake value were independent predictors of SOL component whereas no independent predictor of micropapillary component was found. Among pre- or intra-operative cytopathologic examinations, intraoperative touch imprint cytology exhibited the highest detection rate of MIP component (66%), and preoperative TBLB (30%) and bronchial washing cytology (36%) had low detection rates.

Conclusions: Histologic high-grade components are associated with radiology-pathology discordance and poor prognoses in early-stage lung adenocarcinoma eligible for sublober resection. The preoperative prediction of high-grade components varied between histologic subtypes, and radiologic assessment would be beneficial for predicting the SOL subtype, but not MIP. Alternatively, intraoperative cytologic assessment would complement the detection of MIP subtype.

Keywords: lung cancer, pathology, grading

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.03 Mucoepidermoid Carcinoma of the Lower Respiratory Tract With Few to None Intermediate/Squamoid Cells: A Challenging Tumor Series

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Introduction: Mucoepidermoid carcinoma (MEC) of the lower respiratory tract is a malignant salivary gland-type tumor comprising mucin-secreting cells, squamoid cells and intermediate-type cells, which usually arises in central airways (WHO classification 2021). Little is known, however, about MECs of the lower respiratory tract composed exclusively or to large extent of mucin-secreting cells, which really make up diagnostic challenges.

Methods: Five MECs of the lower respiratory tract with few to none intermediate-type/squamoid cells were retrieved from the pathology archives and consultation files of the participating Institutions. Immunoreactivity for p40, CK5, calponin and S100 protein, which highlight intermediate, squamoid and myoepithelial cells, was carried out on formalin-fixed and paraffin-embedded tumor tissue by means of standard staining methods on a Ventana BenchmarkXT autostainer (Ventana Medical Systems, Tucson, AZ, USA). Fluorescence in situ hybridization (FISH) analysis for the 11q21 rearrangement, which include the MAML2 gene, was performed by using the ZytoLight SPEC MAML2 Dual Color Break Apart Probe (ZytoVision, Bremerhaven, Germany).

Results: The tumor series included 3 females and 2 males, aged 29 to 69 years and 15 to 16 years, respectively. Tumors were endotracheal (one case) or endobronchial (four cases), the latter on either the left (3 cases) or the right (one case) side, and appeared limited to tracheal or bronchial walls in all but two instances, with minimal extraparietal extension. Histologically, just glandular aggregates of mucin-secreting cells were observed, featuring variably sized cystic structures repleted and distended by mucin, with no discernible intermediate or squamoid cells. The immunohistochemical study revealed complete absence or just sparse reactivity for CK5 or p40 in rare tumor cells, with no elements being decorated with calponin and S100 protein. As any conclusive interpretation was challenging because of the inconsistency of intermediate/squamoid cells and the differential diagnosis comprised various alternatives, such as mucous gland adenoma, hyalinizing clear cell carcinoma or even metastases of mucinous or clear cell adenocarcinomas of either pulmonary or extrapulmonary origin, a MAML2 gene FISH was conducted in three out of our five cases. This analysis documented the presence of the corresponding gene translocation in most tumor cells, whereby confirming the final interpretation of MEC. Clinical correlation ruled out metastasis from synchronous or previous head and neck salivary gland tumors.

Conclusions: MECs of the lower respiratory tract with few to none intermediate/squamoid cells are diagnostic challenges, inasmuch as immunohistochemistry may be of little help or even misleading. In these cases, MAML2 FISH analysis is the most effective tool to get the correct final interpretation, provided metastasis from a head and neck salivary gland tumor sharing the same translocation has been clinically excluded. It is important to keep in mind such an unusual presentation of MECs in the lower respiratory tract, because turns out outside its semantic definition of tumors composed of mucin-secreting, intermediate-type and squamoid cells. To the best of our knowledge, this is the largest series of such a variety of MEC thus far described in the lower respiratory tract.

Keywords: Mucoepidermoid carcinoma, Lung, MAML2 translocation

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.04 Extranodal Extension in Lung Adenocarcinoma: Pathological Insights and Its Role as an Independent Prognostic Factor

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Introduction: Extrapulmonary nodal extension (ENE) has been increasingly recognized as an important prognostic factor in various malignancies. This study aimed to explore its pathological features of ENE in lung adenocarcinoma and to clarify its prognostic impact.

Methods: We retrospectively analyzed 105 patients with N1 or N2 lung adenocarcinoma who underwent anatomical lung resection between January 2016 and December 2020. AI-driven image analysis was used to quantify tumor-infiltrating lymphocytes (CD8+, FoxP3+), tumor-associated macrophages (CD204+), and cancer-associated fibroblasts (podoplanin+). The area of cancer cells and fibrous stroma was measured in both primary and metastatic lesions. An in vitro invasion assay using A549 cancer cells co-cultured with different numbers of CAFs was performed to assess their invasive potential of A549 cells. Moreover, we assessed ENE as a prognostic factor to elucidate its clinical significance.

Results: ENE-positive patients had higher lymph node involvement and were associated with more advanced tumor stages. In contrast, patient demographics and other baseline characteristics showed no notable differences between the two groups. No significant differences in the amount of TILs, tumor-promoting-TAMs, or -CAFs in primary tumors were observed between ENE-positive and ENE-negative groups. However, fibrous stroma in metastatic lymph node, but not of the primary tumor, was significantly more abundant in ENE-positive cases (14.2 mm^2 vs. 4.0 mm^2, $p < 0.001$). In vitro invasion assays demonstrated increased invasiveness of A549 cells when cocultured with higher numbers of CAFs. ENE was an independent poor prognostic factor and was significantly associated with distant metastasis ($p = 0.0198$).

Conclusions: ENE was a pathological prognostic factor characterized by abundant fibrous stroma. Additionally, from the high frequency of distant metastases, ENE could be considered a qualitative factor of malignancy in N classification.

Keywords: Extranodal extension, Cancer-associated fibroblasts, AI-driven image analysis

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.05 Extensive-Stage Small Cell Lung Cancer Compared With Metastatic Extrapulmonary Small Cell Cancers- a Retrospective Study

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Introduction: Extensive-stage small cell lung cancers (ES-SCLC) carry a dismal prognosis and are treated with a combination of chemotherapy and immune checkpoint inhibitors (ICI) in the frontline setting. However small cell cancers are a systemic disease and can have an extrapulmonary (EPSCC) primary and treatment is extrapolated from ES-SCLC. Similarly to ES-SCLC, prognosis of metastatic EPSCC is poor as well. There are only a few institutional case series comparing the two entities. Given its rarity we performed a retrospective study comparing ES-SCLC with metastatic EPSCC in our institution.

Methods: We reviewed the medical records of adults > 18 years age from January 2013- December 2022 with biopsy proven de-novo extensive stage small cell lung cancer and de-novo metastatic extrapulmonary small cell cancer or poorly differentiated non-large cell neuroendocrine cancers. We analyzed these cases till December 31, 2023. Patients must have received at least one cycle of systemic treatment. We analyzed 89 patients [40 EPSCC (21 males and 19 females) and 49 ES-SCLC (24 males and 25 females)] for our final analysis. Of the 40 EPSCC patients, 17 were primary gastrointestinal (GI), 14 were hepatopancreaticobiliary (HPB), 7 were genitourinary (GU) and 2 were unknown primary (CUP). Our primary endpoint was median overall survival (mOS) and median progression-free survival (mPFS). We also assessed whether the primary site could affect survival.

Results: The median age was 62.6 years in EPSCC and 68.6 years in ES-SCLC cohorts. At the time of last data analysis 3 patients were still alive and 2 patients had not yet progressed and they were all in the ES-SCLC cohort. The mOS was [9.5 months (95% CI 2.0-17) versus 10.5 months (95%CI 7.1-13.6), p=0.34] in EPSCC and ES-SCLC respectively. The mPFS was [6.4 months (95% CI 2.1-10.7) versus 8.2 months (95% CI 5.9-10.5), p=0.04] in EPSCC and ES-SCLC respectively. Patients with HBP origin had the worst prognosis with mOS of 4.7 months when compared to all other sites. Primary GI and GU patients had similar survival data with mOS of 11.0 and 12.0 months respectively (p=0.017). Only 4 patients in EPSCC received upfront chemotherapy and ICI as compared to 35 patients in the ES-SCLC cohort.

Conclusions: In our institution the mOS of de-novo metastatic EPSCC was similar to de-novo ES-SCLC, however the mPFS was lower for EPSCC. Our data shows primary HBP EPSCC carried the worse prognosis. EPSCC can be similarly treated to ES-SCLC, however currently upfront ICI has not been approved in EPSCC unlike ES-SCLC, where with the Impower133 and CASPIAN studies revealed atezolizumab and durvalumab respectively with carboplatin and etoposide (CE) were superior to CE alone. Since only 4 patients with EPSCC received upfront ICI, this may be the reason behind the worse mPFS. It would require a large collaborative trial to study whether upfront chemotherapy and ICI in EPSCC can improve survival.

Keywords: small cell lung cancer, extrapulmonary small cell, chemotherapy

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.06 Characterization of SMARCA4 and SMARCA2 Alterations in Early-Stage Pulmonary Adenocarcinomas)

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Introduction: The SWI-SNF complex plays a pivotal role in chromatin remodeling, regulating gene transcription and essential cellular functions. Its catalytic subunit is composed of proteins encoded by either the SMARCA4 or SMARCA2 genes. In thoracic malignancies, SMARCA4 alterations have gained significant interest in recent years and have been described in two clinically aggressive and poorly differentiated tumors: SMARCA4-deficient non-small cell lung cancers (NSCLC) and SMARCA4-deficient undifferentiated tumors (SDUT). These alterations are considered early driver events in tumor pathogenesis, and the co-loss of SMARCA4 and SMARCA2 has been proposed as a key oncogenic mechanism in SDUT. However, little is known about the prevalence and characteristics of these alterations in early-stage NSCLC. In this project, we aimed to characterize SMARCA4 and SMARCA2 alterations in early-stage lung adenocarcinomas.

Methods: We retrospectively selected a cohort of 672 resected early-stage pulmonary adenocarcinomas between 2000 and 2013 for which clinical, pathological, and prognostic data were reviewed. Tissue microarrays (TMA) were built from formalin-fixed paraffin-embedded blocks using 1 mm cores. Immunohistochemistry for SMARCA4/BRG1, SMARCA2/BRM, claudin 4, and SOX2 was performed. We calculated the prevalence of SMARCA4 and SMARCA2 loss and co-loss of expression and association with clinico-pathological data.

Results: Complete loss of SMARCA4/BRG1 expression was observed in 18 cases (2.7%), while SMARCA2/BRM loss was found in 29 cases (4.3%). Co-loss of both markers occurred in 2 cases (0.3%). Patients with SMARCA4-deficient adenocarcinomas had a mean age of 62.1 ± 6.5 years and were predominantly male (61.1%). Those with SMARCA2deficiency were younger (60.2 ± 8.9 years) and mostly female (68.9%). All patients had a history of smoking. The predominant histologic pattern was solid in both groups (77.8% in SMARCA4-deficient and 48.3% in SMARCA2-deficient tumors). Pathologic stage distribution (AJCC 9th edition) was similar between groups. Disease progression occurred in 8 (44.4%) and 9 (31.0%) patients with SMARCA4- and SMARCA2-deficient tumors, respectively, with progression-free survival of 667.1 ± 704.0 days and 631.0 ± 523.4 days. The two tumors with co-loss of SMARCA4 and SMARCA2 were poorly differentiated adenocarcinomas with solid patterns, preserved claudin 4, TTF1 loss, mucin production, and SOX2 positivity in one case. One patient with a stage 1B tumor is still alive after 5444 days and the other with a 1A3 stage tumor died of an unrelated disease after 3240 days.

Conclusions: SMARCA4 and SMARCA2 deficiency is infrequent in resected early-stage lung adenocarcinomas, but can be detected in tumors with poorly differentiated histology and solid patterns. These alterations appear to occur in a subset of smokers and may not be as strongly associated with poor outcomes in early-stage disease as in advanced tumors. Further work is underway to characterize the genomic alterations of these tumors.

Keywords: SWI-SNF complex, SMARCA4 and SMARCA2, Early-stage lung adenocarcinoma

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.07 Clinicopathologic and Genomic Landscape of Lung Cancer Arising in Interstitial Lung Disease: An Expanded Cohort Analysis

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Introduction: Patients with interstitial lung disease (ILD) are at increased risk for developing lung cancer, which often presents with poor prognosis and limited therapeutic options. Despite its clinical significance, comprehensive studies on the clinicopathologic and molecular characteristics of lung cancer arising in ILD (LC-ILD) remain limited. Previously reported with 41 cases, this cohort has now been expanded to 99, enabling a more in depth characterization of LC-ILD.

Methods: We retrospectively analyzed 99 cases of LC-ILD diagnosed between 2018 and 2024 at Korea University Guro Hospital and Seoul National University Hospital. Clinical data, histopathologic features, and genomic profiles obtained via single gene tests, next-generation sequencing (n=13) or whole-exome sequencing (n=9) were compared with a control cohort of 1,255 lung cancer patients without ILD who underwent surgical resection at Korea University Guro Hospital during the same period.

Results: Patients with LC-ILD were older (71.0 ± 7.1 vs. 68.0 ± 9.4 years, P<0.001) and predominantly male (90.9% vs. 59.3%, P<0.001), with a universal smoking history. Usual interstitial pneumonia (UIP) was the most common ILD subtype (82.9%). Squamous cell carcinoma (SqCC) was significantly more frequent in the ILD cohort (45.5% vs. 16.9%, P<0.001), predominantly located in the peripheral lung. Genomic profiling revealed frequent TP53 mutations (66.7% in total, 81.8% in SqCC), whereas key actionable driver mutations were rare: EGFR (2.8%), KRAS (12.5%), and BRAF (2.9%) mutations, with no ALK or ROS1 alterations detected. Rare druggable EGFR mutations (E19del and E20ins) were observed. Tumor mutational burden (TMB) was significantly lower in LC-ILD (1.8 vs. 7.1 mut/Mb, P<0.001). PD-L1 expression showed no significant differences by histologic subtype.

Conclusions: Lung cancers arising in ILD exhibit unique clinicopathologic and genomic features, including a predominance of peripheral SqCC, frequent TP53 mutations, low TMB, and rare actionable driver mutations. These findings suggest limited responsiveness to targeted and immune-based therapies, underscoring the need for tailored therapeutic strategies and further biomarker development in this high-risk population.

Keywords: Lung cancer, interstitial lung disease, clinicopathologic features

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.08 Mutation Spectrum of EGFR Mutations in South Indian Population Identified by Next Generation Sequencng and Real TIME PCR

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Introduction: Lung cancer (LC) predisposes significant morbidity and mortality in India. The survival rates for lung cancer in India are lower than in Western countries due to late-stage diagnosis and limited access to advanced treatments. The prognosis largely depends on the stage of lung cancer diagnosis. A wide majority of our patients present in stage IV with multiple sites of metastasis. It is very challenging to introduce high-throughput molecular diagnostics in a low-resource setting due to the cost implications. However, these are mandatory to offer targeted therapy to improve lung cancer outcomes. In the current observational study, we aim to share the mutation spectrum of the EGFR gene, the well-established driver in lung cancers, both by real-time PCR and targeted massive parallel sequencing technologies.

Methods: We performed real-time PCR for the EGFR gene mutation detection (hotspots) and detected ALK, RET, ROS, and RET fusions in lung cancer FFPE tissue-derived DNA and RNA (n=548), respectively. Real-time PCR was done using a clinically validated IVD-approved assay using the protocol as given by the manufacturer. We also performed next-generation sequencing on an Illumina sequencer for lung cancer patients (n=103). The targeted panel (Oncotarget, Onecell Dx, Pune, India) with 100 actionable genes at 1000x coverage was evaluated. The data analysis was done using iCARE, an AI-driven software to decipher the SNVs, Indels, and fusions in the panel studied.

Results: EGFR mutations were positive in 278 patients (42.7%) out of 651 lung cancer patients tested using both technologies. The EGFR positivity rate derived by qPCR was 44.3% (243/548), and that of NGS was 34% (35/103). We found significantly high EGFR mutants among Indian females with 58.8% (127/243), compared to males, with 34.9% (116/243), as tested by qPCR and NGS. Among the EGFR mutations, exon 19 deletion and L858R in exon 21 were the most common mutations found by both qPCR and NGS, as expected. Additionally, we identified some rare EGFR mutants by NGS, like EGFR p.E709_710del in exon 18 and EGFRp.G724S in exon 18, indicating resistance to Afatinib, and exon 20 insertions EGFR H773_V774insGVNPH, leading to activation of the EGFR pathway. We found 80% (28/35) EGFR mutants occurring along with nonactionable genes like p53, APC, PDGFRA, RB1, and ATM1, of which mutant EGFR along with p53 was found in 60% (21/35) of the Indian lung cancer patients. The outcome of lung cancer has not improved despite the availability of targeted TKIs. It is therefore important to understand the impact of co-mutation on prognosis and treatment resistance. Mutations in p53 are associated with poor prognosis, faster progression, and increased resistance to TKIs. Patients with p53 mutations along with EGFR mutations may benefit from checkpoint inhibitors.

Conclusions: Next-generation sequencing technology has revolutionised the diagnosis, treatment, and management of lung cancer, even in a low-resource setting, proving its feasibility. It offers a multiplexed approach to detect the combination of mutations and fusions in lung cancer, emphasizing the need to consider the combinations of non-actionable gene mutations along with actionable drivers like EGFR in lung cancer.

Keywords: Lung Cancer in India, EGFR, NGS

EP.06 PATHOLOGY AND BIOMARKERS
TUESDAY, SEPTEMBER 9, 2025

EP.06.09 Integrated Clinical, Radiological and Molecular Profile of Lung Cancer Patients From an Incidental Nodule Detection Program

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Introduction: Comprehensive molecular and immunohistochemical profiling is critical for guiding therapeutic strategies in individuals diagnosed with lung cancer. In routine practice, however, testing is often incomplete or inconsistently applied. This study aimed to characterize clinical, radiological, histological, and biomarker features in a cohort of individuals diagnosed with lung cancer within a structured nodule management program, emphasizing associations between molecular alterations, histological subtypes, and clinical variables.

Methods: Between January 2023 and December 2024, 25,358 chest CTs were performed, identifying 2,200 nodules (689 >7 mm). Follow-up adherence occurred in 237 cases, resulting in 74 lung cancer diagnoses (44 early-stage, 59,4%). Among these, 61 individuals with molecular or immunohistochemical data were included in this retrospective analysis from a tertiary center in Brazil. Descriptive statistics and chi-square tests were applied to assess associations.

Results: The median age was 74 years, and 49.2% were female. A substantial proportion (42.6%) reported no history of tobacco exposure. Most nodules were solid (85.2%) and located in upper lobes. Adenocarcinoma was the most frequent histologic subtype (85.2%). Among 59 staged individuals, stage 4 was most common (39%), followed by stage 1 (34%), stage 2 (14%), and stage 3 (10%).Immunohistochemistry revealed high TTF-1 positivity (75.4%), consistent with adenocarcinoma predominance. P40 and P63 showed low positivity (11.5%). PD-L1 expression was assessed in 38 individuals (62.3%), with significant variation across histologic subtypes (p=0.002). Low expression (<1%) occurred in 76.9% of cases, intermediate (1-49%) in 19.2%, and high (≥50%) in 3.8%. Intermediate expression was more common in acinar (33.3%) and squamous carcinomas (66.7%), while other subtypes (non-mucinous invasive, mucinous, solid, lepidic) mostly exhibited PD-L1 <1%. The only high-expression case was an invasive mixed carcinoma.EGFR testing was performed in 41.0% of individuals, with 40% positivity. Mutations occurred exclusively in adenocarcinomas and were significantly associated with histologic subtype (p=0.004), particularly non-mucinous, acinar, and lepidic patterns. EGFR positivity was more frequent in individuals without tobacco exposure (85.7%) than in former (27.3%) or current users (14.3%) (p<0.05), and more prevalent in women.No significant associations were observed between sex or smoking status and other molecular markers. ALK was tested in 39.3% of patients, with 8.7% positivity. KRAS mutations were found in 60% of those tested (16.4%), suggesting clinical relevance despite limited testing. No positive results were observed for BRAF or MSI. ROS1 was positive in 12.5% of tested individuals, but over 80% remained untested for these markers. No correlation was found between molecular alterations or PD-L1 expression and cancer stage.

Conclusions: Strong correlations were observed between biomarker profiles and histological or clinical variables, particularly for EGFR and PD-L1. These findings underscore the importance of standardized molecular testing and multidisciplinary workflows. In Brazil, testing access remains limited, with most performed externally via pharmaceutical support programs.

Keywords: Molecular profiling, Biomarkers in lung cancer, Early detection

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.10 Hypoxia-Induced Cancer Stemness, Metastasis, Angiogenesis and Immune Modulation in Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma is the most common type of non-small cell lung cancer (NSCLC) and leading cause of cancer-related deaths in the United States and worldwide. Yet this cancer remains a major therapeutic challenge due to its adaptability and resistance to treatment. Hypoxia, a key feature of the tumor microenvironment, drives tumor aggressiveness and therapy resistance. Understanding hypoxia-driven transcriptional changes is critical for improving diagnostics and targeted therapies. This study investigated the transcriptomic and proteomic responses of Stage 1 NSCLC H1437 cells under hypoxic conditions to identify key biomarkers and pathways involved in angiogenic, inflammatory, and immunosuppressive responses.

Methods: In-depth bulk RNA-sequencing (RNA-seq) analysis was performed on Stage 1 lung adenocarcinoma H1437 cells under hypoxic (1% O2 for 24 hours) or normoxic conditions to elucidate the molecular adaptations of these cancer cells to hypoxia. RNA was isolated and sequenced to create raw RNA-seq reads, which were processed and analyzed through RStudio and edgeR. Biomarkers identified through RNA-seq data analysis were verified by the Enzyme-Linked Immunosorbent Assay (ELISA) and immunohistology studies.

Results: Hypoxia upregulated hypoxia-inducible transcription factors ARNT, EPAS1, and ARNT2, while maintaining HIF1A expression, thereby facilitating tumor survival. Metabolic shifts included a transition from mitochondrial beta-oxidation to glycolysis and increased lipid biosynthesis via upregulation of FASN, ACLY, and SREBF1, which supports tumor progression. Hypoxia downregulated the cell cycle-related genes, likely mitigating the proliferation of H1437 cells. The MTT assay was performed to demonstrate the lower cell proliferations in hypoxic H1437 cells. Hypoxia also disrupted genomic stability by downregulating ATR-CHK1 cell cycle arrest pathways and suppressing BRCA1 and MDC1, thus enabling DNA-damaged cells to persist. Additionally, hypoxic H1437 cells exhibited elevated secretion of pro-angiogenic growth factors (VEGFA-C, PDGFB, and TGFB) and upregulated M2-like macrophage markers (CSF1R, IL4R, VEGFA, and CCL22) as well as osteoclast-like markers (TNFRSF11A and ACP5), which induces an angiogenic, immunosuppressive, and inflammatory microenvironment. The elevation of CCL22 and ACP5 in the supernatant of the hypoxic H1437 cells was verified by ELISA. The ACP5-positive H1437 cells were stained by TRAP. Notably, hypoxia induced stem-like phenotypes by upregulating known NSCLC stem-like markers (CD44, ALDH3B1, and PLAUR) as well as stem-like markers for other cancer types (IL3RA, ALCAM, SOX4, CEACAM6, CD24, NOTCH2, ICAM1, and NTF3). Moreover, SOX4, TGFB, and JAK/STAT emerged as key regulators of hypoxia-driven tumor progression. Additionally, hypoxia conferred apoptotic resistance through upregulation of BCL3, BCL6, BCL9, and CFLAR. Hypoxia also promoted metastatic potential by upregulating markers such as MUC1, MUC16, CEACAM5, CEACAM6, KRT19, FUT3, PLAUR, SERPINE1, NTF3, and FSCN. FUT3, an enzyme involved in CD15 (Lewis X) biosynthesis, was highly expressed, and CD15-positive H1437 cells were detected under hypoxic conditions.

Conclusions: These findings elucidated hypoxia-induced molecular adaptations and revealed key regulators of the progression, metastasis, and therapy resistance of lung adenocarcinoma. The findings demonstrate the potential of targeting HIFs and hypoxia-responsive pathways for improved diagnostic and therapeutic strategies. The biomarkers and pathways identified herein provide promising avenues for developing novel treatments and predictive tools in lung adenocarcinoma.

Keywords: lung adenocarcinoma, hypoxia, metastasis

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.11 Comprehensive Genomic Profiling in Lung Cancer Management: Insights From North Sweden

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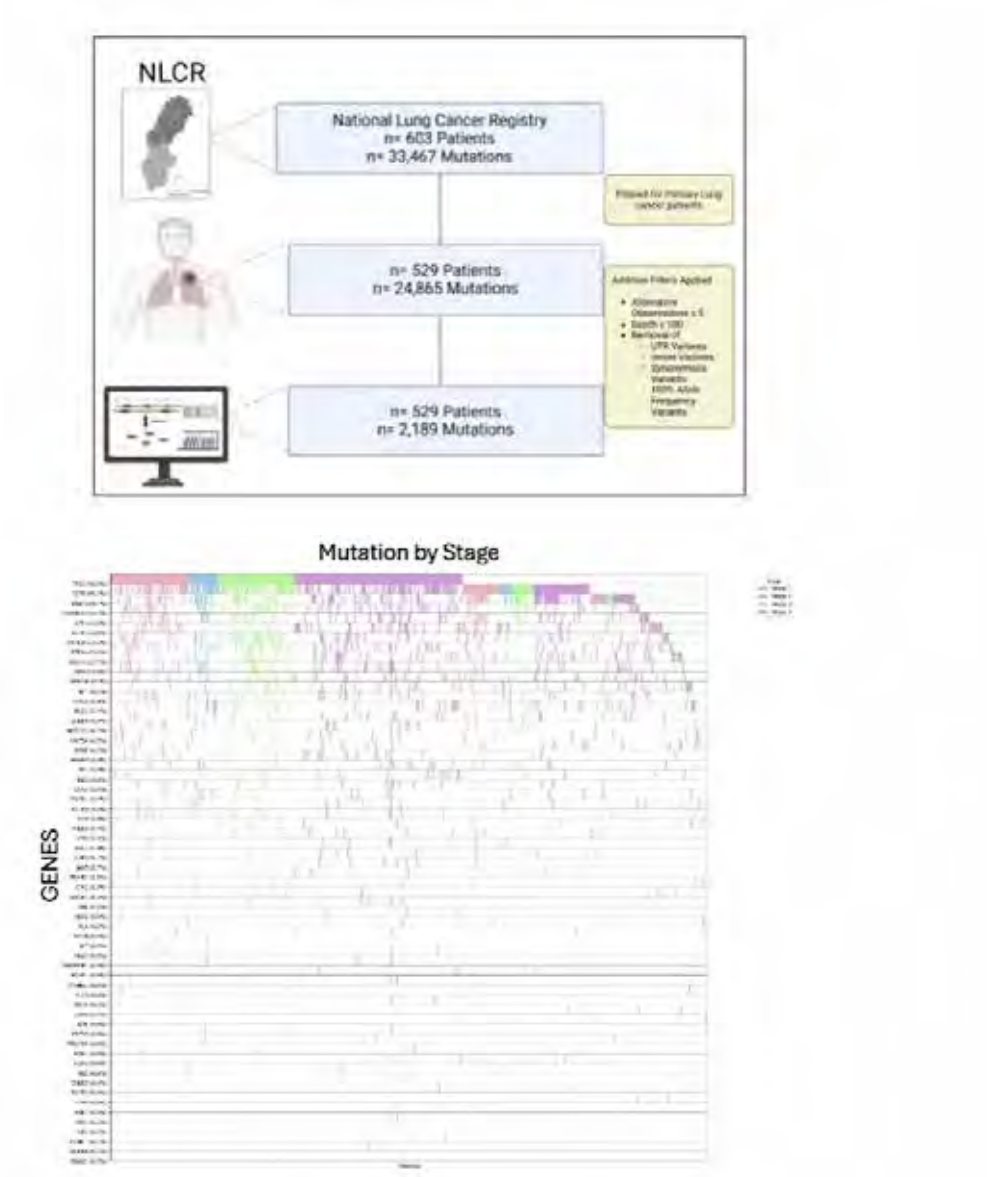
Introduction: The present study is a real-world in-silico study of the mutational landscape of lung cancer In the North Swedish Health Care Region. Real world data from routine genomic profiling have been used to study the mutational landscape of lung cancer. This research leverages existing genomic datasets to examine the interplay between genetic variations and a range of clinical factors, aiming to enhance our understanding of cancer genetics in a well-defined demographic setting.

Methods: This study utilized data from the Archer VariantPlex Solid Tumor 67 gene assay to analyze targeted sequencing genetic data from 529 lung cancer patients diagnosed 2011 to 2021. Individual clinical and demographic data were obtained from the Swedish National Lung Cancer Registry and matched to the genetic profiles. The relationship between clinical data, mutational patterns and patient outcomes is reported below.

Results: After quality filtration mutations in 60 unique genes were found across the cohort. The analysis revealed a mean of 2.5 mutations per tumor with a range of 0-27 mutations, indicating significant heterogeneity in mutational profiles. Geographic and demographic variations, such as lower EGFR mutation frequencies, were observed and linked to clinical factors. Mutation patterns varied significantly with age, gender, smoking status, and disease stage. Notably, early-stage lung cancer featured mutations in genes related to cellular differentiation and growth, while late-stage disease was associated with disruptions in cell cycle control and metabolic processes. Survival analysis highlighted the context-dependent prognostic value of mutations, with certain co-mutations altering the expected outcomes.

Conclusions: The findings underscore the importance of considering a broad, integrated mutational profile when evaluating prognostic markers in lung cancer. This approach could lead to more effective, personalized treatment strategies by acknowledging the complex interplay between genomic profiles and clinical characteristics



EP.06 PATHOLOGY AND BIOMARKERS

EP.06.12 Kita-Kyusyu Lung Cancer Antigen-1 Positive Is Associated With Pathological High-Grade in Lung Adenocarcinoma

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Introduction: Kita-Kyushu Lung Cancer antigen-1 (KK-LC-1) is one of the cancer-testis antigens and is reported to be an effective treatment using T cell receptor (TCR) gene-engineered T cells. In lung cancer, KK-LC-1 expression was observed in about 30%, and the association between KK-LC-1 expression and lymph node metastasis has been reported. This study aimed to evaluate the prognostic impact of KK-LC-1 in resected lung adenocarcinomas.

Methods: We reviewed the medical records of 110 patients who underwent curative resection for lung adenocarcinoma. We evaluated an original monoclonal antibody against KK-LC-1 (Kmab34B3). The staining intensity was scored as 0 (negative), 1 (weak staining), 2 (moderate staining) or 3 (strong staining). We defined moderate staining and strong staining as positive and divided into positive and negative groups. The overall survival (OS) and recurrence-free survival (RFS) were compared according to KK-LC-1 positivity. Cox regression analyses were performed to identify prognostic factors.

Results: In total cohort, 39 patients (35%) were KK-LC-1 positive. KK-LC-1 positive was significantly associated with larger invasive size, advanced stage, presence of lymphatic invasion and vascular invasion, and lymph node metastasis. Furthermore, KK-LC-1 positivity rate was significantly higher in papillary/acinar predominant and solid/micropapillary predominant than in lepidic predominant (43.0% vs 11.1% P = 0.001, 50.0% vs 11.1%, P = 0.023) and multivariable logistic analyses revealed invasive size as independent factors with KK-LC-1 positive (Odds ratio:4.184, 95% confidential interval (CI), 1.597-10.96, P=0.003). There were no significant prognostic differences in OS (5-year OS, 79.8% vs. 94.0%, respectively, P =0.072), whereas cases with KK-LC-1 positive showed poorer RFS than those without (5-year RFS, 85.5% vs. 67.7%, respectively, P =0.020). In multivariate analysis of OS, KK-LC-1 was not found to be an independent factor (Hazard Ratio (HR) = 1.413, 95% CI, 0.444-4.499, P= 0.558). On the other hand, in multivariate analysis of RFS, pathological stage was an independent factor (HR = 5.022, 95% CI, 1.659-15.20, P = 0.004). However, KK-LC-1 was not an independent factor in RFS (HR = 1.230, 95% CI, 0.518-2.918, P= 0.638).

Conclusions: KK-LC-1 positive was significantly associated with pathological high-grade and poor RFS of lung adenocarcinoma. KK-LC-1 may be one of the prognostic factors for lung adenocarcinoma and KK-LC-1 positive cases may be candidates for TCR reconstitution therapy.

Keywords: Lung cancer, KK-LC-1, pathology

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.13 Molecular Alterations in Octogenarians With Early-Stage Lung Cancer: A Real-World Study

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Introduction: As the U.S. population ages, an increasing number of octogenarians (≥80 years) are presenting with early-stage lung cancer. However, they remain an under-studied population. We aimed to assess the frequency and types of molecular alterations in this group and examine their family history of lung cancer.

Methods: We analyzed data from the Initiative for Early Lung Cancer Research on Treatment (IELCART), a prospective multi-institutional cohort study initiated in 2016, including patients who underwent surgical resection for lung tumors ≤30 mm. Our objective was to evaluate the frequency and distribution of clinically actionable variants in octogenarians compared to younger patients and examine variations across racial groups and smoking status. We also assessed the prevalence of family history of lung cancer in this population.

Results: Among 864 patients with surgically resected lung cancer (tumors ≤30 mm), 112 (13.0%) were octogenarians. Family history of lung cancer was comparable between octogenarians (14.3%) and younger patients (19%, p=0.2). Oncogenic driver mutations were analyzed in 568 patients (65.7% of the cohort), including 97/112 octogenarians (86.6%) and 471/752 younger patients (62.6%). Clinically actionable variants were identified in 313 patients (55.1%), with similar distribution between age groups. KRAS mutations were the most frequent, identified in 193 patients (34.0%), including 27 octogenarians (27.8%) and 166 younger patients (35.2%). The G12C variant was detected in 13/27 octogenarians (48.1%) and 79/166 younger patients (47.6%), showing no age-related difference. Octogenarians exhibited a similar prevalence of EGFR mutations (32/97, 33.0%) compared to younger patients (116/471, 24.6%). Among these, classical variants included exon 19 deletions (12/32, 37.5%) and L858R substitutions (20/32, 62.5%). Other targetable alterations—including MET exon 14 skipping (9/97, 9.3% vs. 20/471, 4.2%), ROS1 fusions (2/97, 2.1% vs. 5/471, 1.1%), RET fusions (1/97, 1.0% vs. 5/471, 1.1%), ALK fusions (1/97, 1.0% vs. 9/471, 1.9%), and BRAF V600E (2/97, 2.1% vs. 19/471, 4.0%)—showed no significant differences between age groups. Clinically actionable variants varied significantly by race (p<0.001). Among 568 tested patients, 14.3% were African American, 12% Asian, 61.8% White, and 12% other races. EGFR mutations were more prevalent in Asian patients (48.5%) compared to the overall cohort (26.1%). This trend was consistent among octogenarians, with Asians representing 7.2%, African Americans 7.2%, Whites 76.3%, and other races 9.3%. Among Asian octogenarians, 71.4% harbored EGFR mutations. Smoking status significantly influenced clinically actionable variants (p<0.001). Among 568 patients, 24.0% were never smokers, 64.4% former smokers, and 12.0% current smokers. EGFR mutations were more common in never-smokers (66.2%) than former (24.6%) and current smokers (4.4%). In octogenarians, 21.6% were never smokers, 75.3% former smokers, and 3.1% current smokers. EGFR mutations were more frequent in never-smokers (66.7%) than former smokers (24.7%), mirroring the overall trend (p<0.05).

Conclusions: Among 568 patients with resected lung cancer ≤30 mm who underwent NGS analysis, 17.1% were octogenarians, with 14% reporting a family history of lung cancer. Distribution of clinically actionable variants was similar between octogenarians and younger patients but varied significantly by race and smoking status. Future studies should address outcomes and therapeutic strategies in this underrepresented population.

Keywords: octogenarians, molecular alterations, family history of lung cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.14 Decreased Expression of DAAM2 Is Correlated With Poor Prognosis and Tumor Immune Microenvironment in Lung Adenocarcinoma

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Introduction: Disheveled-associated activators of morphogenesis 2 (DAAM2) has been shown to promote tumorigenesis and progression of various cancers, but its role in lung adenocarcinoma (LUAD) remains unknown. This research aimed to explore the role of DAAM2 in LUAD progression.

Methods: We used The Cancer Genome Atlas and TIMER2.0 databases to study DAAM2 expression in LUAD tissue samples, and we verified it in a tissue microarray. The correlation between DAAM2 expression and prognosis, clinicopathological characteristics, and the tumor immune microenvironment (TIME) of LUAD patients were investigated using survival, Cox regression, and correlation analyses. Functional enrichment analysis was used to investigate possible biological functions and mechanisms of DAAM2 in LUAD progression. The role of DAAM2 in the proliferation, migration, and invasion of LUAD cells were confirmed using Cell Counting Kit-8 assay, cell scratch assay, and invasion experiment.

Results: DAAM2 expression was downregulated in LUAD tissue samples and correlated with inferior survival and treatment outcome of LUAD patients. Functional enrichment analysis revealed that DAAM2 may promote LUAD progression through the cell cycle, P53, Wnt, and TGF-β signaling pathways. Furthermore, DAAM2 overexpression subdued the capacity of LUAD cells to proliferate, migrate, and invade. The number of immune cells and cellular markers infiltrated in the tumor microenvironment was significantly associated with the DAAM2 expression level.

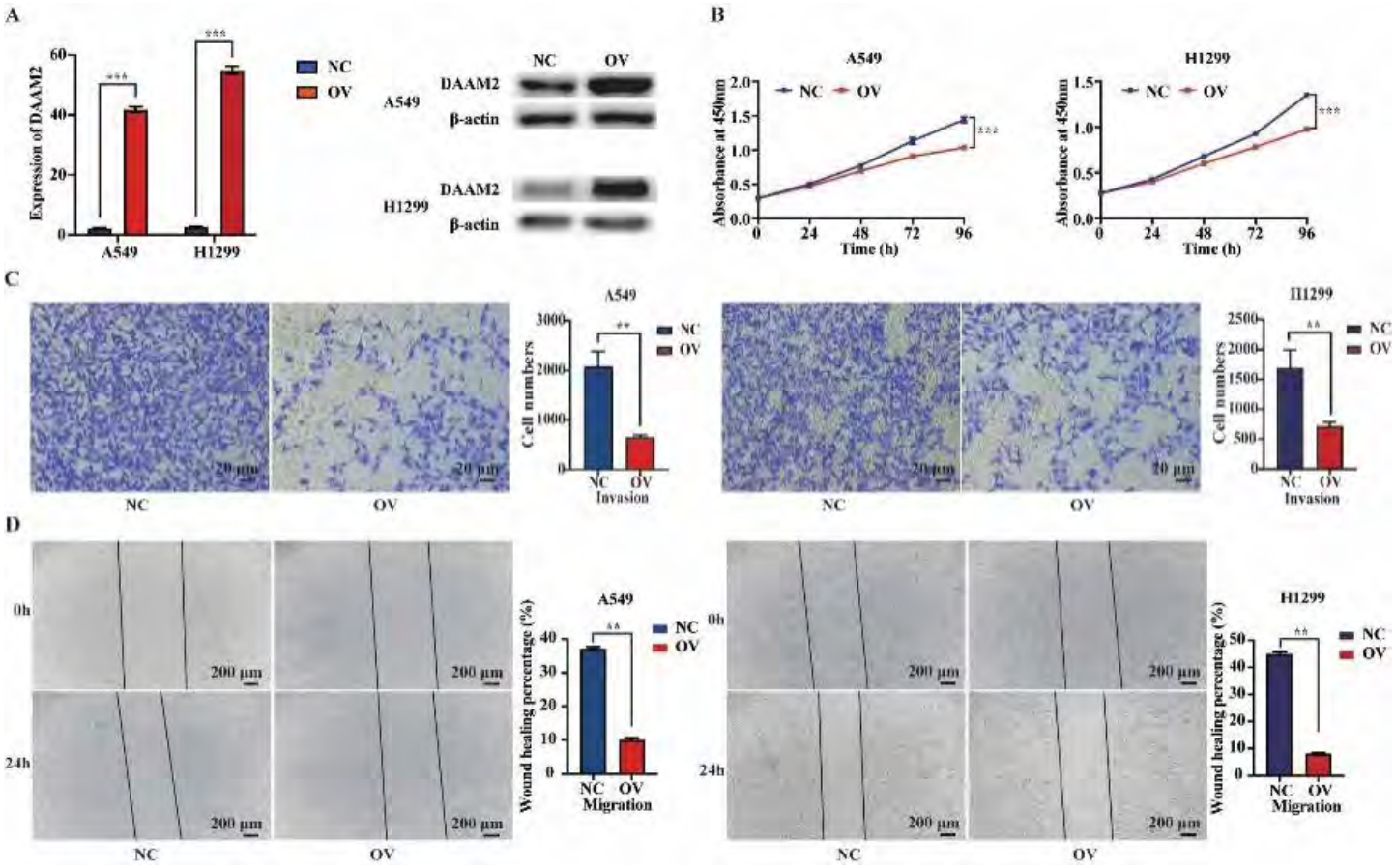

Figure1 DAAM2 overexpression inhibited the growth, migration, and invasion. (A) The cell model of DAAM2 overexpression. (B) Analysis of cell proliferation using the CCK-8 assay. (C) Analysis of cell invasion using the Transwell experiment. (D) Analysis of cell migration using the cell scratch assay.

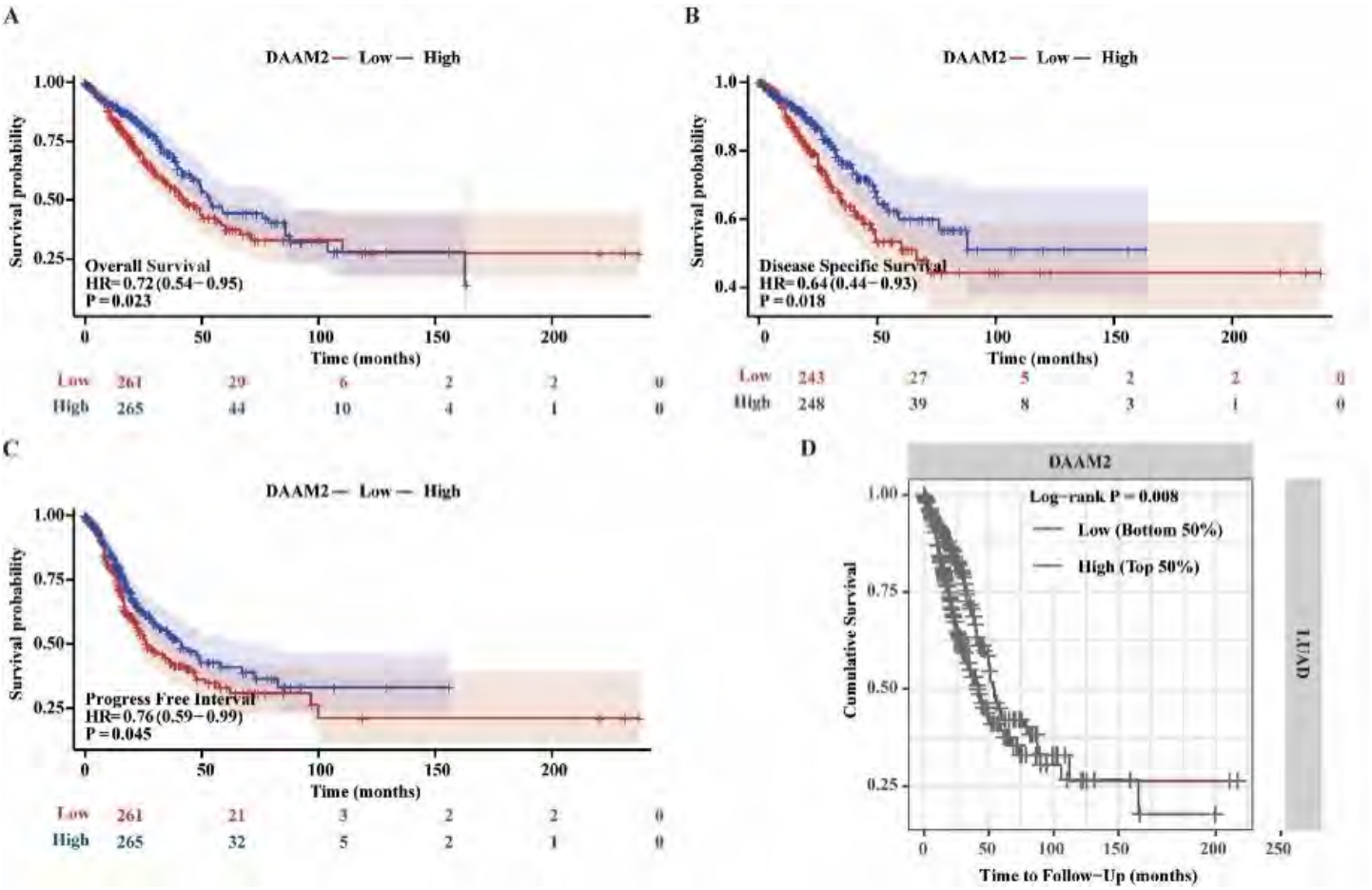

Figure2 Decreased expression of DAAM2 was correlated with poor prognosis. (A) OS; (B) DSS; (C) PFI; and (D) Cumulative survival.

Conclusions: These results indicate that DAAM2 can block tumor progression and may serve as a prognostic biomarker and therapeutic target for the treatment of patients with LUAD.

Keywords: Lung adenocarcinoma, The Cancer Genome Atlas, DAAM2

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.15 Reflex Next Generation Sequencing Testing in NSCLC: Overcoming Barriers to Equitable Molecular Profiling in an Urban Healthcare Network ?

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Introduction: Next-generation sequencing (NGS) enables comprehensive genomic and transcriptomic profiling. As the treatment landscape for non-small cell lung cancer (NSCLC) quickly changes, these molecular markers guide treatment selection across disease stages. However, implementation challenges, such as tissue sufficiency, provider awareness, and logistical constraints, can hinder adherence to these guidelines. Temple University Health System (TUHS) is a non-profit academic healthcare network in Pennsylvania (United States) with diverse patient populations and subspecialty services. At the start of 2023, a reflex molecular testing policy was implemented for NSCLC across multiple sites of TUHS. This study evaluates the rates of NGS DNA and RNA testing from intrathoracic samples of NSCLC obtained from pulmonary and interventional radiology (IR) procedures.

Methods: We retrospectively identified patients who underwent pulmonary or IR procedures in 2023 at three sites across TUHS that resulted in an NSCLC diagnosis. Sites included Temple University Hospital-Main Campus (TUH-MC), Fox Chase Cancer Center (FCCC), and Temple University Hospital-Jeanes Campus (TUH-JC). Reflex ordering was done by pathology and NGS testing was performed internally at FCCC and TUH-MC. We examined completion rates of NGS-DNA, NGS-RNA, and both NGS-DNA and RNA. We collected patient demographic information, comorbid diseases, tumor histology, geographic site of sampling, type of procedure performed (bronchoscopy, EBUS, CT-guided), biopsy type (transbronchial, core, fine needle aspiration) and location from which the sample was obtained (lung tissue vs. lymph node).

Results: Using search terms inclusive of pulmonary or IR procedures resulting in the diagnosis of NSCLC across sites in 2023, 306 patients were identified. Patients with histological subtypes other than NSCLC, non-lung primary malignancies, inconclusive diagnoses, or procedures that did not result in a malignancy diagnosis were excluded from further review. 277 patients remained: 232 (83.8%) received NGS DNA testing, 227 (81.9%) received NGS RNA testing, and 224 (80.9%) received both NGS DNA and RNA testing. Of the 42 (15.2%) patients that did not undergo any NGS testing, 21 (50%) did not require NGS testing for clinical management given stage IB < 4cm. Multivariate analysis is ongoing to elucidate patient and procedural factors associated with NGS-DNA and RNA testing.

Conclusions: Within a large urban healthcare network, where disparities in cancer care are prevalent, reflex DNA and RNA-based NGS testing ensures that patients diagnosed with NSCLC receive comprehensive molecular profiling, even on small samples from intrathoracic procedures. By systematically integrating NGS into routine diagnostic workflows, we hope to overcome known traditional barriers to testing, such as provider awareness and logistical constraints. Future studies should focus on providing guidance on tissue sufficiency for NGS testing and the role of circulating tumor DNA, along with identifying remaining gaps in adherence, addressing logistical and financial barriers, improving access to genetic counseling for germline risk variants, and refining strategies to further standardize biomarker testing.

Keywords: NGS, genomics, NSCLC

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.16 Immunophenotyping of the Molecular Subtypes of Small Cell Lung Cancer and Its Correlation With Prognostic and Therapeutic Implications

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Introduction: Molecular stratification of small cell lung carcinoma based on mRNA expression consist of four categories: achaete-scute homologue 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), POU class 2 homeobox 3 (POU2F3) and yes-associated protein 1 (YAP1) transcriptional regulators. However, there is paucity of literature regarding the expression of these markers at protein level/ immunohistochemistry and their prognostic and therapeutic relevance including survival analysis

Methods: Formalin-fixed paraffin embedded tissue samples of 120 consecutively diagnosed unresectable SCLC patients were subjected to IHC (ASCL1, NEUROD1, POU2F3 and YAP1) and analyzed for their immunoexpression. The subtypes identified were correlated with expression of neuroendocrine marker (NE): INSM-1 and also with the response after 6-cycles of platinum-based chemotherapy: Responder (R; complete or partial response /stable disease) vs Non responder (NR; progression). Overall survival was also evaluated in correlation with these molecular IHC subtypes

Results: Majority were males (81.7%) and elicited history of smoking (70.8%). Four distinct categories were identified on the basis of relative immunoexpression of these IHC markers: ASCL1-dominant (58.5%), NEUROD1 dominant (12.1%), POU2F3+/ASCL1-/ NEUROD1- (7.8%), and ASCL1-/ NEUROD1- NOS (21.6%). All the POU2F3 positive cases were ASCL1-/NEUROD1- and were associated with absent/reduced NE (INSM-1) expression ($p < 0.0001$). Overall expression of YAP1 was very low (2.5 % cases) and not exclusive of other subtypes. NEUROD1 dominant and POU2F3+/ASCL1-/ NEUROD1- categories were significantly associated with NR ($p = 0.027$). The survival rates were 59% in responders and 50% in non-responders at 1 year (p-value= 0.928). The OS was 53% at 1year and was not significantly associated with any of the IHC subtypes (p-value 0.137). YAP1 expression although had low frequency, however, was associated with poor overall survival (p=0.013)

Conclusions: We found NEUROD1 dominant and POU2F3 dominant subtypes were associated with poor response to chemotherapy while none of the molecular subtypes were significantly associated with OS. YAP1 expression was rare and could not establish itself as a distinct molecular subtype, however, was associated with poor OS. POU2F3 can be utilized as a useful NE IHC marker, to diagnose small cell carcinoma in absence of other established NE IHC markers.

Keywords: immunoexpression, molecular stratification, small cell carcinoma

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.17 Immunological and Genetic Profile and Efficacy of Immunotherapy in NSCLC Patients With Mutations in KRAS and STK11 Genes

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Introduction: Mutations in KRAS gene are among the most common genetic abnormalities in patients with non-small cell lung cancer (NSCLC) and often coexist with mutations in STK11 gene. Such co-occurrence is associated with resistance to immune checkpoint inhibitors (ICIs). This study aimed to examine the immune status and genetic profile that may affect the efficacy of ICIs.

Methods: In 20 patients with NSCLC qualified to immunotherapy or chemo-immunotherapy, we performed targeted next-generation sequencing based on the SureSelect CD Glasgow Cancer Core Panel. In addition, we assessed peripheral blood mononuclear cells' immunophenotype using flow cytometry. We performed immunological analysis before and during therapy. This study was funded by the Polish National Centre for Research and Development (LIDER/46/0237/L-12/20/NCBR/2021).

Results: Mutations in KRAS/STK11 genes co-occurred in 3 patients. The chemoimmunotherapy long-responding patient (38 months and ongoing) - NK2 - additionally had abnormalities in RAD50, PMS2, JAK1, KDR and NOTCH4, the patient with short disease stabilization (NK9) following chemoimmunotherapy (4 months) - in ATM, PMS2 and SMARCA4, while the patient with rapid progression (NK5) during pembrolizumab therapy (<2 months) - in PIK3CA, PDGFRA, H3-3A, and NOTCH4 genes. Patients NK2 and NK9, compared to the non-responder, before therapy had high percentages of CD3+ and CD4+ T cells and low percentages of CD8+/PD-1+ cells and Tregs. In NK2 and NK9 patients, in contrast to the NK5 patient, the percentages of CD8+ T cells CD8+/PD-1+ cells, CD4+/EOMES+ cells and Tregs were increasing. In the non-responding patient, an increase in the percentage of T cells with TIM-3 and LAG-3 molecules was observed.

Conclusions: Coexistence of KRAS/STK11 mutations with mutations in genes encoding DNA repair proteins: PMS2, RAD50, and ATM appears to be a favorable predictor for immunotherapy. This is probably related to DNA repair deficit in tumor cells, accumulation of somatic mutations and high number of neoantigens, and thus high immunogenicity of the tumor and activation of the immune system supported by immunotherapy. Additional mutations in oncogenes (PIK3CA, NOTCH4) may be an unfavorable predictor. Immune system analysis may be important in predicting the immunotherapy efficacy.

Keywords: NSCLC, mutations in KRAS and STK11 genes, immunotherapy

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.18 Is There Any Association Between EGFR Alterations and PD-L1 Expression in NSCLC a Single Center Experience

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Introduction: Epidermal growth factor receptor (EGFR) mutation is the most common mutation in non-small cell lung cancer (NSCLC), approximately 15-45%. EGFR amplification is sometimes the only detectable molecular alteration in patients with NSCLC, also it sometimes co-occur with EGFR mutations. Previous studies reported that EGFR amplifcation occurred in about 9-64% NSCLC patients. They were distinct situations, and treatment schedules were different.

Methods: We conducted a retrospective observational study in our medical oncology department, enrolling advanced non-squamous NSCLC patients with EGFR alterations (mutation or amplification) between 2019 and 2024. Next-generation sequencing (NGS) or polymerase chain reaction (PCR) was used to detect genetic alterations in tumor tissue, and immunohistochemistry (IHC) was used to determine PD-L1 expression. The Chi-square test was used to compare these proportions in two groups. PD-L1 expression cut-off was calculated as PD-L1:1.

Results: A total of 85 advanced NSCLC patients with EGFR alterations were included in this study. EGFR amplification was found in 37 of 85 (43.5%) and EGFR mutation was found 48 of 85 (56.5%) patients with EGFR alterations. Of 48 patients with EGFR mutations, 22 patients harbored EGFR 19 del, 16 patients with 21-L858R, 8 patients harbored with rare mutations. In chi-square analysis, EGFR amplification was identified as an independent factor for the PD-L1 expression (p = 0.01).

Conclusions: We found that EGFR amplification is an independent factor for PD-L1 expression in advanced non-squamous NSCLC patients. Nevertheless, further research is needed in larger populations.

			PD L1 expressions		
			<1	>1	Total
EGFR	amplification	Count	6	31	37
		% within EGFR	16,2%	83,8%	100,0%
	mutantion	Count	25	23	48
		% within EGFR	52,1%	47,9%	100,0%
Total		Count	31	54	85
		% within EGFR	36,5%	63,5%	100,0%

Keywords: NSCLC, EGFR amplification, PD-L1

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.19 The Relationship Between PD-L1 Expression and Tumor Microenvironment in Lung Squamous Cell Carcinoma

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Introduction: PD-L1 expression status is very important factor in order to predict therapeutic effect of immune checkpoint inhibitor (ICI). Tumor cells interact with surrounding stromal cells via complex mechanisms, and together these cells make up the tumor microenvironment (TME). Within the last decade, the TME has been shown to be important for the proliferation, invasion, metastasis, and treatment resistance of tumor cells. Stromal cells include fibroblasts, vascular cells, and immune cells. Common immune cells, including lymphocytes, neutrophils, and monocytes/macrophages, also make up the TME. Tumor infiltrate lymphocyte (TIL), tumor-associated macrophage (TAM), and cancer-associated fibroblast (CAF) are main components of TME. The aim of this study is to examine the relationship PD-L1 expression status and the density of TIL and TAM and CAF expression status in surgically resected lung squamous cell carcinomas (SQCCs).

Methods: A total of 104 SQCCs were examined. The male:female ratio was 97:7; the age range was between 51 and 87 years of age and the mean age was 71 years. Pathological stage's ratio (I:II:III) was 57:32:15. Adjuvant chemotherapy was performed in 62 patients. The mean follow-up period was 58.2 months (range, 4.9-135.3 months). Tissue microarray was built and the expression status of PD-L1, CD3 and CD8 as TILs marker, CD68 and CD163 as TAMs marker, AEBP1, α-SMA, FAP, Tenascin-C, Podoplanin, CD10, PDGFRα, PDGFRβ, FSP1 as CAFs marker was analyzed using immunohistochemistry. PD-L1 expression status of both tumor cells (TC) and immune cells (IC) were examined and classified as follows: (Negative, <1%; Positive, 1%≤). The relationship between the status of PD-L1 expression and the expression status of TME factors (TILs, TAMs, and CAFs) was investigated.

Results: The status of PD-L1 expression was as follows: Negative, 60 (58%); Positive, 44 (42%) in TCs and Negative, 63 (61%); Positive, 41 (39%) in ICs. PD-L1 expression in TCs was correlated with the density of CD3 and CD163 expression (p=0.029 and p=0.029, respectively) and PD-L1 expression in ICs was correlated with the density of CD3, CD8, CD68, CD163 expression and the status of CAFs expression (p=0.009, p=0.032, p=0.098, p=0.067 and p=0.075, respectively). The status of CAFs expression was also correlated with the density of CD8 and CD163 expression (p=0.01 and p=0.023, respectively).

Conclusions: PD-L1 expression was correlated with the status of TME, particularly in ICs. In addition, Inter-correlation among TME was found. Therefore, examining the status of TME is very important and useful because of therapeutic strategy of lung SQCC.

Keywords: PD-L1, Tumor microenvironment, squamous cell carcinoma

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.20 Stage-Dependent Increase in EGFR Mutation Rates in Early-Stage Lung Cancer at National Taiwan University Cancer Center

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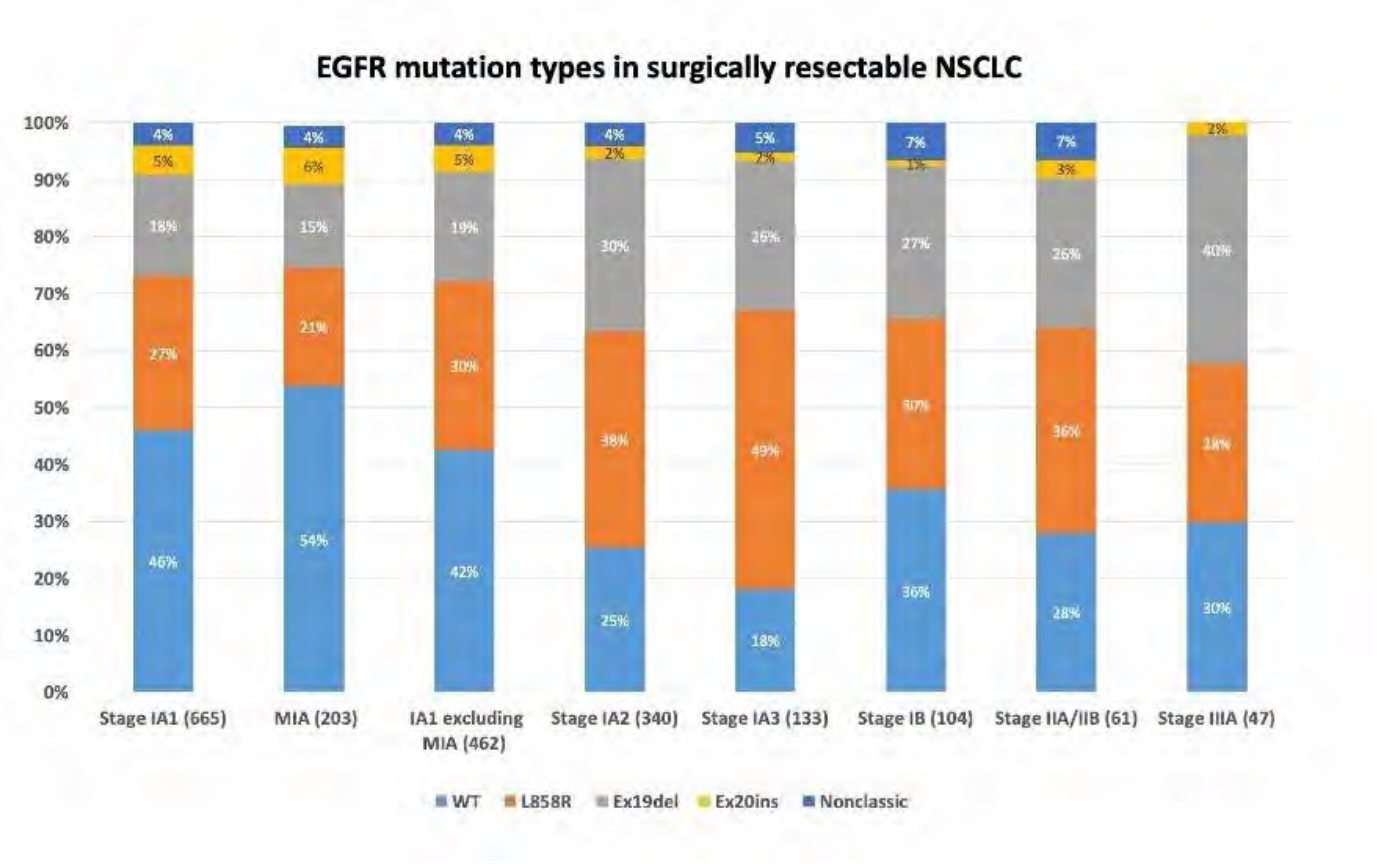
Introduction: Epidermal growth factor receptor (EGFR) mutation is the most common driver mutation of lung cancer in Asia. This study aims to analyze the prevalence of EGFR mutations and their clinicopathological characteristics among different stages of surgically resected lung cancer at National Taiwan University Cancer Center. Specifically, we intend to examine the differential expression patterns of EGFR mutations in early-stage versus advanced-stage lung cancers, in order to elucidate their distinct roles in tumor invasiveness and early-stage oncogenesis.

Methods: This retrospective study meticulously compiled data from all surgically resected lung cancer cases, spanning stages IA1 to IIIA, who underwent EGFR mutation testing at the National Taiwan University Cancer Center between January 1, 2023, and December 31, 2024. Comprehensive clinical and pathological information for each eligible case was systematically extracted from electronic medical records. The retrieved data encompassed detailed EGFR mutation test results, precise histologic typing, histologic grading, and the complete TNM staging components.

Results: From 2023-2024, 1,351 stage I-IIIA lung cancers underwent cobas EGFR v2 testing, identifying EGFR mutations in 887 (64.2%) cases. The most frequent mutations were EGFR exon 21 L858R (32%), EGFR exon 19 deletions (Ex19del) (24%), and EGFR exon 20 insertions (Ex20ins) (4%). A striking trend emerged: the overall EGFR mutation rate and the prevalence of classic EGFR mutations (L858R/Ex19del) progressively increased with advancing tumor stage, from IA1 (53.9% and 44.8%, respectively) to IA3 (81.9% and 75.2%, respectively). Furthermore, tumor grade influenced mutation frequency, with grade 2 adenocarcinomas showing the highest EGFR mutation rate (70.0%) and grade 1 the lowest (49.0%). This finding hints at a possible link between EGFR mutation prevalence and the differentiation status or biological aggressiveness of lung adenocarcinoma.



Conclusions: Across all stages and grades, L858R was the most common mutation type. In early-stage lung cancer (stage IA1-IA3) with tumors not exceeding 3 cm, the EGFR mutation rate increased from minimally invasive adenocarcinoma (MIA) to stage IA3, suggesting that early-stage lung adenocarcinoma with EGFR mutations has a growth advantage. Regarding different EGFR mutation types, this study also showed that early-stage lung adenocarcinoma with typical EGFR mutations (L858R/Ex19del) had a growth advantage over those with atypical mutations (Ex20ins/G719X/L861Q). Consequently, the proportion of typical EGFR mutations gradually increased from MIA to stage IA3, whereas the proportion of atypical EGFR mutations decreased.

Keywords: EGFR mutation, Early-stage lung cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.21 Genomic and Demographic Predictors of Survival in Patients With ALK Fusion NSCLC: Insights From a Single-Center Cohort

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Introduction: Patients with anaplastic lymphoma kinase (ALK) fusion non-small cell lung cancer (NSCLC) generally exhibit prolonged survival rates. In multiple phase III studies evaluating the efficacy of tyrosine kinase inhibitors (TKIs) targeting the ALK receptor, the median overall survival (OS) has not yet been reached. However, a subset of patients experiences significantly reduced OS. We aim to characterize the demographic and genomic profiles of this patient group.

Methods: We reviewed consecutive electronic medical records of patients with ALK fusion NSCLC whose next-generation sequencing (NGS) was performed and who were treated at Cedars-Sinai Cancer Center between the years 2019 to 2024. Data on demographic factors (age, sex, race, ethnicity, and smoking status), clinical information (date of initiation of ALK inhibitor TKI and date of death, if applicable), and pathological characteristics (including NGS analysis and co-mutations) were evaluated. Patient characteristics by mortality were compared using two-sample t-tests, Chi-squared tests, or Fisher's exact tests, as appropriate. Overall survival since the treatment start was compared across sex, ethnicity, race, and co-mutation status using Kaplan-Meier curves and the log-rank test.

Results: Our cohort included 68 patients with ALK fusion. At the time of analysis, 15 patients (22%) had died (median OS 43 months), while 53 patients (78%) were still alive (median OS not reached). The median age of patients who died was younger than that of the long-survival group (56 years vs. 65 years, p-0.05). Both groups were well-balanced in terms of other characteristics, including sex, ethnicity, race, smoking status and ALK Fusion variant. Genomic analysis of the cohort revealed a shorter OS for patients whose tumors harbored co mutation of TP53 mutation (median OS was not reached in both groups, p-0.014) and MTAP deletion (18.5 months versus not reached, p-0.026).

Conclusions: Our findings highlight the heterogeneity within patients with ALK fusion NSCLC, demonstrating that certain genomic alterations, specifically TP53 mutations and MTAP deletions, are associated with shorter OS despite the generally favorable prognosis seen in this population. These findings underscore the need for further research into the biological mechanisms underlying these differences, which may guide the development of more personalized treatment strategies and improve outcomes for patients with poor prognostic factors.

Keywords: NSCLC, ALK Fusion, co-mutation

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.22 Genomic Insights Into ALK-Rearranged NSCLC: A Comprehensive Study

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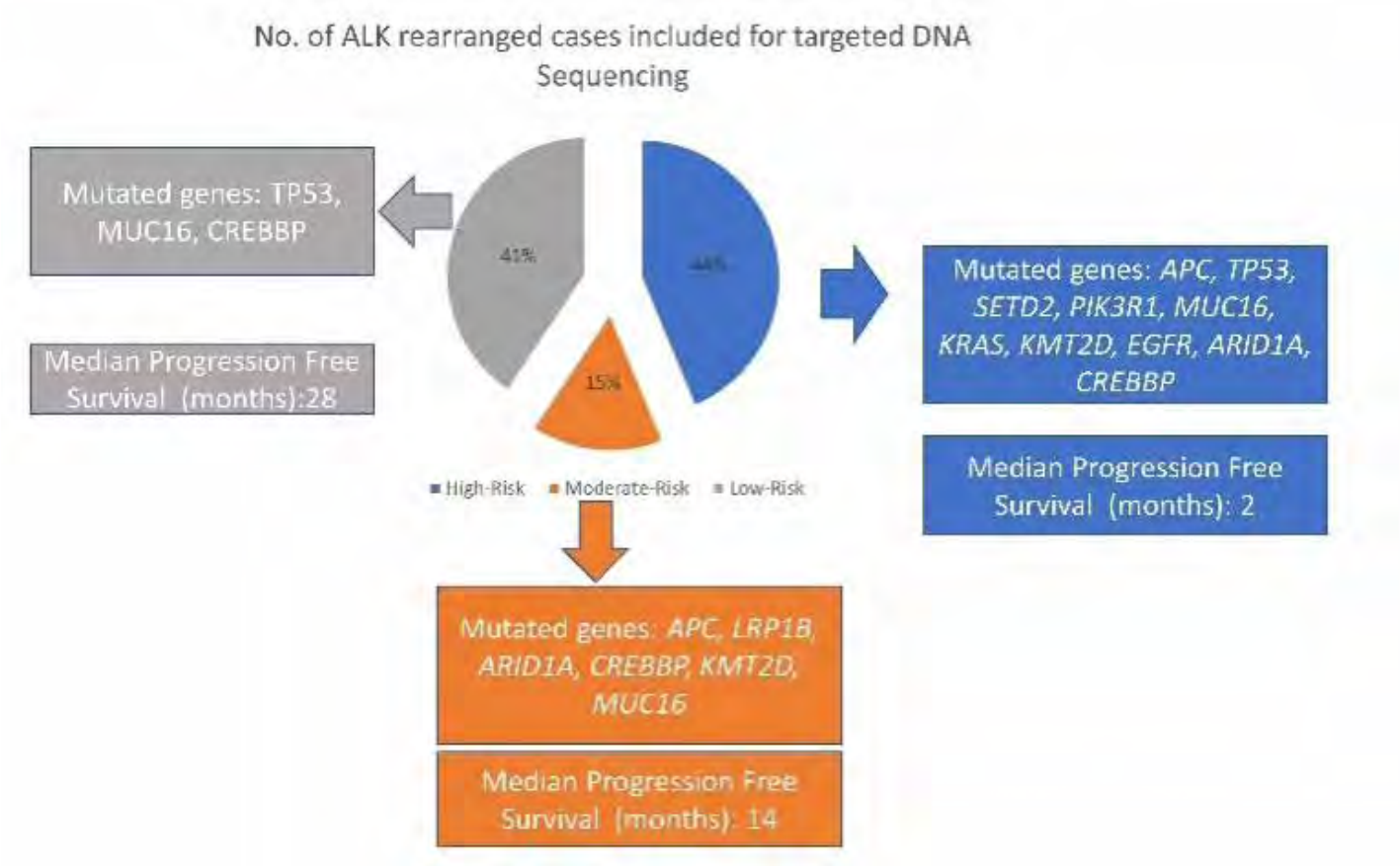
Introduction: The discoveries of targetable molecular alterations are leading to the advancement in precision medicine. The discovery of rearrangement in the Anaplastic lymphoma kinase (ALK) gene in Non-Small Cell Carcinoma (NSCLC), makes it another subtype of NSCLC. The ALK tyrosine kinase inhibitor (TKI) is used for treatment of such subtype, despite this treatment some patients have rapidly progressive disease, which necessitates the understanding of major risk factors.In our study, the genetic profile of different risk patients was done to identify signatures for rapid disease progression, that can be incorporated into routine molecular testing panels alongside ALK testing.

Methods: We collected ALK Immunohistochemistry and/or Fluorescence In Situ Hybridization positive 46 Formalin-Fixed, Paraffin-Embedded (FFPE) block of ALK-rearranged NSCLC patients from 2014 to 2024, from the department of pathology. On the 41 Samples, RNA fusion was detected using a custom RNA fusion panel and based on tissue availability the 32 samples were tested for 72 genes that are crucial in lung cancer using the Qiagen 72 gene panel.

Results: Out of 41 samples, 17 samples were from High-risk group (MPFS:2), 6 samples were from moderate risk group (MPFS:13.5), and 18 samples were from the low-risk group (MPFS:39), the ALK fusion partner was detected in 26 patients and 12 samples were negative, and 3 samples failed at QC level. The RNA sequencing result showed V1 as the most common variant (53.8 %, 14/26) and V5 being the least common (3.8 %, 1/26) and no direct correlation was found between ALK fusion variants and risk groups. In addition to RNA sequencing, targeted DNA sequencing was performed to identify mutations that may further define the molecular risk stratification, results are shown in figure 1. Mutations like TP53, MUC16, and CREBBP are common in all three groups and may not be genes defining the risk, whereas mutation in tumor suppressor genes including APC, ARID1A, KMT2D can be included to define the moderate risk and High-risk group. Mutation in SETD2, PIK3R1, KRAS, and EGFR along with ALK rearrangement may promote the tumor progression and contribute to poor treatment response.

Conclusions: This finding suggests that mutations in genes such as APC, ARID1A, KMT2D, SETD2, PIK3R1, KRAS, and EGFR may help in determining the aggressiveness of the tumor. Evaluating the efficacy of ALK TKIs in the context of baseline genetic alterations is essential, and combination therapies may be required for cases with co-occurring oncogenic drivers like EGFR and KRAS.



Keywords: ALK, NSCLC, Genomic Profiling

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.23 Comprehensive Genomic Profiling as a Key Determinator in Clinical Staging and Treatment Planning

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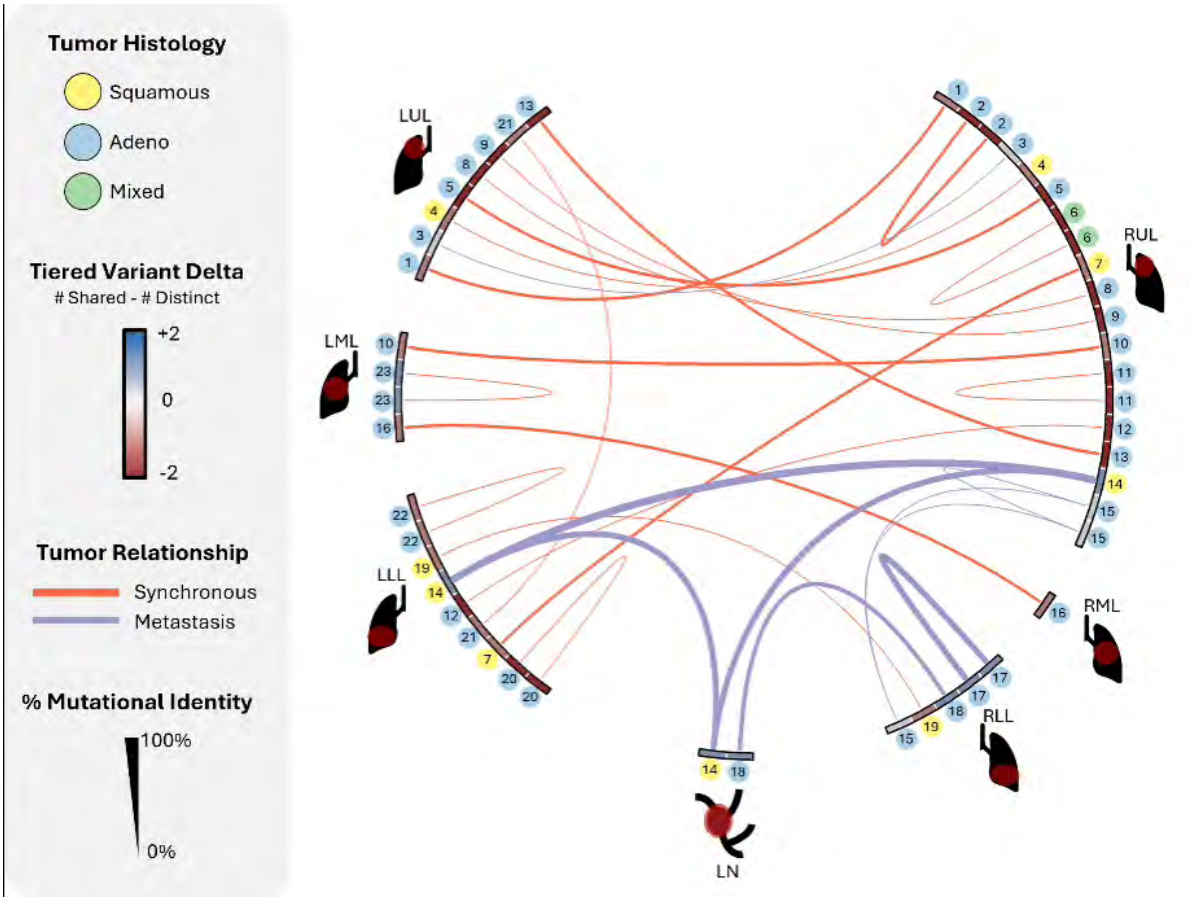
Introduction: NSCLC patients who present with multiple distinct lesions present a clinical conundrum. Distinguishing between synchronous primaries or metastasis can serve as a prognostic indicator, facilitate staging, and therefore influence treatment decisions. Recommended criteria for staging proximal lesions primarily relies upon histologic characterization, with one paper describing criteria to consider, yet no formal guideline has been issued. We present evidence for a valuable role of comprehensive genomic profiling (CGP) to facilitate staging in the setting of multiple lung nodules and outline guiding principles for the interpretation of composite results.

Methods: A cohort of 23 NSCLC patients encompassing 48 intrapulmonary lesions of distinct spatial localization or histologic subtype were evaluated. CGP was performed on each lesion using an FDA-cleared 505 gene NGS assay. Clinical history, morphology, and mutational profiles were cross evaluated to infer staging for each patient. Variants were tiered according to AMP/ASCO/CAP guidelines.

Results: Of the 23 patients, 22% (n=5) were designated as harboring a single primary with local or advanced metastasis, while 78% (n=18) favored the presence of synchronous primaries. Of patients with synchronous primaries, 94% harbored more unique Tier I/II variants than shared between lesions and averaged a 16% (95% CI, 11.3% to 20.7%) shared identity between mutational profiles. Comparatively, all patients with lesions denoted as being of a single primary with metastasis harbored an equal or higher ratio of shared to unique tiered variants but displayed variable levels of shared identity (average, 50%; SD, 36%). Further, we exhibit individual patients where treatment decisions were altered considering CGP results.

Conclusions: The utilization of mutational profiles to infer tumor staging has largely been unincorporated due to multiple factors including limitations in assay sensitivity, germline mutations, and known discordance between primary and metastatic sites. However, interpretation of the mutational profiles between lesions can still inform stage determination if caveats are factored into the final decision. In our experience, this approach has facilitated staging in ways that are not possible by morphology alone. The data herein often lowers staging thereby driving treatment decisions, including the possible avoidance of unnecessary treatment options. As such, we propose CGP should be recommended as a standard approach to navigate these clinical scenarios, and that payors support the use of these assays in such a way. We also hope to inspire additional discussion for the review of the use of CGP to inform staging in NSCLC patients with multiple lesions with more formal guidance.



Keywords: Staging, Genomic profiling

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.24 Update of Mutation Status and PD-L1 Expression in Lung Cancer

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Introduction: Significant progress has been made in understanding the biology of non-small cell lung cancer (NSCLC), particularly through the characterization of molecular alterations including oncogene activations (mutations, translocations, amplifications) and immune checkpoint expressions, which serve as predictive biomarkers

Methods: This study analyzed molecular alterations in EGFR, ALK gene fusion, Ros1 and PD-L1 in Caucasian and Hispanic populations from 2015 to 2025. PD-L1 expression was assessed in 146 of 260 NSCLC samples, including biopsies and surgical resections from various Cordoba institutions. Molecular testing included EGFR mutations (TheraScreen PCR kit targeting exons 18-21), ALK translocations (FISH Vysis Break-Apart and IHC clone D5F3), and PD-L1 expression (Dako Autostainer Link 48, kit PD-L1 IHC 22C3 pharmDx). Molecular profiles and PD-L1 expression were correlated with clinical variables (age, gender, smoking habits), using chi-squared or Fisher's test for qualitative variables and T-test for quantitative variables.

Results: The study included 260 NSCLC adenocarcinoma pts (165 males, mean age 63; 95 females, mean age 61). Smoking was significantly higher in males (60%) compared to females (29.62%, p=0.006). EGFR positivity was more frequent in females (11.51%) compared to males (6.35%, p=0.0001), while ALK alterations were infrequent overall (positive cases: males 1.2%, females 1.6%; p=0.4276). PD-L1 expression positivity was identified in 26% of males and 16% of females (p=0.9726), without significant gender differences. ROS-1 positivity was very rare (0.74% each gender).Of the 149 adenocarcinoma cases specifically tested for PD-L1, positivity was found in 63 cases (42.28%).PD-L1 positive and negative groups showed no significant differences regarding to age (mean 60.98 vs. 62.21 years, p=0.3736), gender (male 26% positive vs. 36% negative, female 16% positive vs. 22% negative; p=0.9726), or smoking habits (smokers: 37.58% PD-L1 positive vs. 54.36% negative; p=0.3613). EGFR and ALK status did not significantly correlate with PD-L1 expression.

Conclusions: The observed frequencies of EGFR mutations and ALK fusions are comparable to those reported in Western populations. The molecular profiling of EGFR, ALK, and PD-L1 tumor proportion scores (TPS) in NSCLC adenocarcinomas is crucial for accurate diagnosis and appropriate therapeutic decisions, underscoring the importance of personalized medicine in lung cancer management.

Keywords: Molecular Profile, PDL1 expression, Lung cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.25 Analysis of LAT1 Protein Expression and Clinical Characteristics of Patients With Primary Lung Cancer

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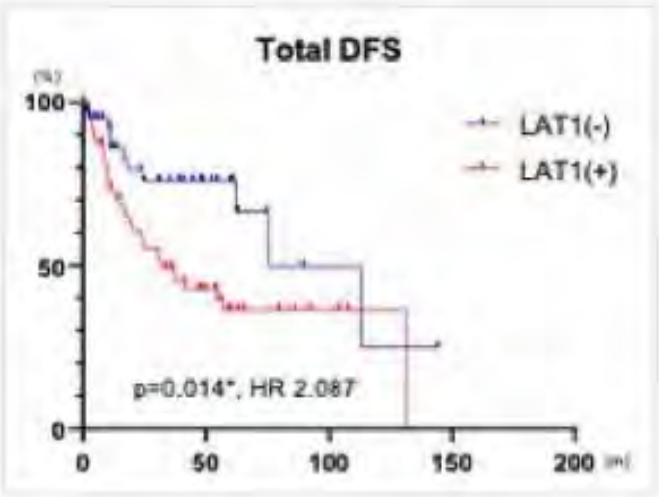
Introduction: The L-type amino acid transporter 1 (LAT1) is a membranous transporter that transports neutral amino acids for cells and is dysregulated in various types of cancers. One of this study aims is to investigate the correlation between prognosis or histological features of lung cancer and LAT1 expression, and the other is to clarify the heterogeneity of expression levels between primary and metastatic lesions.

Methods: We collected lung cancer specimens by surgical resection or pathological autopsy, administered from 2019 to 2021 in Kanazawa University Hospital. LAT1 protein expression of cancer cells were accessed by immunohistochemistry staining. Patient characteristics were extracted from electric record retrospectively.

Results: Totally 127 patients were corresponded for our study. The positive rate for LAT1 protein in small cell carcinoma, adenocarcinoma and squamous cell carcinoma were 58%, 50% and 94%, respectively. In the survival analysis, disease-free survival in LAT1 positive group was significantly shorter than that in LAT1 negative group (31.7m vs 76.8m, p=0.034, HR=1.99). Overall survival in LAT1 positive group was also significantly shorter than that in LAT1 negative group (84.1m vs NR, p=0.034, HR=2.35). Multiple lesions could be accessed in 27 cases in the analysis about autopsy. 22 out of 27 cases were homologous among the metastases.

Conclusions: Our study suggested LAT1 protein expression had a potency of the prognostic factor, especially in adenocarcinoma. These results were consistent with previous reports. It thinks that recruited amino acid contributes not only protein synthesis but stimulation of cancer growth. LAT1 expression heterogeneity among the metastases was low. We think further investigation as a new therapeutic target is warranted.



Keywords: LAT1, heterogeneity

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.26 Resectable Lung Cancer With KRAS Mutation May Have Less Lymphatic Metastasis

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Introduction: Multigene panel testing has mainly been performed in advanced lung cancer, and there is little data accumulated in resected specimens from early-stage lung cancer. At our institution, all resected specimens are tested for driver gene mutation using the the AmoyDx® Multi-Gene Mutations Detection Kit (AmoyDx). We report on the association between genetic mutations and pathological factors.

Methods: We collected pathological data from 291 patients with non-small cell lung cancer who were submitted to AmoyDx after surgical resection at Tohoku University Hospital between January 2022 and July 2024. We investigated the association between driver gene mutations and pathological factors.

Results: The median age of the patients was 72 years, and 157 were men (54%) and 134 were women (46%). The pathological stage was 0/IA/IB/II/III in 1/177/49/43/21 cases, respectively. The driver gene mutations were EGFR in 109 patients (37%), KRAS in 40 patients (14%), BRAF in 2 patients (0.7%), HER2 in 7 patients (2.4%), RET in 3 patients (1.0%), MET in 15 patients (5.1%) and ROS1, ALK and NTRK in 0 patients. The more advanced the pathological stage, the lower the rate of EGFR mutation and the higher the rate of KRAS mutation. There was no consistent trend was observed for other mutations. The proportion of KRAS mutations increased with the progression of pathological T-factors, but the proportion of positive lymph node metastases and lymphatic invasion was 5.0% (2/40) and 7.5% (3/40), respectively, in KRAS mutation-positive lung cancer, both of which were low (Table 1). On the other hand, vascular and pleural invasion were observed in a reasonable proportion of KRAS mutation-positive lung cancers, at 28% (11/40) and 35% (14/40), respectively.

Conclusions: KRAS mutation-positive lung cancers are generally considered to have a high malignant potential, but this may not be due to lymphatic metastasis but may depend on other metastatic modalities such as hematogenous metastasis or pleural dissemination.

Table 1. Association of KRAS mutation with lymphatic invasion and lymph node

		Lymphatic invasion (+)	Lymph node metastasis (+)
KRAS mutation	+	3/40 (7.5%)	2/40 (5.0%)
	-	43/251 (17%)	48/251 (19%)
Total		46/291 (16%)	50/291 (17%)

Keywords: driver gene mutation, KRAS, early-stage lung cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.27 Challenges in Implementing Targeted Panel NGS for Biomarker Testing in Non-Small Cell Lung Carcinoma in Resource-Constrained Settings

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Introduction: The number of clinically actionable biomarkers for inoperable non-small cell lung carcinoma has increased significantly in the last decade, necessitating routine multiplex biomarker testing. In resource-constrained settings, transitioning from single-gene tests (e.g., EGFR, ALK, ROS1) to NGS-based multiplex testing requires major changes in tissue processing, biopsy reporting, and molecular testing workflows. This study aims to analyze the cost-benefit ratio of routine multiplex NGS implementation and identify potential pitfalls and challenges.

Methods: This prospective study (November 2024 to June 2025) includes baseline biopsies from patients with advanced non-small cell lung carcinoma with a pathological diagnosis of adenocarcinoma, or not-otherwise-specified, negative for EGFR mutations, ALK rearrangements, and ROS1 rearrangements. Biopsies with >30% tumor fraction were subjected to multiplex NGS using AmoyDx Handle NGS kits followed by Illumina sequencing. Post-treatment biopsies were subject to upfront NGS. Representative cases of ALK and ROS1-rearranged samples diagnosed on single gene testing were also included for validation.

Results: As of date, 75 patient samples have been included for study. Complete data is available from 40 patients including 35 treatment-naive and 5 treated patients with progression (see Figure), excluding patients whose sequencing data output lacked adequate DNA depth (DNA QC fail, n=5) and/or showed inadequate RNA controls (RNA QC fail, n=2). One or more clinically actionable predictive biomarkers were detected in 30/40 (75%) of the patients, including two post-EGFR TKI patients detected with MET exon 14 skipping mutation (n=1) and EGFR T790M mutation (n=1), undetected on single gene testing. KRAS mutations (n=6), MET exon 14 skipping mutations (n=4), ERBB2 mutations (n=6). RET fusions (n=2), ROS1 fusions (n=3), BRAF mutations (n=1) were among the ESCAT Tier 1/2 actionable drivers detected only on NGS. Further updated data will be presented in the conference.

Conclusions: Routine implementation of limited panel NGS is urgently required in any centre treating patients with lung cancer as is evident from the high numbers of clinically actionable targets that are identified only on NGS. With the availability of multiple commercial NGS kits, it is possible to standardise, validate and establish testing algorithms and workflows for cost-effective delivery of NGS results even in resource constrained settings.

Keywords: Non-small cell lung carcinoma, Multiplex Predictive biomarker testing, Resource constrained settings

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.28 Circadian CLOCK Expression in Non-Small Cell Lung Cancer

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Introduction: The circadian clock consists of multiple sets of transcription factors resulting in autoregulatory transcription-translation feedback loops. Disruption of this cellular pathway has been recently proven to be associated with cancer risk, development and progression. BMAL1 and CLOCK are the central modulators of circadian output in cells and their pathological functions in cancer. CLOCK may harbor tumor-suppressive roles that are conserved among humans and rodents. In previous reports, epigenetic or genetic inactivation of Bmal1 and/or Clock has been shown to increase tumor proliferation or growth rates in several types of cancer, such as lung cancer. On the other hand, overexpression of these circadian activators suppresses proliferative and malignant phenotypes in tumor cells. Colon cancer with higher expression levels of CLOCK were associated with lymph node metastasis and tended to be more advanced. The expression of core circadian clock genes is frequently dysregulated in human tumors; however, the specific effects and underlying mechanisms are not fully understood.

Methods: Formalin-fixed, paraffin-embedded samples were stained with CLOCK antibody by immunohistochemical (IHC) analysis. Extent of staining of CLOCK was scored as 1 (0-25%), 2 (26-50%), 3 (51-75%), 4 (76-90%), and 5 (91-100%) according to the percentages of the positive staining areas in relation to the whole cancer area. The IHC scores were analyzed for correlation to clinicopathological parameters and prognosis using Kaplan-Meier method and Cox proportional hazard regression models in patients with non-small cell lung cancers.

Results: From January 2020 to October 2022, totally 98 consecutive patients (57 males/41 females) who underwent complete resection were collected with median age 72 years (range, 54-88) at the time of operation. Extent of CLOCK protein expression in lung cancer was score 1 in 5 cases (5%), score 2 in 10 cases (10%), score 3 in13 cases (13%), score 4 in 17 (17%) and sore 5 in 53 cases (54%). The patients were divided into CLOCK normal expression group (score 4-5) and CLOCK low expression group (score 1-3). No difference in CLOCK expression were observed between sex and smoking status, and histological types. In pathological stage, normal expression rate of CLOCK for p-stage 0-IA and IB-IIIB was 87% (40/46) and 58% (30/52). CLOCK expressions were significantly decreasing in advanced disease (p=0.001). Recurrent rate (32%) of CLOCK low expression group was higher than that of high expression group (13%). However, three-year disease-free survival was 69% in normal expression group and 73% in low expression group. There was no significant difference in prognostic analysis depend on CLOCK expression, nor there any other factors.

Conclusions: Expression level of CLOCK in lung cancer were decreased in advanced disease stages. These were contrary to previous reports, which showed that the expression increased in advanced colon cancer. However, expression of CLOCK was not related to prognosis, and this result was the same as in colon cancer. In this study, we evaluated one protein level of many circadian clock factors and also the number of analyzed cases was small. Then we plan to conduct further studies by increasing the number of analyzed factors and cases.

Keywords: Circadian CLOCK, Non-Small Cell Lung Cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.29 Prognostic Impact of Lepidic Growth in Intermediate and High-Grade Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma is characterized by heterogeneous pathologic features and a variable growth pattern composition that can profoundly influence prognosis. Grade 1 lung adenocarcinomas, which are characterized by predominantly lepidic growth and less than 20% high-risk patterns, have a favorable survival rate compared to higher-grade tumors. However, the prognostic significance of lepidic components in intermediate and high-grade lung adenocarcinomas is still controversial. A positive prognostic impact of non-predominant lepidic growth has been observed in Asian populations, but this has not yet been validated in different populations around the world. Therefore, the aim of this study was to investigate the presence of lepidic growth in grade 2-3 non-mucinous lung adenocarcinomas and to evaluate its impact on survival in a large, European lung cancer population.

Methods: 479 consecutive patients who underwent curative resection for non-mucinous lung adenocarcinoma in pathologic grade 2-3 and stage I were enrolled in this retrospective, single-center study. The impact of lepidic components and other predictors on survival was assessed in multivariable cox regression.

Results: Of 479 patients in the total study cohort, 300 (62.6%) exhibited tumors with lepidic components. The presence of lepidic growth was significantly associated with older age (median 67 vs. 65, p=0.0149), a higher proportion of never-smokers (22.1% vs. 9.9%, p = 0.0011), predominance of acinar growth (69.0% vs. 53.1%, p = 0.0005), and a lower proportion of solid-predominant tumors (7.0% vs. 26.8%, p<0.0001). Pathologic stage according to the 8th edition of the TNM system was T1a in 37 patients (7.1%), T1b in 134 (28.0%), T1c in 72 (15.0%) and T2a in 239 patients (49.9%) without significant association to the presence of lepidic components. We observed a trend towards more lymphatic and vascular invasion in lepidic-negative patients (15.0% vs. 20.7%, p = 0.1110 and 21.0% vs. 30.7%, p = 0.0168, respectively). Median follow-up was 67 months (IQR 47 - 92 months). A cox proportional hazards analysis revealed that the presence of lepidic growth was not significantly associated with OS or RFS both in the univariable and multivariable model. Further stratification for patients with 1-10% or over 10% lepidic growth did not enhance predictive power. Significant risk factors affecting RFS were age over 70 years (HR 1.402 (1.006-1.954), p= 0.046), pathologic stage IB (HR 1.515 (1.077-2.130), p = 0.017), grade 3 (HR 1.422 (1.016-1.990), p = 0.040) and lymphatic invasion (HR 1.668 (1.123-2.477), p= 0.011).

Conclusions: The prognostic impact of lepidic components in intermediate and high-grade lung adenocarcinoma was not confirmed in this study. Our findings highlight that considerable differences between patient demographics around the world exist, and careful consideration of conflicting observations between different patient populations is warranted in order to correctly estimate the prognostic impact of lepidic growth.

Keywords: adenocarcinoma, lepidic, survival

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.30 Single-Cell RNA Sequencing Reveals a Subset of FSIP1 Cancer Cells and Verified Its Value of Prognosis in Lung Adenocarcinoma

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Introduction: Lung adenocarcinoma (LUAD) is the most prevalent subtype of non-small cell lung cancer. The prognostic role of Fibrous sheath interacting protein 1 (FSIP1) in LUAD remains unclear. Thus, this study aims to identify and validate the prognostic value of FSIP1 in LUAD and explore its molecular functions.

Methods: Single-cell RNA sequencing (scRNA-seq) data of LUAD patients were collected from Gene Expression Omnibus (GEO) database, the major cell types were identified based on known markers. Additionally, the expression of FSIP1 was detected in 180 LUAD samples, Kaplan-Meier (KM) analysis of high- and low-expression patients was conducted. Univariate and multivariate Cox regression analyses were utilized to assess the prognostic ability of FSIP1. Then, FSIP1-silenced human LUAD cell lines were constructed, and the functions of FSIP1 were explored. Finally, immune infiltration analysis was also performed in LUAD patients.

Results: In this study, we identified LUAD FSIP1+ cancer cells by using scRNA-seq data from GEO database. Additionally, we investigated the protein level and prognostic value of FSIP1 in 98 LUAD patients using Tissue Microarray. Compared with the adjacent, FSIP1 was higher expressed in LUAD tissues. KM analysis revealed that the 5-year OS rate to be 30% to 59% (FSIP1High vs FSIP1Low) in Tissue Microarray. Univariate and multivariate COX regression showed that FSIP1 should be an independent factor in poor prognosis. The receiver operating characteristic curve (ROC) and time-ROC curve both indicated that FSIP1 had a good performance in prognostic model. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed that FSIP1 was associated with migration. Migration assay and Western blotting showed that FSIP1 influenced cell migration and PI3K/AKT pathway. FSIP1 could influence the immune cell infiltration in lung adenocarcinoma patients.

Conclusions: This study verified that FSIP1 could serve as a valuable prognostic biomarker in LUAD and analyzed its impact on the disease and its association with the immune infiltration. The findings of this research provide valuable insights into the understanding of LUAD and could potentially lead to the development of new treatment strategies.

Keywords: FSIP1, Lung Adenocarcinoma, Biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.31 Prognostic Impact of Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5 Expression in Non-Small Cell Lung Cancer

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Introduction: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is overexpressed in various solid tumors including non-small cell lung cancer (NSCLC). Its expression has been associated with tumor invasion and metastasis. However, the prognostic significance of CEACAM5 expression has not been investigated in patients with NSCLC. We aim to examine the prognostic effect of CEACAM5 expression by immunohistochemistry (IHC) in a large cohort of patients with resected NSCLC.

Methods: We retrospectively evaluated CEACAM5 expression by IHC on resected NSCLC specimens from 2005 to 2012 at our institution, using the anti-CEACAM5 clone 769 antibody assay protocol developed for the tusamitamab ravtansine clinical trials. Expression levels were categorized as high (≥ 50% tumor cells at ≥ 2+ intensity), moderate (1-49% tumor cells at ≥ 2+ intensity), and low (0 or 1+ intensity), and were scored independently by three thoracic pathologists. Interrater reliability was assessed by Kendall's coefficient of concordance (KCC) and Fleiss' Kappa. Discordant classification was reviewed to achieve a consensus score. Association with categorical PD-L1 tumor proportion score (TPS <1%, 1-49% and ≥ 50%) was calculated by Fisher exact test. Association with driver mutation results was determined by Chi-squared test. Correlation with recurrence free survival (RFS) and overall survival (OS) were determined by log-rank tests.

Results: The study cohort consisted of 394 patients, including 290 with adenocarcinomas, 94 with squamous cell carcinomas, and 10 with other histologies. The cohort was composed of 210 (53%) female and 184 (47%) male patients. Two hundred twelve (54%) were stage I, 103 (26%) stage II, 69 (18%) stage III and 10 (3%) were stage IV. Eleven cases were excluded from CEACAM5 scoring due to suboptimal tumor sections for evaluation. The prevalence of high CEACAM5 expression was 16% (n = 62). Interrater reliability was moderate (KCC 0.67, Fleiss' Kappa 0.56). CEACAM5 expression was not associated with PD-L1 TPS (p=0.15), EGFR mutation (p=0.79) or KRAS mutation (p=0.19). High CEACAM5 expression was not associated with tumor stage (p=0.4), RFS (p=0.8), or OS (p=0.7).

Conclusions: In our cohort of predominantly early-stage resected NSCLC including adenocarcinoma and squamous cell carcinoma, we did not observe a significant prognostic impact of CEACAM5 expression on RFS or OS.

Keywords: CEACAM5, Biomarker

EP.06.32 Elevated SERPINA3 Expression in Bronchoalveolar Lavage Fluid Predicts Poor Prognosis in Non-Small Cell Lung Cancer

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Introduction: SERPINA3 is a protease inhibitor and acute-phase protein that is elevated in inflammatory conditions and several cancers, including lung, breast and colon cancer. It is associated with tumor growth and progression. The aim of this study was to evaluate whether SERPINA3 expression in non-small cell lung cancer (NSCLC) patients could predict prognosis.

Methods: A total of 362 patients from a respiratory research registry, with bronchoalveolar lavage fluid (BALF) and blood samples collected between April 2019 and May 2021, were initially reviewed. After excluding 282 patients based on various criteria, 148 primary NSCLC patients were analyzed. Of these, 147 plasma and 135 BALF samples were used. The Institutional Review Board and Ethics Committee of Severance Hospital approved the study (IRB number: 4-2021-0228).

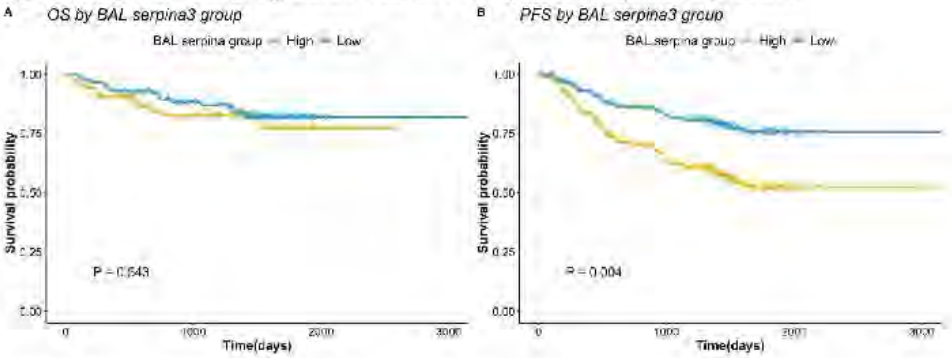
Results: Patients were divided into high and low SERPINA3 expression groups based on BALF levels. In the high SERPINA3 group, there were significantly fewer men (P=0.028) and the rate of progression/recurrence was significantly higher (P=0.012). Cox regression analysis showed that high BALF SERPINA3 expression was significantly associated with increased risk of death (P=0.027) and progression/recurrence (P=0.007). Other significant factors for mortality were male sex (P=0.012) and stage IV cancer (P=0.032). For progression/recurrence, stage III (P=0.001) and IV (P=0.003) were also significant. Furthermore, the high SERPINA3 group showed a significant decrease in progression-free survival (P=0.004).

Conclusions: Elevated SERPINA3 expression in BALF is associated with poor prognosis in NSCLC patients, including increased risk of mortality and progression/recurrence. It may serve as a potential biomarker for predicting outcome in these patients.

Table 3. Cox Regression Analysis of Clinical Factors Associated with Progression/Recurrence.

Variable	HR (univariable)	HR (multivariable)
Age	1.006 (0.980-1.033, p=0.637)	1.030 (0.993-1.068, p=0.109)
Sex, male	1.618 (0.934-2.802, p=0.086)	1.540 (0.752-3.151, p=0.238)
BALF Serpina3	1.007 (1.001-1.012, p=0.020)	1.010 (1.003-1.018, **p=0.007**)
Plasma Serpina3	1.002 (0.999-1.005, p=0.290)	1.002 (0.998-1.006, p=0.381)
EGFR, positive	0.873 (0.486-1.568, p=0.649)	0.674 (0.313-1.452, p=0.314)
Stage (Ref. Stage I)		
II	2.596 (0.974-6.918, p=0.056)	1.714 (0.560-5.244, p=0.345)
III	6.871 (2.997-15.752, p<0.001)	5.531 (2.002-15.281, **p=0.001**)
IV	8.565 (3.820-19.207, p<0.001)	18.780 (2.672-131.974, **p=0.003**)
Operable status (Ref. ≥ stage IIIB)		
Cancer pathology, SCC (Ref. others)	0.244 (0.145-0.409, p<0.001)	2.008 (0.383-10.519, p=0.409)
Age	1.685 (0.908-3.129, p=0.098)	0.000 (0.000-Inf, p=0.997)

Figure 1. Overall and progression-free survival by BALF serpina3 expression



* Adjusted for age, sex, operable status, cancer pathology.

Table 1. Baseline Characteristics of NSCLC Patients by BALF SERPINA3 Expression

	High (N = 75)	Low (N = 73)	Total (N = 148)	P value
Age, median [IQR]	65.00 [60.00, 73.00]	67.00 [62.00, 75.00]	66.00 [60.00, 74.00]	0.079
Sex, male (%)	40 (53.3)	52 (71.2)	92 (62.2)	**0.028**
Stage (%)				0.806
I	29 (38.7)	28 (38.4)	57 (38.5)	
II	11 (14.7)	13 (17.8)	24 (16.2)	
III	15 (20.0)	17 (23.3)	32 (21.6)	
IV	20 (26.7)	15 (20.5)	35 (23.6)	
Pathology (%)				0.091
Adenocarcinoma	64 (85.3)	53 (72.6)	117 (79.1)	
Squamous carcinoma	10 (13.3)	19 (26.0)	29 (19.6)	
Others	1 (1.3)	1 (1.4)	2 (1.4)	
SP263, median [IQR]	0.00 [0.00, 10.00]	1.00 [0.00, 10.00]	1.00 [0.00, 10.00]	0.72
C22-3, median [IQR]	0.00 [0.00, 10.00]	0.00 [0.00, 10.00]	0.00 [0.00, 10.00]	0.828
EGFR, positive (%)	34 (52.3)	24 (44.4)	58 (48.7)	0.462
ALK, positive (%)	2 (3.0)	5 (9.3)	7 (5.8)	0.241
ROS1, median [IQR]	0.00 [0.00, 40.00]	0.00 [0.00, 50.00]	0.00 [0.00, 45.00]	0.637
Progression/Recur (%)	37 (49.3)	21 (28.8)	58 (39.2)	**0.012**
Death (%)	13 (17.3)	13 (17.8)	26 (17.6)	1

Table 2. Cox Regression Analysis of Clinical Factors Associated with Mortality

Variable	HR (univariable)	HR (multivariable)
Age	1.029 (0.988-1.072, p=0.174)	1.105 (0.982-1.243, p=0.096)
Sex, male	17.185 (2.328-126.857, p=0.005)	21.562 (1.992-233.411, **p=0.012**)
BALF Serpina3	1.006 (0.997-1.015, p=0.216)	1.033 (1.004-1.064, **p=0.027**)
Plasma Serpina3	1.001 (0.997-1.006, p=0.536)	0.999 (0.991-1.007, p=0.841)
EGFR, positive	0.407 (0.128-1.298, p=0.129)	0.296 (0.063-1.383, p=0.122)
Stage (Ref. Stage I)		
II	9.667 (1.080-86.493, p=0.042)	1.322 (0.073-23.887, p=0.850)
III	12.085 (1.454-100.428, p=0.021)	3.513 (0.187-65.903, p=0.401)
IV	33.562 (4.429-254.333, p=0.001)	114.443 (1.487-8806.911, **p=0.032**)
Operable status (Ref. ≥ stage IIIB)	0.184 (0.082-0.413, p<0.001)	3.026 (0.103-89.008, p=0.521)
Cancer pathology, SCC (Ref. others)	4.404 (2.030-9.550, p<0.001)	0.000 (0.000-Inf, p=0.999)

Keywords: non-small cell lung cancer, SERPINA3, prognosis

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.33 Unique Features of the Tumor-Microenvironment in PL3 Non-Small Cell Lung Cancer and Their Association With Post-Operative Outcomes

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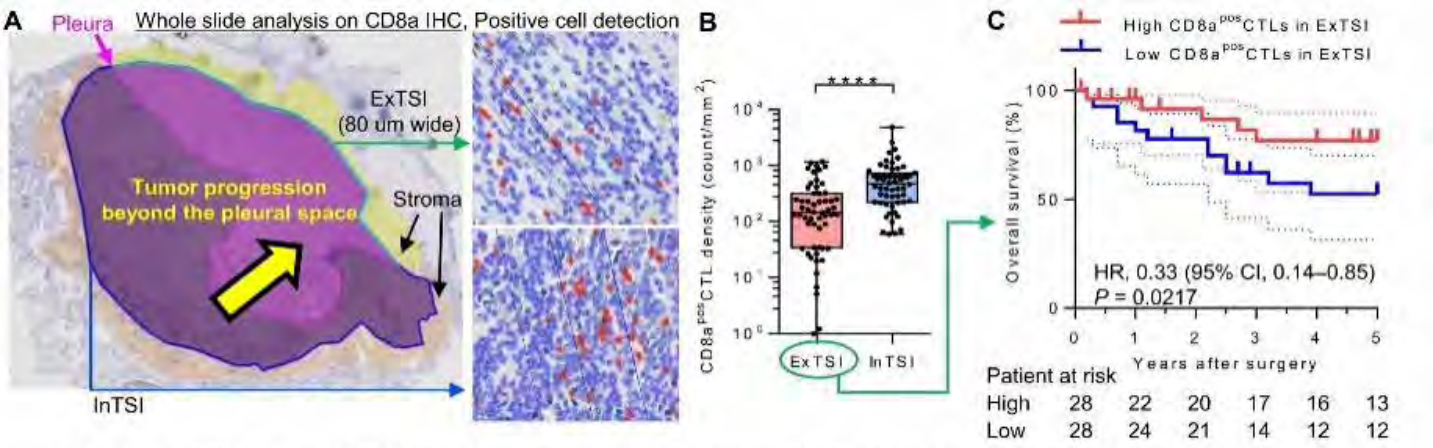
Introduction: Understanding the tumor microenvironment (TME) is critical for predicting the prognosis of patients with non-small cell lung cancer (NSCLC). Tumor progression to neighboring structures (i.e. PL3) is a significant factor influencing treatment decision-making and prognosis of patients with PL3-NSCLC. TME of PL3-NSCLC has intrapleural and extrapleural parts. However, the extrapleural TME of PL3-NSCLC which contains the front of tumor progression remains to be elucidated.

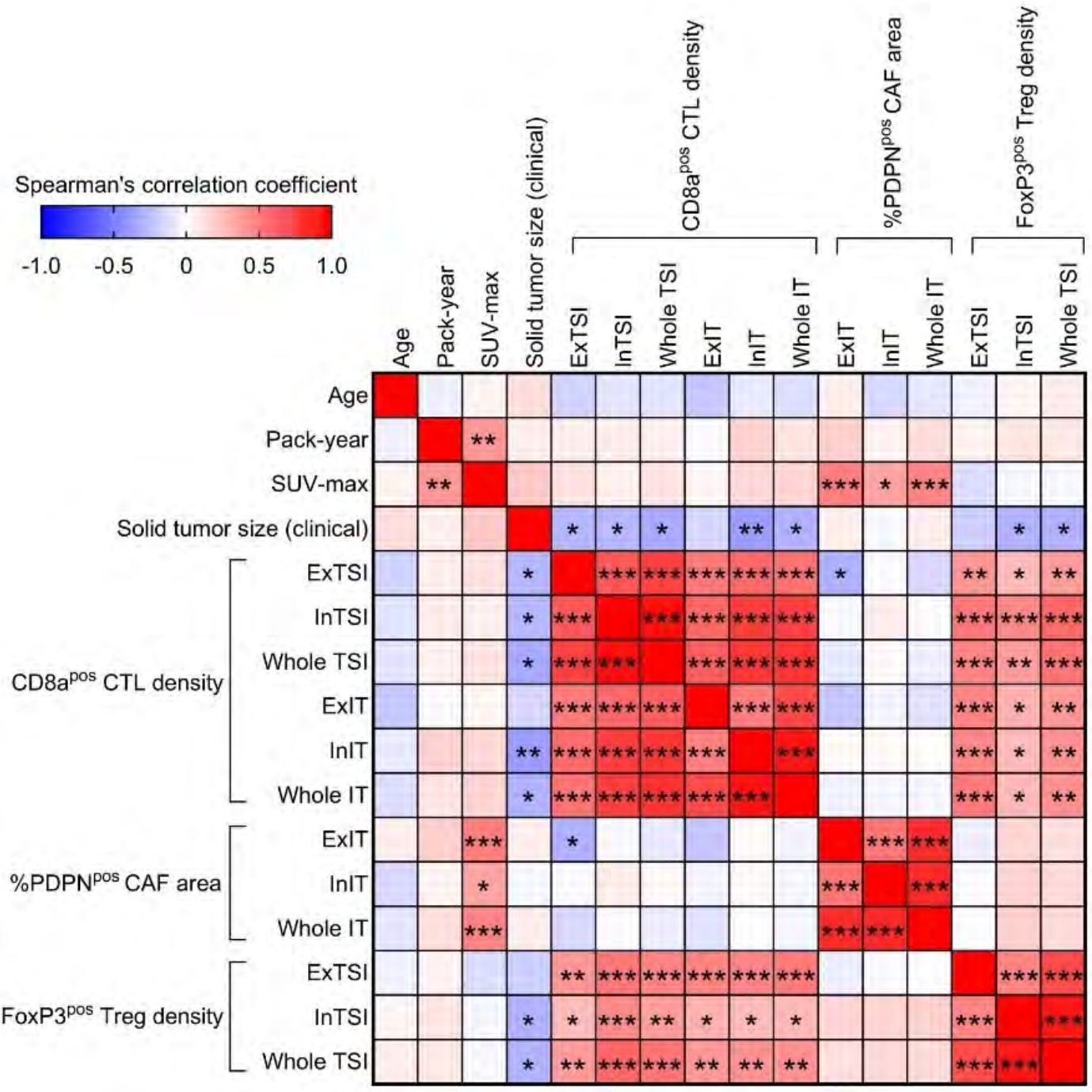
Methods: We retrospectively reviewed patients with pathologically proven treatment-naïve PL3-NSCLC who underwent lung resection between 2010 and 2021 at our institute. Immunohistochemical staining was performed to identify CD8a-expressing cytotoxic T lymphocytes (CD8aposCTLs) and FoxP3-expressing regulatory T cells (FoxP3posTregs) in the extrapleural and intrapleural tumor-stroma interface (ExTSI and InTSI, respectively) and podoplanin-expressing cancer-associated fibroblasts (PDPNposCAFs) in the extrapleural and intrapleural intratumoral areas (ExIT and InIT, respectively).

Results: Fifty-six patients were evaluated. CD8aposCTLs (Figure 1A-B) and FoxP3posTregs were sparsely distributed in ExTSI compared to InTSI. Conversely, PDPNposCAFs were more abundant in ExIT than in InIT. Decreased CD8aposCTLs in ExTSI were associated with significantly worse overall (Figure 1C) and recurrence-free survival post-surgery, a larger solid tumor size, a lower prevalence of tertiary lymphoid structures, and increased PDPNposCAFs in ExIT (Figure 2). Increased FoxP3posTregs in ExTSI were associated with the presence of pleural dissemination and malignant pleural effusion at surgery. PDPNposCAFs in ExIT were more abundant in tumors invading the chest wall, parietal pleura, and mediastinum than in those invading the interlobe only.

Conclusions: Our findings support the concept that the TME in PL3-NSCLC has unique features specific to the extrapulmonary components and functions as an oncological immunomodulatory niche.



NSCLC, Non-Small Cell Lung Cancer; ExTSI, Extrapleural Tumor-Stroma-Interface; InTSI, Intrapleural Tumor-Stroma-Interface; CTL, Cytotoxic T Lymphocyte; IHC, Immunohistochemical



Keywords: PL3 NSCLC, Tumor microenvironment, Cytotoxic T lymphocyte

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.34 Retrospective Analysis of Genomic Testing and Survival Outcomes in Lung Cancer Patients From Western India

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Introduction: NGS-based mutational findings are increasingly utilized in oncology practice to tailor treatment strategies. This study highlights the impact of comprehensive genomic profiling compared to cost-effective short molecular panel testing and explores its potential for personalized precision medicine in a developing country setting.

Methods: This retrospective study included consecutive lung cancer patients from community oncology centers in Western India, diagnosed between March 2018 and September 2024. Clinical characteristics, including testing panels, mutational distribution, and survival outcomes, were obtained from the EMR and analyzed for progression-free survival and overall survival using Kaplan-Meier analysis

Results: A total of 2281 lung cancer patients were evaluated from a community oncology practice who underwent next generation testing (64.05%; 1461/2281) and the mean age was 65 years (IQR 56-73); with Male:Female ratio being 1:1.41 and stage distribution being 1.3%, 2.5%, 17.5% and 77.6% for Stage I, II, III and IV respectively. Comprehensive genomic panel (CGP) was performed in 52.49% (767/1461) to evaluate SNVs, CNVs, and indels spanning across over 15000 loci for 1080 tumor while short panel testing was done in 47.50% (694/1461) to assess mutation detection rates for key genes (EGFR, ALK, ROS1, MET, KRAS, BRAF, NTRK, RET, TP53, and Her2). The cohort comprised 94.9% of Non-small cell lung cancer (NSCLC) cases, with adenocarcinoma being the predominant subtype (85.2%). The mutational differences observed between the two panels were significant, with MET/RET/NTRK/BRAF alterations being more prevalent in the CGP group 7.3% (56/767) compared to the short molecular panel group 1.2% (8/694) (P<0.001). Similarly, KRAS mutations were more frequently detected in the CGP group 8.9% (68/767) vs. 2.1% (14/694) (P<0.001), as were TP53 mutations 21.4% (164/767) vs. 3.6% (25/694) (P<0.001) while HER2 alterations showed no significant difference between the two groups 2.3% (18/767) vs. 1.3% (9/694) (P=0.1362).Rare mutations were significantly more frequent in the CGP group 16.1% (87/539 mutated cases) compared to the short panel group 1.6% (6/364 mutated cases). Among the rare mutations identified in the CGP cohort, the most frequently reported alterations included PIK3CA (n=28), STK11 (n=8), RB1 (n=4), and BRCA (n=2). The median overall survival (mOS) for the entire cohort was 25.7 months (95% CI: 22.7-28.8), with a progression-free survival (PFS) of 16.0 months (95% CI: 14.4-17.6) and a median follow-up time of 29.0 months (95% CI: 26.8-31.3). Patients tested with CGP demonstrated a longer but statistically non-significant improvement in survival with mOS of 29.2 months (95% CI: 25.3-33.2) in CGP group compared to 24.3 months (95% CI: 20.7-27.8) in those tested with the short panel (P = 0.384).

Conclusions: This study from a developing country demonstrated that comprehensive genomic profiling (CGP) achieved superior detection of actionable and rare mutations compared to short molecular panel testing. Additionally, CGP was associated with improved overall survival, highlighting its potential to enhance precision oncology and the need to improve its accessibility in resource-limited settings.

Keywords: Genomic Testing, Western India, Survival Outcomes

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.35 Role of PD-L1 Expression and TP53Mutation as a Prognostic Factor in Early Stage NSCLC

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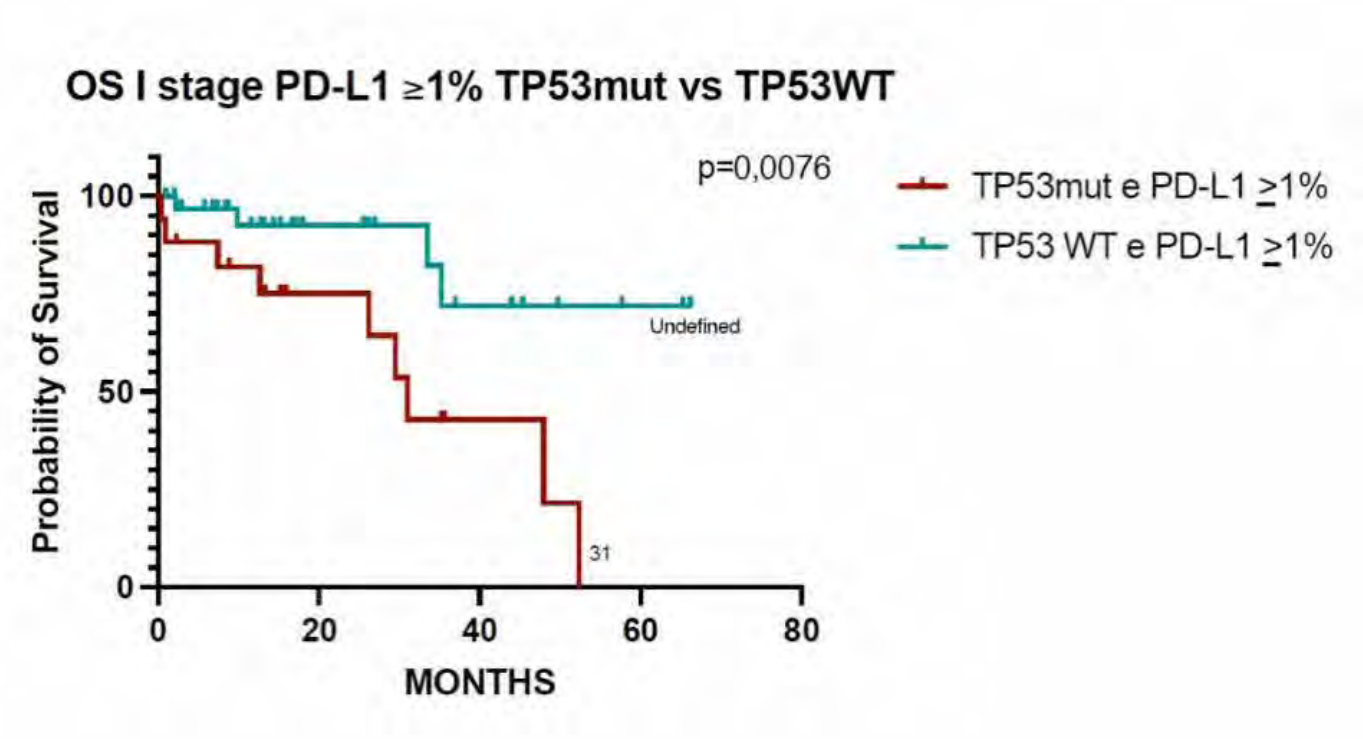
Introduction: Lung adenocarcinoma is a complex and heterogeneous disease. Although programmed death-ligand 1 (PD-L1) expression is an essential biomarker in treatment algorithms, its prognostic role remains unclear. While various molecular alterations have been studied for their prognostic and predictive value, their implications in early stages are less well defined. This study aimed to investigate the impact of PD-L1 expression and co-mutations on outcomes in early-stage non-small cell lung cancer (NSCLC) patients.

Methods: Single center retrospective cohort of patients diagnosed with non-squamous NSCLC between January 2018 and July 2022. A targeted NGS analysis including 22 genes (Ion TorrentTM, panel AmpliSeq Colon and Lung Cancer v2) was performed on all patients. PD-L1 expression was assessed by Immunohistochemistry (SP263 Antibody, Ventana). Statistical analyses were made using log-rank test, the two-tailed Fisher's exact test and Kaplan-Meier survival curves.

Results: Clinical data were collected for 464 patients, including 100 cases with stage I disease (21.5%), 42 with stage II (9%), 63 with stage III (13.5%), and 259 with stage IV (56%) as per the TNM 7th edition. All patients were treated according to international guidelines. High PD-L1 expression (≥50%) was predominantly observed in advanced stages (III and IV), with only 10 patients in stage I (10%). TP53 mutations were identified in 202 patients. In stage I patients (16%), TP53 mutations were mainly associated with PD-L1 expression < 50%. Analysis of overall survival (OS) in stage I revealed that patients with high PD-L1 expression had a median OS (mOS) of 26.2 months, compared to 52.3 months for those with PD-L1 expression < 50% (p=0.0016). Additionally, when comparing PD-L1 positive (≥1%) versus negative (<1%) patients, mOS was 47.9 months versus not reached, respectively, though this difference was not statistically significant. In the PD-L1 positive subgroup, patients harboring TP53 mutations had an mOS of 31 months, in contrast to a not reached mOS in those without TP53 mutations (p=0.0076).



Conclusions: These findings suggest that high PD-L1 expression is associated with worse prognosis even in early-phase lung adenocarcinoma, with TP53 mutations having an additive detrimental effect. In stage I NSCLC patients with positive PD-L1 expression, the presence of TP53 mutations significantly influenced OS. Our results underscore the importance of mutation testing in early-stage NSCLC and raise the question of whether adjuvant treatment should be considered for stage I patients with both TP53 mutations and high PD-L1 expression. Further research in this population is warranted.

Keywords: Early stage NSCLC, PD-L1, TP53 mutation

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.36 Non-Small Cell Lung Cancer With Diffuse Coexpression of TTF-1 and P40:A Clinicopathologic and Molecular Study of 19 Casess

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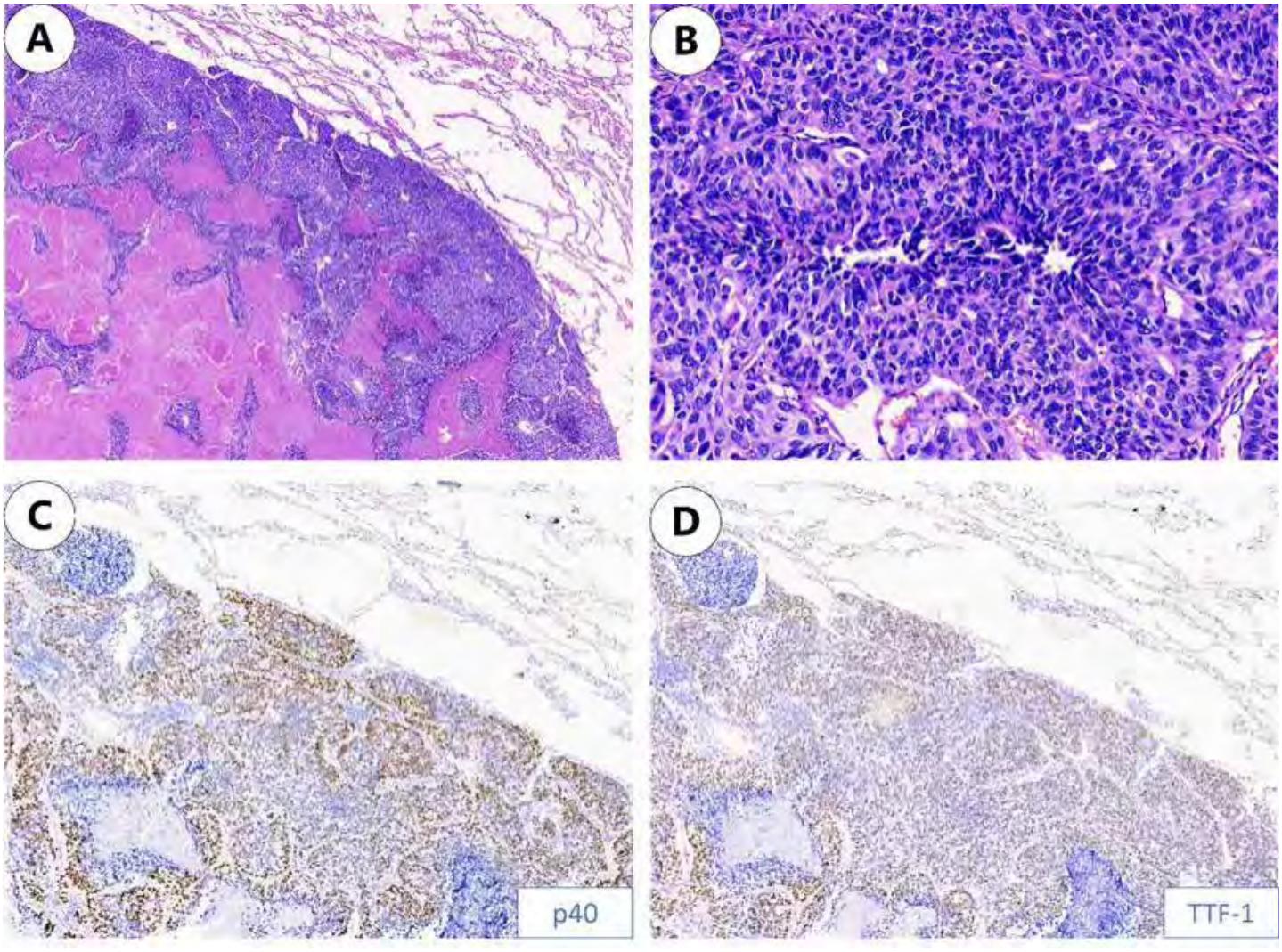
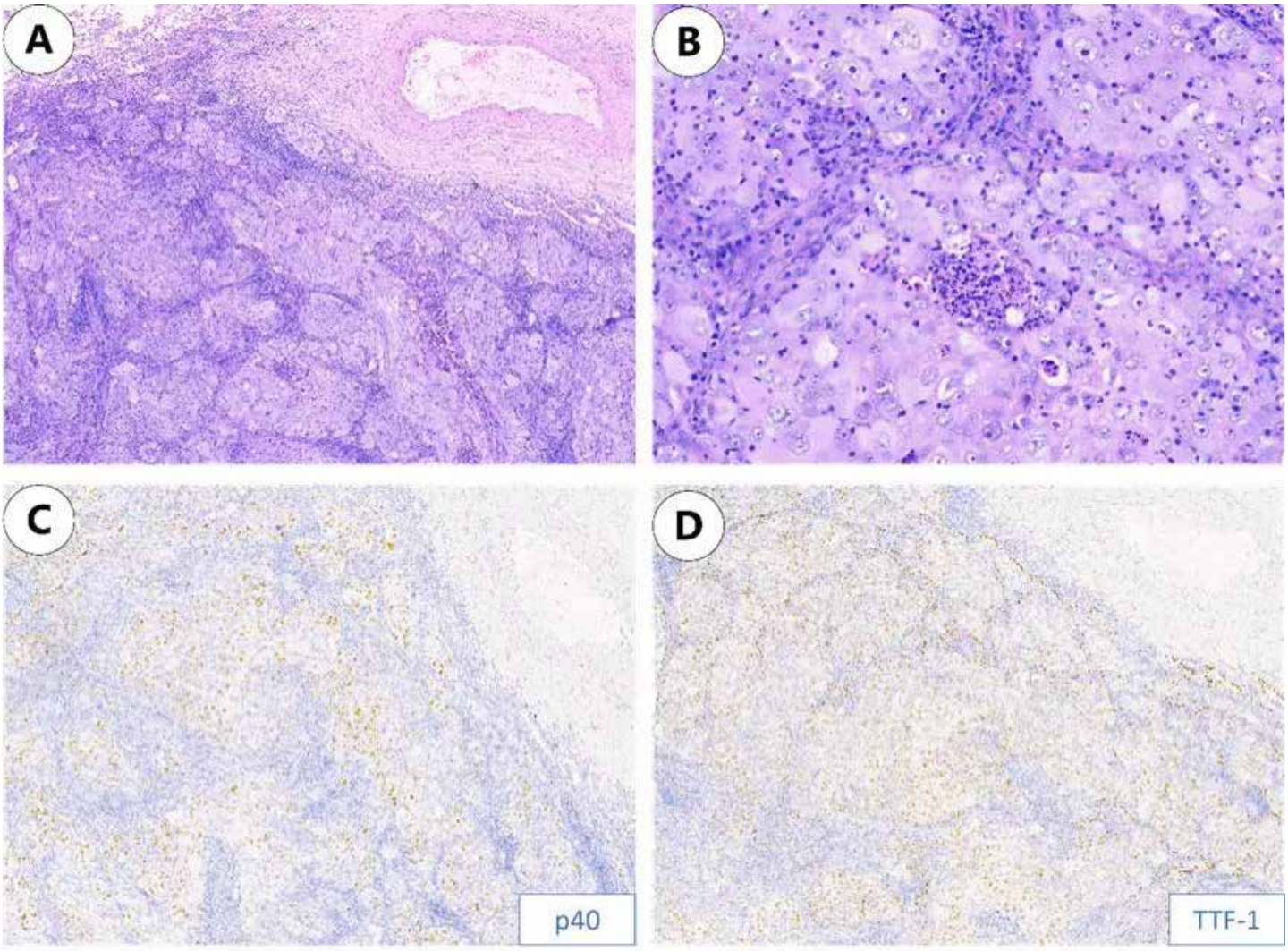
Introduction: The diffuse co-expression of TTF-1 and p40 in non-small cell lung carcinomas (NSCLCs) is extremely rare. Despite limited reports, comprehensive pathobiology of this NSCLC subtype—including diagnostic criteria, pathological characteristics, molecular profiles, biological behavior, and postoperative outcomes—remain largely uncharacterized.

Methods: We identified nineteen cases of NSCLCs co-expressing TTF1 clone 8G7G3/1 and p40. Their clinical, pathological, and molecular characteristics were systematically analyzed, supplemented with a review of the relevant literature.

Results: Patients with co-expression of TTF-1 and p40 were predominantly older males who smoke, with 66.7% (12/18) diagnosed at stage III-IV. All tumors were poorly differentiated NSCLCs, lacking keratinization and glandular formation and displayed either basaloid features (31.6%, 6/19) or distinct histological morphology (68.4%, 13/19) characterized by high-grade plasma-rich tumor cells with significant lymphocytic infiltration. Molecular analysis revealed recurrent mutations in TP53 (42.9%, 3/7), EGFR (26.7%, 4/15), and KRAS (13.3%, 2/15). Copy number alterations included amplifications of MCL1 (57.1%, 4/7) and MYC (42.9%, 3/7), with MCL1 amplification confirmed by FISH. Metastasis was observed in 61.1% (11/18) of cases, including 4 with distant spread and 7 involving thoracic or supraclavicular lymph nodes or the pleura. Three patients succumbed to the disease within 10-64 months following diagnosis.

Conclusions: NSCLCs with co-expression of TTF-1 and p40 display unique clinicopathological features, molecular alterations, and clinical outcomes, characterized by rapid progression and poor prognosis. The multigenic, targetable alterations in MCL1, KRAS, and EGFR underscore the critical importance of comprehensive molecular testing in these tumors.





Keywords: non-small cell lung carcinoma, coexpression, biphenotype

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.37 Clinical and Pathological Features of a High Altitude-Peruvian Population With Metastatic EGFR Mutated Lung Cancer

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Introduction: Lung cancer ranks second in incidence and first in mortality (1). In Peru, lung cancer is an important cause of incidence and mortality (2,3), and the late diagnosis is the most common presentation. Motta-Guerrero et al, reported 13% of patients were diagnosed in stage III and 69.3% in stage IV (4). The Regional Institute of Neoplastic Diseases (IREN) - Center is located in a high altitude region which is a protector factor against lung cancer (5,6).

Methods: Retrospective, cross-sectional study of patients with metastatic lung cancer who underwent EGFR mutation testing from March 2020 to December 2023. Of the 112 records obtained, 18 were included. A database was created considering age, sex, origin, risk factors, symptoms, ECOG, clinical stage, histological type and grade, immunohistochemistry and EGFR gene mutation status. A descriptive analysis of the main characteristics of the patients was performed. Subsequently, a univariate analysis was performed to investigate the association with EGFR mutation. For each statistical test, significance was considered when p was less than 0.05. Statistical analysis was performed using SPSS software version 26

Results: Eighteen patients were registered. The EGFR mutation frequency was 16.07%. Among the main features, 94.4% came from high altitude regions, 44.4% were exposed to wood smoke, and the place of origin was related to the EGFR mutation (p = 0.044); the most frequent location of metastasis was bone (44.4%). The most frequent histological type in patients with exon 19 deletion was adenocarcinoma type NOS (16.7%); and in patients with point mutation in exon 21, was acinar and lepidic adenocarcinoma (11.1%). There was a higher frequency of presentation with histological grade II and III (11.1%) in patients with exon 19 deletion.

Conclusions: In a high altitude populaation, EGFR mutation was related with the place of origin, clinical stage and immunohistochemical markers.

Table 1: Sociodemographical features and relationship with EGFR mutation in a high-altitude population with metastatic lung cancer

VARIABLES	NO.	%	p
• Age			
52-61	9	50,0	
62-71	6	33,3	0.557
72-81	3	16,7	
• Sex			
Female	9	50,0	
Male	9	50,0	0,381
• Origin			
Ayacucho	1	5,6	
Cerro De Pasco	1	5,6	
Huancavelica	1	5,6	0,044
Huánuco	1	5,6	
Junín	14	77,8	
• Risk factors			
None	5	27,8	
Exposure to wood smoke	8	44,4	0,946
Air pollution	2	11,1	
Inheritance	2	11,1	
Smoking and exposure to wood smoke	1	5,6	
• Comorbidities			
None	13	72,2	
Arterial hypertension	2	11,1	0,215
Mellitus diabetes	1	5,6	
Previous lung disease	2	11,1	
TOTAL	18	100	

Table 2: Relationship between clinical stages and immunohystochemical markers with type of EGFR mutation in a high-altitude population with metastatic lung cancer.

Variables	Exon19 deletion		Exon 21 point mutation		Exon 18 mutation		Exon 20 mutation		p
Clinical stages	N°	%	N°	%	N°	%	N°	%	
IVA	4	22.2	4	22.2	0	0	0	0	
IVB	1	5.6	0	0	0	0	1	5.6	0.042
IVC	5	27.8	2	11.1	1	5.6	0	0	
Immunohystochemical markers	N°	%	N°	%	N°	%	N°	%	
TTF-1	2	11.1	3	16.7	0	0	1	5.6	
TTF-1 and Napsin A	5	27.8	0	0	1	5.6	0	0	0.021
Non reported	3	16.7	3	16.7	0	0	0	0	

Keywords: metastic lung cancer, EGFR mutation, high-altitude

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.38 HLA-DQB1 Predicts Immunotherapy Response in NSCLC Through Augmented TCR Signaling

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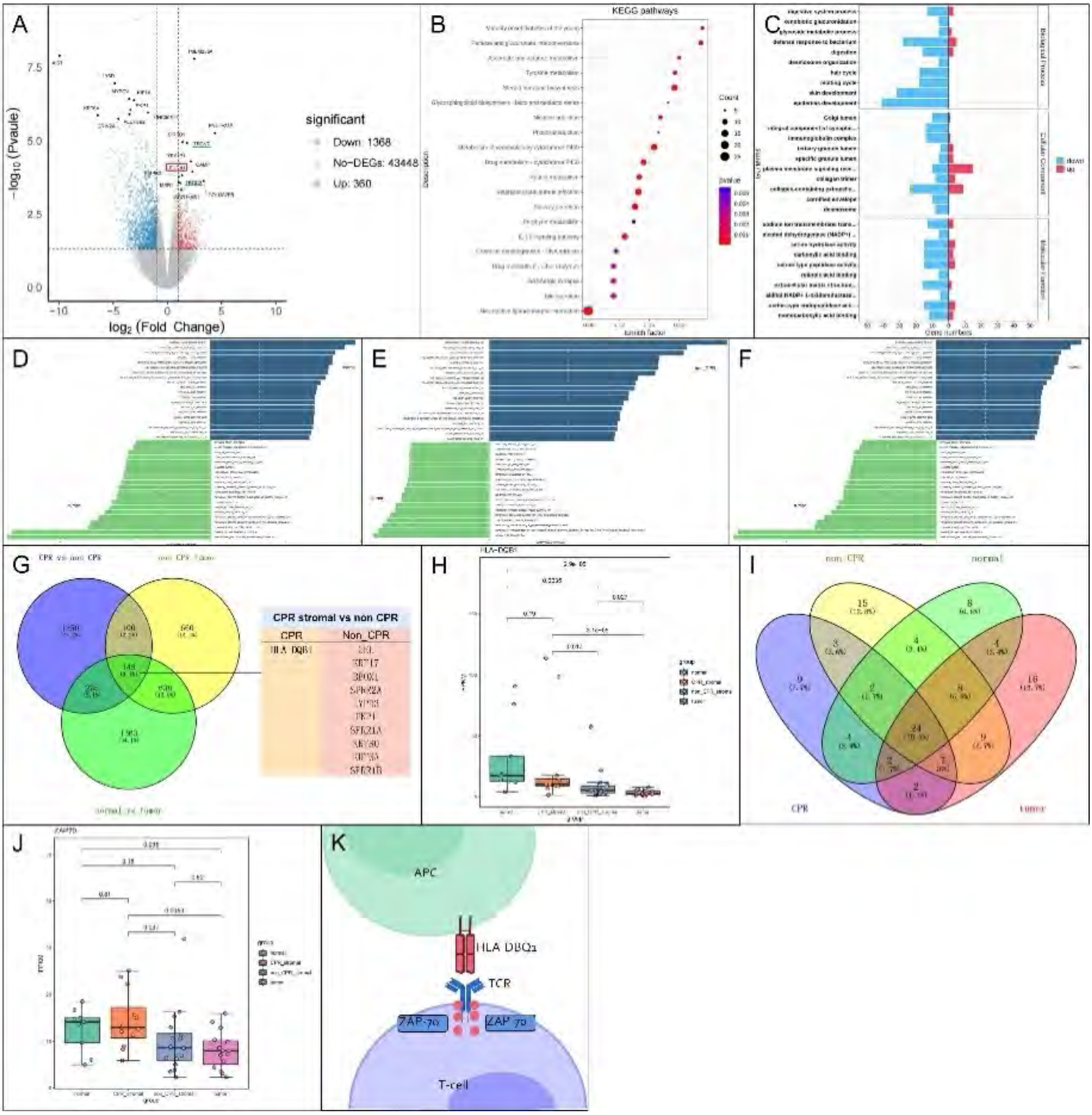
Introduction: Complete pathological response (CPR) following immunotherapy is associated with improved survival in non-small cell lung cancer (NSCLC). However, the molecular mechanisms underlying distinct immune landscapes and their prognostic implications remained unclear. This study aimed to identify molecular signatures and clinically relevant biomarkers in immunotherapy of NSCLC.

Methods: Transcriptomic sequencing was performed on tumor, and normal lung tissues of CPR (n=6), non-CPR (n=13) patients. Differential gene expression analysis was conducted using DESeq2, with thresholds set at |log2FC| >1 and adjusted P <0.05. Enrichment of KEGG/GO pathways was evaluated via clusterProfiler. Pathway activation scores were calculated using ssGSEA, and sample heterogeneity was analyzed using correlation matrices.

Results: Compared with the non-CPR group, 1368 genes were significantly down regulated and 360 genes were upregulated in the CPR group. These genes were enriched in metabolic pathways and immunoglobulin-related biological processes. TCR-associated genes (CD3D, CD8A) and FUCA1 (a p53-regulated tumor suppressor) were upregulated in CPR, while EMT-related markers (KRT6A) were suppressed. Compared to non-CPR, the top pathways activated in the CPR group are almost all related to immune processes, including T (helper) cell differentiation, TCR related pathways. Compared to the tumor sample, the non-CPR matrix sample showed activation of interleukin-6 and vascular endothelial growth factor related pathways, downregulation of tumor characteristics and E2F transcription factor related pathways, and activation of cell cycle regulation related pathways in the tumor sample. Compared with normal tissues, tumor samples showed activation of pathways such as tumor necrosis factor, interleukin 3/6, and CD40 in normal samples, while pan cancer common characteristic pathways were activated in tumor samples. Intersection analysis identified 143 shared DEGs, including progressively downregulated HLA-DQB1(CPR>non-CPR>tumor). HLA-DQB1 linked to TCR signaling through ZAP70 activation, with sequential ZAP70 reduction across groups. HLA genotyping revealed no allelic heterogeneity among groups, excluding HLA type-driven biases and underscoring expression-level differences as prognostic determinants. HLA-DQB1 was linked to the TCR signaling pathway (Generation of second messenger molecules) in CPR samples, with its high expression driving ZAP70 activation—a kinase essential for phosphorylating substrates to initiate second messenger release. Progressive downregulation of ZAP70 from CPR to non-CPR and tumor tissues suggested that HLA-DQB1-mediated TCR engagement suppresses tumorigenesis by sustaining ZAP70 expression.

Conclusions: HLA-DQB1 is a prognostic biomarker for NSCLC immunotherapy, enhancing TCR signaling via ZAP70. Its progressive loss in non-responders suggests a mechanistic role in immune evasion. These findings support HLA-DQB1 as a predictor of therapeutic efficacy and a potential target for combination strategies.



Keywords: NSCLC immunotherapy, Prognostic biomarker, HLA-DQB1

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.39 Better Prediction of Resistance to Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer : Immunoresist Project

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Introduction: Immune checkpoints inhibitors (ICI) targeting PD1 and PDL1 have transformed the treatment of non-small cell lung cancer (NSCLC) at the metastatic stage. However, around 80% of patients do no benefit from treatment. In this work, we integrated clinical and immunohistochemical factors and set the foundation for a composite predictor of outcome with ICI.

Methods: A total of 130 patients with NSCLC who received ICI between 2015 and 2022 in Strasbourg (France) either as a monotherapy or in combination with chemotherapy, at any line of treatment, with available archival tissue samples were included. Resistance was defined by a progression-free survival (PFS) ≤ 3 months (63 patients) and sensitivity by a PFS ≥ 1 year (67 patients). Using immunohistochemistry, the expression of PDL1 and eleven other biomarkers (table 1) were assessed by two independent observers.

Results: The expression of PDL1, CD3, CD4, CD8, FOXP3 and TIM3 was statistically significant different between the two groups. Using expression thresholds determined with receiver-operating curves, we found statistically significant differences in expression status of PDL1 (1% threshold, p<0.001), CD8 (750 cells at hotspot, p=0.03), CD56 (10 cells at hotspot, p=0.02), FOXP3 (200 cells at hotspot, p= 0.03) and TIM3 (20%, p=0.01) between the two groups. The OR for sensitivity of patients who scored positive forPDL1, CD56 and FOXP3 was two times greater than negative PDL1 alone (OR 7.59[2.63, 25], p<0.001 and OR 4.27 [1.85, 10], p<0.001, respectively), andwas also greater than double negative PDL1/CD8 (OR 4.71 [1.80, 13.59],p<0.001). Using logistic regression, a multivariate explanatory model for resistance to ICI included a level of expression of PDL1 < 1% (OR 0.30 [0.12, 0.78], p=0.015) and TIM3 < 20% (OR 0.28 [0.09, 0.84], p=0.022), and low amounts of FOXP3+ cells (hotspot < 200 : OR 0.23 [0.08, 0.7], p=0.009) and CD56+ cells (hotspot < 10 : OR 0.32 [0.12, 0.87], p=0.021). This model also includes clinical factors at baseline: TNM stage IVB, corticoid treatment, platelet blood count ≥ 250,000 per microliter and the presence of bone metastases.

Conclusions: A combination of clinical and biological markers performs better at predicting resistance to ICI than PDL1 alone. We aim to expand this model with genetic data (currently being processed) before refinement and validation on independent cohorts.

Table 1 : scoring methods for immunohistochemistry slides

PDL1	Tumour proportion score
CD23	Present at the core of tertiary lymphoid structures or absent
CD3, CD4, CD8, CD56, FOXP3	Two methods were used and compared : 1. Percentage of stromal infiltration by stained cells 2. Highest count of stained cells achievable in a single microscopic frame at the 400th power (hotspot)
TIM3, VISTA	Percentage of stained non-tumour cells in the stroma
STAT3, PTEN, B2M	Histoscore method : the percentage of tumour cells stained for each of four levels of staining intensity was multiplied by the corresponding index of intensity (0 : no staining, 1 : mild, 2 : moderate, 3 : strong) ; all weighted percentages were added

PDL1 : programmed death-ligand 1 ; CD : cluster differentiation ; FOXP3 : forkhead box protein 3 ; TIM3 : T cell immunoglobulin and mucin domain-containing protein 3 ; VISTA : V-domain immunoglobulin (Ig)-containing suppressor of T-cell activation ; STAT3 : signal transducer and activator of transcription 3 ; PTEN : phosphatase and tensin homolog ; B2M : beta-2-microglobulin

Keywords: Immunotherapy, Prediction, Biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.40 The Role of Histology and Metabolic Parameters in Predicting Spread Through Air Spaces

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Introduction: Spread through air spaces (STAS) is a recently validate prognostic factor for survival in NSCLC, but the possibility to pre-operatively individuate it remains challenging. In this study, we consider clinical, pathological and metabolic factors with the aim to individuate possible STAS predictors.

Methods: Clinical and pathological characteristics of patients who underwent anatomical lung resection from 1/01/2018 to 31/12/2023 were reviewed and retrospectively analyzed. Patients with GGO tumors, MIA, AIS, and/or distant metastases, receiving neoadjuvant treatment were excluded. Only patients underwent pre-operative 18-FDG Positron Emission Tomography(PET) were included. Operatory and pathological report were reviewed to collect data on histology, STAS, pleural invasion, lymphovascular invasion and necrosis.The PET parameters considered were SUVmax, SUVmean, SUVpeak,Total Lesion Glycoysis(TLG) and Metabolic Tumours Volume(MTV).The primary end-point was the association between clinical, metabolic and pathologic characteristics with STAS presence. Odds Ratios (ORs) with 95% confidence intervals(95% CIs) were estimated for each variables of interest. A P-value<0.05 was considered significant. A multivariable logistic regression model was developed using stepwise regression (forward selection, enter limit and remove limit, p = 0.10 and p = 0.15, respectively), to identify independent predictors of STAS.

Results: The final analysis was conducted on 224 patients that met the inclusion/exclusion criteria. Histology consisted in adenocarcinoma in 164 (72.3%) patients, while stage Ia was present in 160 (71.4%) cases.STAS was detected in 24(10.7%) cases.Metabolic parameters did not correlated with STAS presence (table), while pathological characteristics did. High grade adenocarcinoma tumors (solid, papillar and micropapillary) presented a statistically significant higher risk of STAS presence compared to low grade histology (acinar, lepidic): 20.8% vs 4.3%, p=0.003, OR 5.87 , 95%CI 1.83-18.78. Also tumour grading significantly correlated with STAS: 4.6% in G1-G2 tumors vs 23.5 % in G3 tumors (p=0.001, OR 5.79, 95%CI 2.12-15-78).Multivariable confirmed as independent prognostic factor the tumours grading: OR 5.44, 95% CI 1.75-16.84, p=0.003. Considering stage Ia tumours only, STAS occurred in 20 cases (12.5%). High grade adenocarcinoma(p<0.001), high tumour grading (p=0.001),lymphovascular invasion (p=0.034) and pT>2cm (p=0.017) resulted significantly correlated with STAS presence. Multivariable confirmed as independent risk factors the high grade adenocarcinoma histology(OR 6.10,95%CI1.17-31.74,p=0.032) and high tumour grade(OR4.73, 95%CI 1.16-19.23,p=0.030).

Conclusions: In our study, STAS presence risk is not correlated with metabolic parameters, while adenocarcinoma subtype and tumours grading seem to stratify the STAS occurrence risk. This information may be used to plan appropriate anatomical lung resection and follow-up schedules in patients with pre-operative diagnosis.

VARIABLE	N(%) or median	RISK OF STAS	
		Univariable p value	Multivariable p Value(OR;95%CI)
SEX		0.131	
Male	126(56.1)		
female	98(43.9)		
AGE	71(40-86) years	0.846	
SMOKER		0.392	
Yes	63(27.9)		
no	161(72.1)		
LOBE		0.142	
upper	151(67.4)		
lower	73(32.6)		
SIDE		0.851	
Right	136(60.7)		
left	88(39.3)		
pT			
1a	44 (19.8)		
1b	93 (41.2)		
1c	44(19.8)		
2a	24 (10.7)		
2b	8 (3.6)		
3	5 (2.2)		
4	6 (2.7)		
pT		0.348	
1	181(80.8)	REF.	
2	32(14.3)	0.740	
3-4	11(4.9)	0.438	
pT size		0.257	
<2 cm	136 (60.7)		
>2cm	89(39.3)		
HISTOLOGY		0.538	
adenocarcinoma	164(73.2)	Ref.	
squamous cell carcinoma	34(15.2)	0.392	
other	26(11.5)	0.275	
Adenocarcinoma subtype		0.003	NOT SIGNIFICANT
Low grade (acinar-lepidic)	93(41.5)		
High grade (papillar, micropapillary, solid)	67(29.9)		
GRADING		0.001	0.003 (5.44, 1.75-16.84)
1-2			
3			
Pathological N		0.222	
0	203 (90.6)		
1	7 (3.1)		
2	14(6.3)		
SUVmax	4.9(0.8-34.3)	0.947	
SUVpeak	2.9(0.69-23.9)	0.894	
SUV mean	2.9(0.56-21.7)	0.899	
Metabolic total volume	2.1(0.14-39.4)	0.545	
Total Lesion Glycolysis	5.7(0.19-262)	0.919	
STAS		-	
Yes	24(10.7)		
No	200 (89.3)		
NECROSIS		0.472	
Yes	49(21.9)		
NO	175 (78.1)		
LYMPHOVASCULAR INVASION		0.053	NOT SIGNIFICANT
Yes	27 (12.1)		
NO	197(87.9)		
VISCERAL PLEURAL INVASION		0.848	
YES	49(21.9)		
NO	175 (78.1)		

Keywords: NSCLC, stas, early stage

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.41 CD200 as a Novel Prognostic Biomarker in Early-Stage Lung Adenocarcinoma Immune Microenvironment

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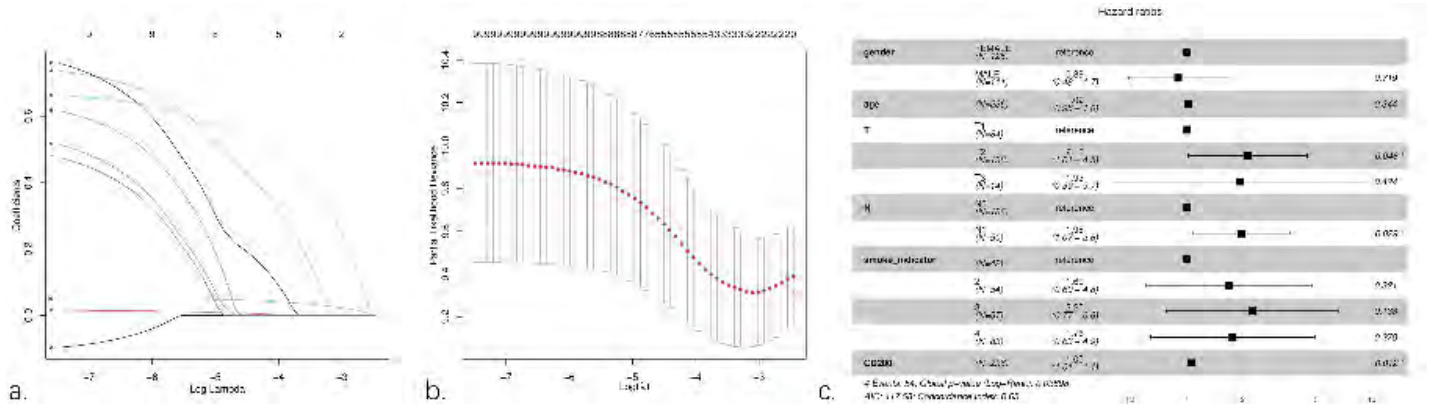
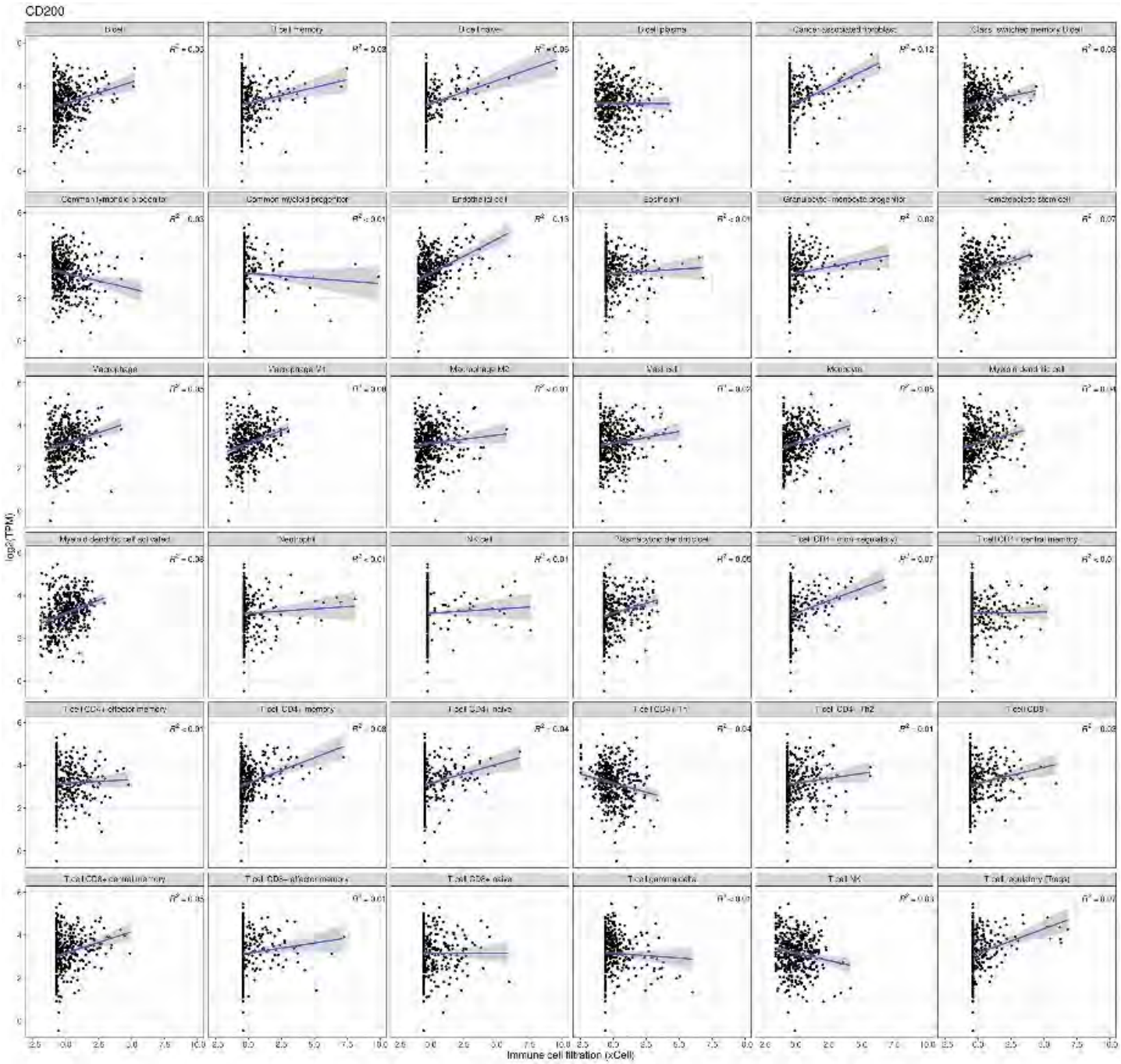
Introduction: Early-stage lung adenocarcinoma (LUAD) prognosis remains challenging, with immune microenvironment dynamics and recurrence biomarkers poorly defined. This study aimed to characterize immune infiltration patterns and identify prognostic biomarkers linked to recurrence.

Methods: Public TCGA data (421 early-stage LUAD samples) were analyzed via bioinformatics tools (DESeq2, edgeR, xCell) to evaluate immune cell infiltration and differential gene expression. A prognostic model integrating Cox regression and LASSO was developed. Clinical validation included 123 early-stage LUAD patients, with immunohistochemistry (CD3, CD8, CD20, CD68, CD200) and digital pathology (QuPath) to quantify immune cells. Survival analysis and multivariate Cox regression assessed independent prognostic factors.

Results: CD200 emerged as a key independent prognostic biomarker. High CD200 expression correlated with increased recurrence risk (HR=2.30, p=0.015) and immune infiltration (B cells, macrophages, CD8+ T cells). Tumor tissues exhibited reduced CD200 expression versus normal (p=0.036). Immune infiltration analysis revealed CD4+ naïve T cells as a risk factor and NKT cells as protective. Mature tertiary lymphoid structures (TLS) were associated with higher CD200 density (p<0.001). CD68+ macrophages independently predicted poor DFS (AHR=1.87, p=0.045).

Conclusions: CD200 and immune cell infiltration (CD68+ macrophages, CD8+ T cells) are critical prognostic indicators in early-stage LUAD. CD200's role in immune evasion highlights its potential as a therapeutic target. Validation in larger cohorts and functional studies are warranted to optimize personalized immunotherapy strategies.





Keywords: Lung Adenocarcinoma, Immune Microenvironment, CD200

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.42 Clinical Characteristics and Treatments of Patients With Advanced Non-Squamous NSCLC KRAS-Mutated With or Without STK11

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Introduction: KRAS is a frequently mutated oncogene in non-squamous (NSQ) Non-Small Cell Lung Cancer (NSCLC) with significant molecular and clinical heterogeneity and different prognostic and therapeutic implications. The impact of KRAS mutations on survival remains ambiguous due to co-mutations, such as STK11. Current KRAS-targeting drugs focus on the specific KRAS mutation, G12C, with varying treatment responses and intrinsic resistance, often influenced by co-mutations. Therefore, understanding the biological context of KRAS-mutated NSCLC, including the PD-L1 expression associated with KRAS mutations, may support the development of treatment strategies. We aimed to describe demographic characteristics, treatment, and survival outcomes of advanced NSQ NSCLC patients KRASm with or without STK11m (KRASm±STK11m).

Methods: Patients diagnosed with advanced NSQ NSCLC between January 1, 2017, and December 31, 2022, in Denmark were identified in the Danish National Cancer Register. Information on KRAS and STK11 mutations status [tested by polymerase-chain reaction (PCR), and since 2018 at increasing frequency next-generation sequencing (NGS)] as well as PD-L1 expression (by immunohistochemistry) from the diagnostic biopsy was collected from the National Pathology Register. Details on comorbidities and treatments were retrieved from the National Patient Register and the National Hospital Medication Register, respectively. Patient characteristics were assessed at diagnosis, and first-line (1L) treatments were defined as chemotherapy (CT), radiotherapy (RT), immunotherapy (IO), and combinations of them, administered between diagnosis and the 1st follow-up scan post-diagnosis. Overall survival (OS) was assessed by the Kaplan-Meier estimator.

Results: In total, 9822 patients were identified with advanced NSQ NSCLC between 2017 and 2022. Of these, 2024 were reported with KRASm±STK11m, 1934 with only KRASm, 68 with only STK11m, 90 with co-mutated KRAS and STK11, and 565 with KRAS wild type. The remaining 7233 patients had either an inconclusive result or were not tested. Approximately, 54% of the KRASm±STK11m patients were diagnosed in 2021 and 2022, compared to 46% between 2017 and 2020, which may reflect an increase in NGS testing practice in Denmark. Females were predominant among patients with KRASm±STK11m (63%), while males were predominant among patients with STK11m only (69%). At diagnosis, patients with KRASm±STK11m were on average 69.8 years of age, and they had a comorbidity index of 0.6. PD-L1 expression levels above ≥50% were observed in 46.2% of patients with KRASm±STK11m, 47.8% with only KRASm, 16.2% with only STK11m, and 12.2% with co-mutations. About 80% of KRASm±STK11m patients received 1L treatment, most frequently as RT (22.3%, n= 451), IO (18.5%, n=374), CT (18.2%, n=369), and CT+IO (9.9%, n=200). Notably, 20% did not receive 1L treatment. OS in patients with KRASm±STK11m at 6 and 12 months was 54.4% and 36.8%, respectively, while median OS was 7.03 months.

Conclusions: Overall, 20.6% of Danish patients diagnosed with NSQ NSCLC included in our study were reported with KRASm±STK11m during the period 2017-2022. In addition, our data show that a large proportion of patients in the study cohort had an inconclusive test or was not tested. Therefore, broader usage of molecular testing nationwide can provide more accurate epidemiological evaluation of this patient population and its unmet therapeutic needs.

Keywords: KRAS mutation, STK11 mutation, molecular testing

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.43 Using Artificial Intelligence to Leverage Phenotypic, Genomic and Proteomic Correlations in Lung Carcinoma Patients With MET Alterations

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Introduction: Oncogenic MET activation in patients with non-small cell lung carcinoma (NSCLC) can occur due to gene mutations, amplification, fusions, and protein overexpression. Accordingly, these dysregulation mechanisms have been investigated for the development of targeted therapies and antibody-drug conjugates. Although MET exon 14 skipping mutations (M14M) and high-level MET copy number gain (MCNG) are established or emerging predictive biomarkers in most guidelines, the predictive role of MET overexpression as detected by immunohistochemistry (IHC) remains unclear. Furthermore, the correlation among M14M, MCNG, and MET IHC is controversial. We hypothesize that using artificial intelligence (AI) in this setting can advance our understanding of genomically mediated MET overexpression. This strategy could serve as a first step toward the potential deployment of MET IHC as a predictive biomarker for antibody-drug conjugates.

Methods: We retrospectively identified all NSCLC patients tested with Oncomine (Thermo Fisher Scientific) next-generation sequencing (NGS) panels between 2020 and 2025 who exhibited M14M. In addition, high-level MCNG (≥10 copies) was also recognized by NGS through DNA analysis. Automated IHC for MET (Ventana SP44 clone) was performed on all cases with these MET alterations, and subsequently scanned and analyzed using off-label software (NDP). MET IHC was also evaluated by three pathologists, each providing a four-tier classification based on staining intensity (0 and 1+: negative, 2+ and 3+: positive). The consensus human score was compared with the AI result. Since the reliability of NGS for detecting gene amplifications (compared to FISH) has been questioned in specimens with low tumor content, we opted to use an additional AI algorithm (PathAI AIM-tumorCellularity) to confirm that samples with high-level MCNG contained ≥20% tumor content.

Results: In the NGS cohort of 2,170 NSCLC patients, 30 (1.4%) exhibited M14M and 12 (0.5%) had high-level MCNG, with no overlap between these groups. The majority of the samples analyzed were core-needle biopsies (42.8%), followed by surgical specimens (33.3%). Of these 42 patients, 21 were male and 21 were female, and 31 (73.8%) had adenocarcinoma. The median high-level MCNG was 13.7 (range: 10-27.1). Among patients with M14M, six (20%) also exhibited low-level MCNG (range: 4.5-7.9). Manual scoring of MET IHC was 3+ in 36.7% (11/30) of M14M cases (including all cases with low-level MCNG) and 66.7% (8/12) of MCNG cases. Interestingly, four (13.3%) M14M cases and two (16.7%) MCNG were scored as 1+. When evaluated using AI, all samples with M14M or high-level MCNG showed at least 2+ immunoreactivity. The proportion of patients with 3+ scores was higher in the AI group compared with the consensus manual scoring (66.7% versus 45.2%).

Conclusions: There was substantial agreement between MET IHC and the two currently established MET predictive biomarkers, particularly when AI algorithms were applied. AI-powered MET IHC scoring has the potential to refine the identification of MET alterations in patients with NSCLC.

Keywords: Biomarkers, Artificial intelligence, MET

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.44 Tertiary Lymphoid Structures in the Tumor Micro Immune Environment of EGFR Positive Lung Cancer Are Associated Prognosis

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Introduction: We have been studying the tumor micro immune environment(TME) in lung cancer such as tertiary lymphoid structure(TLS), and there are still many unknowns about TME in EGFR mutation-positive lung cancer. We investigated TME in EGFR mutation-positive lung cancer patients.

Methods: We included 213 patients with non-small cell lung cancer who underwent surgery at our institution between January 2007 and December 2015, who were positive for EGFR mutations and were further considered for TLS; TLS was defined as a population of lymphocytes containing PNAd-positive epithelial vessels.

Results: The median age was 67 years (37-90 years), 34% were male, 66% were female, and 62 patients had a history of smoking. The histological type was adenocarcinoma in 209 cases: Stage I in 172 cases and II-IV in 41 cases; L858R in 132 cases and Exon19 del in 81 cases; TLS High in 75 (57%) of L858R-positive cases and 31 (37%) of Exon19 del-positive cases (P=0.011). DFS was significantly higher in TLS High in all cases (P=0.028). There was no clear difference in Stage I, but in Stage II and above, the TLS High group tended to do better, especially in L858R. In univariate and multivariate analysis of DFS, p-Stage and TLS were independent predictors of prognosis.

Conclusions: There are reports that TLS is associated with DFS in EGFR-positive lung cancer, although L858R-positive lung cancer is more likely to have TLS, and there are scattered reports that Exon19del has better PFS and TKI efficacy. On the other hand, the ATTLAS trial reported that ICI tended to be more effective than L858R. This study suggests that differences in EGFR mutations may be related to the tumor microenvironment, especially TLS expression, and may affect the efficacy of TKIs and ICIs.

Keywords: Lung cancer, EGFR, TLS

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.45 Heterogeneity of Tumor Microenvironment and PD-L1 Expression in NSCLC and Tumor Draining Lymph Nodes After Solid Organ Transplantation

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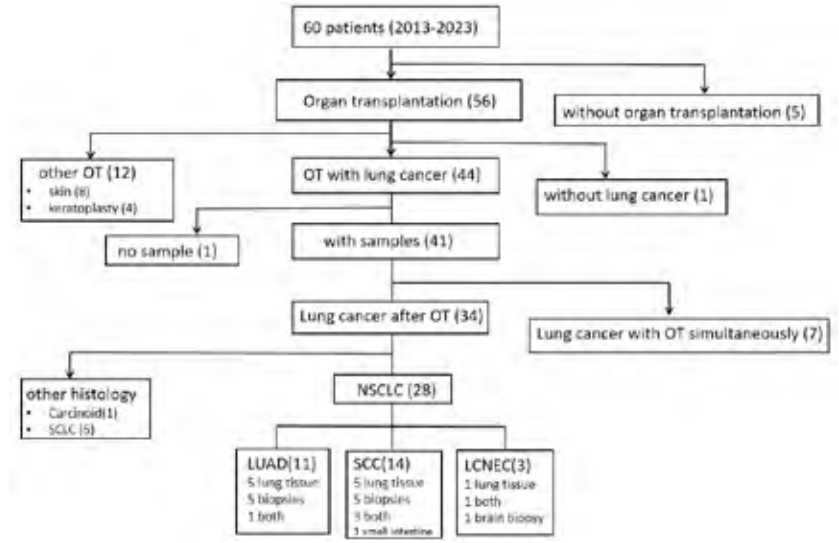
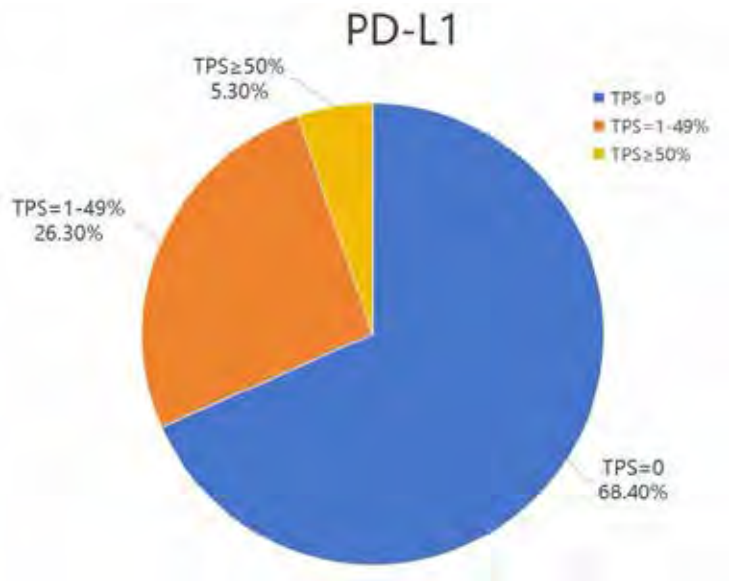
Introduction: Lung cancer is one of the most common malignant tumors after solid organ transplantation (SOT). This study aims to reveal the heterogeneity of the tumor microenvironment (TME) and PD-L1 expression in NSCLC after SOT.

Methods: We performed a retrospective study of NSCLC patients after SOT from 2013 to 2023 and the clinical characteristics were described and summarized. Immunohistochemistry was used to quantify expression of PD-L1. Statistical analyses were completed in GraphPad Prism.

Results: 28 patients who developed NSCLC after SOT were ultimately included (lung [n=10], kidney [n=6], liver [n=3], heart [n=5], other [n=4]) (Figure 1). At diagnosis, 13 patients (46.4%) were in stage I and II, while 15 patients (53.6%) were in stage III and IV. 16 patients (57.1%) underwent surgical treatment after diagnosis. The median survival time after diagnosis was 18 months, with a 1-year OS rate of 61.2% (95% CI: 40.3-76.7%) and a 2-year OS rate of 34.2% (95% CI: 16.8-52.5%). PD-L1 testing was performed on 19 samples, among which 5 cases (26.3%) showed 1-49% expression, 1 case (5.3%) showed high expression (TPS=70%), and 13 cases (68.4%) showed negative PD-L1 expression. Multiple clinical studies have shown that among the general NSCLC population, 40-60% of patients exhibit PD-L1 positivity, with 20-30% of patients having TPS ≥50% (Figure 2).

Conclusions: Our data indicate that PD-L1 expression in NSCLC after SOT is lower compared to the general NSCLC population. Our cohort describes NSCLC after SOT. Most patients were treated with surgery, which is consistent with the literature. PD-L1 expression levels in NSCLC after SOT are lower than in NSCLC in a non-immunosuppressed and may reflect differences in the TME which should be explored in further experiments. The next step is to examine the differences in immune-related genes by using microarrays.





Keywords: NSCLC, SOT, PD-L1

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.46 Frequent Co-Existence of RBM10 Mutation in Patients With Non-Squamous NSCLs Harboring EGFR Point Mutationse

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Introduction: Mutations of the RBM10 (RNA-binding motif 10) gene that encodes for a regulator of alternative splicing has been implicated in lung cancer pathogenesis as well as drug tolerance to EGFR-tyrosine kinase inhibitors (TKIs). However, there are insufficient data on which non-small cell lung cancer (NSCLC) patients are more likely to develop RBM10 mutations.

Methods: We analyzed 190 NSCLC specimens obtained from surgical resection at Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine between June 2022 through April 2024 by NGS analysis.

Results: RBM10 mutation was not detected in 38 patients with squamous cell carcinoma (0%), while 18 patients out of 152 non-squamous NSCLC patients (12%) had RBM10 inactivating mutations (nonsense or frameshift mutations). The prevalence of RBM10 mutation was significantly higher in EGFR-mutated tumors (14/68 patients, 21%, $p < 0.01$) and KRAS-mutated tumors (3/25 patients, 12%, $p < 0.01$) compared with EGFR/KRAS wild-type non-squamous NSCLC patients (1/60 patients, 2%). Among patients with non-squamous NSCLCs with EGFR mutation, the prevalence of RBM10 mutation was numerically higher in patients with point mutations (26% in L858R, 9% in exon 19 deletion, and 38% in uncommon point mutations, Figure 1). In contrast, the prevalence of TP53 co-mutation were equivalent between these EGFR mutation subtypes (31% in L858R, 32% in exon 19 deletion, and 38% in uncommon point mutations, Figure 1).

Conclusions: RBM10 mutations were enriched in EGFR- or KRAS-mutated non-squamous NSCLCs, especially in tumors with EGFR point mutations.

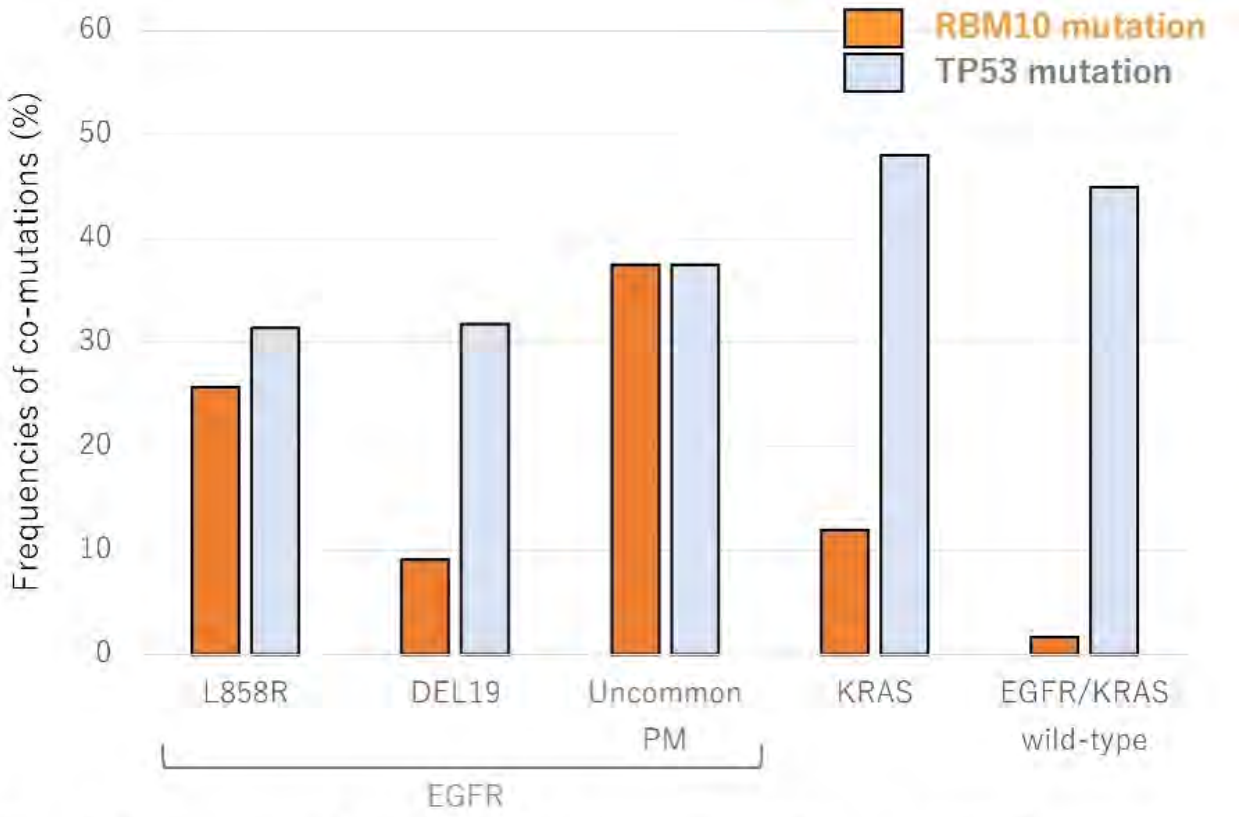

Figure 1. Frequencies of RBM10 or TP53 mutations in EGFR-mutated, KRAS-mutated, or EGFR / KRAS wild type non-squamous NSCLC patients.

Keywords: EGFR mutation, Co-mutation, non-squamous NSCLC

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.47 A Ten-Gene DNA Damage Repair-Related Signature for Predicting Prognosis and Treatment Response in Non-Small Cell Lung Cancer

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Introduction: DNA damage repair (DDR) plays a crucial role in maintaining genomic integrity and regulating cancer risk, progression, and therapeutic response. DDR alterations are frequently observed in non-small cell lung cancer (NSCLC), presenting both challenges and opportunities for treatment strategies. A deeper insight into DDR molecular characteristics in NSCLC can greatly enhance patient management by improving prognosis prediction and guiding personalized treatment strategies. This study aimed to investigate the association between DDR alterations and NSCLC prognosis and to develop a DDR-based prognostic model for risk stratification in NSCLC patients.

Methods: Biomarker discovery was conducted using the GSE68465 dataset (n = 462). We employed machine learning approaches, including LASSO and Cox regression models, to identify a DDR-associated gene signature. From an initial pool of 644 DDR-related genes, 128 were selected using univariate Cox regression, and a ten-gene DDR prognostic model was established using LASSO Cox regression. This model was validated in the TCGA cohort (n = 589) for overall survival (OS). Model performance was evaluated using the concordance index (C-index) and area under the curve (AUC) in both the training and validation cohorts. Furthermore, clinical validation was conducted, and a nomogram was developed for personalized risk assessment. Immune infiltration analysis was conducted to evaluate the impact of the DDR signature on the tumor microenvironment.

Results: We identified a ten-gene DDR signature comprising WDHD1, PIAS1, WRNIP1, DDIT4, SMARCA4, PIK3R1, ARID1A, TP53BP1, ZBTB40, and APTX, which demonstrated a strong correlation with NSCLC prognosis. This signature was significantly associated with poor OS in the training cohort (HR=1.8, 95% CI: 1.6-2.1, p<0.0001) and was robustly validated in the TCGA cohort (HR=1.96, 95% CI: 1.08-3.57, p=0.025). High-risk DDR patients demonstrated significantly poorer overall survival (OS) in clinical validation. To enhance personalized patient management and treatment planning, a nomogram was developed by integrating the DDR signature with clinical factors such as TNM stage, age, and gender. Immune infiltration analysis revealed that NSCLC samples with a high DDR signature exhibited significant alterations in immune cell infiltration, including: Increased infiltration of myeloid-derived suppressor cells (MDSCs) (z-score=3.5, p<0.001) and decreased infiltration of plasma B cells (z-score=-2.4, p<0.01), CD8+ T cells (z-score=-2.3, p=0.02), and myeloid dendritic cells (z-score=-2.19, p=0.03). These findings suggest that a high DDR signature is associated with an immunosuppressive tumor microenvironment, characterized by reduced infiltration of key immune effector cells and increased MDSC accumulation.

Conclusions: We present a novel DDR-related gene signature for risk stratification and identification of NSCLC patients with poor prognosis. This DDR-based prognostic model holds promise for guiding personalized treatment strategies. Furthermore, immune infiltration analysis highlights the impact of DDR alterations on the tumor immune microenvironment, offering insights into potential implications for NSCLC immunotherapy.

Keywords: Non-small cell lung cancer, DNA damage repair, Immunotherapy

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.48 Complementary Role of IHC in ALK Fusion Detection: A Validation Study of NSCLC NGS-Based Screening in Seven Laboratories

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Introduction: Next-generation sequencing (NGS) is the recommended technology for the assessment of non-small cell lung cancer (NSCLC) biomarkers. Gene fusion detection presents methodological challenges especially when using amplicon-based technologies. Furthermore, these alterations have low incidence, making it difficult to standardize the assay validation phase. The objective of this study is to verify ALK fusion NGS results by retesting negative samples using immunohistochemistry (IHC) in seven reference centers in Catalonia.

Methods: A total of 553 negative (without alterations in EGFR, KRAS, BRAF, ALK, ROS1, NTRK, RET, or MET) from 1,910 NSCLC samples assessed in 2022, were retested using VENTANA anti-ALK (D5F3) antibody. Resulting ALK NGS-IHC discordant cases were further studied using fluorescence in situ hybridization (FISH). Information regarding the screening test, the results obtained, and the number of cases non-assessable by NGS were compiled.

Results: Among the 1,910 NSCLC samples analyzed by NGS in 2022, 35 were ALK-positive (1.8%), 990 were negative (51.8%), and 48 were non-assessable (2.5%). Of the negative cases, the NGS ALK result was verified by IHC in 553 samples (113 studied with SureSelect Agilent NGS panels, and 440 with Thermo Fisher Oncomine technology). Only 2 samples presented a discordant ALK result, both assessed with the Oncomine Comprehensive Assay (Thermo Fisher) in the same center. One of them presented a positive ALK FISH pattern but the other was negative, leading to only one misdiagnosed ALK-positive case out of 1,910 (0.05%). Regarding the screening method, only one center analyzed fusions using DNA-based NGS by hybrid-capture (SureSelect Agilent Custom panel and Illumina sequencing). The remaining centers analyzed fusions at the RNA level using amplicon panels: Oncomine Focus Assay, Oncomine Precision Assay, and Oncomine Comprehensive Assay (Thermo Fisher). This panel is the only one that does not perform alternative fusion analysis using ALK gene expression differences (imbalance score) for detecting novel or rare fusions. In all seven centers, alternative ALK techniques used are primarily IHC and FISH, and to a lesser extent, the Idylla GeneFusion Assay (Biocartis).

Conclusions: The reliability of the ALK-fusion results obtained by NGS in NSCLC patients is very high, despite the methodological differences among the NGS panels used across centers. As with any other technique, there is a possibility of false negative results, that can be minimized in this case using NGS panels that perform alternative fusion analysis for novel or rare fusions. IHC is a reasonable option to retest a negative NGS result, when clinical or histological evidence suggests an ALK fusion.

Keywords: ALK fusions, NGS, Biomarkers

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.49 Analysis of EGFR Mutations Using Highly Sensitive Digital Droplet PCR for EGFR Mutation-Positive NSCLC

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Introduction: It has been reported that the T790M mutation, which cannot be detected using the usual test for EGFR mutations, can be detected using highly sensitive digital PCR (ddPCR). However, prospective studies on the relationship between the detection of the T790M mutation by ddPCR and the efficacy of EGFR-TKIs are scarce. This study aimed to explore how EGFR T790M mutation detectable only by ddPCR in tissue prior to treatment affects EGFR-TKI treatment.

Methods: This was a single-institution prospective cohort study. Patients with EGFR mutation-positive, advanced, or recurrent NSCLC were eligible. T790M was quantified using ddPCR in tumor tissues before treatment with EGFR-TKIs. The threshold to determine positivity for T790M by ddPCR was analyzed using an experimental system in which plasmids containing the EGFR T790M mutation were mixed with nucleic acids to adjust the ratio of wild-type EGFR to EGFR T790M.

Results: A total of 21 patients participated in this study between December 2019 and May 2022. The median age of the patients was 72 years (range, 42-84 years). There were 12 females (57.1%), 13 at Stage IV (61.9%), 20 patients with PS 0-1(95.2%), and 12 patients never smoked (57.1%). The most common EGFR mutation was del19 (57.1%). Twelve patients (57.1%) were treated with osimertinib. The thresholds were considered “negative” at 1.1 copies/mL or less, “positive” at 5.47 copies/mL, and “not determinable” at all other levels. Six patients (28.6%) were determined to be positive for T790M. The median T790M EGFR detected by ddPCR was 1.8 (range: 0.43-350) copies/μL. The median PFS was 12.5 months and the median OS was 31.9 months in the overall population. The patients were divided into two groups. Osimertinib (OSI) and other drugs (OTH). Median PFS was 13.5 months in the OSI group and 11.0 months in the OTH group (HR: 01.53, 95%CI: 0.55-4.24). Median OS was 31.9 months in the OSI group and 27.3 months in the OTH group (HR: 0.59, 95%CI: 0.16-2.08). In the OTH group, all patients were treated with afatinib, except for one patient who was treated with erlotinib and ramucirumab. Additionally, the patients was divided into two groups. T790M positive (T790M POSI) and T790M not positive group (T790M NON-POSI) . Median PFS was 19.6 months in the T790M POSI group and 12.5 months in the T790M NON-POSI group (HR: 0.45, 95%CI: 0.10-2.06). OSI group was further divided into two groups according to T790M status. Median PFS was 39.6 months for the T790M POSI group and 12.5 months for the T790M NON POSI group (HR: 0.34, 95%CI: 0.08-1.45). NON-OSI group was further divided into two groups according to T790M status. Median PFS was 34.9 months for the T790M POSI group and 9.9 months for the T790M NON POSI group (HR: 0.25, 95%CI: 0.06-1.15).

Conclusions: There was a trend toward better PFS in the T790M POSI group in both the OSI and NON-OSI groups. EGFR T790M positivity by ddPCR may be a predictor of the response to EGFR-TKIs.

Keywords: digital droplet PCR, EGFR, NSCLC

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.50 Development of a Novel AI-Augmented Small Cell Lung Cancer (SCLC) Algorithm for Accurately Classifying Cell Types From H&E

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Introduction: Small cell lung cancer (SCLC) is an aggressive cancer with 5-year survival rate of <10%. Recent treatment advances have primarily been from immunomodulatory agents including checkpoint inhibitors and t-cell engagers. However, understanding the tumor microenvironment with standard pathological assays like H&E remains challenging as SCLC tumor cells closely resemble the surrounding immune cells and are difficult to distinguish by pathological review. While deep learning models have predicted outcome for SCLC patients from H&E, they have focused on learning patient-level characteristics. In contrast to other tumor indication models, SCLC models have not provided cell-level classification of the tumor tissue due to challenges in appropriately annotating and learning this information. We developed a novel AI model for SCLC using slides sequentially stained with a duplex chromogenic IHC and H&E that accurately phenotypes cell-level information from H&E slides.

Methods: Commercially sourced samples from SCLC resections were sequentially stained with a duplex chromogenic IHC of CD45 (immune) and TTF1 (tumor) followed by H&E staining. The slides were scanned and the digitized images were split into training and validation sets for deep learning pathologist annotation and model assessment. H&E and duplex IHC scanned images were co-registered to allow for pathologist driven deep learning based on ground truth staining of duplex IHC. Nucleai's baseline tumor H&E model was optimized for SCLC based on annotation of tumor, immune (including lymphocyte, granulocyte, macrophages), and stromal cells. Results were compared to a SCLC model trained by pathologist annotation without access to duplex staining.

Results: Analysis of withheld validation samples against duplex staining ground truth pathological annotation found that the H&E only model faired significantly worse at distinguishing between key cell classes than the one informed by duplex stains. Tumor cells (n = 3,709) had higher specificity in the duplex trained model (89.9%) compared to the H&E only model (61.4%) and retained comparable sensitivity (92.8% duplex model, 98.8% H&E alone). Similarly, lymphocytes (n = 698) had poor detection in an H&E only model and improved significantly by deep learning to the duplex stain (sensitivity: 83.6% duplex model, 51.1% H&E alone; specificity: 93.0% duplex model, 98.9% H&E alone).

Conclusions: We propose that this novel AI algorithm that is capable of differentiating tumor cells from surrounding microenvironment within SCLC on H&E slides and provides researchers a new tool for interrogating the tumor-immune interactions critical for a mechanistic understanding of key therapeutic interventions in this indication.

Keywords: Artificial Intelligence, Small Cell Lung Cancer, H&E slides

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.51 Development of Novel IHC Assay for PD-L1 Detection in Non-Small Cell Lung Cancer

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Introduction: Non-small cell lung cancer (NSCLC) is globally a leading cause of cancer-related deaths. Each year, around 2 million new cases are attributed to lung cancer, and the same number of yearly deaths are reported. Due to the poor overall survival rate, this cancer type results in high mortality.

PD-L1 is one of the biomarkers associated with NSCLC progression and can be a valuable cancer immunotherapy target. Hence, accurate PD-L1 estimation in tumor cells can better inform treatment regimens and improve patient care. Leica Biosystems has developed a novel PD-L1 immunohistochemistry (IHC) assay and analyzed its initial performance by comparing it to Ventana's PD-L1 SP263 assay.

Methods: The study objective was to ascertain the concordance of the Leica Biosystems CAL10 assay with the comparator (SP263 assay) at 50% tumor proportion score (TPS). If the TPS was ≥50%, then the sample was scored positive; if the TPS was<50%, then the PD-L1 status was categorized as negative. Additionally, concordance was similarly assessed at a 1% cut off.

A total of 150 unique formalin-fixed, paraffin-embedded (FFPE) cases cut to 4µm serial sections were enrolled in the study. Each case was randomly assigned a unique ID and had triplicate glass slides stained with CAL10 antibody, BOND negative rabbit control, and H&E. Similar triplicate glass slides were generated with SP263 antibody, Ventana negative control, and H&E. Each slide set (stained with CAL10 or SP263) was read and scored independently by the 2 pathologists. Both pathologists first read SP263 stained slide set. After a washout period of 5 weeks, the CAL10 stained slide set of the same cases was read by the same study pathologists, following which the concordance between the 2 assays was estimated by the study biostatistician.

Results: The inter-assay concordance was estimated by measuring overall percent agreement (OPA), negative percent agreement (NPA), and positive percent agreement (PPA). For 50% TPS assessment, a total of 260 (133 case reads by the first pathologist plus 127 case reads by the second pathologist) paired estimates by the 2 reading pathologists were generated for the unique FFPE cases. Out of the 260 paired reads, OPA was 90.3% (235 total agreements/260 total paired reads*100), NPA 86.3% (127 negative agreements/147 negative paired reads*100), and PPA 95.5% (108 positive agreements/113 positive paired reads*100).

For analysis at the 1% cut off, OPA was 96.9% (252 total agreements/260 total paired reads*100), NPA 91.8% (45 negative agreements /49 negative paired reads*100), and PPA 98.1% (207 positive agreements/211 positive paired reads*100).

The lower bound of the estimated OPA at 50% cut off was 86.1% while for 1% TPS, it was 94.0%, which met the pre-defined target of a minimum OPA lower bound value of 85%.

Conclusions: The Leica Biosystems CAL10 assay-which is under development-has demonstrated that its preliminary performance is comparable to that of the comparator SP263 assay. Although these results look promising, further verification and validation studies are required to confirm these initial findings.

Keywords: PD-L1, NSCLC, CAL10

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.52 TTF-1 Negativity Predicts Poor Outcomes in Advanced Non-Squamous NSCLC Also in the Immunotherapy Era: A Multicenter Cohort and Meta-Analysis

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Introduction: Immune checkpoint inhibitors (ICIs) significantly improved outcomes in advanced non-squamous non-small cell lung cancer (NSCLC), yet robust prognostic biomarkers beyond PD-L1 remain critically needed. We systematically evaluated the prognostic role of Thyroid Transcription Factor-1 (TTF-1), previously known as favorable in chemotherapy-treated NSCLC, in patients receiving first-line immunotherapy-based regimens.

Methods: We conducted a multicenter retrospective analysis involving 163 advanced non-squamous NSCLC patients treated with first-line immunotherapy or chemo-immunotherapy, and a historical chemotherapy-only cohort (n=37) for comparison. Patients were stratified by TTF-1 expression. Primary endpoints were progression-free survival (PFS) and overall survival (OS). To robustly validate our retrospective findings, and to weigh the role of TTF-1 in the immunotherapy era, we performed a comprehensive systematic literature review and meta-analysis following PRISMA-guidelines, integrating results from 9 studies encompassing 14 cohorts and 2,019 patients.

Results: TTF-1 negativity (25.5%) correlated with significantly poorer median PFS (6.7 vs 16.0 months; HR 2.22, 95% CI 1.59-3.13, p<0.001) and OS (11.5 vs 26.4 months; HR 2.33, 95% CI 1.64-3.45, p<0.001), independent of PD-L1 status and treatment regimen. Multivariate analysis confirmed TTF-1 negativity as an independent adverse prognostic factor for both PFS (HR 2.17; p<0.001) and OS (HR 2.08; p<0.001). A four-level composite analysis combining TTF-1 and PD-L1 expression revealed significant prognostic interplay. Patients in the TTF-1−/PD-L1low (<50%) group exhibited the worst outcomes and served as the reference. TTF-1+/PD-L1high (≥50%) patients showed the most favorable prognosis for PFS (HR 0.29, 95% CI 0.17-0.50, p<0.001) and OS (HR 0.25, 95% CI 0.14-0.44, p<0.001), followed by TTF-1+/PD-L1low (PFS: HR 0.51, 95% CI 0.32-0.80, p=0.004; OS: HR 0.53, 95% CI 0.33-0.84, p=0.008). Conversely, the TTF-1−/PD-L1high subgroup did not significantly differ from the double-negative group in either PFS (HR 0.63, p=0.23) or OS (HR 0.62, p=0.23). Stratified analyses confirmed that among TTF-1 positive patients, PD-L1 ≥50% significantly predicted better outcomes (PFS HR 0.56, p=0.01; OS HR 0.46, p=0.003), whereas among TTF-1 negative patients, PD-L1 status did not significantly influence survival (PFS HR 0.68, p=0.31; OS HR 0.67, p=0.32).The meta-analysis confirmed TTF-1 negativity as a predictor of inferior outcomes across multiple immunotherapy and immunochemotherapy regimens (PFS HR 1.75, 95% CI 1.50-2.04; OS HR 1.76, 95% CI 1.45-2.14; both p<0.0001).

Conclusions: TTF-1 negativity is a strong independent prognostic biomarker for poor outcomes in advanced non-squamous NSCLC patients treated with immunotherapy-based regimens, even among those with high PD-L1 expression. Integrating TTF-1 assessment in clinical practice could enhance patient stratification and treatment personalization, warranting prospective validation.

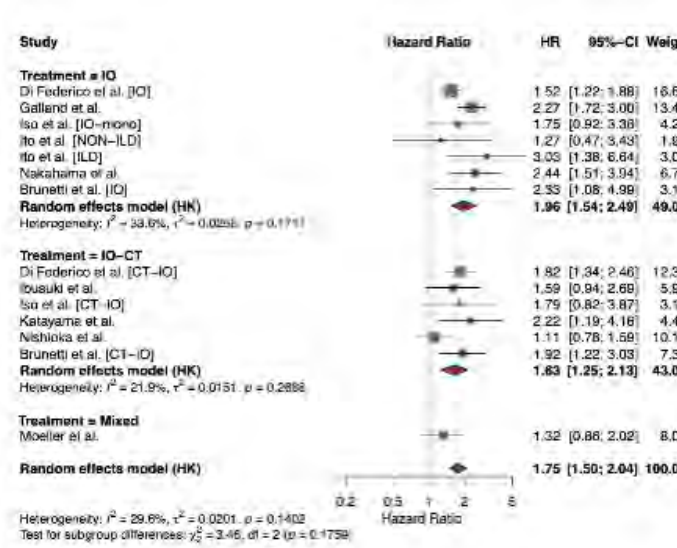

Figure 1A. Forest plot for PFS

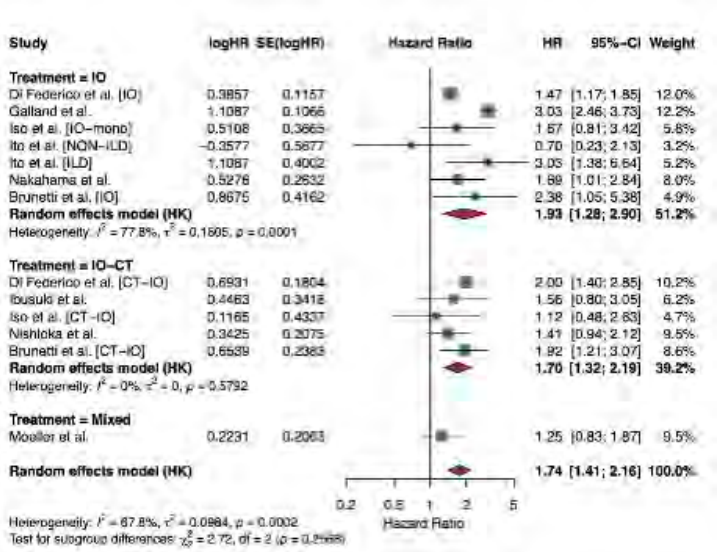

Figure 1B. Forest plot for OS

Keywords: TTF-1, NSCLC, Immunotherapy

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.53 c-MET Expression in Non-Squamous NSCLC: Molecular Correlation and Interobserver and Intersample Concordance on Scoring

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Introduction: Emerging therapies targeting c-MET overexpression in non-squamous non-small cell lung cancer (NSCLC) have recently demonstrated promising results. However, evaluating c-MET expression can be challenging due to heterogenous expression within the tumor. Furthermore, little is known about the relationship between c-MET expression and driver alterations, nor the effect of treatment on c-MET expression.

Methods: c-MET expression was assessed on resected lung adenocarcinomas without neoadjuvant therapy, available pre-operative biopsies, and excision/biopsy/cytology (non-resection) specimens from patients with advanced stage non-squamous NSCLC with/without tyrosine kinase inhibitor (TKI) therapy. All specimens underwent molecular profiling using targeted next-generation sequencing. Immunohistochemistry for c-MET (clone SP44; Roche Ventana) was evaluated using H-score and 2-tiered classifications with the cut-off of 3+ in ≥25% or ≥50% of tumor cells. Resections were evaluated by 3 (2 senior and 1 junior) pathologists, and the interobserver reproducibility was assessed via interclass correlation coefficient (ICC) and Fleiss Kappa coefficient (ƙ). c-MET expression was compared between driver alterations using t-Tests and Fisher's exact tests. c-MET expression was also compared between specimens procured at different time points in a subset of patients.

Results: The study cohort consisted of 281 patients with non-squamous NSCLC (age 22-94 [mean 67] years; Female: Male = 172:109, Stage I/II/III/IV =71/41/43/126). Of those, 150 underwent lung resections (all adenocarcinomas, pathologic Stage I/II/III/IV =71/41/34/4) with pre-operative biopsies available in 31. In the analysis of interobserver concordance of 3 pathologists assessing c-MET expression on resections, global ICC for H-score was 0.772 to 0.845, and the ƙ for the 25% and 50% cut-offs were 0.4855 to 0.7324 and 0.5300 to 1.0000, respectively. The ƙ was higher between senior pathologists and for biopsy samples. In the 31 biopsy/resection pairs, the intrasample reproducibility for H-score was ICC 0.246, and the ƙ for the 25% and 50% cut-offs were -0.1932 and -0.2000, respectively. With the 25% and 50% cut-offs, 12 (38.7%) and 8 (25.8%) cases were positive in the resection and negative in the pre-operative biopsy, respectively, while 2 (6.5%) and 0 cases were negative in the resection and positive in the biopsy. In the resection cohort, c-MET expression was associated with pathologic Stage (mean H-score: I vs II-IV = 173 vs 251, p<0.0001). In TKI-naïve tumors, c-MET expression was higher in fusion positive tumors (p = 0.026 in the resection cohort) or in ALK positive tumors only (p = 0.0079 in the non-resection cohort) than the rest of the cohort. Paired pre- and post-TKI specimens were available from 28 patients with advanced non-squamous NSCLC. Of those, c-MET expression was increased (from <25% to ≥25%/≥50% or from ≥25% to ≥50%) in 6 (21.4%) cases, decreased (from ≥50% to <25%) in 3 (10.7%), and similar in 19 (67.9%) after TKI therapy.

Conclusions: Interobserver agreement for c-MET expression was moderate to excellent in both resections and biopsies. However, c-MET expression may be underestimated in biopsies due in part to significant intratumoral heterogeneity. c-MET expression correlated with tumor stage and was relatively high in fusion-positive tumors. c-MET expression was the same or higher post TKI in 90% of treated patients.

Keywords: c-MET, reproducibility, tyrosine kinase inhibitor

EP.06.54 The Landscape of Actionable Genomic Alterations in Non-Small Cell Lung Cancer. A Single Institution Quality Improvement Initiative

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Introduction: Identification of actionable genomic alterations (AGA) in non-small cell lung cancer (NSCLC) is crucial to guide appropriate therapy for patients. Molecular profiling (accuracy and timeliness) can be inconsistent between centers and countries. Our centre adopted a new Next Generation Sequencing (NGS) panel, Oncomine Comprehensive Assay version 3 (OCAv3) ®, in 2021. Through our QI initiative, we will try to identify whether our test detected AGAs at an anticipated rate.

Methods: This is a retrospective single center QI project of patients diagnosed with NSCLC at a Canadian tertiary academic hospital with in-house testing, from July 1, 2021, to June 30, 2023, representing the initial 24 months after adopting OCAv3. All adult patients with confirmed NSCLC, of any stage, who had NGS by OCAv3 were reviewed, including those with attempted but unsuccessful tests. Patients with other active malignancies were excluded. With an ethics board waiver for QI projects, patient charts and pathology reports were reviewed, collecting simple patient demographics, molecular testing results and treatment details. Here we report the results of the molecular testing.

Results: Overall, 1276 consecutive cases where the OCAv3 lung NGS panel was used were included. Demographics: 42% male; median age 69 years; 90% adenocarcinoma; 48% stage 4 at time of testing. Of the 1276 cases, the sample was insufficient, or the test failed in 88 (6.9%) cases. The rates of AGAs are shown in Table 1, overall and by early vs advanced stage. PDL1 was tested in 1218 cases (95.4%), of whom 437 (34.3%) were PDL1 <1%, 356 (27.9%) were PDL1 1-49%, and 425 (33.3%) were PDL1 >=50%, There were single cases with NRG1 , PTEN and NTRK.

Conclusions: In this large QI series, we broadly identified AGAs at an anticipated rate, although the rates of ALK and ROS1 fusions are slightly lower than in other published series. This data will inform clinical trial portfolio planning. Ongoing work will look at how many patients received appropriate targeted therapy, and survival outcomes.

Table

Mutation	Number of cases in entire cohort (n=1276)	% overall	Number (%) stage 1-3	Number (%) stage 4
EGFR mutations				
EGFR (all types)	181	14.1%	81 (44.8%)	100 (55.2%)
Common EGFR	134	10.5%	64 (47.7%)	70 (52.2%)
EGFR exon 19 del	74	5.8%	37 (50%)	37 (50%)
EGFR L858R	60	4.7%	27 (45%)	33 (55%)
Atypical EGFR	34	2.6%	10 (30.3%)	24 (72.7%)
EGFR exon 20	13	1.0%	7 (53.8%)	6 (46.2%)
Non-EGFR mutations				
MetEx14	33	2.6%	13 (39.4%)	20 (60.6%)
KRAS G12C	209	16.4%	113 (54.1%)	96 (45.9%)
KRAS (non-G12C)	299	23.4%	168 (56.2%)	129 (43.1%)
BRAF V600E	20	1.6%	12 (60%)	8 (40%)
BRAF (non-V600)	55	4.3%	30 (54.4%)	25 (43.6%)
Her2 mutation	18	1.4%	10 (55.6%)	8 (44.4%)
PIK3CA mutation	36	2.8%	16 (44.4%)	20 (55.6%)
Fusions				
ALK fusion	27	2.1%	7 (26%)	20 (74%)
RET fusion	16	1.3%	5 (31.2%)	11 (68.8%)
ROS1 fusion	9	0.7%	4 (44.4%)	5 (55.6%)

Note: NRG1 fusions, PTEN mutations and NTRK fusions were identified in 1 patient each in this cohort.

Keywords: NSCLC, NGS, Mutations

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.55 Racial Differences in ERBB2 Mutations in Lung Adenocarcinoma: Insights From a Multi-Cohort Study

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Introduction: ERBB2 (HER2) mutations, particularly exon 20 insertions, are increasingly recognized as key oncogenic drivers in lung adenocarcinoma. However, racial variations in mutation prevalence and subtype distribution, especially between Asian and Western populations, remain poorly characterized. This study examines ERBB2 mutation profiles across racial groups in a multi-cohort dataset.

Methods: Whole-exome sequencing data from 380 lung adenocarcinoma patients (72% Asian) were analyzed. ERBB2 mutations were identified in 9 patients (detection rate: 2.3%), including 3 from Taiwan. Mutation subtypes (exon 20 insertions vs. S310F/Y), co-occurrence with EGFR and KRAS mutations, and racial background (Asian vs. non-Asian) were evaluated using descriptive statistics.

Results: Among ERBB2-mutated cases, 88.9% were EGFR/KRAS wild-type, confirming ERBB2 as an independent driver. Exon 20 insertions predominated (66.7%), with 50% occurring in Taiwanese patients, despite Taiwan comprising only 33.3% of the cohort. S310F/Y mutations (22.2%) exceeded global averages. Asians, constituting 66.7% of ERBB2-mutated cases, reflected higher mutation rates in East Asian populations.

Conclusions: Exon 20 insertions are the dominant ERBB2 mutation subtype in lung adenocarcinoma, with potential enrichment in Taiwanese patients, suggesting racial disparities. The elevated S310F/Y frequency merits further study. Larger multi-ethnic cohorts are essential to confirm these trends and guide targeted therapies.

Keywords: ERBB2, Race, lung adenocarcinoma

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.56 Genomic and Immune Characteristics Linked to Second-Line Combination Immunotherapy Outcome in EGFR-Mutated Advanced NSCLC

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Introduction: Immune checkpoint inhibitors (ICIs) combined with anti-angiogenic agents and chemotherapy have demonstrated safety and tolerability as second-line treatment options for patients with EGFR-mutated advanced NSCLC resistant to EGFR tyrosine kinase inhibitors. However, reliable predictive biomarkers of treatment outcome remain to be explored.

Methods: Eleven patients with EGFR-mutated advanced NSCLC were enrolled in this study. All patients received ICIs plus anti-angiogenic agents and chemotherapy as second line therapy following progression on EGFR-TKI treatment. FFPE biopsy tissue and peripheral blood samples were collected from all patients before initiating second-line treatment. Comprehensive genomic profiling of tissue and circulating tumor DNA (ctDNA) was performed using a panel of 437 cancer-related genes. Tumor-infiltrating immune cells were characterized using multiplex immunohistochemistry (mIHC).

Results: Of the ten patients with evaluable genomic characteristics, 100% had detectable EGFR mutations, predominantly 19del (40.0%) and L858R (50.0%) mutations. The remaining patient carried EGFR S768I and V769L mutations along with EGFR amplification. The most frequent concurrent genetic event detected in tumor samples was TP53 mutation (40.0%), followed by MYC amplification (20.0%) and SMAD4 mutation (20.0%). Notably, the presence of TP53 mutations was significantly associated with shorter progression-free survival (PFS) outcome (HR=8.25, P=0.028). A higher tissue mmVAF (minVAF/maxVAF) level (>0.3) was associated with longer PFS (HR=0.10, P=0.016). In contrast, in plasma ctDNA, a higher mmVAF was associated with shorter PFS (HR=6.99, P=0.039). Moreover, a high density of tumor-infiltrating CD56bright NK cells associated with longer PFS (HR=1.71E-10, P=0.003).

Conclusions: These findings highlight the potential of TP53 status, mmVAF and immune cell infiltration as biomarkers for guiding personalized treatment strategies in patients with EGFR-mutated advanced NSCLC undergoing second-line immunotherapy combined with anti-angiogenic agents and chemotherapy. Further validation in large cohorts is warranted to confirm these results and optimize therapeutic approaches.

Keywords: non-small cell lung cancer, combination immunotherapy, biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.57 Molecular Analysis of Driver Negative Lung Cancer for Rearrangements and Fusions Using a New HiC Sequencing Assay

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Introduction: Molecular testing in lung cancer has led to the identification of driver mutations that can be effectively targeted by new therapeutics. In addition to single point mutations that activate signaling proteins such as EGFR and KRAS, the presence of various fusion proteins that lead to protein overexpression and activation of key pathways have become prominent drug targets. Detection of these fusion proteins by FISH or sequencing is possible but may be limited due to changes in breakpoint regions, the panel may not target the fusion partner, or RNA expression may be affected by sample fixation or processing. This study aims to improve detection rate of targetable fusions and rearrangements in non-small cell lung cancer (NSCLC) using a new method called FusionPlus sequencing.

Methods: FusionPlus sequencing is a novel whole genome DNA-sequencing assay for detection of structural variation based on Hi-C chemistry method leveraging the sequencing of linked pairs of reads which occur nearby one another in 3-dimensional and linear space, from FFPE samples. Linking reads amplifies the rearrangement signal giving it much higher sensitivity. In previous studies, FusionPlus has been shown to detect gene fusions and rearrangements in many different tumor types missed by other clinical testing modalities such as FISH and RNA sequencing.

Results: In a pilot set of NSCLC samples, FusionPlus sequencing demonstrated 100% concordance with FISH and/or RNA sequencing results (10/10, including 4 ALK, 2 MET, 2 ROS, 1 NTRK, and 1 RET fusions). In this current study, we have examined 100 NSCLC FFPE specimens (25 complete, to date), which were previously determined by DNA and RNA sequencing to be negative for drivers such as EGFR and KRAS mutations and fusions of ALK, MET, NTRK, RET, and ROS. In the first 25 samples, we have detected eleven total rearrangements in FGFR1 (7), RAD51B (2), ERBB2 (1) and FGFR4 (1). We have also detected two amplifications, one MET and one KRAS. The other 75 samples have been sequenced and are currently being analyzed.

Conclusions: Encouraging results from this study suggest that FusionPlus sequencing may be a valuable tool in the molecular classification of lung cancers and could lead to improvement in patient care. FusionPlus can detect gene fusions and rearrangements that are known to drive cancer and may be used for therapy selection, including in cases which were negative by standard genetic testing.

Keywords: fusion, rearrangements, biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.58 CEACAM5 as a Biomarker for Differentiating Ground-Glass Opacities From Other Lung Cancers

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Introduction: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell adhesion molecule implicated in tumor cell migration, invasion, and resistance to apoptosis. Its role as a circulating biomarker in the form of CEA is well-established in some gastrointestinal malignancies. However, CEACAM5 is also overexpressed in approximately 25% of non-small cell lung cancer (NSCLC), particularly lung adenocarcinoma, yet its role as a biomarker and therapeutic target remains unclear. Previously, we demonstrated elevated CEACAM5 RNA expression in ground-glass opacities (GGO). In this study, using a separate patient cohort, we assess CEACAM5 protein expression as a potential biomarker for GGO compared to other solid NSCLC tumors.

Methods: CEACAM5 immunohistochemistry (IHC) was performed in a CLIA setting on surgically resected GGO (n=42) and NSCLC (n=200) with known clinical demographics and radiographic growth characteristics. Expression was quantified with standardized H-score by an expert thoracic pathologist and compared between GGO and solid NSCLC. Sub-group comparisons were also performed based on gender, smoking status, tumor histology, and tumor stage. GGO specimens underwent multiplex immunofluorescence (mIF) to characterize the immune microenvironment and quantify CD8+ and CD20+ immune cell infiltration to explore immune correlations with CEACAM5 expression.

Results: GGO exhibited significantly higher mean CEACAM5 expression than the overall NSCLC cohort (H-score:53vs27, P<0.001). This increase was also observed when comparing GGO to specific NSCLC subtypes including lung adenocarcinoma (n=57, H-score:53vs35, P=0.009), squamous cell (n=20, H-score:53vs5, P=0.003), and large cell carcinoma (n=10, H-score:53vs12, P=0.024). Among the adenocarcinoma cohort, stage 1 adenocarcinoma showed lower levels of CEACAM5 compared to stage 2-4 adenocarcinoma (H-score:28vs50, P=0.089). Among the GGO cohort, specimens with H-score≥100 exhibited a tumor microenvironment with higher density of PanCK+ tumor cells (5.5%vs2.2%, P=0.017)(Figure 1). Among patients with ≥2 documented preoperative CT scans, all GGO specimens with H-score≥100 (n=6) developed a new radiographic solid component compared to GGO with H-score<100 (100%vs38%, P=0.035).

Conclusions: Our findings demonstrate that CEACAM5 is significantly overexpressed in GGO compared to other forms of solid NSCLC, suggesting its potential utility as a biomarker for identifying and monitoring these lesions. Notably, within the GGO cohort, higher CEACAM5 expression was associated with increased tumor cell density and development of a new solid component on imaging. These findings provide insight into the biological significance of CEACAM5 in lung cancer evolution and its possible role in tumor progression. Future studies should explore the clinical utility of CEACAM5-targeted strategies for early detection of invasive lung cancer and lung nodule risk stratification.

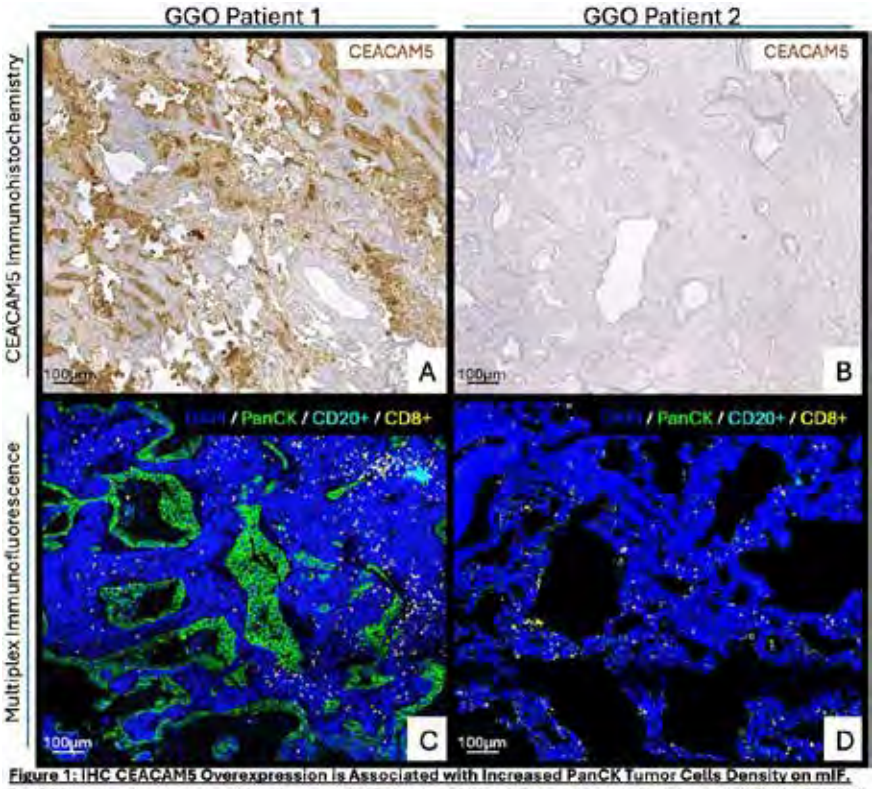

Figure 1: IHC CEACAM5 Overexpression is Associated with Increased PanCK Tumor Cells Density on mIF.
Two GGO specimens are represented by columns labeled Patient 1 and Patient 2. Top row is immunohistochemistry (IHC) with CEACAM5. The bottom row is multiplex immunofluorescence (mIF) for DAPI (all cell types), PanCK (malignant epithelial cells), CD8 (cytotoxic T cells), and CD20 (B cells). Increased CEACAM5 expression (Figure 1A) is associated with increased PanCK cell density (Figure 1C).

Keywords: Ground-Glass Opacities, CEACAM5, Biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.59 Dna+RNA-NGS Testing in NSCLC Patients With Primary Resistance to First-Line Non-Targeted Therapy and Negative Driver Genes (Dream Study)

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Introduction: Immunotherapy is the first-line standard treatment for advanced NSCLC patients with negative driver genes. However, primary resistance is relatively common. Gene fusion mutations are a key cause of this primary resistance. Research shows RNA-NGS has a higher gene fusion detection rate than DNA-NGS, effectively preventing fusion mutation miss-detection and helping identify therapeutic targets. This study enrolls NSCLC patients with DNA-NGS confirmed negative driver genes and primary resistance to first-line non-targeted therapy. Through DNA+RNA co-testing, it aims to determine the proportion of patients with poor first-line non-targeted therapy efficacy due to missed driver gene detection, especially fusion mutations. Driver gene positive patients can get targeted treatment, highlighting the importance of DNA+RNA co-testing for better NSCLC treatment and prognosis.

Methods: Research Design: The prospective study is divided into two parts. Part A collects samples from NSCLC patients whose driver genes are negative as detected by traditional DNA-NGS and who have primary resistance to first-line non-targeted therapy. These samples will undergo simultaneous DNA+RNA-NGS co-testing to analyze relevant proportions and characteristics. Part B enrolls patients with positive driver genes identified in Part A. According to patients' wishes, they are divided into a targeted therapy group and a non-targeted therapy group. Sample Selection: It is estimated that 508 cases will be included in Part A and 64 cases in Part B. Evaluation **Methods:** The primary research endpoints are the proportion of patients with positive driver genes redetected by DNA+RNA NGS co-testing and the objective response rate (ORR) of different treatment groups. Secondary and exploratory endpoints include the first-line median progression-free survival (PFS) of drug-resistant patients, clinical characteristics, and the impact of different factors on the testing. Statistical analysis will be performed using SPSS 26.0, and appropriate testing methods will be selected based on the data type.

Results: The main endpoints of this study are the proportion of patients with positive driver genes (especially fusion mutations) detected by simultaneous DNA+RNA-NGS co-testing and the ORR comparison in driver-gene-positive patients with or without targeted therapy. The further updated data will be presented at the Conference.

Conclusions: Through simultaneous DNA+RNA-NGS co-testing, it will be elucidated that in a subset of patients, suboptimal efficacy of first-line non-targeted therapies and compromised overall prognosis will be attributable to the failure to detect driver genes, particularly fusion variants.These findings provide a scientific rationale for the implementation of simultaneous DNA+RNA-NGS co-testing in NSCLC patients at the time of initial diagnosis.

Keywords: Immune resistance, Driver Gene, DNA+RNA NGS

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.60 Exploring the Role of the Oral Microbiome in Saliva Sputum Bronchoalveolar Fluid and Tissue Tumor in Lung Cancer a Systematic Review

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Introduction: To investigate the relationship between the oral microbiome and the development or progression of lung cancer (LC) using metagenomic sequencing techniques

Methods: Databases, including PubMed and EMBASE, were reviewed from January 2015 to July 2024. Eligible studies included investigations of oral microorganisms through genomic sequencing and the molecular mechanisms associated with lung cancer (LC) in saliva, sputum, bronchoalveolar lavage fluid (BALF), or tumor tissue from patients with LC. A quality analysis of the studies was conducted using the New Castell scale (NCS), and a qualitative synthesis was performed according to the localization and sample type

Results: Of the 1,880 scrutinized articles, 50 studies were selected, comprising 29 cross-sectional, 7 case-control, and 14 cohort studies. The quality analysis sheds light on potential biases. The findings revealed a conspicuous overgrowth of specific microbial taxa in the saliva and BALF samples of LC patients, including Veillonella and Streptococcus. However, Veillonella was associated with a better response to ICIs therapy. Conversely, samples from the Bacteroides genus, related to periodontal disease, exhibited no significant correlation with LC. Although oral microorganisms in the tumor tissue varied, their presence was associated with a poor prognosis in LC. However, Prevotella nigrescens was associated with longer PFS. Fusobacterium nucleatum had an inadequate response in ICs. Oral microorganisms are related to the biodegradation of xenobiotics, amino acid and sugar metabolism, including sucrose, as well as a proinflammatory environment that can inhibit the immune response and disrupt cellular redox homeostasis

Conclusions: The Overgrowth of certain oral microorganisms in saliva and BALF is associated with diagnosis, poor prognosis, and a low response to immunotherapy. Further, well-designed studies should evaluate the impact of the oral microbiome on the response to ICs

Keywords: Oral microbiome, Lung cancer, Metagenomic sequencing

EP.06 PATHOLOGY AND BIOMARKER

EP.06.61 FGRF-2: A Prognostic Biomarker and Potential Therapeutic Target in NSCLC

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Introduction: Fibroblast growth factors (FGFs) and their receptors (FGFR1-4) regulate a number of cellular processes and are known to be involved in tumorigenesis. The overexpression, amplification, mutation and fusion of FGFR genes in lung cancer are closely linked to tumor initiation, progression and resistance, suggesting that targeting the FGF-FGFR axis is an attractive therapeutic strategy for the treatment of lung cancer. Evaluating the efficacy and safety of selective FGFR inhibitors in lung cancer patients with FGFR abnormalities are currently ongoing. The development of novel FGFR2-targeted therapies hold promise for mitigating the toxicities and resistance reported with the use of small molecular inhibitors targeting FGFR-1 and FGFR-4. In this study, a role for FGFR-2 as a biomarker in NSCLC was examined.

Methods: Expression of total FGFR-2 and its isoform, FGFR-2b, was examined in a panel of 20 NSCLC cell lines by RT-qPCR. A tissue microarray (TMA) consisting of 209 surgically resected tumor tissues from NSCLC patients resected at St James's Hospital was generated. A cell line microarray (CMA) was also prepared which consisted of lung adenocarcinoma (H3122, H2228, H1975) and large cell lung carcinoma (H460) cells. Immunohistochemical (IHC) staining for FGFR-2 (Novus Biologicals, clone 1G3) and FGFR-2b (clone Fc-FGF1) was optimized using the Benchmark Ultra (Roche Diagnostics). Tissue staining was independently assessed and graded by a Consultant Histopathologist using the H-score (staining intensity × percentage cell positivity). FGFR-2 protein expression was correlated with demographic and clinicopathological parameters such as age, gender, histology, tumor grade, stage, smoking status and overall survival. Statistical analyses were performed using SPSS v26.0 or GraphPad Prism v6.01 statistical software.

Results: Total FGFR-2 and FGFR-2b were differentially expressed across different NSCLC cell line genotypes and histology. The lung adeno-squamous cell line, NCI-H596, expressed significantly higher levels of total FGFR-2 relative to the normal bronchial epithelial cell line, BEAS-2B ($p<0.001$). Of interest, FGFR-2b gene expression was increased by 40- and 70-fold in SNU2535 (ALK+) and H358 (KRAS, CTNNB1) cells, respectively ($p<0.001$). Immunocytochemical analysis of the CMA showed intense staining for FGFR-2 (H-score=300) in H3122 (ALK+) cells. Diffuse membranous and cytoplasmic FGFR-2 staining patterns were evident in NSCLC tissues, with notable positive staining of lung alveolar macrophages. Optimization of FGFR-2b staining was unsuccessful using different antibody clones. FGFR-2 expression was significantly higher in females vs. males ($p<0.05$), between adenocarcinoma (ADC) tissue vs. squamous cell (SqCC) tissue ($p<0.001$) and in non-smokers compared to current ($p<0.01$) or former smokers ($p<0.01$). There were significantly higher levels of FGFR-2 in stage I, II and III lung tumors relative to stage IV ($p<0.05$) and in patients with N0 vs. N1 disease ($p<0.05$). NSCLC patients with ADC histology and high FGFR-2 expression had worse 5-year ($p=0.20$) and overall survival ($p=0.40$) outcomes. Similar findings were found at 5-year ($p=0.09$) and overall survival ($p=0.05$) in patients with SqCC tumors expressing high levels of FGFR-2.

Conclusions: These data provide evidence for the potential use of FGFR-2 as a prognostic biomarker for enabling better patient selection in future clinical trials for novel FGFR-2 targeted therapies.

Keywords: FGFR2, Tissue, Biomarker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.62 Based on Labyrinth Microfluidic Chip in Evaluating Therapeutic Efficacy for Leptomeningeal Metastasis of Lung Cancer

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Introduction: The assessment of therapeutic efficacy for leptomeningeal metastasis (LM) in lung cancer relies on the RANO criteria, yet its clinical utility remains limited. Cerebrospinal fluid (CSF) circulating tumor cells (CTCs) may serve as a real-time biomarker to overcome current limitations. This study evaluates the clinical value of the Labyrinth microfluidic chip in isolating and analyzing CTCs, aiming to explore its feasibility for efficacy assessment.

Methods: A prospective study enrolled six LM patients (cytologically confirmed) from the Second Affiliated Hospital of Nanchang University (January-December 2024). All patients received systemic therapy and intrathecal chemotherapy. The Labyrinth chip dynamically quantified CTCs in CSF samples collected pre-treatment, post-treatment cycles, and at progression. CTC dynamics were compared with RANO criteria for consistency.

Results: Among six patients (5 males, 1 female; median age 59.5 years), Patient 1 achieved partial response (PR) after three intrathecal pemetrexed cycles (CTCs decreased from 312 to 0.4 cells/mL). On February 22, CTCs rebounded to 5 cells/mL but stabilized (stable disease, SD at 0.6 cells/mL) after combined fumetinib therapy by May 28. Patient 3 exhibited initial CTCs of 1,651.8 cells/mL post-chemotherapy. Upon progression (PD on May 9, CTCs: 2,693.4 cells/mL), afatinib combined with bevacizumab reduced CTCs to 294.6 cells/mL (PR by July 11), followed by PD on July 30 (CTCs surged to 3,318.6 cells/mL). CTC dynamics provided an average 14-day earlier warning of progression compared to RANO criteria.

Conclusions: The Labyrinth microfluidic chip enables precise CTC quantification in CSF, offering a novel approach for early therapeutic efficacy assessment in lung cancer LM.

Keywords: Therapeutic monitoring, Cerebrospinal fluid circulating tumor cells, Leptomeningeal Metastasis

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.63 New Approaches for Enhancing the Efficacy of "Liquid Biopsy" in Non-Small Cell Lung Cancer

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Introduction: "Liquid biopsy" is a modern technology for diagnosing various molecular-genetic abnormalities in tumors. The main drawback of currently used cfDNA analysis methods is their low diagnostic sensitivity. There are numerous approaches aimed at improving this parameter: increasing the volume of analyzed blood plasma, enhancing coverage in NGS studies, and employing technologies with high analytical sensitivity (Beaming-PCR). However, the use of expensive technologies significantly raises the overall cost of ctDNA analysis. One of the alternative approaches aimed at increasing the levels of ctDNA in the bloodstream of patients may be a single irradiation of tumor sites, leading to the massive apoptosis of malignant cells. The aim of current study is to enhance the effectiveness of ctDNA detection in patients with lung cancer.

Methods: The study will include 40 patients with III-IV st. NSCLC (adenocarcinoma and squamous cell lung cancer) who will undergo a standard radiotherapy (III st.) or single local irradiation of the tumor site at a dose of 4 Gy (IV st.), as well as 20 patients in the control group. Plasma samples (8 ml) will be collected at the following time points: before irradiation and 6, 12, 24, and 48 hours after. ctDNA analysis will be conducted using droplet digital PCR, targeting pathogenic variants in the EGFR, KRAS, BRAF genes, and methylation of the promoter region of the RASSF1A gene. If a statistically significant increase in ctDNA concentration will be detected during a specific time point, an additional 5 pts with NSCLC progressed on therapy with EGFR inhibitors (Erlotinib, Gefitinib) and negative for EGFR T790M in plasma will be included. The study protocol has been approved by the Ethics Committee of the N.N. Alexandrov National Cancer Centre of Belarus.

Results: Currently, 29 patients with NSCLC have been included in the study, and patient recruitment is ongoing. The concentration of ctDNA has been assessed in 11 patients with NSCLC. Before irradiation ctDNA was detected in 82% of cases with an observed increase in cfDNA levels in the bloodstream after irradiation in 91% of cases. CtDNA was detected in 100% of cases at the 6 and 48-hour time points.

Conclusions: We expect to obtain data that will improve ctDNA diagnostics in patients with NSCLC. The study will determine the feasibility of using single local irradiation of tumor sites in patients with NSCLC to induce cfDNA release into the bloodstream. Successful outcomes could enhance the diagnostic sensitivity of tests for detecting the T790M mutation in ctDNA from patients undergoing EGFR inhibitor therapy.

Keywords: NSCLC, ctDNA, Irradiation

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.64 ISET CTC-DNA shows higher sensitivity then ctDNA in early stage lung cancer patients

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Introduction: Lung cancer (LC) is a leading cause of cancer deaths in the world. Early detection of lung cancer can reduce mortality, as demonstrated by low-dose computed tomography (LDCT) screening. However, there is a need to complement LDCT screening to increase adoption, reduce patients' exposure to radiation and increase specificity/sensitivity. Several molecular approaches have been developed for non-invasive early-stage detection of LC based on the analysis of circulating tumor DNA (ctDNA), however, this marker is barely detectable and present in very small quantities in the plasma of early-stage lung cancer patients.The present work explores the combined analysis of CTC (Circulating Tumor Cells)-DNA, extracted from blood using the hypersensitive ISET® platform from Rarecells, and ctDNA, extracted from plasma according to standard procedures.

Methods: We analyzed DNA extracted from the isolated CTC, plasma, tumor tissue, and leucocytes from 50 patients undergoing surgery for early stage lung cancer. Next Generation Sequencing was performed on all the DNA samples using a panel (Agilent Technologies, Inc.) targeting 983 regions from 53 target genes. Libraries were prepared with the SureSelectXT technology (Agilent Technologies, Inc.) following the manufacturer's instructions. Pairedend (2x111 bases) sequencing was performed on a MiSeq device (Illumina, Inc.).

Results: Direct comparison of tumor-tissue related variants detected in CTC-DNA, in corresponding cfDNA and paired primary FFPE tumor tissues from 6/6 cases clearly show increased number of tumor-tissue related variants in CTC-DNA as compared to cfDNA.

Conclusions: (Preliminary): These preliminary results, if confirmed by the coming data from the whole cohort, suggest that CTC-DNA obtained with an hypersensitive approach could improve early stage lung cancer detection and early lung cancer recurrence detection by increasing the sensitivity of ctDNA-based results.

Note: Further updated data from the 50 patients included in the study will be presented at the Conference.

Keywords: Liquid Biopsy DNA Markers, Lung Cancer, Early Detection

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.65 Mosaic Chromosomal Alterations and the Risk of Incident Lung Cancer: A Systematic Review and Meta-Analysis

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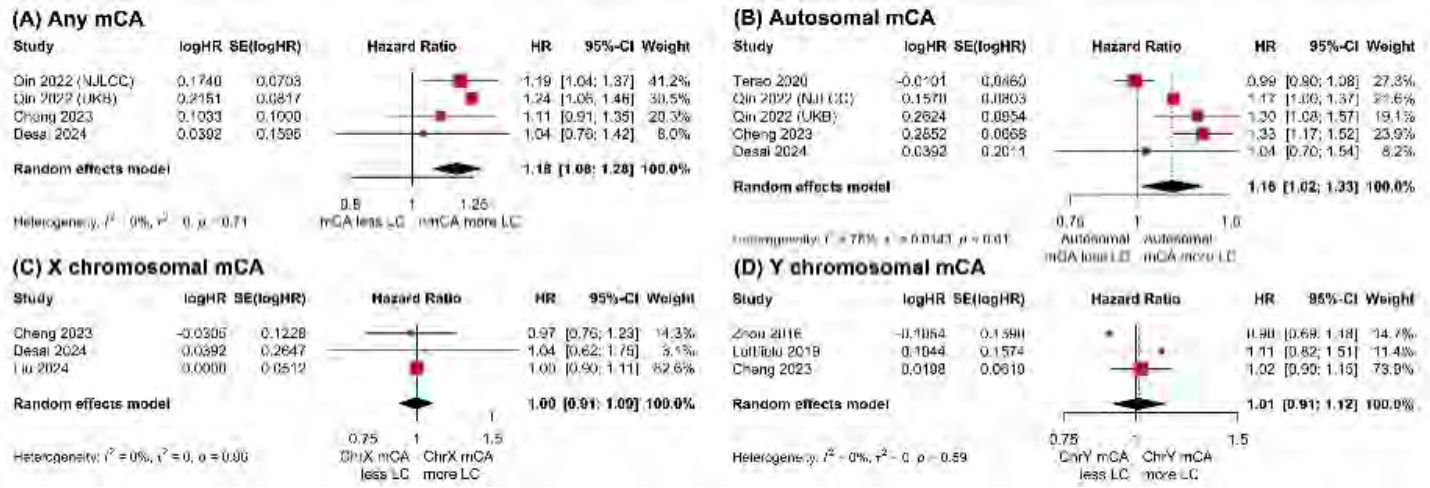
Introduction: Mosaic chromosomal alterations (mCA) are somatic alterations in hematopoietic stem cells designated by large-size chromosome loss, gain, or copy-neutral loss of heterozygosity, whose prevalence increases by age. Despite the presence of mCA being associated with an elevated risk of developing hematologic cancers, the data on mCA and incident lung cancer risk are still conflicting. We aim to evaluate the risk of developing lung cancer in individuals harboring mCA.

Methods: All articles related to mCA and lung cancer were retrieved from Embase and Medline databases from inception to February 2025. Eligible studies must be cohort studies that evaluated mCA status upon study entry, then compared lung cancer incidence among individuals with mCA and those without. All participants in the study must not have prior lung cancer diagnoses. Hazard ratios (HR) or odds ratios (OR), along with their 95% confidence intervals (CI), were extracted and combined using the generic inverse variance method. We also performed subgroup analyses based on the type of chromosome alteration (autosomal vs X chromosome (ChrX) vs Y chromosome (ChrY)). All statistical analyses were performed in R version 4.3.2.

Results: In total, seven studies were included in the meta-analysis: four for autosomal mCA in both sexes, three for ChrX mCA in females, and three for ChrY mCA in males. mCA was associated with an increased incidence of lung cancer (HR 1.19, 95% CI 1.08-1.28), especially in those with autosomal mCA (HR 1.16, 95% CI 1.02-1.33; Figure 1A-B). However, sex chromosome mCA was not associated with incident lung cancer (HR 1.00, 95% CI 0.91-1.09 and 1.01, 95% CI 0.91-1.12 for ChrX and ChrY mCA, respectively; Figure 1C-D).

Conclusions: The occurrence of mCA was associated with an elevated risk of incident lung cancer and was mainly driven by autosomal mCA, but not those involving sex chromosomes mCA. This observation might result from the limited number of major oncogenes or tumor suppressor genes on the sex chromosomes that are associated with lung carcinogenesis. mCA detection may serve as a valuable tool for lung cancer risk stratification, and further studies to validate this role are sought.



Keywords: mosaic chromosomal alteration, lung cancer, risk factor

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.66 Prediction of Immune-Related Adverse Events by Human Leukocyte Antigen (HLA) and Other Biomarkers in Patients With Non-Small Cell Lung Cancer

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Introduction: Immune-related adverse events (AEs) in patients (pts) with non-small-cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs) lead to treatment interruptions and toxic deaths. The mechanisms responsible for their occurrence are unknown and biomarker research is needed to help us reduce the associated morbidity and mortality. The association between HLA-I and autoimmune diseases has been described, and recent studies seem to find a similar association between HLA-I and irAEs.

Methods: We analyzed the clinical characteristics of 233 patients with stage IV NSCLC receiving ICIs monotherapy (antiPD1/PDL1) in first or second line at our center between 2018-2024. In addition, a high-resolution HLA-I assay was performed in 75 pts. The impact of clinical and pathological variables affecting the risk of developing irAEs was assessed using a univariate and multivariate logistic regression model and Fisher's test was used to analyze the association between HLA-I zygosity and HLA-I types with irAEs.

Results: 57 pts (24.5%) presented possible irAEs (28.5% grade >= 3). 6.4% discontinued ICIs definitively due to toxicity. The most frequent irAEs were skin toxicity (26.3%), endocrinopathies (19.3%), pneumonitis (15.3%) and arthritis (10.2%). The median time to onset of irAEs was 146 days. Homozygosity at one or more HLA-I loci was not associated with a lower risk of irAEs (p= 0.7). Patients with HLA C*06:02 were associated with an increased risk of endocrinopathy (p=0.036) and HLA C*05:01 with skin toxicity (p=0.04). After multivariate analysis in the total sample, irAEs were associated with a higher % PDL1 expression (OR 1,02 95% CI (1-1,036) p=0,04) and a lower neutrophil-to-lymphocyte ratio baseline (OR 1,19 95% CI (1,03-1,39) p= 0,02). Finally, we found an association between irAEs and the clinical benefit of treatment (partial response + complete response + stable disease) (p<0,001)

Conclusions: irAEs could be related to low NLR and expression of PDL-1, in addition to some HLA-I types seem to be related to the presence of irAEs. Further studies with more patients in our setting would be necessary to corroborate our findings.

Keywords: HLA, irAEs, NSCLC

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.67 Longitudinal ctDNA Profiling in HER2-Altered NSCLC Treated With HER2 Adc: Preliminary Results From the RESOLUTION Trial

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Introduction: Circulating tumor DNA (ctDNA) testing offers a non-invasive approach to identify actionable genetic alterations and monitor treatment response in advanced non-small cell lung cancer (NSCLC). In patients with HER2-mutant NSCLC, ctDNA profiling enables dynamic assessment of tumor burden and molecular changes, supporting more precise therapeutic decision-making. RC48, a novel antibody-drug conjugate (ADC) targeting HER2, has demonstrated promising anti-tumor activity in various solid tumors. ctDNA-guided strategies may enhance the clinical utility of ADCs like RC48, particularly in the context of combination regimens with immunotherapy or anti-angiogenic agents. Further investigation is warranted to explore ctDNA-informed treatment approaches in HER2-altered NSCLC.

Methods: RESOLUTION is a single-arm, phase II clinical trial investigating the efficacy and safety of a novel combination therapy in treatment-naïve patients with locally advanced or metastatic NSCLC harboring HER2 alterations. A total of 28 eligible patients will receive disitamab vedotin (2.0 mg/kg), tislelizumab (200 mg), and bevacizumab (7.5 mg/kg), all administered intravenously every 3 weeks, until disease progression or unacceptable toxicity. To enable non-invasive, real-time monitoring of tumor dynamics, longitudinal circulating tumor DNA (ctDNA) testing is incorporated as a key exploratory component of the trial. Peripheral blood samples are collected at baseline (C1D1), on-treatment (C3D1, C5D1, C7D1, and C10D1), and at the time of disease progression (PD). ctDNA profiling is performed using PredicineCARE, a targeted next-generation sequencing (NGS) assay covering 152 cancer-related genes, and PredicineEPIC, a genome-wide methylation assay. These assays are employed to characterize mutation and methylation patterns in ctDNA, enabling the evaluation of molecular response and potential mechanisms of resistance throughout the course of treatment.

Results: From April 2024 to January 2025, 11 patients were enrolled in the study, and 9 patients were evaluable for efficacy. Among these patients, 3(33.3%) achieved a partial response and 6(66.6%) had stable disease. The confirmed ORR was 33.3%, and the median duration of response was 5.1 months.A total of 29 blood samples from 9 patients were analyzed using the PredicineCARE assay. Across all samples, the assay detected 167 mutations and 148 copy number variations (CNVs). At baseline, 56 mutations and 79 CNVs were identified. The most frequently altered genes at baseline (>50% of patients) were ERBB2 (7/9), TP53 (7/9), and AKT3 (5/9). Tumor fractions were estimated based on the allele frequencies of detected mutations in each sample. A reduction in tumor fraction was observed at C3D1 in 5 of 9 patients, while the remaining patients maintained stable levels. Notably, an increase in tumor fraction was detected as early as C5D1 in 6 patients, which was concordant with and preceded clinical progression. Methylation analyses are currently ongoing.

Conclusions: Our result suggested the combination therapy is a promising treatment strategy for NSCLC with HER2 alteration. The first-stage interim analysis revealed acceptable efficacy to support proceeding to the further stage. Longitudinal ctDNA analysis enabled dynamic monitoring of tumor burden and early detection of disease progression, underscoring its potential as a non-invasive tool for real-time treatment response assessment.

Keywords: HER2-ADC, ctDNA, Longitudinal Monitoring

EP.06.68 Clonal Hematopoiesis (CH)-Derived Mutations Detected in Non-Small Cell Lung Cancer (NSCLC) Liquid Biopsies (LBx)

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Introduction: CH results from fitness-enhancing mutations in hematopoietic stem cells. Although many CH mutations are in hematological driver genes, some occur in genes with solid tumor relevance (e.g. TP53, ATM, CHEK2). We report the prevalence of CH mutations in genes relevant to NSCLC.

Methods: For LBx from 762 patients with NSCLC, plasma cell-free DNA and white blood cell (WBC) DNA were sequenced in parallel at equal depth on the FoundationOne®Liquid CDx platform. A variant origin prediction (VOP) algorithm leveraging fragmentomics and other features, trained and validated using WBC, was used to classify mutation origins in 21,456 additional NSCLC LBx.

Results: In the WBC-sequenced cohort (N=762), CH mutations in EGFR were detected in 2 (0.3%) samples (T415K and V843I), in BRAF in 3 (0.4%) (T244P, K499Q, D594N), and in KRAS in 4 (0.5%) samples (G12D, V14I, I24N, A59G). Established driver mutations were detected as tumor-somatic [EGFR in 86 (11.2%) (L858R, exon19 deletions, exon20 insertions, G719X, S768I, L861Q), ERBB2 in 9 (1.2%), BRAF V600E in 8 (1.0%), and MET exon14 skipping in 8 (1.0%)]; none of these were CH. CH mutations in genes with emerging clinical implications in NSCLC were detected at low frequencies: 16 (2.0%) NF1, 4 (0.5%) TP53 Y220C and RB1, and 1 (0.1%) KEAP1 and SMARCA4. For the VOP cohort (N = 21,456), Figure 1 shows the prevalence of predicted CH origin mutations in relevant genes. Figure 2 shows the predicted tumor-somatic versus CH origin distribution of specific variants in KRAS, EGFR, and BRAF.

Conclusions: CH does not appreciably confound detection of established targets in NSCLC LBx. However, emerging targets such as TP53 Y220C, BRAF nonV600E, and SMARCA4 mutations may be CH-derived in some LBx and ruling out CH origin via tissue testing, equal depth WBC sequencing, or algorithmic prediction of origin may be advisable.

Figure 1 Prevalence of predicted CH origin of NSCLC targetable variants and emerging targets in 21,456 LBx

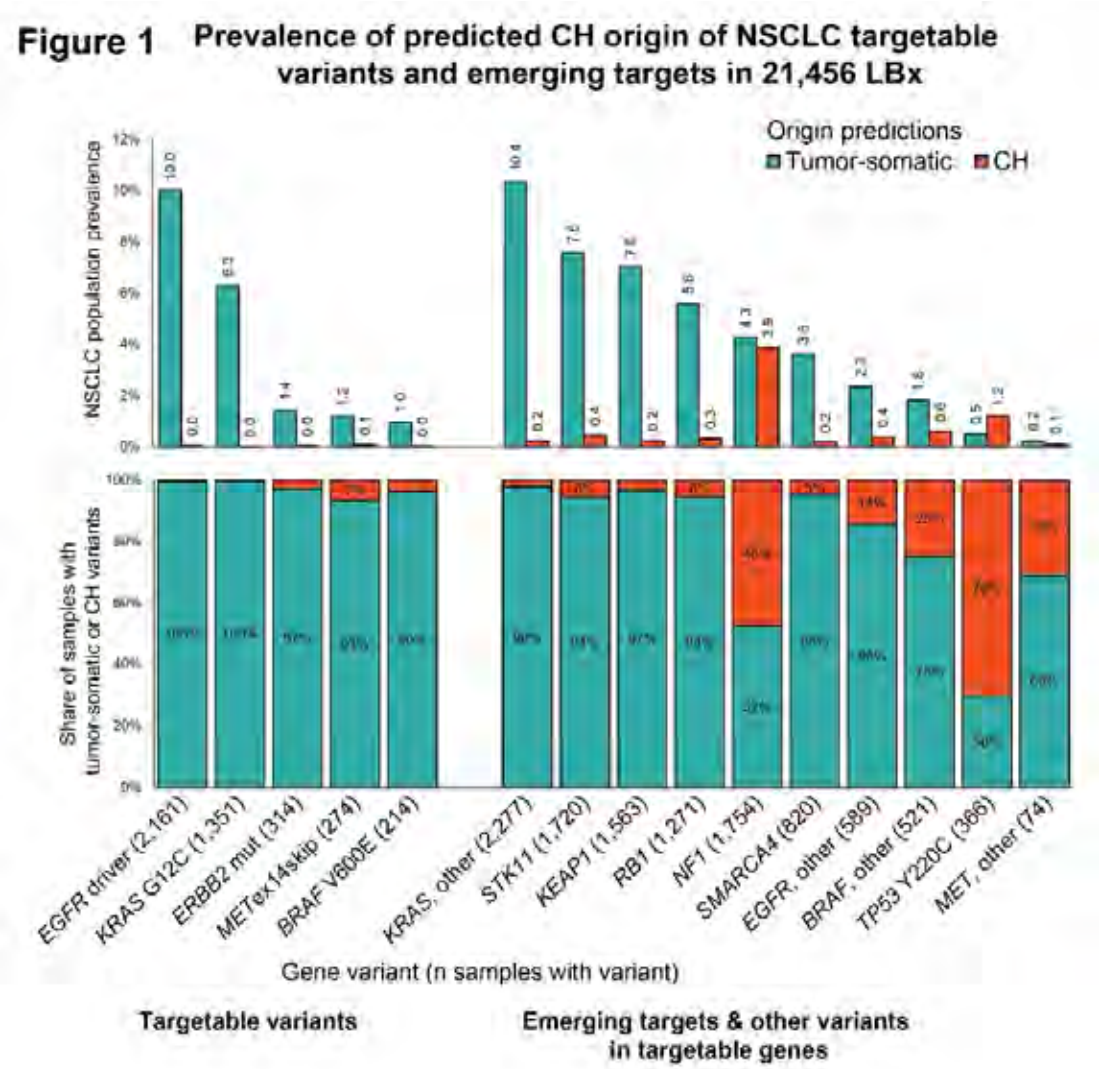
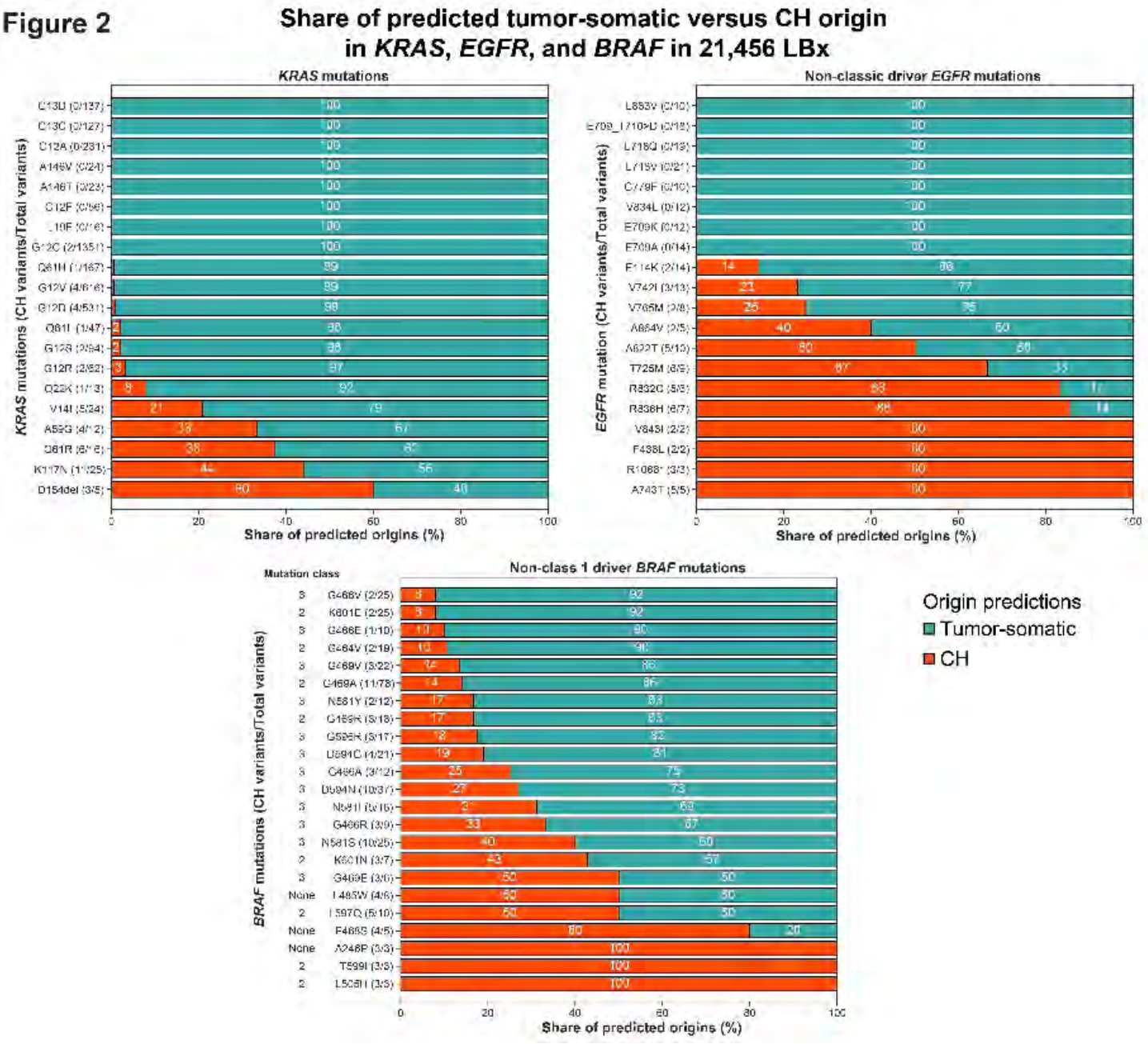


Figure 2



Keywords: Clonal hematopoiesis, Liquid biopsy, Precision medicine

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.69 Real-World Utilization of Tissue-Free ctDNA Monitoring in Patients With Lung Cancer on Targeted Therapies +/- Chemotherapy

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Introduction: Evidence increasingly supports utilizing circulating tumor DNA (ctDNA) monitoring for early treatment response and emerging resistance in patients with advanced or metastatic disease receiving targeted therapy (TT). However, little is known about the real-world utilization of ctDNA monitoring in this setting. Here we describe the use of a tissue-free ctDNA monitoring assay in patients with lung cancer receiving TT.

Methods: The clinical laboratory developed test, FoundationOne®Monitor, was available on a limited pilot to 90 physicians familiar with liquid biopsy to use in their practice. The schedule and number of tests were at the physician's discretion. Enrollment was on a rolling basis. Current/planned therapy abstraction was requested but not required. ctDNA was detected and quantified by ctDNA tumor fraction (TF), and variants were tracked with variant allele frequency (VAF).

Results: Across multiple US oncology practices, 34 physicians ordered FoundationOne®Monitor for lung cancer patients between 09/30/2024-02/17/2025. A total of 535 tests for 349 patients were ordered, with 526 tests (98.3%) yielding results and a median turnaround time of 8 days. Therapies were abstracted for 193 patients and included 59 (31%) TT and 11 (6%) chemotherapy+TT (chemo+TT). 3 patients switched to or added TT, and 8 switched away from TT or removed TT from chemo+TT during testing. At data cutoff, the median time on the pilot was 46.5 days (interquartile range [IQR]: 29.3-65). Restricting to patients enrolled ≥65 days to allow for serial monitoring (n=179), the median number of tests per patient was 2. The median interval between first and second tests was 51 days (IQR: 35-72) and was similar among patients receiving TT or chemo+TT. The median cadence of serial testing (3+ tests, n=42 patients) was 33.3 days (IQR: 27.8-42). Patients receiving TT (n=13) or chemo+TT (n=2) had similar cadence. Among patients receiving TT or chemo+TT, the range of ctDNA TF across all timepoints was 0-43% with 0.19% being the lowest detected value. The lowest known/likely pathogenic, targetable variant VAF detected was 0.06%. 28.6% (12/42) of patients exhibited dynamic ctDNA TF throughout testing (timepoint results: newly detected TF: 4; increase: 5; <50% decrease: 1; >=90% decrease: 3; clearance: 7). Of patients with ctDNA TF detected, 31.6% (6/19) cleared ctDNA TF in a median of 46.5 days from the first test, all but 1 receiving TT alone. A total of 298 unique known/likely pathogenic alterations were detected. Changes in ctDNA TF, copy number alterations, and VAF of target genes were complementary. New variants emerged after the first test in 23 patients. Emergence of new known/likely pathogenic variants co-occurred with increased or stable ctDNA TF in 30.4% (7/23) of patients with new emerging variants and included known resistance alterations. When new variants emerged while ctDNA TF decreased, variants were in known clonal hematopoiesis-associated genes.

Conclusions: ctDNA-based monitoring at the discretion of physicians across US-based institutions indicated a preference for monitoring every 4-6 weeks across lung cancer subtypes and therapy classes. Among patients receiving TT or chemo+TT, dynamic changes in ctDNA TF and detected variants were observed that informed response and interpretation of imaging.

Keywords: targeted therapy, circulating tumor DNA, tumor fraction

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.70 Development and Clinical Application of Ultra-Sensitive Digital EV Assay Targeting GLUT1 for Early Diagnosis of Non-Small Cell Lung Cancer

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide. The five-year survival rate for lung cancer patients diagnosed at an advanced stage is dismal; however, early detection significantly improves clinical outcomes. In this study, we have developed a novel liquid biopsy method for the early diagnosis of non-small cell lung cancer using intratumoral extracellular vesicles (EVs) extraction technology and an ultrasensitive digital EV assay (UDA). UDA captures target EVs by coupling magnetic beads with capture antibodies and detection antibodies and then enhances the fluorescent signal with tyramide and detects them by flow cytometry. This is an assay that achieves ultrasensitive results that surpass those of conventional ELISA.

Methods: We extracted intratumoral EVs from four lung adenocarcinoma and squamous cell carcinoma specimens from surgical cases at our hospital, and four normal lung specimens from the same patient, and performed proteomic analysis using 10 plex TMT labeling together with two lung cancer cell line EVs. We also integrated lung cancer gene expression data from The Cancer Genome Atlas (TCGA) and predicted location data from the Human Protein Atlas (HPA) to identify candidates for lung cancer-specific EV surface proteins. We also performed UDA targeting candidate proteins using patient plasma.

Results: Proteomic analysis of intratumoral EVs detected 1653 proteins. Using these, PCA analysis made it possible to distinguish between lung cancer and normal lung. By calculating the fold change between lung cancer and normal lung from tissue EVs and TCGA data and comparing the two data, 50 common proteins were detected, and further integrating HPA data, GLUT1 was identified as a lung cancer-derived EV surface protein. UDA targeting GLUT1 was performed using 38 lung cancer plasma samples and 9 non-cancer plasma samples from our department, and ROC analysis was performed, resulting in an AUC of 0.776. When this was analyzed in combination with CEA and CYFRA, the AUC was 0.860. In the study of stage I lung cancer, UDA alone showed an AUC of 0.833, and when combined with CEA and CYFRA, the AUC was 0.883.

Conclusions: By combining tissue EV analysis and UDA, we have developed an innovative liquid biopsy method that targets previously unknown extremely low-abundance EV surface proteins. We will continue to utilize this liquid biopsy method to develop biomarkers that contribute to early diagnosis and precision medicine for lung cancer.

Keywords: Ultra-sensitive digital EV assay, GLUT1, Early diagnosis

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.71 Clinical Application of Expert Software Based on Tumor Biomarkers to Stratify Lc-Risk in a Hospital Thoracic Tumor Committee

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Introduction: Lung cancer (LC) is responsible for 1.8 million deaths annually. While low-dose computed tomography (LDCT) aids early detection, its availability is limited. Tumor biomarkers (TBs) provide a complementary diagnostic tool, though their optimal combination remains uncertain. We collaborated with Dr. Molina's group to develop an expert software to interpret TB panels. This study evaluates the effectiveness of the expert software "CLAUDIA", enhancing clinical decision-making in the Thoracic Tumor Committee.

Methods: A prospective study was conducted at Macarena University Hospital, including all patients evaluated by the Thoracic Tumor Committee for suspected LC in 2023. Patients were assessed following international guidelines. TB levels were measured and analyzed using CLAUDIA, an expert software trained on over 5,000 cases. The software classified the LC risk as high, moderate, or low. With moderate-risk cases, we recommend reanalyzing after 3-4 weeks. The software's reports were compared with final histopathological diagnoses, classified per WHO 2015 guidelines. Serum TB concentrations were measured using electrochemiluminescent assays.

Results: Among 138 cases assessed, 16 patients with renal failure were excluded as it may interfere with TB levels. Of the remaining 122 patients, 89 (73%) were diagnosed with cancer: 32 (36%) adenocarcinomas, 22 (25%) squamous cell carcinomas, 17 (20%) nonspecific NSCLC cases, and 12 (13%) small cell carcinomas (SCLC) (6 other histologies). Radiographic nodules were the primary diagnostic trigger. The CLAUDIA software correctly identified 89.57% of cases, showing a Sensitivity: 91%, Specificity: 84.6%, positive predictive value: 95.3% and negative predictive value: 73.3%. 12 patients were classified as moderate risk, of which 4 were finally no cancer and 8 LC. In addition to the risk of LC, the software suggests the most likely histological subtype taking into account the different TB expression patterns. The percentage of success in discriminating between SCLC and NSCLC was 99%.

Conclusions: This study confirms the effectiveness of a six-TB panel (CEA, CA 15-3, SCC-Ag, CYFRA 21-1, NSE, and ProGRP) combined with CLAUDIA software in diagnosing LC. The software enhances diagnostic accuracy (89,5%) and facilitates rapid decision-making, improving patient care. CLAUDIA provides a valuable tool for risk stratification and clinical decision support, particularly in Rapid Diagnostic Units.

Keywords: Tumor Biomarkers panel, Lung cancer diagnosis., Expert software

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.72 Lung Cancer EGFR Mutation Prediction via cfDNA Fragmentome Profiling

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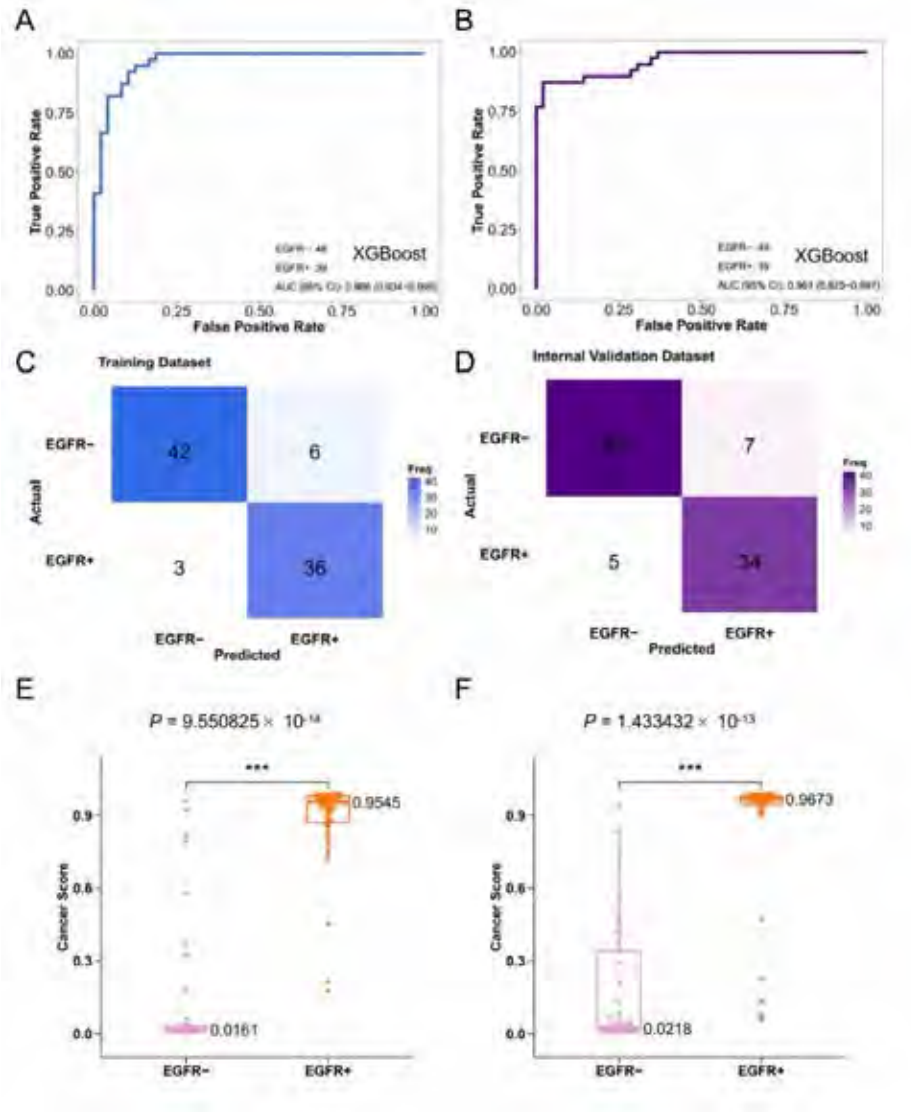
Introduction: Lung cancer is a leading cause of cancer-related deaths worldwide, and early detection of EGFR mutations has become one of the key indicators in lung cancer gene alterations. cfDNA (Circulating free DNA) is a novel biomarker that enables non-invasive detection of tumor-related mutations through blood samples. This study combines cfDNA sequencing technology with various machine learning models to explore the EGFR mutation prediction.

Methods: We enrolled 175 early lung cancer patients and analyzed their plasma cfDNA samples using whole-genome sequencing (WGS). In the training cohort, multiple features were extracted, including fragment length, 3' end motif, methylation motif, N-index, E-index, and CNV, which were used as input features for analysis. We predict EGFR mutation-positive population using generalized linear models (GLM) and support vector machines (SVM), while also combining XGBoost models. We conducted extensive evaluation on the validation dataset. By comparing the predictions of different models, we were able to validate the accuracy, sensitivity, specificity, and generalizability of these models in EGFR mutation prediction, thus providing strong data support for clinical application.

Results: This study employs deep learning algorithms to conduct multimodal integrated analysis of cfDNA molecular omics, copy number variations, and epigenetic characteristics, aiming to achieve the precise prediction of EGFR mutation. Through the analysis of relevant features, differences were revealed in various features, including terminal motifs and breakpoint features. The EGFR mutation prediction model built based on these features showed excellent performance in the training set (n = 87, specificity 87.5%, sensitivity 92.3%, AUC: 0.966) and maintained consistency in the validation cohort (n = 88, specificity 65.3%, sensitivity 97.4%, AUC: 0.953).

Conclusions: This study developed a deep learning model based on cfDNA multi-dimensional omics features, focusing on the precise analysis of EGFR mutation prediction. This approach provides a highly sensitive, non-invasive solution for early detection of EGFR mutation.



Keywords: blood omics, machine learning, EGFR mutation

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.73 Co-Driver Mutations in Fusion-Positive NSCLC: Liquid Biopsy Insights From 2,369 Patients

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Introduction: While kinase fusions represent established therapeutic targets in non-small cell lung cancer (NSCLC), the co-occurrence of additional driver mutations may influence treatment response and resistance mechanisms. This study characterizes the landscape of co-driver mutations across different fusion architectures in ALK, RET, and ROS1 fusion-positive NSCLC from liquid biopsy.

Methods: Comprehensive genomic profiling of 2,369 lung cancer patients with fusion genes was performed using liquid biopsy (Guardant360) from October 2016 to September 2022. Patients were stratified by primary driver (ALK: n=1,506; RET: n=594; ROS1: n=269) and fusion architecture: nonreciprocal fusions (NRF: 5 -partner-3 -kinase), reciprocal fusions (RF: 5 -kinase-3 -partner), or bidirectional reciprocal and nonreciprocal fusions (BRNRF: concurrent RF and NRF). Co-occurring genomic alterations were analyzed for frequency, distribution, and association with fusion partners and breakpoints.

Results: Notable differences in co-mutation profiles were observed across kinase fusions. EGFR alterations demonstrated fusion-specific distributions: amplifications were more prevalent in RET fusions (9.2% overall; 16.4% in BRNRF) compared to ALK (7.8%) and ROS1 (3.0%), while Exon 19del mutations were enriched in RET fusions (10.6% overall; 14.1% in NRF). Partner-specific analysis revealed EGFR Exon 19del was predominantly detected in CCDC6-RET NRF (11.1%), and EGFR amplifications in EML4-ALK NRF (6.1%) and KIF5B-RET BRNRF (16.7%). KRAS G12* mutations were more frequent in RET (4.0%) than ALK (2.0%) or ROS1 (0.7%) fusions, with the highest prevalence in RET-NRF (4.7%) and were primarily observed in EML4-ALK NRF (1.9%), CCDC6-RET NRF (3.3%), and CD74-ROS1 BRNRF (2.0%). MET amplifications showed distinct patterns: ALK (5.6% overall), RET (6.2% overall with enrichment in BRNRF at 9.4%), and rare in ROS1 (1.0%), with highest frequencies in EML4-ALK NRF (4.7%) and KIF5B-RET BRNRF (5.1%). These co-mutations followed specific patterns across fusion architectures, with EGFR and MET alterations enriched in BRNRF and RF architectures, particularly in RET fusions, compared to NRF variants.

Conclusions: This large-scale genomic analysis reveals distinct co-driver mutation landscapes across kinase fusion architectures in NSCLC, with RET fusions showing the highest frequency of actionable co-alterations. The partner-specific and architecture-dependent distribution of co-driver mutations suggests potential functional implications in disease biology and therapeutic response. These findings provide molecular rationale for incorporating comprehensive genomic profiling into diagnostic protocols and considering co-driver mutation status in therapeutic decision-making for kinase fusion-positive NSCLC patients.

Keywords: Fusion, Reciprocal, Driver

EP.06.74 Clinical Validity of Repeated CTCs and CAM-L Enumeration in Treatment Monitoring of Metastatic Non-Small Cell Lung Cancer

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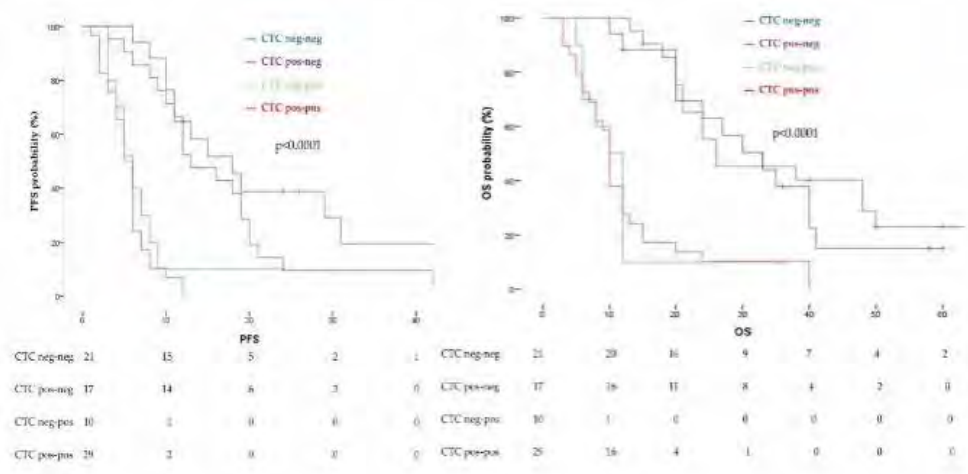
Introduction: The introduction of targeted therapies and immune checkpoint inhibitors (ICIs) has improved survival in metastatic non-small cell lung cancer (mNSCLC). However, reliable biomarkers to predict patient prognosis are needed. Circulating tumor cells (CTCs) have been identified as a prognostic factor associated with poor overall survival (OS). Moreover, cancer-associated macrophage-like cells (CAM-Ls), circulating macrophages that have internalized dying tumor cells before re-entering circulation, are emerging as a promising biomarker. Nevertheless, the role of their combined enumeration for mNSCLC is unexplored.

Methods: Serial CTC/ CAM-L levels were analyzed in 77 patients with mNSCLC treated with first-line regimens, specifically ICIs (39%), targeted therapies (22%), or chemotherapy (39%). Blood samples were analyzed for CTC and CAM-L levels at baseline (T0) and after three months (T1) using the CellSearch platform. The association of these biomarkers with progression-free survival (PFS) and OS was evaluated. Multivariate analysis adjusted for tissue PD-L1, treatment type, number of metastasis, and age was performed.

Results: Using a ≥1 CTC cut-off for positivity, 21 patients had 0 CTCs at both T0 and T1 (neg/neg), 10 and 17 patients converted between CTC negative and positive (neg/pos, pos/neg), and 29 patients had ≥1 CTC at both time points (pos/pos). MedianOS for the groups was 26, 33, 10, and 10 months, respectively (p<0.0001), and medianPFS was 13, 18, 5, and 6 months, respectively (p<0.0001). CTC non-responders (pos/pos) showed shorter PFS and OS compared to CTC responders (pos/neg). T1-CTC negativity and T1-CAM-L positivity were associated with better PFS and OS, independent of clinical factors. CAM-L positivity was more frequent in the ICIs-treated population (OddsRatio 3.53, 95% CI 1.34-9.25; p=0.009).

Conclusions: Serial assessments of CTCs and CAM-Ls are strong independent predictors of PFS and OS. These findings suggest their potential as prognostic biomarkers in mNSCLC and highlight the need for further clinical trials to validate their utility.



	PFS			OS		
	HR	CI 95%	p	HR	CI 95%	p
Overall population (77 patients)						
T1 CTC pos vs T1 CTC neg	5.91	2.58-13.54	<0.0001	6.68	2.72-16.44	<0.0001
CTC resp vs CTC non-resp	15.47	3.63-65.95	<0.0001	8.94	2.35-33.92	0.001
T1 CAM-L pos vs T1 CAM-L neg	0.23	0.11-0.48	<0.0001	0.28	0.12-0.62	0.002
ICIs population (30 patients)						
T1 CTC pos vs T1 CTC neg	5.25	1.70-16.25	0.004	8.17	2.41-27.64	0.001
T1 CAM-L pos vs T1 CAM-L neg	0.10	0.02-0.41	<0.0001	0.07	0.01-0.28	<0.0001
Non-ICI population (47 patients)						
T1 CTC pos vs T1 CTC neg	7.63	3.20-18.21	<0.0001	3.84	1.83-8.03	<0.0001
T1 CAM-L pos vs T1 CAM-L neg	0.34	0.18-0.66	0.002	0.40	0.20-0.78	0.008

Keywords: liquid biopsy, CTC, CAM-L

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.75 Identifying Emergent Resistance Alterations in Patients With Advanced NSCLC Using Plasma Genotyping (DISCOVER)

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Introduction: Targeted therapies have revolutionized treatment and outcomes for patients with advanced non-small cell lung cancer (NSCLC). Despite these advances, treatment resistance eventually occurs. To better understand mechanisms of resistance to targeted therapy, patients require a repeat tissue biopsy and genomic testing which is often challenging for patients. Liquid biopsy with circulating tumor (ct)DNA analysis may yield a less invasive, faster approach for molecular diagnosis of resistance.

Methods: Targeted therapies have revolutionized treatment and outcomes for patients with advanced non-small cell lung cancer (NSCLC). Despite these advances, treatment resistance eventually occurs. To better understand mechanisms of resistance to targeted therapy, patients require a repeat tissue biopsy and genomic testing which is often challenging for patients. Liquid biopsy with circulating tumor (ct) DNA analysis may yield a less invasive, faster approach for molecular diagnosis of resistance.

Results: As of January 2025, 75 eligible patients were enrolled, with a median age of 66 years; 56% were female, 99% had adenocarcinoma and 72% were never-smokers. The most common baseline actionable genomic alterations (AGAs) at enrollment were EGFR mutations (53/75, 71%) and ALK rearrangements (13/75, 17%). At the time of analysis, plasma ctDNA testing was completed for 67 patients (1 insufficient ctDNA, 7 pending). Compared to pre-treatment NGS results, 14% (9/66) gained AGAs and 36% (24/66) had loss of AGAs (Table 1). Gains included EGFR C797S, BRAF V600E, KRAS G12C, ERBB2 ex20ins and EGFR amplification. In addition, 36% (24/66) had variants reported consistent with clonal hematopoiesis (variant allele frequency =>2%).

Conclusions: Preliminary data demonstrate that plasma-based ctDNA NGS with the TSO500™ can detect emergent alterations in 14% of patients in a real-world setting. This has the potential to inform targeted therapeutic strategies and avoid costly and invasive repeat tissue biopsies. The observed loss of AGAs could be explained by post-therapy driver mutation clearance or insufficient ctDNA levels, although further exploration is needed.

Keywords: target therapy, liquid biopsy, Mechanism of resistance

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.76 Real-World Use of Tissue-Free ctDNA Monitoring in Patients With Lung Cancer Receiving Immunotherapy And/Or Chemotherapy

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Introduction: Circulating tumor DNA (ctDNA) is an emerging biomarker for monitoring early treatment response in patients with advanced lung cancer receiving immunotherapy (IO) and/or chemotherapy (chemo). However, optimal monitoring timing and cadence in this setting is unknown. Here we describe the real-world use of a tissue-free ctDNA monitoring assay in patients with lung cancer receiving IO and/or chemo.

Methods: The clinical laboratory developed test, FoundationOne®Monitor, was available in a limited pilot to 90 physicians familiar with liquid biopsy. The schedule and number of tests were determined by each local medical team as appropriate for their practice. Enrollment was rolling. Therapy abstraction was requested but not required. ctDNA was detected and quantified by ctDNA tumor fraction (TF), and variants were tracked with variant allele frequency (VAF).

Results: The range of ctDNA TF was 0 - 83%. The lowest ctDNA TF and pathogenic variant VAF values detected were 0.15% and 0.09% respectively. Changes in ctDNA TF were observed in 56% (27/50) of patients during their course of testing (timepoint results: newly detected: 8; increase: 17; <50% decrease: 5; 50-89% decrease: 7; 90-99% decrease: 1; clearance: 7). Of patients with ctDNA TF detected, those receiving IO monotherapy were less likely to have clearance of ctDNA TF in the observed time (chemo: 30.8%, 4/13; chemo+IO: 20.0%, 2/10; IO: 12.5%, 1/8,), and only 25.0% (2/8) had 50-90% reduction in ctDNA TF, occurring 47 days after the first test for one patient and after a switch in therapy for the other patient. A total of 458 unique known/likely pathogenic alterations were detected. In patients with multiple tests, 68% (34/50) had new variants emerge after the first test. Emergence of new known/likely pathogenic variants co-occurred with increased or stable ctDNA TF in 28% (14/50) of patients with new emerging variants. For patients in which emerging new variants occurred with ctDNA TF reduction, variants were in known clonal hematopoiesis genes: TP53, DNMT3A, CHEK2.

Conclusions: In real-world ctDNA-based monitoring across lung cancer subtypes, physicians monitored plasma approximately every 1-2 cycles, with a preference for every cycle for patients on chemo+/-IO. A broad range of ctDNA dynamics and emerging variants were observed that informed therapy response and reinforced changes on imaging.

Keywords: anti-PD1 therapy, circulating tumor DNA, tumor fraction

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.77 Exploring the Impact of Peripheral Immune Landscape on Immunotherapy Outcomes in Non-Small Cell Lung Cancer

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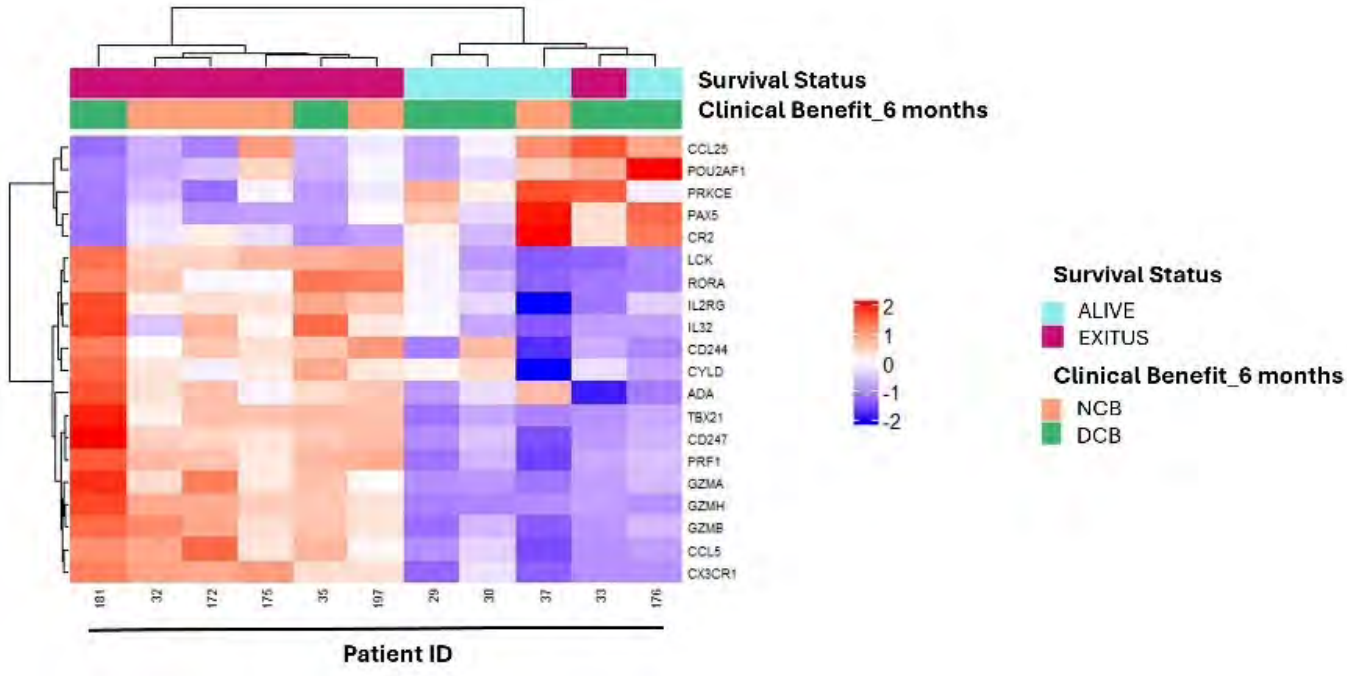
Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, yet their efficacy in non-small cell lung cancer (NSCLC) remains limited. Peripheral immunity plays a key role in antitumor responses, emphasizing the need to look beyond the tumor microenvironment. This study aims to assess changes in peripheral blood cell subsets and their potential correlation with therapeutic efficacy and clinical prognosis in NSCLC patients undergoing ICI treatment, providing insights into the interplay between systemic immunity and treatment outcomes.

Methods: 11 patients with NSCLC and receiving first-line ICI treatment from Consorcio Hospital General Universitario de Valencia were included. Peripheral blood samples were collected in EDTA K2 tubes before treatment initiation. PBMCs were isolated using Ficoll-Paque Plus, and RNA was extracted and analyzed with the nCounter® SPRINT Profiler using the PanCancer Immune panel. Normalized counts were obtained using the nSolver platform. Bioinformatic analysis was performed in R Studio, including heatmaps and principal component analysis (PCA) to explore gene expression patterns. The association between gene expression and survival was assessed using Kaplan-Meier analysis and Cox regression.

Results: PCA analysis did not show a clear distinction between sample groups, preventing the definition of clusters using ellipses. However, the top 20 genes contributing most to sample variability were identified. Unsupervised clustering of these genes stratified patients based on clinical benefit and survival (Figure attached). Gene Ontology (GO) analysis showed that the most highly expressed genes in surviving patients were related to B cell differentiation and activation, while the least expressed genes were associated with Th17 lymphocyte differentiation. Kaplan-Meier analysis revealed that 9 of these 20 genes were significantly associated with patient survival.

Conclusions: Our findings highlight the critical role of peripheral immune dynamics in shaping immunotherapy outcomes in patients with NSCLC. While global gene expression did not clearly differentiate patient groups, a subset of 20 genes was identified as key contributors to sample variability and was associated with clinical benefit and survival. These results underscore the potential of peripheral immune markers in predicting response to ICIs and warrant further investigation in larger cohorts.

AI Disclaimer: AI assistance (ChatGPT) was used to refine the text by reducing word count and correcting grammatical errors in English. Study supported by GIDO 2024, nCounter Loaner Grant 2023 and PI22/01277.



Keywords: lung cancer, biomarker discovery, peripheral blood

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.78 T Lymphocyte Subpopulations as Predictive Biomarkers in Non-Small Cell Lung Cancer Patients Treated With Anti-Pd(L)1 Inhibitors

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Introduction: Immune Checkpoint Inhibitors (ICIs) have revolutionized NSCLC treatment. However, patient response varies significantly, highlighting the need for reliable predictive biomarkers. This study investigated peripheral blood T lymphocyte subpopulations in lung cancer patients receiving anti-PD(L)1 therapy, analyzing their relationship with tumor characteristics, treatment response, and tumor progression.

Methods: Peripheral blood T lymphocyte subpopulations were analyzed in 50 NSCLC patients receiving anti-PD1/PDL1 in monotherapy as first and second line or consolidation after chemoradiotherapy. Immunophenotyping was performed using multiparametric flow cytometry with a comprehensive panel of memory/differentiation markers and expression of co-stimulatory/activation molecules. Cytometry data analysis was conducted using conventional gating strategies and multiparametric high-dimensional approach. Clinical stratification was based on tumor stage (III vs IV) according to TNM classification, and treatment response using RECIST criteria. Statistical analyses for conventional cytometry data were performed using R software and high-dimensional cytometry data underwent unsupervised multiparametric analysis using the R-edge algorithm. Currently, single-cell RNA sequencing analysis and TCR clonotype profiling are being completed in a subset of patients (N= 14).

Results: Significant differences in peripheral T lymphocyte subpopulations correlated with tumor stage, with stage IV patients exhibiting higher proportions of naive-like T cells compared to stage III patients. Effector memory (EM) T cells with mixed Th1/17 phenotype showed significant reduction in non-responders and at tumor progression. Double-positive (CD27+CD28+) EM T cells correlated with improved treatment outcomes

Conclusions: The study identified distinct T-cell immunological signatures that serve as potential biomarkers for advanced tumor stage characterization, therapeutic response and tumor progression monitoring. These findings could provide a more precise immune status assessment for patient stratification and treatment response evaluation in patients with PD(L)1 blockade therapy

Keywords: peripheral blood T lymphocyte subpopulations, anti-PD(L)1 therapy, Non-small cell lung cancer

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.79 Liquid Biopsy Shortens Time to Diagnosis and Treatment Selection: Primary Results From the International L1St Study

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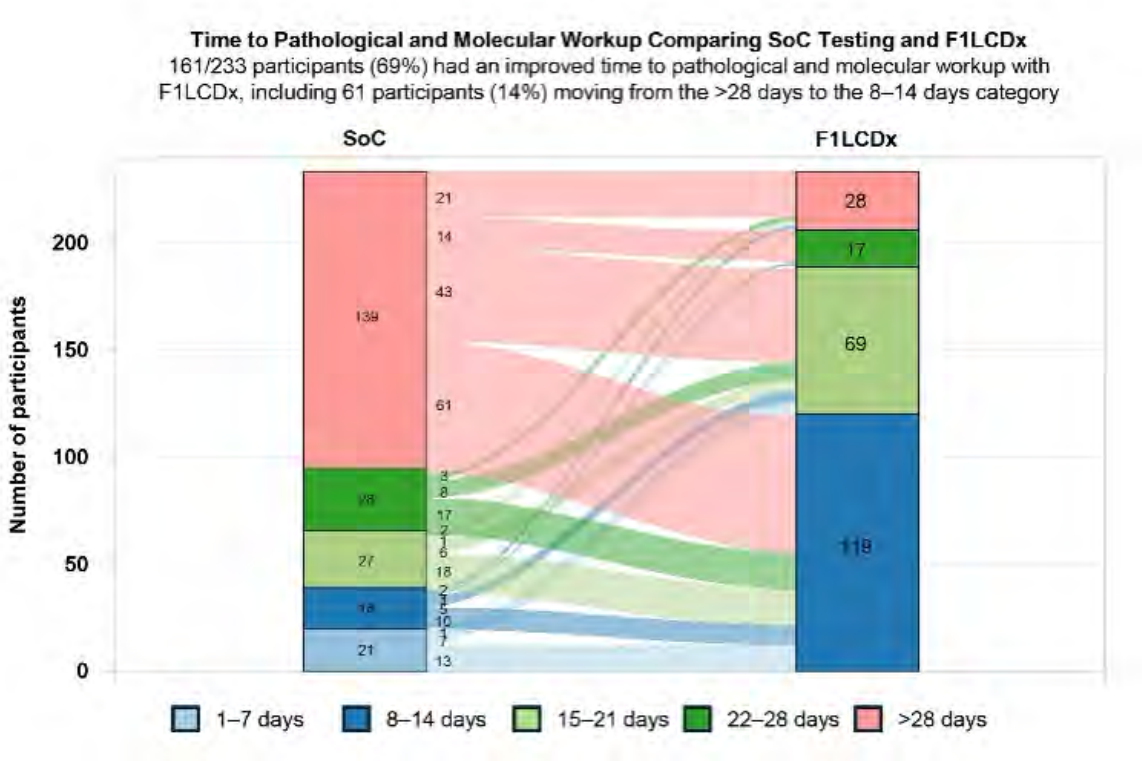
Introduction: Timely, comprehensive (tissue/liquid) molecular testing is required to identify effective molecularly guided treatment for advanced cancer. Standard sequential assessments often delay decisions by weeks; minimising this is critical to improving patient outcomes. L1st (NCT05846594) assesses the potential of liquid-based comprehensive genomic profiling (by FoundationOne®Liquid CDx; F1LCDx®) to streamline standard of care (SoC) diagnostic workup and expedite clinical decision-making and treatment start in people with clinical suspicion of advanced lung (presented here)/gastrointestinal cancers.

Methods: F1LCDx was performed in participants who did not/did have tissue biopsy prior to enrolment (basic/extended workup, respectively). The report was provided to the treating physician as soon as results were available. Primary endpoint: time from diagnostic pathway initiation (date of first request for biopsy/tissue/blood by a healthcare professional) to complete pathological and molecular workup (time to diagnosis; TTD), per ESMO/national guidelines, in the basic workup group. Secondary endpoints: time from diagnostic pathway initiation to anticancer treatment recommendation after complete pathological diagnosis (TTR); concordance between F1LCDx and SoC treatment recommendation (TR).

Results: By clinical cutoff (23 Oct 2024), 159 participants had basic workup; 98, extended. Median F1LCDx vs SoC TTD: 15.0 vs 34.0 days (median difference -14.0; Wilcoxon signed rank P < 0.0001) with basic workup (primary endpoint); 14.0 vs 35.0 days (median difference -17.0; P < 0.0001), with any workup (Figure) (also significant with extended workup). Median F1LCDx vs SoC TTR with any workup: 20.0 vs 43.0 days (median difference -16.0; P < 0.0001). F1LCDx and SoC TR concordance with any workup was 78% (57/73 participants with F1LCDx- and SoC-based TR). 199/242 participants (82%) had genomic alterations. Key alterations, filtered for ESCAT, included BRCA2 (42/242; 17%), EGFR (34/242; 14%), BRCA1 (32/242; 13%), KRAS (28/242; 12%), ALK (25/242; 10%), MET (24/242; 10%), PIK3CA (18/242; 7%), ERBB2 (17/242; 7%) and RET (6/242; 2%). Non-ESCAT-filtered key genomic alterations included RB1 and TP53 (151/242; 62%). 125/187 participants (67%) had a tumour fraction >1%. 41/257 participants (16%) were assigned a first-line targeted therapy based on F1LCDx (vs 31/257 [12%] with SoC).

Conclusions: In advanced lung cancer, high-quality liquid biopsy should become best practice: it allows for significantly improved diagnostic workup and the potential to improve TTR vs SoC by several weeks, as molecular diagnostics can be initiated before tumour specimen collection and reveals complex genomic alterations (e.g., MET Exon 14) that can inform TRs in the first-line (and in subsequent lines) of therapy.



Keywords: Diagnosis, Liquid biopsy, Treatment recommendation

EP.06.80 Immunological Markers of Prognosis in Lung Cancer: T-Cell Subpopulations and Their Correlation With Clinical Outcomes

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Introduction: Immune checkpoint inhibitors (ICIs) have improved outcomes for patients affected by lung cancer (LC), but reliable predictors of treatment efficacy are lacking. T-cell subpopulations have shown promise as biomarkers, since their presence at tumor sites and in peripheral blood seems to correlate with immune responses and clinical outcomes in patients undergoing immunotherapy. Identifying specific circulating T-cell phenotypes could help tailor immunotherapy strategies and optimize patient selection.

Methods: Peripheral blood samples were collected at baseline from patients affected by advanced LC treated with ICIs at the 'Maggiore della Carità' Hospital in Novara, Italy. Analyses were conducted on a subgroup of patients participating in the Immuno-EGA study (n = 32). Flow cytometry was used to assess circulating CD3+, CD4+ (Th), CD8+ (Tc), exhausted (CD28+LAG3+PD1+TIGIT+, Exh), exhausted-like (CD28+PD1+TIGIT+, ExhL), and senescent (CD28-CD57+KLRG1+, Sen) lymphocytes. Associations with overall survival (OS) and progression-free survival (PFS) were evaluated using the Log-rank test and Cox regression. Potential confounders, including age, sex, BMI, and smoking status, were considered in multivariable analyses. The correlation between the percentage of T-cell subpopulations and plasma metabolic biomarkers was assessed using the Spearman test.

Results: Patients with a higher proportion of circulating CD4+ Sen lymphocytes had improved OS (HR 1.02E-06 [1.62E-12 - 0.64], p = 0.043) and PFS (HR 1.17E-11 [1.61E-21 - 0.086], p = 0.030). These associations remained significant after adjusting for age, sex, BMI, and smoking status (table below). Conversely, a higher percentage of peripheral CD4+ Exh cells showed a trend toward worse PFS (HR 63.96 [0.53 - 7729.67], p = 0.089). This subpopulation also positively correlated with plasmatic carboxyhemoglobin (CoHb) percentage (r = 0.55, p = 0.011).

Conclusions: Our preliminary data suggest that characterizing T-cell subpopulations may provide valuable insights into the clinical outcomes of patients with advanced LC treated with ICIs. Further studies on larger patient cohorts are necessary to confirm these observations and explore their potential in guiding personalized immunotherapy.

		Multivariate Cox model adjusted for: age (<65 vs ≥65), BMI (<25 vs ≥25), sex (M vs F) and smoking status (smokers vs non-smokers)			
	T-cell population	HR	Lower HR	Upper HR	Pvalue
OS	CD4+CD28-CD57+KLRG1+	7.83E-13	1.02E-24	0.60	0.0459
PFS	CD4+CD28-CD57+KLRG1+	1.20E-12	2.04E-23	0.07	0.0301

Keywords: T cell populations, advanced NSCLC, Immunotherapy

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.81 Observational Study of Concordance Between Tissue-Based ODxTT CDx and In-House Plasma OPA Gene Analysis in NSCLC Patients

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Introduction: Genomic profiling is important in the treatment of non-small cell lung cancer, and the Oncomine Dx Target Test multi CDx system® (ODxTT CDx) is widely used in Japan. However, it is less likely to use in cases where the treatment is rushed because the test requires many slices, and the turnaround time (TAT) takes about 10 days. The Oncomine Precision Assay® (OPA) can be examined on plasma or pleural fluid, and since the test can be performed in our hospital, the TAT takes about one day, so it is expected to be used in cases that require early intervention. The purpose of this study was to investigate the reliability of plasma-based gene profiling using OPA and to examine its consistency with the results of tissue-based ODxTT CDx.

Methods: We retrospectively reviewed the concordance rate and the clinical course of 51 patients who had plasma based OPA and FFPE based ODxTT CDx retrieved at the same time from May 2022 to February 2025 at our hospital.

Results: The sex was 27 males and 24 females, the median ages were 73 years old (40-89years old), and the histology was Ad 39/Sq 10/NOS 2. The median difference between OPA and ODxTT CDx was 5 days (0 - 53 days), and none of the patients received systemic chemotherapy between the examinations. The concordance rate of detectable genetic variants in both OPA and ODxTT CDx was calculated. 36 of 51 cases were matched, with a concordance rate of 70.6% (95% Confidence Interval [CI], 56.2 - 82.5). Next the concordance rate of detectable genetic variants in both OPA and ODxTT CDx was calculated, limited to the driver oncogene. 43 of 51 cases were matched, with a concordance rate of 84.3% (95% CI, 71.4 - 93.0). The positive predictive value of OPA for ODxTT CDx was 95.7% (22/23 cases, 95% CI, 78.1 - 99.9). Three of the four OPA-positive and ODxTT CDx-negative cases were non-driver oncogenes such as PIK3CA, and ERBB2 S310F was detected in one case.

Conclusions: Plasma OPA can detect gene mutations that are useful as first-line therapy, and the concordance rate was high when limited to the Driver oncogene. We suggest that treatment can be initiated without waiting for ODxTT CDx results once a gene mutation is detected in OPA.

Keywords: Genomic profiling, Plasma-based testing, Driver oncogene concordance

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.83 Prognostic Impact of PD-L1 Expression in a Swiss Cohort ofEGFR-Mutant Non-Small Cell Lung Cancer Patients Treated With First-Line Osimertinib

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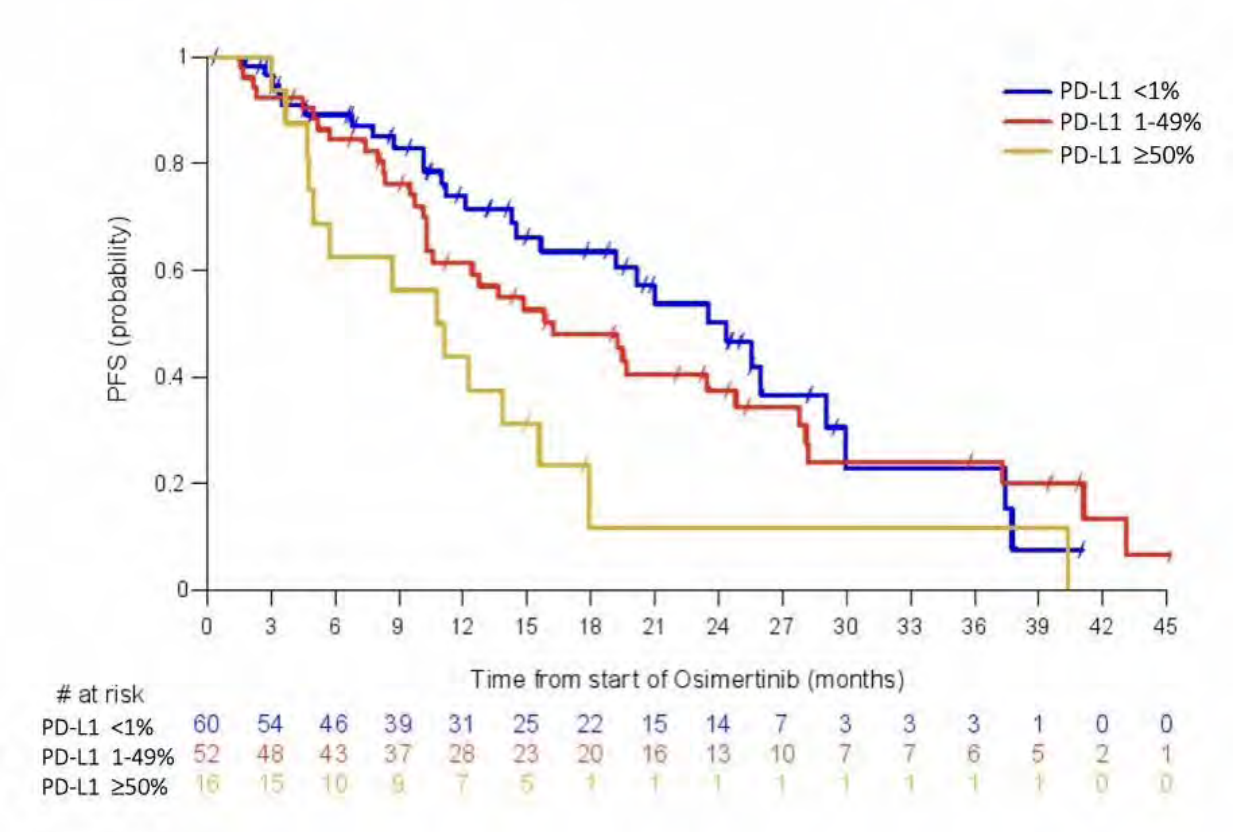
Introduction: Osimertinib monotherapy is a first-line treatment option for patients (pts) with metastatic non-small cell lung cancer (NSCLC) with a common epidermal growth factor (EGFR) mutation. Recently, osimertinib in combination with chemotherapy and lazertinib in combination with amivantamab have shown improvement in progression free survival (PFS) and overall survival (OS) compared to osimertinib alone. However, increased efficacy comes at the price of more toxicity and patient selection for treatment intensification remains uncertain. Therefore, it's important to identify predictive biomarkers for efficacy of osimertinib. Previous studies suggested a prognostic role of PD-L1 in this setting. We investigated the association of PD-L1 expression with osimertinib outcomes.

Methods: 128 EGFR-mutated pts from 13 Swiss centres with osimertinib first-line treatment and available PD-L1 tumour proportion score (TPS) were retrospectively analysed. Three PD-L1 groups were defined: No expression (<1%), PD-L1 low (1-49%) and PD-L1 high (≥50%). Survival outcomes were compared using the log-rank test. Primary resistance was defined as progressive disease as best response or progression free survival (PFS) < 6 months.

Results: Out of 128 patients 60, 52 and 16 pts had PD-L1 <1%, low and high. Median age was 68 years (range 38-93), 61% were females, 84% had PS ≤ 1, 57% were never smokers, 59% had an exon 19 deletion and 38% L858R exon 21. Patients and tumour characteristics among PD-L1 groups were well balanced except for more pts with exon 21 L858R mutations in the PD-L1 high vs. low vs. PD-L1 <1% group (63% vs. 29% vs. 38%, p=0.009). There was a significant difference in median PFS with 24.4 months (95% CI, 15.6-29.0) for PD-L1 <1% vs. 16.2 months (95% CI, 10.3-24.8) for PD-L1 low vs. 10.9 months (95% CI, 4.7 - 15.6) for the PD-L1 high group (p=0.023). Primary resistance occurred more frequently in PD-L1 high vs. low vs. <1% pts (38% vs. 15% vs. 10%, p=0.027). Median OS was similar among the groups: 65.3 months (95% CI, 38.4-NR) for PD-L1 <1%, 58.1 months (95% CI, 26.7 - 65.0) for PDL-1 low and not reached (95% CI, 18.2-NR) for PD-L1 high pts (p=0.365).

Conclusions: In our real-world data analysis of a Western population with EGFR mutated NSCLC high PD-L1 expression was associated with significantly shorter PFS and a higher proportion of primary resistance to first-line osimertinib. These results indicate that osimertinib may suffice in PD-L1 negative pts, and treatment intensification should be evaluated in PD-L1 positive, particularly PD-L1 high pts.



Keywords: osimertinib, PD-L1, prognostic marker

EP.06 PATHOLOGY AND BIOMARKERS

EP.06.84 Impact of Preoperative Brain Natriuretic Peptide Levels on Postoperative Outcomes in Lung Cancer Patients

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Introduction: Recent advancements in lung cancer treatment, including surgical intervention and drug therapy have dramatically improved patient prognosis. However, both treatments carry risks of cardiac complications, and cardiovascular hormones like brain natriuretic peptide (BNP) have been known to be associated with the occurrence of these complications. These days, several studies have reported that serum levels of cardiovascular markers could serve as markers for early diagnosis and assessment of disease progression for certain cancers. However, most studies included patients with advanced cancer, without surgical indication, and no reports have focused on lung cancer. This study examines the relationship between preoperative BNP levels, tumor characteristics, and long-term prognosis in lung cancer patients undergoing curative resection.

Methods: Patients who underwent radical resection for lung cancer at our institution from January 2012 to June 2019 were divided into high (≥18.5 pg/ml) and low (<18.5 pg/ml) BNP groups. The cutoff value was determined according to the guideline on heart failure in Japan. Continuous variables were analyzed through the Mann-Whitney U test, while categorical data were examined using Fisher's exact test. Kaplan-Meier curves were used to analyze postoperative overall survival (OS) and relapse-free survival (RFS). To adjust for baseline characteristic imbalances between two groups, an analysis with propensity score matching focusing on the cohort excluding cases in which limited resection was performed due to the risks of lobectomy was conducted. Cumulative incidence function was analyzed using the Gray's test. Multivariate Cox proportional hazards models were used to identify the independent predictors of postoperative OS.

Results: The final cohort includes 430 patients, composed of 222 higher BNP patients and 208 lower BNP cases. In the group with higher BNP, patients tended to be older ($p<0.01$) and had a higher prevalence of underlying comorbidities such as ischemic heart disease ($p<0.01$) and interstitial pneumonia ($p<0.01$). To evaluate the association among tumor size, maximum standardized uptake value (SUVmax) on positron emission tomography, and BNP levels, we calculated the Spearman's rank correlation coefficients. No significant correlation was found between BNP levels and tumor size (Spearman's rho=0.021, p=0.66) or SUVmax (Spearman's rho=0.075, p=0.12) . The patients with elevated BNP levels had lower OS (p=0.03) but no significant difference was observed in the RFS (p=0.09). In a subgroup limited to patients who can tolerate lobectomy, blood BNP levels were associated with OS before (p=0.03) and after propensity score marching (p=0.03) as well. Competing risk event analysis revealed higher mortality due to diseases other than lung cancer in the high BNP group ($p<0.05$), but there was no association between blood BNP levels and postoperative recurrence (p=0.86). Multivariate analysis showed male sex (HR: 2.10, 95% CI: 1.37-3.23) and pathological stage ≥II (HR: 2.32, 95% CI: 1.56-3.45) were independently associated with the OS. The HR for preoperative BNP levels was 1.49 (95% CI: 0.96-2.30).

Conclusions: Preoperative BNP levels in patients with lung cancer may reflect potentially compromised patient condition and show an association with postoperative OS. Nevertheless, no significant association was observed between tumor progression and BNP levels.

Keywords: Brain Natriuretic Peptide, Lung cancer, Overall survival

EP.06 PATHOLOGY AND BIOMARKERS

EP06.85 Real-World Performance of NGS Panels in Detecting Actionable Genomic Alterations in NSCLC

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Introduction: NGS testing is now routine in non-small cell lung cancer (NSCLC), with multiple panels used in clinical practice to identify clinically relevant actionable genomic alterations (AGAs). This study aimed to assess the performance of different NGS panels, including RNA-based events, in a large single-institution population evaluated since 2016.

Methods: Patients (pts) diagnosed with advanced NSCLC between 2016 and 2024 underwent molecular characterization using a range of NGS panels: Oncomine Solid Tumor DNA (OST) with customized nCounter RNA, Oncomine Focus Assay DNA/RNA (OFA), Oncomine Comprehensive Assay DNA/RNA (OCA), and Oncomine Precision Assay DNA/RNA (OPA).

Results: A total of 1,465 pts were included, the majority with stage IV (54%) and adenocarcinoma histology (63%). The overall NGS success rate was 91.6%, with 122 samples deemed non-evaluable. Panel-specific success rates were: OST + nCounter (91.3%, 367/402), OFA (85.6%, 430/502), OCA (91.7%, 132/144), and OPA (95.2%, 401/421). The overall AGA detection rates were: OST + nCounter (50.7%), OFA (44.0%), OCA (39.6%), and OPA (47.5%). Statistically significant differences in AGA detection were observed between OST + nCounter and both OFA and OCA ($p < 0.05$), with a trend toward significance for OPA vs. OCA ($p = 0.09$). Detection of non-AGA alterations also varied across panels ($p < 0.05$), with OCA reporting the highest incidence (48.6%) compared to OFA (22.1%), OST + nCounter (29.4%), and OPA (36.6%). Both METex14 skipping and ALK fusion showed a declining detection trend over time. Although no statistically significant, detection rates were numerically lower with newer panels: METex14, 3.0% (12/402) with OST + nCounter vs. 1.9%, (8/421) with OPA; ALK fusion, 2.5% (10/402) vs 0.7% (1/144) with OCA.

Conclusions: These results reinforce the value of NGS in routine clinical practice and suggest that panel selection may influence detection sensitivity for certain AGAs. This is particularly relevant for low-prevalence alterations such as METex14 and ALK fusions, where even modest reductions in detection rates may significantly impact the identification of patients eligible for targeted therapies.

EP.06 PATHOLOGY AND BIOMARKERS

EP06.86 Evaluating Sustainment of Results in Quality Improvement Focused on Molecular Testing in Non-Small Cell Lung Cancer Patients

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Introduction: In June 2022, Integra Connect (IC) published positive results of a quality improvement project (QI) focused on stage IV NSCLC patients (pts) conducted in partnership with the University of Pittsburg Medical Center (UPMC) aimed at improving EGFR testing rates, molecular testing rates across all NCCN recommended markers, and rates of pts who received EGFR test results prior to first-line treatment1. IC and UPMC sought to reassess those same measures two years later to see if UPMC sustained the improvement.

Methods: Pts included were treated at UPMC and identified via manual chart abstraction as newly diagnosed with stage IV NSCLC that received first-line therapy. The initial baseline of the QI was 1/1/2017-8/31/2020, followed by a first-post-baseline period 9/1/2020-12/31/2020, and second-post-baseline period of 1/1/2021-9/30/2021. To assess whether results were sustained two additional evaluation periods were observed in the calendar years 2022 and 2024.

Results: Median age in the initial QI was 68 (range 36 - 89) and 49% male. In the additional observation periods 2022 and 2024 the median age was 70 (range 45 - 89) and 54% male. The EGFR testing rate for pts at baseline was 94% and increased to 96% by the second post-baseline period and in 2022 reached 98%, but in 2024 reduced to 93%. Testing across all NCCN recommended markers increased from 52% at baseline to 76% by the second post-baseline and in 2022 reached 89% followed by 92% in 2024. The rate of pts receiving their EGFR test results prior to initiating first-line treatment was 72% at baseline and increased to 88% by the second post-baseline and in 2022 remained at 88%, but in 2024 dropped to 77%.

Conclusions: The QI implemented at UPMC for stage IV NSCLC led to continuous improvement in full panel biomarker testing climbing to 92% of pts tested for all actionable mutations. However, the rate of pts with EGFR test results in hand prior to initiating first-line treatment dropped after the completion of the QI, yet the rate remained above the baseline. This demonstrates the importance of continuous monitoring to ensure quality improvement efforts are sustained.

Keywords: Quality Improvement, Stage IV, Molecular Testing

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.01 Prediction of Pathologic Low-Grade Malignant Adenocarcinoma in Radiologically Invasive C-Stage IA Non-Small Cell Lung Cancer Measuring >2-3 Cm

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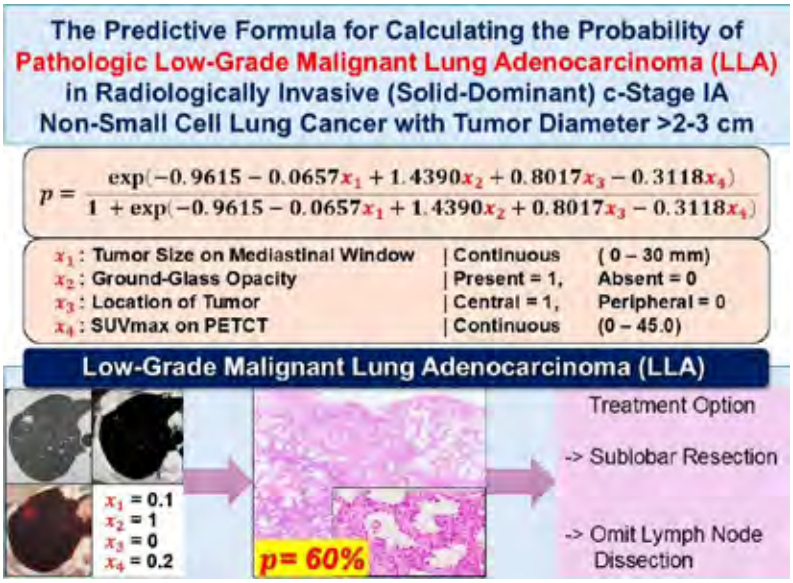
Introduction: Despite the recent trend toward sublobar resection, lobectomy with lymph node dissection (LND) remains the standard treatment for radiologically invasive (solid-dominant) clinical stage IA non-small cell lung cancer (NSCLC) measuring >2-3 cm. We aimed to develop a predictive model for pathologic low-grade malignant lung adenocarcinoma (LLA) to identify potential candidates for limited surgery, such as sublobar resection or simple lobectomy without LND, depending on tumor location. This study was conducted as an early supplementary analysis of JCOG1413, a randomized phase III study evaluating the clinical benefits of the extent of LND in patients with c-stage I-II NSCLC. This primary analysis results will be released in 2026 or later.

Methods: Among 1,711 patients enrolled in JCOG1413 from January 2017 to August 2021, we analyzed 633 patients with radiologically invasive (solid-dominant on thin-section computed tomography [TSCT], consolidation-to-tumor ratio [CTR] >0.5-1.0) c-stage IA tumors measuring >2-3 cm. All patients underwent lobectomy with either systematic or lobe-specific LND. In this study, LLA was defined as adenocarcinoma with a lepidic-predominant pattern, without pleural and lymphovascular invasion, and without pulmonary and nodal metastases. A multivariable logistic regression analysis with stepwise selection method was performed to develop a predictive model based on clinical and radiological factors. Leave-one-out cross-validation was conducted, and sensitivity, specificity and concordance statistics were calculated to evaluate diagnostic performance.

Results: LLA was detected in 71 patients (11%), and the developed prediction model for LLA included the following four variables: (1) tumor size in the mediastinal window setting on TSCT (x1), (2) presence or absence of ground-glass opacity (x2), (3) tumor location (central or peripheral) (x3), and (4) maximum standardized uptake value on positron emission tomography (x4). The predictive formula was p = (exp [-0.9615 - 0.0657x1 + 1.4390x2 + 0.8017x3 - 0.3118x4]) / (1 + exp [-0.9615 - 0.0657x1 + 1.4390x2 + 0.8017x3 - 0.3118x4]). Continuous variables (x1, x4) and categorical variables (x2, x3) were used to predict the probability. The concordance statistics was 0.8439. The risk of incorrectly predicting LLA was low, at only 4.7%, when Youden's index was maximized with a specificity of 95%. When the cut-off value was set to 34.5, sensitivity and specificity were 37.1% (95% confidence interval [CI]: 25.9-49.5%) and 95.3% (95% CI: 93.2-96.9%), respectively.

Conclusions: The proposed model is a clinically accessible and non-invasive tool for predicting pathologic low-grade malignant adenocarcinoma in patients with radiologically invasive (solid-dominant) clinical stage IA NSCLC measuring >2-3 cm.



Keywords: lung cancer, adenocarcinoma, low grade malignant

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.02 Development and Validation of a High-Speed and High-Throughput 3D Reconstruction Algorithm in Pulmonary Vasculature and Nodules Localization

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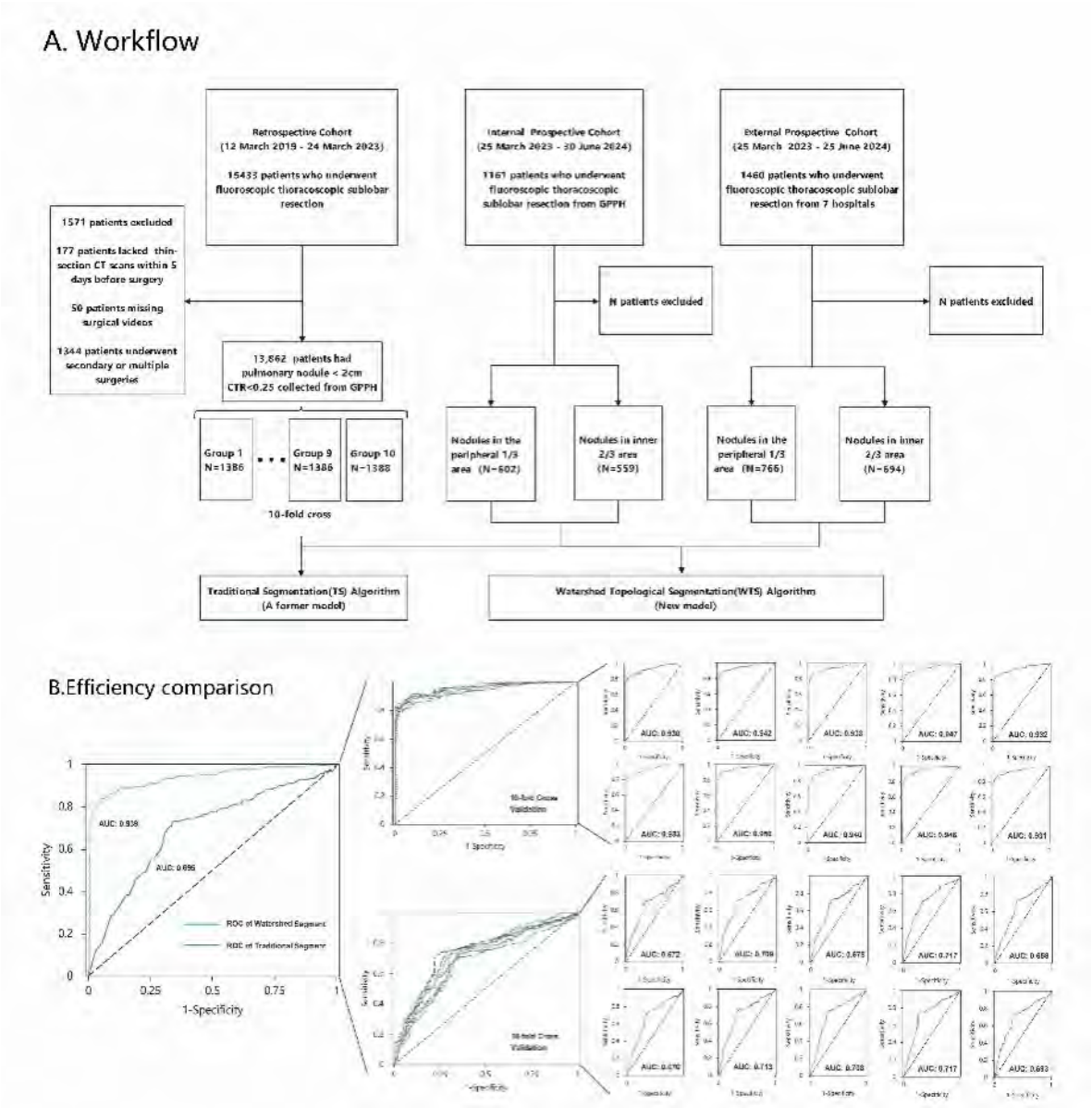
Introduction: Efficient vascular systems are vital for organ function, yet existing anatomical models often overlook vascular structures, limiting their effectiveness in precision medicine. Enhanced understanding of vascular anatomy could improve patient-specific treatment strategies, particularly for early-stage lung cancer.

Methods: We developed an AI algorithm named watershed topographical segmentation (WTS) using a 3D U-Net architecture, augmented by InceptionV3 units and a graph neural network (GNN). The model was trained on a retrospective cohort of 15,433 patients with ground-glass pulmonary nodules (GGNs) from multiple hospitals in China. We utilized an internal prospective validation cohort (1,161 patients) and an external validation cohort (1,460 patients) to evaluate localization accuracy and guide wedge resections.

Results: The WTS model achieved an area under the curve (AUC) of 0.939 in internal ten-fold cross-validation, significantly outperforming traditional segmentation methods (AUC 0.695). In prospective cohorts, the model demonstrated localization accuracy of 92.25% for peripheral nodules and 94.45% for intrapulmonary nodules, with external validation showing similar results (90.90% and 83.00%, respectively).

Conclusions: Our findings indicate that the WTS model can accurately simulate vascular watershed boundaries, enhancing surgical planning and intraoperative navigation. Improved precision in pulmonary nodule localization may reduce surgical trauma and complications, ultimately benefiting lung cancer treatment outcomes. The watershed topographic map is a valuable resource for clinicians and educators, especially in settings with limited access to experienced surgeons.



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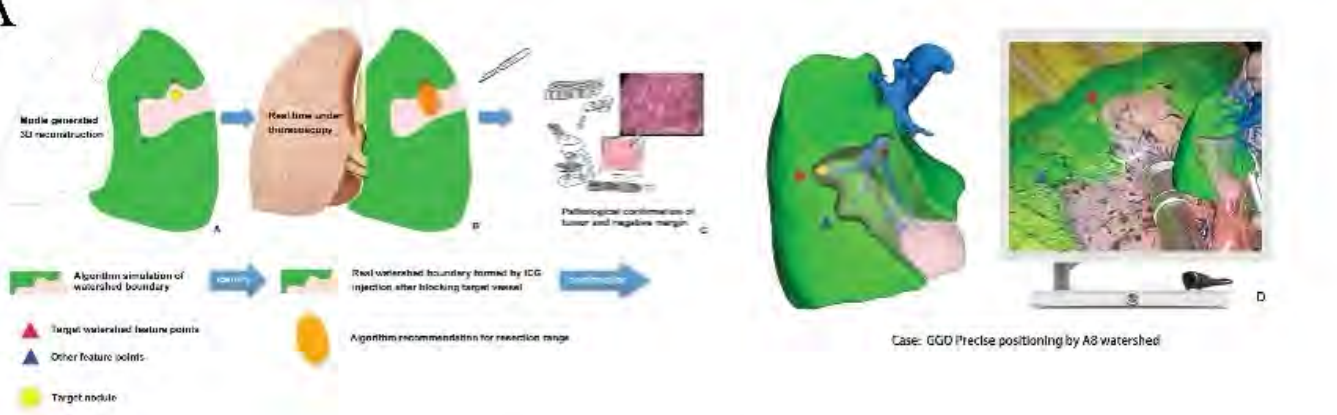

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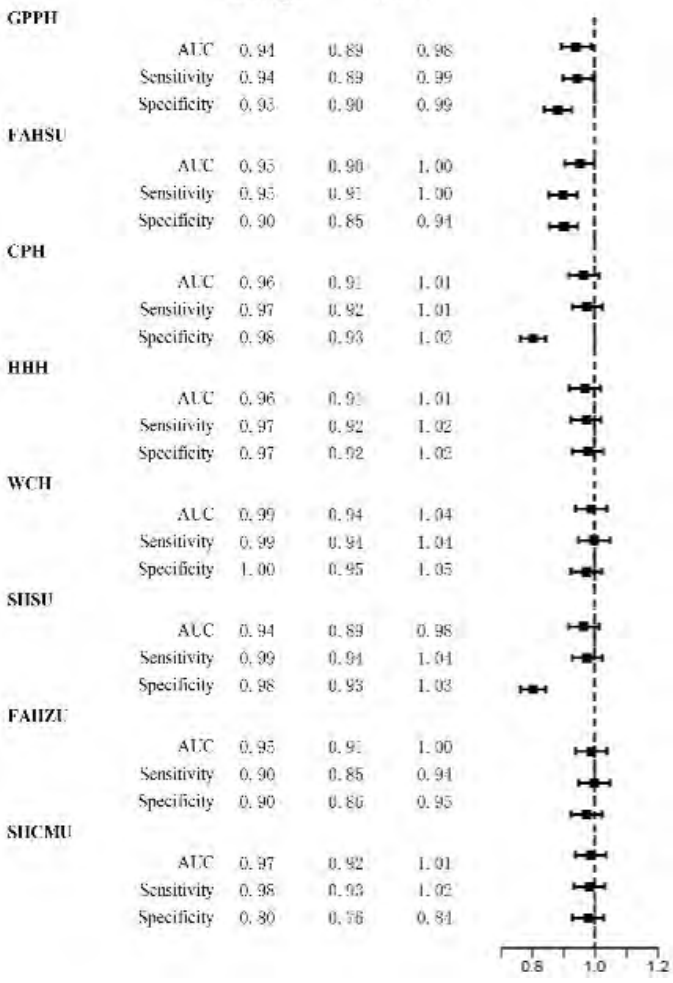

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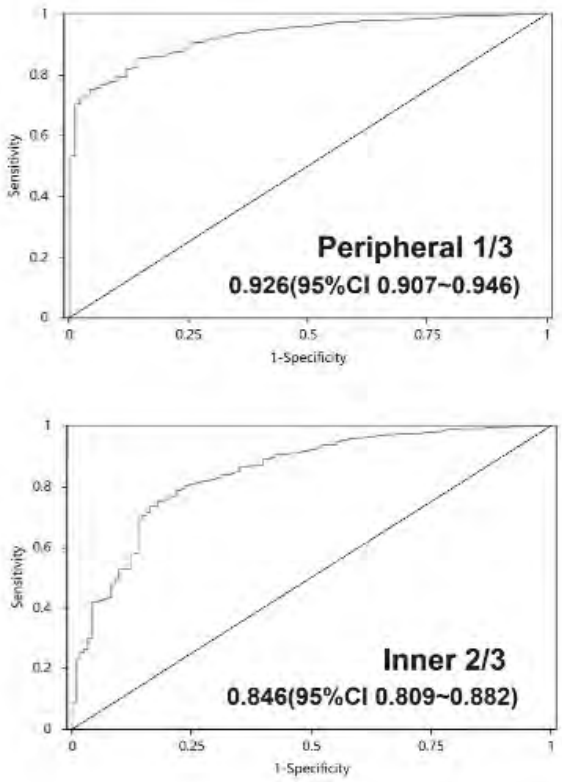

Keywords: Early-Stage NSCLC, Surgery, 3d reconstruction

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.03 Lung Cancer: Artificial Intelligence, Biometrics and Modeling of Alive Supersystems for Best Management

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Introduction: Non-small cell lung cancer (LC) is an extremely complex global problem. 5-survival (5YS) and life span after radical surgery for patients wih LC (LCP) (T1-4N0-2M0) - alive supersysems was analyzed. The importance must be stressed of using complex system analysis, artificial intelligence (neural networks computing), synergetics, simulation modeling and biometrics in combination, because the different approaches yield complementary pieces of prognostic information.

Methods: We analyzed data of 786 consecutive LCP (age=57.7±8.3 years; tumor size=4.1±2.4 cm) radically operated and monitored in 1985-2025 (m=674, f=112; upper lobectomies=284, lower lobectomies=180, middle lobectomies=18, bilobectomies=46, pneumonectomies=258, mediastinal lymph node dissection=786; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=199; only surgery-S=629, adjuvant chemoimmunoradiotherapy-AT=157: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=328, T2=260, T3=137, T4=61; N0=528, N1=133, N2=125, M0=786; G1=199, G2=248, G3=339; squamous=423, adenocarcinoma=313, large cell=50; early LC=221, invasive LC=565; right LC=422, left LC=364; central=298; peripheral=488. Variables selected for study were input levels of 45 blood parameters, sex, age, TNMG, cell type, tumor size. Regression modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine significant dependence.

Results: Overall life span (LS) was 2245.9±1741.5 days and cumulative 5-year survival (5YS) reached 73.4%, 10 years - 65.2%, 20 years - 42.5%. 516 LCP lived more than 5 years (LS=3118.2±1527.7 days), 148 LCP - more than 10 years (LS=5054.4±1504.1 days).199 LCP died because of LC (LS=562.7±374.5 days). 5YS of LCP after bi/lobectomies was significantly superior in comparison with LCP after pneumonectomies (78.2% vs.63.5%, P=0.00001 by log-rank test). AT significantly improved 5YS (65.6% vs. 34.8%) (P=0.00001 by log-rank test) only for LCP with N1-2. Cox modeling displayed that 5YS of LCP significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0—N12, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), G1-3, AT, blood cell circuit, prothrombin index, age, bilirubin, procedure type (P=0.000-0.044). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT early-invasive LC (rank=1), PT N0—N12 (rank=2), thrombocytes/CC (3), healthy cells/CC (4), eosinophils/CC (5), erythrocytes/CC (6), segmented neutrophils/CC (7), lymphocytes/CC (8), monocytes/CC (9); stick neutrophils (10); leucocytes/CC (11). Correct prediction of 5YS was 100% by neural networks computing (area under ROC curve=1.0; error=0.0).

Conclusions: 5YS of LCP after radical procedures significantly depended on: 1) PT early-invasive cancer; 2) PT N0--N12; 3) cell ratio factors; 4) blood cell circuit; 5) biochemical factors; 6) hemostasis system; 7) AT; 8) LC characteristics; 9) LC cell dynamics; 10) surgery type: lobectomy/pneumonectomy; 11) anthropometric data. Optimal diagnosis and treatment strategies for LC are: 1) screening and early detection of LC; 2) availability of experienced thoracic surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

Keywords: lung cancer, surgery, survival

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.04 Pathological Investigation of Bronchial Stump and Bronchopleural Fistula After Anatomical Pulmonary Resection for Lung Cance

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Introduction: Bronchopleural fistula (BPF) after anatomical pulmonary resection for lung cancer is a severe complication that continues to be of concern despite advances in medical devices. However, little is known about the physiological mechanism that leads to BPF formation, and there has been no detailed pathological study of natural bronchial stump formation after anatomical pulmonary resection.

Methods: The aim of this study was to examine features of BPF from a clinco-pathological perspective. A total of 1002 cases that underwent anatomical pulmonary resection for lung cancer at Kanagawa Cardiovascular and Respiratory Center from April 2011 to April 2021 were reviewed retrospectively. BPF was diagnosed based on bronchoscopic findings such as fistula or fluid bubbling. Clinical-pathological data were collected from medical records and correlations of BPF with clinical features were evaluated. In addition, natural microscopic bronchial stump formation after anatomical pulmonary resection was examined in autopsy cases without lung cancer recurrence. After careful removal of staplers from the bronchial stump in autopsy cases, histological specimens were investigated microscopically.

Results: The subjects underwent lobectomy (n=784), segmentectomy (n=185), bilobectomy (n=18) and pneumonectomy (n=2). BPF developed in 6 cases (0.6%), and was significantly associated with right lower lobectomy ($p<0.001$) and presence of interstitial pneumonia (IP) ($p<0.001$). The median period from the procedure to onset of BPF was 25 (20-260) days. Autopsy cases that underwent radical lobectomy and had no recurrence included a 79-year-old female with squamous cell carcinoma (SCC): pStage IA; an 85-year-old male with SCC: pStage IB; a 71-year-old male with SCC: pStage IIB; and an 81-year-old male with large cell neuroendocrine carcinoma: pStage IB. Microscopic investigation revealed fibrosis in the crimped portion of the remaining bronchial wall structure and fibrous tissue surrounding staple holes in concentric circles. The bronchial epithelium had turned around and covered the bronchial lumen at the blind end.

Conclusions: Previously reported risk factors for BPF include right lower lobectomy, diabetes mellitus and poor nutrition. IP was also identified as a risk factor for BPF in this study. Microscopic findings from autopsy cases revealed that after anatomical pulmonary resection the bronchial stump had epithelial damage due to adhesion of the bronchial wall caused by staples, and fibrosis due to the repair reaction. Concentric fibrosis was observed around the hole, suggesting a repetitive repair response to staple movement due to breathing. Thus, under conditions of strong negative intrathoracic pressure, such as those in IP, the patient may be more likely to develop BPF. There was also a wide range of onset times for BPF, which suggests that late onset BPF might be correlated with mechanical factors.

Keywords: anatomical pulmonary resection, bronchial stump, bronchopleural fistula

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.05 Oncologic Outcomes of Segmentectomy Versus Lobectomy in Early-Stage Lung Adenocarcinoma With High-Risk Pathologic Features

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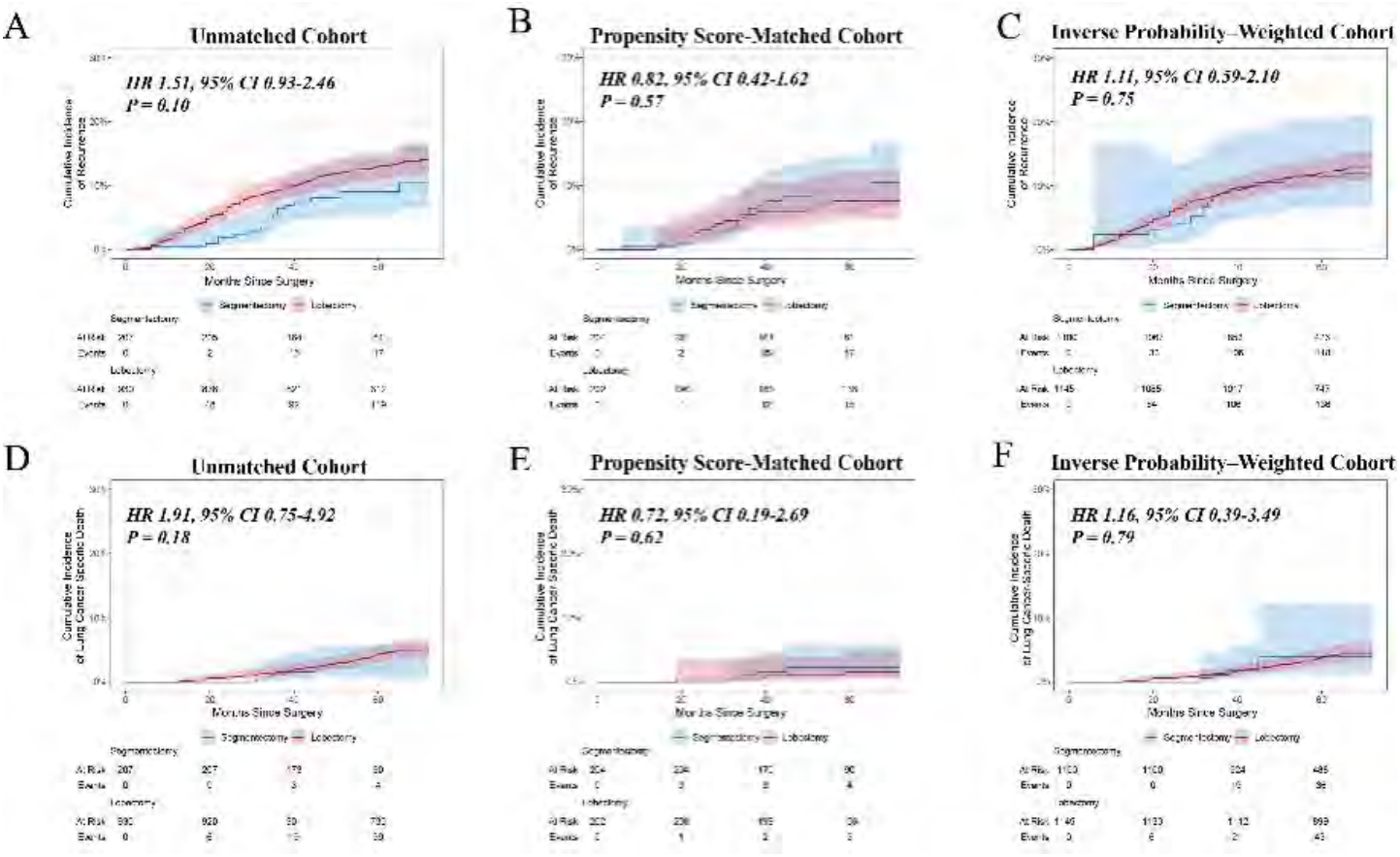
Introduction: Several randomized controlled trials have demonstrated that segmentectomy provides acceptable oncological results for small-sized non-small-cell lung cancer. However, the high-risk pathologic features can significantly influence prognosis of early-stage lung adenocarcinoma (LUAD). The generalizability of JCOG 0802 and CALGB 140503 trial results to patients with these high-risk features remains uncertain. This study aimed to compare oncologic outcomes between lobectomy and segmentectomy in clinically early-stage LUAD patients with high-risk pathologic factors.

Methods: This single-center retrospective study involved patients with clinical stage IA LUAD and high-risk pathologic features who underwent lobectomy or segmentectomy from 2016 to 2020. Patients with occult nodal metastasis were excluded. High-risk pathologic features were defined as visceral pleura invasion, lymphovascular invasion, spread though airspaces or poorly differentiated. Cumulative incidence of recurrence (CIR) and lung cancer-specific cumulative incidence of death (LC-CID) were compared using Fine and Gray's competing risks regression. Death due to other causes was considered as a competing risk. Propensity score matching (1:1) and inverse probability of treatment weighting were employed to reduce selection bias.

Results: A total of 1137 patients were identified, including 930 (81.8%) who underwent lobectomy and 207 (18.2%) who underwent segmentectomy. In unmatched cohort, no significant difference in CIR was observed between segmentectomy (5-year CIR rate, 9.0%) and lobectomy patients (5-year CIR rate, 13.0%; hazard ratio (HR), 1.51; 95% confidence interval (CI), 0.93-2.46; P = 0.10) (Fig 1A). In the propensity score-matched cohort, there was no significant difference in CIR between segmentectomy (5-year CIR rate, 9.1%) and lobectomy patients (5-year CIR rate, 7.6%; HR, 0.82; 95% CI, 0.42-1.62; P = 0.57) (Fig 1B). In inverse probability-weighted cohort, segmentectomy was not a significant predictor of worse CIR (HR, 1.11; 95% CI, 0.59-2.10; P = 0.75) (Fig 1C). Similarly, LC-CID showed no significant differences between segmentectomy and lobectomy across unmatched cohort (HR, 1.91; 95% CI, 0.75-4.92; P = 0.18), propensity score-matched cohort (HR, 0.72; 95% CI, 0.19-2.69; P = 0.62) and inverse probability-weighted cohort (HR, 1.16; 95% CI, 0.39-3.49; P = 0.79) (Fig 1D-1F).

Conclusions: Segmentectomy demonstrates comparable oncologic outcomes to lobectomy in clinically early-stage LUAD patients with high-risk pathologic features, including visceral pleural invasion, lymphovascular invasion, spread through airspaces, and poorly differentiated. These findings support the feasibility of segmentectomy in this population.



Keywords: segmentectomy, lung adenocarcinoma, high-risk pathologic feature

EP.07.06 Preserved Ratio Impaired Spirometry Are Associated With Poor Postoperative Outcomes in Clinical Stage I Non-Small Lung Cancer

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Introduction: The preserved ratio impaired spirometry (PRISm) is an airflow limitation status that identifies a group of individuals with impaired lung function who do not meet the spirometry-assessed definition of chronic obstructive pulmonary disease (COPD). PRISm is defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ≥ 0.7 and percent predicted FEV1 < 80%. Although PRISm is recognized as a risk factor for elevated complication rates of cardiovascular disease and mortality of respiratory disease, the association between PRISm and postoperative outcomes in lung cancer remains unclear. We investigated the association between PRISm without restrictive spirometric pattern (RSP) and postoperative outcomes in early-stage lung cancer.

Methods: Patients who underwent surgery for non-small cell lung cancer (NSCLC) with clinical stage I at Iwakuni Clinical Center between January 2015 and December 2021 were included. The patients were divided into two groups: patients with normal pulmonary function (the normal group) and those with FEV1/FVC ≥ 0.7 and percent predicted FEV1 < 80% (the PRISm group). Patients with RSP on pulmonary function test or those with COPD were excluded. We compared postoperative complications, the duration of postoperative hospital stay, recurrence-free survival within three years after surgery (3-year RFS), and survival within three years after surgery between the two groups.

Results: Of 443 patients who underwent surgery, 23 patients were conducted in the PRISm group. Although there were no significant differences between the normal group and the PRISm group regarding postoperative complications (21 (5.2%) vs. 2 (5.3%), P = 1.00) and postoperative hospital stay (6 (2-8) days vs. 6 (3-21) days, P = 0.68), 3-year RFS (Fig.1) and 3-year OS (Fig. 2) had significant differences between them (3-year RFS, 0.94 (0.91-0.96) vs. 0.77 (0.54-0.90), P < 0.001; 3-year OS, 0.94 (0.91-0.96) vs. 0.83 (0.60-0.93), P = 0.033).

Conclusions: PRISm was associated with poor 3-year RFS and 3-year OS after surgery for NSCLC in stage I. PRISm might be a risk factor of poor outcomes in early-stage NSCLC.

Fig. 1

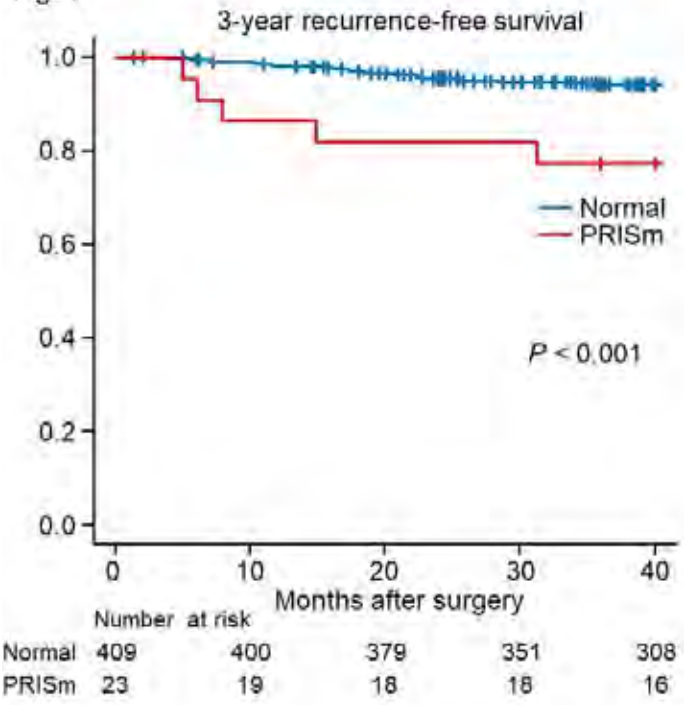
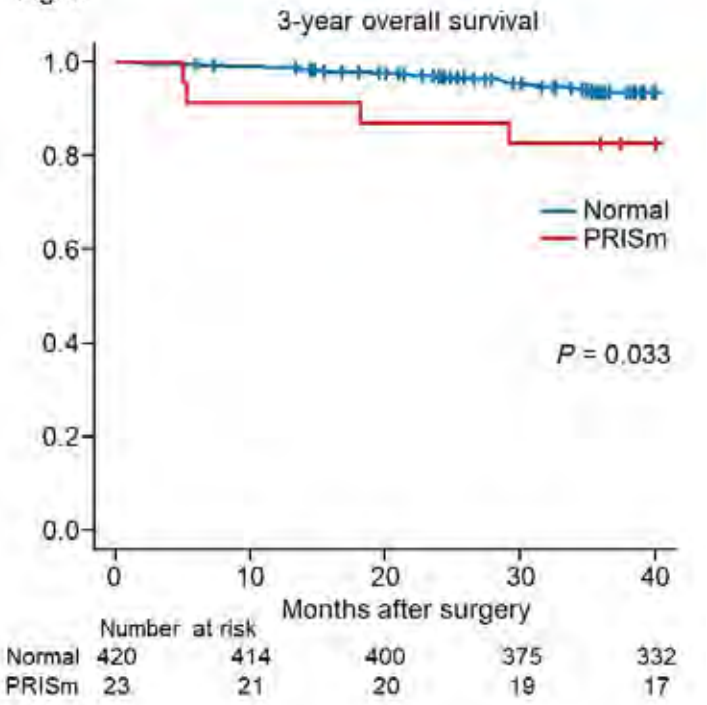


Fig. 2



Keywords: Non-small cell lung cancer, Preserved ratio impaired spirometry, Overall survival

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.07 Prognostic Analysis and Molecular Characteristics of Bubble-Like Appearance-Type Lung Adenocarcinoma

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[1]Kanagawa Cancer Center, Yokohama/JP ,[2]Yokohama City University School of Medicine, Yokohama/JP ,[3]Kanagawa Cancer Center Research Institute, Yokohama/JP

Introduction: Bubble-like appearance (BLA)-type lung adenocarcinoma (LUAD) is a group of LUAD that may be misdiagnosed as chronic inflammatory lesions on imaging and followed up for a long period, as we previously reported. BLA-type LUAD has four imaging features on thin-section CT: polygonal shape, slight ground-glass opacity (GGO) around the tumor, three or more dilated small bronchi (air bronchograms) within the tumor area, and clear pleural indentations. In addition, BLA-type LUAD has a slow growth rate, including a scaly growth pattern, and the main pathological feature is a collapsed tumor center. However, the prognostic significance and molecular characteristics of BLA-type LUAD remain unclear. This study aimed to compare the prognosis and molecular features of BLA-type LUAD with those of non-BLA-type LUAD.

Methods: We retrospectively analyzed the clinical records of 1166 patients who underwent complete surgical resection with lobectomy for LUAD at the Kanagawa Cancer Center between 2010 and 2019. BLA-type LUAD was defined based on the four computed tomography characteristics described earlier. Survival curves were estimated using the Kaplan-Meier method. The prognosis of BLA-type LUAD (BLA group) and non-BLA-type LUAD (non-BLA group) were compared after adjusting for confounding factors. The confounding factors were age, sex, smoking history, CEA level, and CT tumor size. Multivariable analyses were performed using a Cox proportional hazards regression model with the following variables: radiographical GGO component, adenocarcinoma subtype, pathological tumor invasive size, pathological lymph node metastasis, lymphatic permeation, vascular invasion, visceral pleural invasion, and EGFR mutation to explore factors related to RFS and OS of all the patients, including the BLA group. In addition, clinicopathological features, epidermal growth factor receptor (EGFR) mutation status, and programmed death ligand 1 (PD-L1) expression were analyzed.

Results: A total of 2145 consecutive patients with primary LUAD underwent complete surgical resection with lobectomy. Finally, 122 patients in the BLA group and 1044 patients in the non-BLA group were included in the study. The 5-year RFS rates of patients in the BLA and non-BLA groups were 79.0% and 68.6%, respectively, and after adjusting for confounding factors, the RFS was significantly better in the BLA group than in the non-BLA group (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.38-0.85; p=0.006). Similarly, the 5-year OS rates of patients in the BLA and non-BLA groups were 92.9% and 82.6%, respectively, and even after adjusting for confounding factors, the BLA group showed significantly better survival (HR, 0.43; 95% CI, 0.24-0.80; p=0.008). The BLA group had a higher EGFR mutation rate than the non-BLA group (63.1 vs. 45.6%; p<0.001), with a particularly high proportion of exon 21 L858R mutations (58.4%). In contrast, the PD-L1 expression rate (TPS ≥1%) was 9.0%.

Conclusions: The prognosis of BLA-type LUAD was better than that of non-BLA-type LUAD owing to the association of multiple factors, including pathological tumor invasive size, fewer lymph node metastases, and pathological low-grade tumors. BLA-type LUAD exhibited higher EGFR mutation rates than non-BLA-type LUAD and lower PD-L1 expression than previously reported. These results suggest that BLA-type LUAD is more oncologically distinct tumor than regular LUADs.

Keywords: bubble-like appearance, lung adenocarcinoma, collapse

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.08 Quantifying Resection Margins in Lung Cancer Patients Undergoing Sublobar Resection Using CT-Based 3D Reconstruction

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Introduction: Sublobar resection has emerged as a standard treatment option for early-stage peripheral non-small cell lung cancer. Achieving an adequate resection margin is crucial to prevent local tumor recurrence. However, gross measurement of the resection margin may lack accuracy due to the elasticity of lung tissue and interobserver variability. Therefore, this study aimed to develop an objective measurement method, the CT-based 3D reconstruction algorithm, to quantify the resection margin following sublobar resection in lung cancer patients through pre- and postoperative CT image comparison.

Methods: An automated subvascular matching technique was first developed to ensure accuracy and reproducibility in the matching process (Figure 1). Following the extraction of matched feature points, another key technique involves calculating the displacement field within the image. This is particularly important for mapping discontinuous deformation fields around the surgical resection area. A transformation based on thin-plate spline is used for medical image registration. Upon completing the final step of image registration, the distance at the resection margin was measured.

Results: After developing the CT-based 3D reconstruction algorithm, we included 12 cases for resection margin distance measurement, comprising four right middle lobectomies, six segmentectomies, and two wedge resections (Table 1). The outcomes obtained with our method revealed that the target registration error for all cases was less than 2.5 mm.

Conclusions: Our method demonstrated the feasibility of measuring the resection margin following sublobar resection in lung cancer patients through pre- and postoperative CT image comparison. Further validation with a multicenter, large cohort, and analysis of clinical outcome correlation is necessary in future studies.

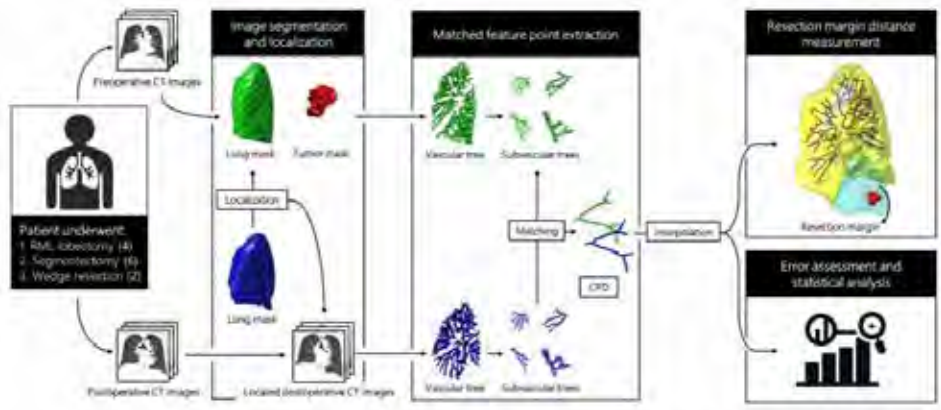

Figure 1. Framework of this study. CPD, Coherent Point Drift; CT, computed tomography; RML, right middle lobe.

Table 1. Resection margin distance measurement results.

Case no.	Surgical procedure/ Location	Margin distance (mm)
#1	Lobectomy/ RML	< 1.00
#2	Lobectomy/ RML	4.69
#3	Lobectomy/ RML	< 1.00
#4	Lobectomy/ RML	11.87
#5	Segmentectomy/ R (S6)	4.12
#6	Segmentectomy/ R (S6)	6.16
#7	Segmentectomy/ R (S7, 8, 9, 10)	5.39
#8	Segmentectomy/ L (S6)	5.74
#9	Segmentectomy/ L (S9, 10)	16.09
#10	Segmentectomy/ R (S8)	1.73
#11	Wedge resection/ LUL	6.16
#12	Wedge resection/ RUL	13.08

Keywords: Resection Margin, Early lung cancer, Sublobar resection

EP.07.09 Preliminary Results of One-Stop Shop: Results From the First Twenty-One Tumor Resections Compared to a Stage-Matched Control Group

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Introduction: We have implemented a one-stop shop (OSS) concept for patients with suspected malignant pulmonary nodules, consisting of: Robotic-assisted navigation-bronchoscopy with integrated cone-beam CT, biopsy, marking of the nodule (fiducial/ICG), fresh-frozen examination and direct oncological resection in one general anaesthesia.

Methods: Comparison of the first 21 patients undergoing our OSS concept to UICC-stage-matched (1:1) control group (n=21), in which patients had preoperative transbronchial biopsy/wedge-resection for diagnostic purposes. Time period was compared from first CT-scan with suspicious lesion to treatment.

Results: There was no relevant difference regarding median age (70 vs. 71 years; p=0.959) and gender (p=0.537) between the two groups. Ten patients had an UICC-Stage IA2, eight IA1, two Tcis and one IB. IN both groups, all surgeries were performed by a minimal-invasive approach (VATS/RATS). Time from first CT-scan with suspicious lesion to treatment was significant shorter in the OSS cohort (41 days vs. 61. days respectively, p=0.0032). There was no difference in overall hospitalisation between the groups (median 4 days in both groups, p=0.5).

Conclusions: With our OSS approach, potentially malignant pulmonary lesions can be diagnosed and treated efficiently, minimizing delays in patient care in patients, which are suitable for primary resection. This concept may also reduce costs by shortening overall hospital stay, as no additional hospitalisation is required for diagnostic intervention. Nevertheless, further analysis is needed to fully evaluate its potential impact.

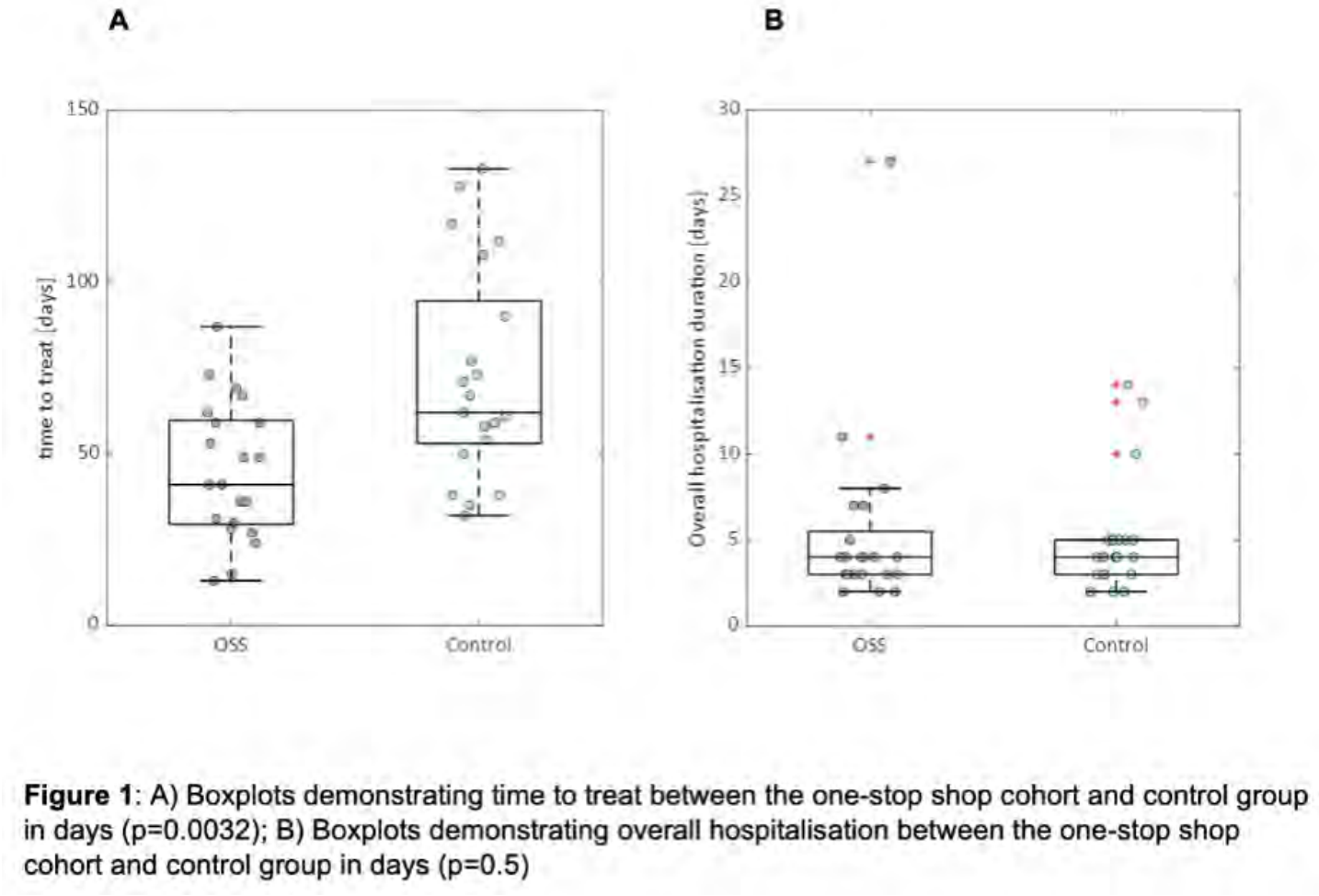

Figure 1: A) Boxplots demonstrating time to treat between the one-stop shop cohort and control group in days (p=0.0032); B) Boxplots demonstrating overall hospitalisation between the one-stop shop cohort and control group in days (p=0.5)

Keywords: Early Stage NSCLC, One-Stop Shop, Minimal-invasive Surgery

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.10 Analysis of Residual Lung Volume After Segmentectomy Using 3DCT and Risk Factors for Decline in Postoperative Pulmonary Function

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Introduction: Lung segmentectomy is increasingly performed as a less invasive alternative to lobectomy, especially in patients with early-stage lung cancer or limited pulmonary reserve. However, some patients experience a decline in pulmonary function equivalent to that after a lobectomy. In particular, the relationship between lung volume loss after segmentectomy and the pulmonary function decline remains unclear. This study aims to investigate the residual lung volume after segmentectomy using detailed 3DCT and to identify the risk factors for pulmonary function decline.

Methods: We retrospectively analyzed 169 patients who underwent lung segmentectomy at our institution between January 2017 and December 2023. All patients had pulmonary function test data between 6 and 18 months postoperatively. The postoperative pulmonary function decline ratios were calculated as the ratios of post- to pre-operative forced expiratory volume in 1 second (FEV1.0) and forced vital capacity (FVC). Patients with both ratios below 0.9 were classified as the pulmonary function decline group, while the remaining were classified as the normal group. Lung volumes were reconstructed and measured using REVORAS™ (Ziosoft) based on pre- and post-operative HRCT images. The predicted residual lung volume was defined as the volume of both lungs excluding the segment to be resected on the preoperative CT. The predicted postoperative lung volume proportion was defined as the proportion of the predicted residual lung volume to the whole lung volume. The predicted postoperative respiratory function was calculated based on this value.

Results: The median age was 73 years, and 85 were male. Lung cancer was diagnosed in 158 patients, and the median tumor diameter was 1.8 cm. Of 169 cases, 139 were classified as the normal group, and 30 as the pulmonary function decline group. The decline group showed a tendency for a larger tumor maximum diameter ($p=0.05$), but there was no significant difference in the predicted postoperative lung volume proportion ($p=0.863$). The ratios of measured postoperative FEV1 and FVC to their predicted postoperative values were significantly higher in the normal group than in the decline group (FEV1: 1.11 vs. 0.92, $p < 0.001$; FVC: 1.14 vs. 0.94, $p < 0.001$). In addition, the ratio of measured postoperative residual lung volume to its predicted value was also significantly higher in the normal group than in the decline group (1.07 vs. 1.00, $p < 0.001$).

Conclusions: Our results suggest that the predicted postoperative lung volume alone was not sufficient to predict decline in postoperative respiratory function. Although the residual lung expansion plays an important role in compensating for lost volume, it can be influenced by factors such as lung compliance and postoperative thoracic adhesions. Future investigations should also consider additional variables, including postoperative pain management, perioperative performance status, and comorbidities.

Keywords: Sublobar resection, Pulmonary function, 3DCT

EP.07.11 Comparison of Robotic Assisted Thoracoscopic Lobectomy and Video-Assisted Thoracoscopic Lobectomy for Early Stage Non-Small Cell Lung Cancer

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Introduction: Robotic-assisted thoracoscopic (RATS) pulmonary resection for early-stage non-small lung cancer (NSCLC) is being increasingly performed in world wide. To evaluate its safety and oncologic efficacy, we compared the outcomes of both RATS and video-assisted thoracoscopic (VATS) lobectomy in patients with stage 0 or IA NSCLC.

Methods: From August 2014 to December 2024, a total of 330 patients with resected stage 0 or IA NSCLC who underwent RATS (n=133) and VATS (n=174) pulmonary lobectomy were included. A da Vinci Si surgical robot (Intuitive Surgical, Inc, Santa Clara, CA) was used to perform RATS lobectomy. A VATS lobectomy was performed using the 4-port technique. Perioperative and clinicopathologic outcomes were evaluated.

Results: The baseline characteristics were similar between RATS and VATS groups. There were more right upper lobectomies and fewer left upper lobectomies in the RATS group compared to VATS group. Intraoperative blood loss was statistically lower in the RATS group than in the VATS group. No significant differences were found in operative time, duration of chest tube drainage, Frequency of postoperative complications and postoperative hospital stay. In lymph node (LN) dissection, the RATS group had significantly a higher number of LN and total number of LN harvested.

Conclusions: Both RATS and VATS lobectomies are safe and feasible for the treatment of early-stage NSCLC. RATS achieved similar perioperative outcomes and higher LN dissection. The minimally invasive nature of RATS surgery and its significance in dissection may contribute to improved long-term outcomes.

Table 1

Factors	VATS (n=186)	RATS (n=144)	p-value
age	68±0.8	68±0.9	0.83
gender			
male	96 (52%)	76 (53%)	0.83
female	90 (48%)	68 (50%)	
Smoking status			
no	82 (44%)	60 (42%)	0.66
yes	104 (56%)	84 (58%)	
Histologic type			
adenocarcinoma	161 (87%)	125 (87%)	0.16
squamous/others	25 (14%)	19 (15%)	
lobe			
Right upper/middle	78 (36%)	96 (53%)	<0.01
Right lower	38 20%)	19 (14%)	

Table 2

Factors	VATS (n=186)	RATS (n=144)	p-value
Operative time(min)	251±5.6	249±5.0	0.78
Blood loss (g)	51.8±4.4	32.8±5.0	<0.01
Duration of chest tube drainage (day)	2.8±0.1	2.7±0.1	0.78
Postoperative hospital stay (day)	9.5±0.3	9.1±0.3	0.32
Conversion to thoracotomy	2 (1%)	1 (0.7%)	0.73
Postoperative complications			
yes	22 (12%)	13 (9%)	0.40
no	164 (88%)	131(91%)	
Number of N1 lymph node	8.3±0.4	9.2±0.4	0.09
Upstaged number of pN1	16 (9%)	10 (7%)	0.57
Number of N2 lymph node	7.7±0.5	9.3± 0.6	0.03
Upstaged number of pN2	12 (6%)	8 (6%)	0.73
Total number of LN dissection	16.0±0.8	18.5±1	0.01

Keywords: Non-small cell lung cancer, Surgery, Robotic surgery

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.12 The Impact of Quantification Parameters and Clinicopathologic Characteristics on the Prognosis of Stage Ia Invasive Lung Adenocarcinoma

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Introduction: The risk factors for postoperative recurrence of stage IA invasive lung adenocarcinoma (LUAD) are still unclear. Studies have shown that consolidation-to-tumor ratio can predict prognosis, but the solid size is difficult to measure accurately. This study aims to identify high-risk factors for postoperative recurrence of stage IA invasive LUAD using deep learning (DL)-based quantitative parameters combined with clinical and pathological characteristics of tumors.

Methods: The maximum total size on axial images (MTSA) and the maximum solid size on axial images (MSSA) were evaluated by two chest radiologists, and the solid component ratio (CTR) was calculated. Maximal total size on multiplanar reconstructed images (MTSMPR), total volume (TV), solid component volume (SV), and solid component volume percentage (SV%) were evaluated by DL, with 0HU, -50HU, -100HU, -150HU, -200HU, -250HU, -300HU, -350HU, and -400HU as the thresholds of solid components, respectively. The DL-based quantification was compared with manual measurements to find the optimal predictor. Combined with clinical and pathological characteristics, competing risk model was used to identify independent risk factors for recurrence.

Results: A total of 2,117 patients with pathological stage IA invasive LUAD were included, and 50 patients experienced recurrence and 26 patients died. The recurrence prediction performance of manual measurements was inferior to that of DL-based quantification. In DL-based quantification, SV0HU% (with 0HU as the solid component threshold) was most closely associated with recurrence, which was superior to other measurements. Univariate and multivariate analysis showed that pathological stage, SV0HU% (HR = 8.95, 95% CI: 4.32-18.57, P < 0.001), pathological stage (HR = 12.14, 95% CI: 1.58-93.13, P = 0.016), pathological subtype (HR = 3.04, 95% CI: 1.46-6.34, P = 0.003), vascular or neural invasion (HR = 3.83, 95% CI: 1.56-9.42, P = 0.003), and spread through air space (HR = 2.34, 95% CI: 1.23-4.44, P = 0.009) were independent risk factors for recurrence of stage IA invasive LUAD.

Conclusions: Among the quantitative parameters of tumors, DL-based SV0HU% was most closely related to postoperative recurrence of stage IA invasive LUAD. In addition, common clinical and pathological characteristics can be used to identify patients at high risk of recurrence and should be considered when assessing the prognosis of patients with stage IA disease.

Keywords: lung adenocarcinoma, stage IA, recurrence

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.13 Thoracoscopic Combined Anatomicalsublobarresection for Deep Intersegmental Small-Sized Non-Small Cell Lung Cancer

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Introduction: The optimal approach for sublobar resection of small-sized nodules in deep-seated, intersegmental locations, as opposed to peripheral lung regions, remains undetermined. This retrospective study compares the surgical and oncological outcomes of deep intersegmental lung cancer (DILC) treated with combined anatomical sublobar resection (CASR) versus combined non-anatomical extended resection (CNER).

Methods: Data were collected from 95 consecutive patients with small (≤2 cm) cN0 DILC who underwent CASR or CNER between March 2019 and November 2024. DILC was defined as a lesion located within the inner two-thirds of the lung parenchyma, involving the junction of adjacent lung segments, as determined by thin-slice (1 mm) and three-dimensional computed tomography. Patients were categorized into two groups: the CNER group, which underwent (sub)segmentectomy with an extended wedge resection of an adjacent segment, and the CASR group, which underwent (sub)segmentectomy combined with (sub)segmentectomy of an adjacent segment.

Results: All patients successfully underwent surgical resection: 38 received CNER and 57 received CASR, with no severe morbidity or perioperative mortality. The CASR group exhibited a significantly lower rate of intraoperative complications (0% vs. 10.5%, P = 0.012), while postoperative complication rates did not differ significantly (7.01% vs. 10.5%, P = 0.546). CASR was associated with a wider surgical margin compared to CNER (2.5 cm vs. 1.6 cm, P < 0.001), while tumor size (1.2 cm vs. 1.2 cm, P = 0.92) and the number of lymph nodes resected (6.3 vs. 6.1, P = 0.71) were comparable between the groups. Local recurrence occurred in six patients (15.8%) in the CNER group at the surgical margin, whereas one patient (1.8%) in the CASR group experienced recurrence in the lymph node basin of the original tumor (P = 0.01). Over a median follow-up of 31 months, the CASR group demonstrated higher local recurrence-free survival (98.2% vs. 84.2%), five-year disease-free survival (96.6% vs. 81.6%), and overall survival (94.7% vs. 89.5%), though the differences were not statistically significant (P = 0.196, 0.403, and 0.724, respectively).

Conclusions: CASR is a safe and effective surgical approach that provides adequate surgical margins, potentially reducing the risk of margin failure—an essential factor in preventing local recurrence. CASR may be a preferable alternative to CNER for patients with DILC.

Keywords: Anatomical sublobar resection, Deep intersegmental nodules, Small-sized lung cancer

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.14 Contemporary Stereotactic Body Radiation Therapy Utilization Trends for Stage I Non Small Cell Lung Cancer

S. Sakowitz, H. Tupper, L. Benjamin, S. Oh, T. He, R. Ronaghi, C. Channick, B. Rosenberg, R. Salehi-rad, M.I. Smith, J. Bando, T. Young, I. Barjaktarevic, M. Velez, A. Gower, A. Cummings, J. Goldman, A. Lisberg, E. Garon, J. Yanagawa, E. Cameron, B. Burt, S. Revels, P. Toste, J. Lee, A. Lee, J. Deng, H. Lee, P. Benharash, D. Moghanaki
David Geffen School of Medicine at UCLA, Los Angeles/CA/USA

Introduction: The utilization of SBRT for stage I non-small cell lung cancer (NSCLC) has been increasing since its introduction in the early 2000s. However, recent trends and reasons for declining preferences for surgery have not been reported.

Methods: A retrospective cohort study was conducted using the National Cancer Database (NCDB) to analyze patients ≥18 years diagnosed with histopathologically confirmed clinical stage I NSCLC diagnosed between 2004 and 2021. Patients were categorized by receipt of Surgery, SBRT, non-SBRT Radiation, or No-Treatment. Exclusion criteria included prior chemotherapy or radiation before surgery and unknown surgical status. Temporal trends were assessed using Cuzick's test, and statistical analyses were performed using Stata 18.0.

Results: Among 343,557 patients with clinical stage I NSCLC, 59% (n=202,517) received surgery, 19% (n=64,159) received SBRT, 12% (n=41,991) underwent non-SBRT Radiation, and 10% (n=34,890) received no treatment. SBRT patients were older, more frequently insured by Medicare, and had greater comorbidity burden. Tumor sizes were smaller, with a predominance of stage IA disease in the SBRT cohort. From 2004 to 2021, SBRT utilization increased from ~1% to 35% (P<0.001), while surgery rates declined from 68% to 41% (P<0.001). The proportion of untreated patients decreased from 16% to 10% (P<0.001). Reasons for patients not undergoing surgery included "not planned for surgery" (74%), "not surgical candidate" (21%), and "refused surgery" (5%). The proportion of patients with surgical contraindications receiving SBRT declined from 22% in 2004 to 18% in 2021 (P<0.001), whereas those for whom surgery was not planned as first-line therapy increased from 74% to 77% (P<0.001).

Conclusions: Utilization of SBRT for stage I NSCLC continues to increase, independent of a rise in surgical contraindications or patient refusal of surgery. This shift may reflect the perceived advantages of SBRT. Until results from ongoing phase III trials become available, patients preferring SBRT should continue to be counseled about surgery, given the potential benefits it can offer patients.

Keywords: Non small cell lung cancer, Surgery, Stereotactic body radiation therapy

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.15 Model Navigated Anchor Based Responsive CT Hybrid Surgery for Intraoperative Localization and Resection for Small Pulmonary Nodules

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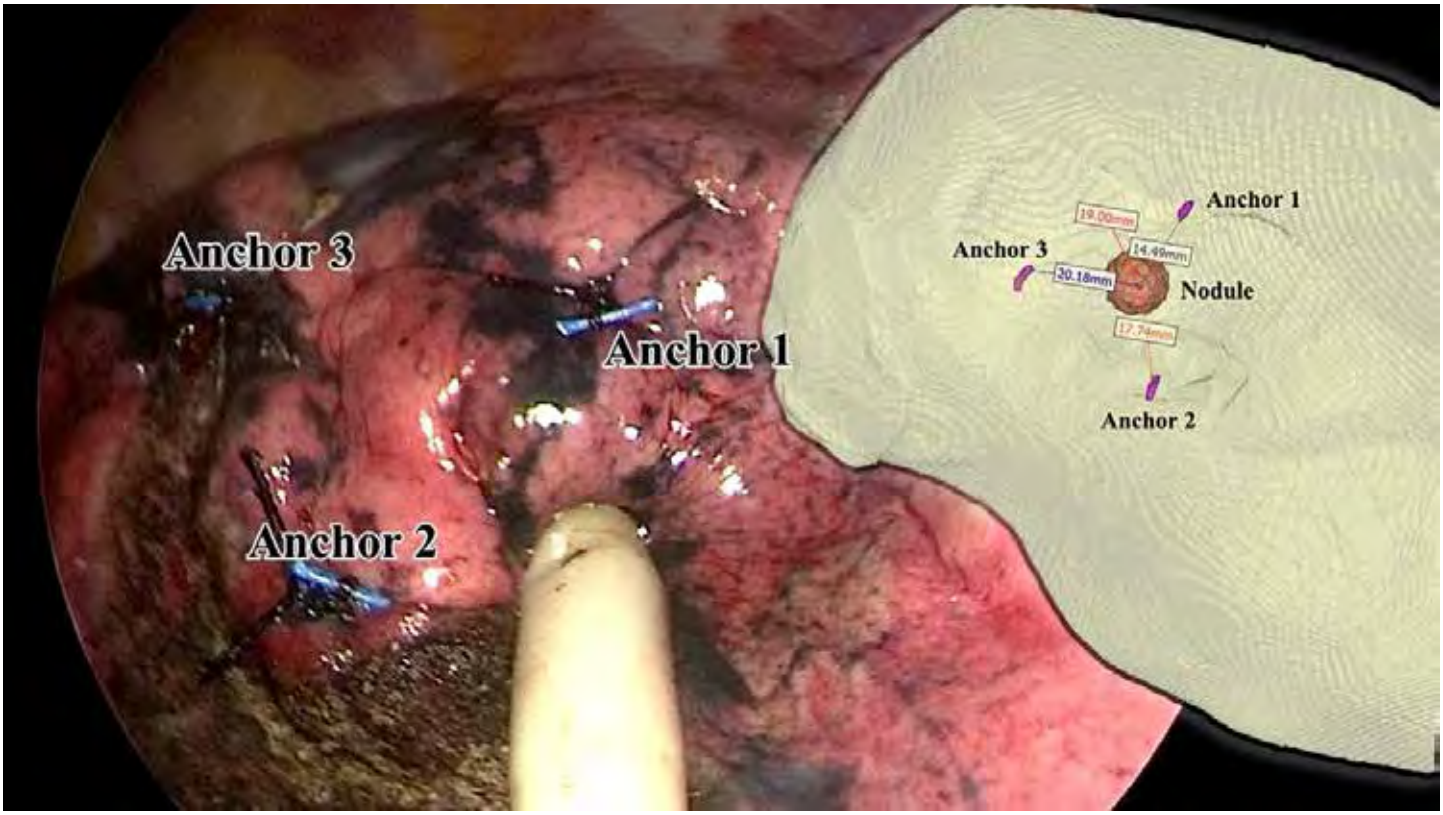
Introduction: With the widespread application of computed tomography (CT) screening and the ever-increasing evidence suggesting the efficacy of sub-lobar resection for early lung malignancies, the precise localization and resection of small pulmonary nodules, especially those that are hard to locate or multiple nodules, calls for attention.

Methods: We collected the consecutive records of patients receiving model-navigated anchor-based responsive CT hybrid (MONARCH) surgery or preoperative CT-guided puncture localization and resection for small pulmonary nodules in our center between 1 January and 31 December 2024. Localization-specific and perioperative parameters were analyzed and compared between the two methods.

Results: All patients underwent localization and resection without significant complications, and the median time for MONARCH localization was 39 minutes. There was no statistical difference in localization outcomes between the two groups (MONARCH: precise 50%, helpful 43.33%, missed 6.67% vs. conventional: precise 49.49%, helpful 42.42%, missed 8.08%, p=1.000). The MONARCH approach displayed superiority in rates of intraparenchymal hemorrhage (0% vs. 16.16%, p=0.022), pneumothorax (0% vs. 29.30%, p<0.001). As for the time of chest tube placement, drainage volume, and postoperative complications, no significant inferiority was found. All the MONARCH surgeries achieved complete resection, and no statistical difference was discovered compared to the conventional approach.

Conclusions: The MONARCH surgery for small pulmonary nodule localization and resection is feasible and effective. Without transthoracic puncture, the technique suits settings like multiple pulmonary nodules or those unfit for puncture or direct tactile localization.



Keywords: VATS, Intraoperative Nodule Localization, Hybrid Surgery

EP.07.16 Minor Ground-Glass Opacity Differences Were Associated With Prognostic Variation in Solid-Predominant Clinical Stage IA Lung Adenocarcinoma

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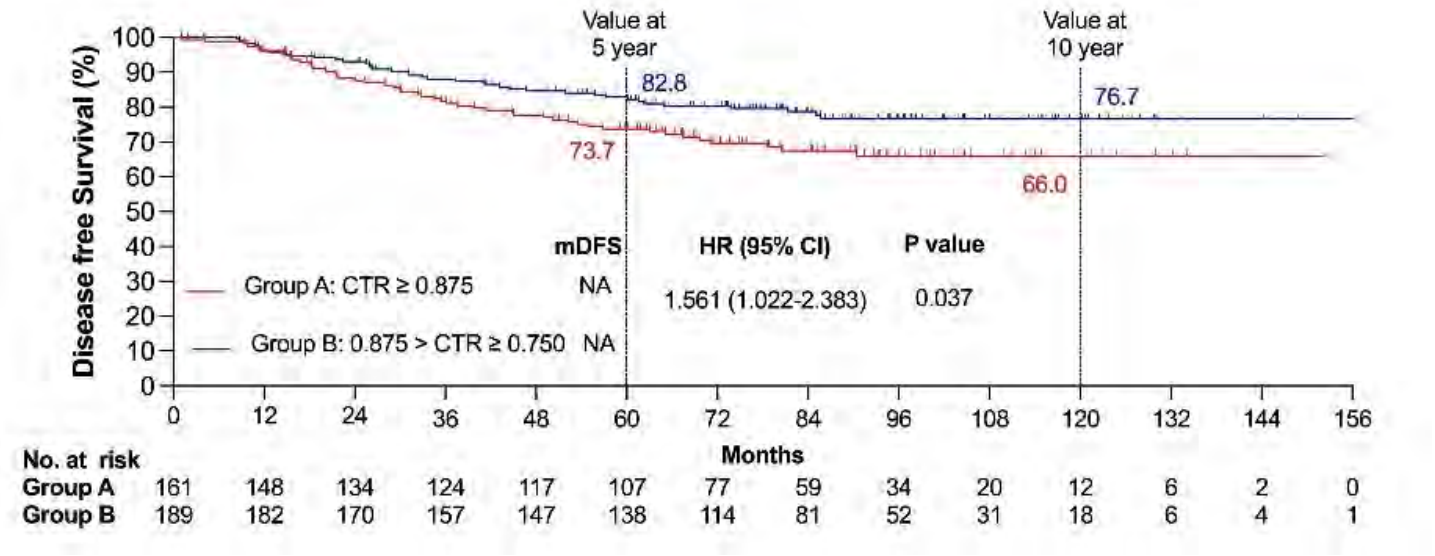
Introduction: Advances in low-dose and multi-slice CT have improved early detection of NSCLC, increasing the diagnosis of small tumors with ground-glass opacity (GGO) components. GGO presence is associated with better prognosis and lower invasiveness, even in tumors with similar solid diameters. The consolidation-to-tumor ratio (CTR) is commonly used to quantify GGO and is considered a potential independent prognostic marker. However, its prognostic significance in solid-predominant tumors (CTR > 0.75), particularly in stage IA adenocarcinoma, remains unclear.This study aims to evaluate whether small differences in GGO influence prognosis in clinical stage IA solid-predominant adenocarcinoma and to clarify the prognostic role of CTR in solid-predominant adenocarcinoma.

Methods: We retrospectively reviewed 3575 NSCLC patients who underwent lung resection from 2011 to 2018 at National Taiwan University Hospital. After applying strict inclusion criteria, 350 patients with clinical stage IA solid-predominant adenocarcinoma (CTR ≥ 0.75, solid component <3 cm) were analyzed. Patients were stratified by average CTR (cutoff: 0.875) into group A (CTR ≥ 0.875, n=161) and group B (0.75 ≤ CTR < 0.875, n=189). Preoperative imaging, clinicopathologic features, and postoperative outcomes were evaluated. Survival analyses were performed using Kaplan-Meier and Cox regression models.

Results: Group B showed significantly better 5-year disease-free survival (DFS) than Group A (82.8% vs 73.7%, HR=1.561, p=0.042), despite only minor differences in GGO components. Overall survival (OS) was comparable between groups (97.3% vs 98.6%, p=0.266). Multivariate analysis identified gender and solid component size on CT as independent preoperative predictors of DFS. The CTR-DFS association remained significant in patients undergoing lobectomy, while DFS did not differ between lobectomy and sublobar resection within either group. Analysis using finer CTR cutoffs (0.75-0.95) also demonstrated significant DFS differences (p=0.0117) in a linear Cox regression model.

Conclusions: CTR demonstrated a significant impact on disease-free survival, even with minor differences, in stage IA solid-predominant adenocarcinoma. Both linear and multivariate Cox regression analyses identified CTR as an independent prognostic factor. Surgical approach (lobectomy vs. sublobar resection) did not significantly affect survival outcomes. Further studies are needed to confirm these findings in non-solid-predominant adenocarcinoma.



Keywords: ground-glass opacity, sublobar resection

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.17 Patient Characteristics, Surgical Outcomes, and Treatment Decisions in Early-Stage Resected NSCLC in Canada

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Introduction: Non-small cell lung cancer (NSCLC) is the most commonly diagnosed type of lung cancer. Of these patients, approximately 50% are diagnosed during the early stages of their disease (I-III), and amongst these, less than 30% are diagnosed with resectable NSCLC. Currently, in Canada, there is limited data characterizing this heterogenous early-stage resectable patient population, treatment pathways, and the molecular testing landscape. The primary aim was to describe the patient characteristics, treatment, and referral patterns of early-stage resected NSCLC patients, estimate the prevalence/frequency of biomarker testing and biomarkers of interest (i.e. EGFRm, PDL1). Secondary objectives included describing the surgical treatment outcomes, short-term follow-up, and testing methods for biomarkers and immunotherapy markers.

Methods: This observational cohort study utilized data from the Canadian Association of Thoracic Surgeons (CATS) national database and prospectively enrolled patients across Canada for 12 months (End date March 2025). The CATS national database includes data from nine thoracic surgery centers across Canada, with another ten centers that have either expressed interest or in the process of being onboarded. Study measures, including patient demographics, clinical characteristics, treatment patterns, and surgical outcomes, were collected. Continuous study measures were reported descriptively with mean and median. Frequencies and percentages were used to document categorical measures of interest. Time to event analysis was conducted for post-surgical timelines and time to testing. These results were presented as median time and IQR time to event.

Results: The study population included 162 patients with a mean age of 70.03 ±7.30 years, 56% females. Stage I was the most common one (39.5%), followed by Stage III (30.9%) with 24.7 % of stage IIIA, and stage II (29.6%). The most frequent histological subtype was acinar adenocarcinoma (24.7%), followed by solid adenocarcinoma (15.5%). The median time from preoperative biopsy to thoracic surgery was 21 days (IQR=33-1), and surgery consultation to operation was 48 days (IQR= 92-28). The median length of stay was 3 days (IQR=6-2) from surgery to discharge. The consultation with thoracic surgeons to medical oncologists was 71 days (IQR=99.8-29.5), and for 8 patients who needed neoadjuvant therapy, consultation with a medical oncologist to the starting of first neoadjuvant treatment was 23 days (IQR=29.5-19). There was variation in biomarker testing across centers: Halifax, McGill, Ottawa, and UBC. Key biomarkers analyzed were EGFR status, ALK rearrangement, ROS1 mutation, BRAF mutation, KRAS mutation, and PD-L1 expression. Pre-operative testing was performed more at the McGill and Ottawa centers. More molecular tests were performed post-operatively than pre-operatively. EGFR testing was performed in 50.7% of post-operative cases, compared to 25.3% pre-operatively. ALK rearrangement testing was conducted in 48.8% of post-operative cases, compared to 24.7% pre-operatively. For PD-L1 expression, testing was more frequently performed post-operatively than pre-operatively.

Conclusions: This study provides important insights about testing patterns, treatment decisions, and surgical outcomes for NSCLC surgical candidates across Canada. Variation in different regions' biomarker testing highlights the need for a national standard. This study is still ongoing, aiming to include a total of 200 persons with lung cancer.

Keywords: Surgical outcome, Early-Stage Resected NSCLC, Canada

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.18 Optimizing Intraoperative Lymph Node Dissection in Stage I NSCLC: A Risk-Stratified Approach Based on CNN Model Predictions

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Introduction: Surgery is now the mainstay of curative local treatment for stage I non-small cell lung cancer (NSCLC) in clinical settings. As an important component, lymph node (LN) resection is a well-established prognostic factor, closely related with recurrence and survival in resectable NSCLC. Therefore, more precise surgical scope involving the resection of LNs is one of the clinical problems that need to be solved urgently. So we aimed to use our conducted model for predicting occult lymphatic metastasis (OLM) to appropriately stratify the risk of OLM and explore the effect of intraoperative lymph node dissection on the prognosis of patients with clinical stage I NSCLC with different OLM risks.

Methods: According to the OLM risk prediction score based on the CNN model conducted in the prospective surgical cohort comprised of 2489 stage I NSCLC patients, 85th percentile in the training set was used as the cut-off value of OLM high- and low-risk groups. Both groups were divided into two groups (1-5 LNs and ≥6 LNs) according to the number of LN dissection, and two groups (less than 3 N2 and 3 N1 and no less than 3 N2 and 3 N1) according to the number of LN stations cleared, respectively. Then, the high-risk group patients were further divided into clinical stage T1 and T2a, which were divided into two groups according to the above number of discharged LNs, respectively. With DFS and CSS as the research endpoints, the survival curve was plotted by Kaplan-Meier analysis, and the Cox proportional risk regression model was used to evaluate the impact of the number and station of intraoperative LN dissection on the prognosis of patients.

Results: Stratified with 85th percentile of risk score of patients in the training set (n=1991) as the cut-off value (0.399), patients in the testing set (n=250) were divided into high- and low-risk group. The results of Kaplan-Meier curve and survival analysis showed that DFS was better in low-risk people with less than 6 LNs or 3 N2 and 3 N1 cleared (P=0.00035 and P<0.0001, respectively), while removal of more than 6 LNs benefit DFS and CSS of clinical T2a high-risk populations (P=0.016 and P=0.00046, respectively). However, no statistical difference in survival due to lymph node dissection factors was observed in other groups.

Conclusions: The results of this study based on the previous OLM prediction CNN model suggested that intraoperative resection of less than 6 LNs and less than systemic LN dissection could bring survival benefit to low-risk people with OLM, while such resection range was insufficient for clinical T2a high-risk patients. Accordingly, it provided a reference for the scope of intraoperation LN dissection of clinical phase I NSCLC, guiding individualized treatment.

Keywords: Lymph Node Dissection, Non-small Cell Lung Cancer, CNN

EP.07.19 Temporal Advances of Surgical Outcomes in Posterior Segment ectomy for Primary Lung Cancer

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Introduction: The JCOG0802 trial demonstrated that segmentectomy was superior to lobectomy in overall survival for small-sized peripheral non-small cell lung cancer. However, segmentectomy was associated with longer operation time, greater blood loss, and prolonged air leakage. Among complex segmentectomies, posterior segmentectomy is considered technically difficult and challenging because segmental structures are deep in the lung parenchyma from the interlobar fissure. This single-institution retrospective study examined periodical changes in surgical outcomes of posterior segmentectomy.

Methods: The study included 95 patients who underwent S10 or S9+10 segmentectomy for primary lung cancer at our institution between January 2012 and December 2023. The interlobar and posterior approaches were defined as surgical procedures where segmental structures were dissected from the interlobar fissure and the inferior pulmonary ligament.

Results: The interlobar approach and posterior approach included 32 and 63 patients, respectively. The number of posterior segmentectomies increased yearly, and the posterior approach became standardized in 2019. The median age was 70 years; 36 were male, and 47 had never smoked. 49 cases were right-sided surgeries. The median operation time, blood loss, and postoperative hospital stay was 116 (interquartile range (IQR), 106-126) minutes, 17.5 (IQR, 4.5-30.5) ml, and 3.5 (IQR, 3.2-3.8) days in the interlobar approaches, and 106 (IQR, 101-111) minutes, 8.0 (IQR, 1.3-14.7) ml, and 3 (IQR, 2.3-3.7) days in the posterior approach. The major (> Grade IIIa) complications occurred in one (2.4%) and five (7.9%) cases, and there were no mortality cases. The median surgical margin was 21.5 (IQR, 17.5-25.5) mm and 20 (IQR, 18-22) mm (P = 0.25).

Conclusions: With the accumulation of surgical cases, the posterior approach that minimizes the unnecessary division of lung parenchyma replaced the interlobar approach for posterior segmentectomy. The operation time became shorter, and perioperative outcomes were encouraging.

Keywords: segmentectomy, non-small cell lung cancer, posterior approach

EP.07.20 Evolution of Overall Survival (OS) After Good Quality Curative-Intent Lung Cancer Surgery in a Population-Based Cohort

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Introduction: Surgical resection is the most effective treatment for non-small cell lung cancer (NSCLC), with OS influenced by both surgical quality, tumor biology, and adjuvant therapy. Having previously demonstrated sequential improvements in surgical quality and OS, we now evaluate survival outcomes specifically among patients who received high-quality surgery.

Methods: The ongoing population-based Mid-South Quality of Surgical Resection (MS-QSR) project involved a pre-intervention era (Era 1: 2004-2008); introduction of a lymph node (LN) collection kit (Era 2: 2009-2013); its widespread adoption (Era 3: 2014-2018), and introduction of a standardized pathology gross dissection protocol (Era 4: 2019-2023). We compared recipients of good quality surgery (defined by IASLC R0 resection and American College of Surgeons' Operative Standard-5.8), evaluated OS with Kaplan-Meier analysis and Cox proportional hazards models with adjusted hazard ratios (aHR) controlling for age, race, sex, insurance status, rurality, comorbidities, pre-radiologic tumor size, histology, IASLC margin classification, receipt of PET/CT, invasive staging, neoadjuvant therapy, final surgical technique, extent of resection, teaching status, and surgeon specialization (with Era 1 for reference).

Results: 7,162 patients underwent curative-intent resection: 987 (14%) in Era 1, 2,219 (31%) in Era 2, 2,057 (29%) in Era 3, and 1,899 (26%) in Era 4. From Era 1 to 4, IASLC R0 resection rates increased from 0% to 32% (p<0.0001), attainment of OS-5.8 increased from 4% to 67% (p<0.0001), 120-day mortality decreased from 10% to 4% (p<0.0001), and five-year OS improved from 48% to 70% (p<0.0001). Among patients with IASLC R0 resections, 5-year OS for Stage I was 67%, 63%, and 72% in Eras 2 to 4 (p=0.0056). Among patients meeting OS-5.8, 5-year OS for Stage I was 63%, 62%, and 73% in Eras 2 to 4 respectively (p<0.0001). OS was stable across eras for Stage II-IV patients in both groups.

Conclusions: Surgical quality improved across all eras, and OS gains were primarily observed in Era 4 Stage I patients. Controlling for high quality surgery eliminated OS differences in stages II-IV patients across eras. However, Stage I patients in Era 4 had improved survival even among those who received high surgical quality, suggesting additional contributing factors beyond surgical improvements. Ongoing research is evaluating potential biologic explanations for these findings.

Era	Era 1 (2004-2008)	Era 2 (2009-2013)	Era 3 (2014-2018)	Era 4 (2019-2023)
Total Cases (N, %)	**987 (14%)**	**2,219 (31%)**	**2,057 (29%)**	**1,899 (26%)**
Age Median (Q1, Q3)	68 (61, 74)	68 (61, 74)	68 (62, 74)	68 (62, 74)
Overall Survival (OS)				
aHR (95% CI)	*Ref*	0.72 (0.63-0.82)	0.62 (0.54-0.72)	0.44 (0.37-0.51)
5-Year OS (%) [CI]	48 (45-51)	53 (51-55)	58 (56-61)	70 (67-73)
Surgical Quality Metrics				
IASLC R-Complete (R0) (%)	-	9%	21%	32%
R0 5-Year OS (%) [CI] by Clinical Stage				
Stage I	-	67 (59-75)	63 (58-68)	72 (65-79)
Stage II	-	55 (37-73)	55 (42-67)	62 (48-75)
Stage III	-	41 (22-62)	32 (16-50)	NA
Stage IV	-	40 (13-70)	42 (17-69)	NA
ACS CoC Standard 5.8 (%)	4%	24%	50%	67%
ACS 5.8 5-Year OS (%) [CI] by Clinical Stage				
Stage I	-	63 (58-68)	62 (59-66)	73 (68-78)
Stage II	-	51 (40-61)	51 (44-59)	63 (53-73)
Stage III	-	51 (39-63)	57 (46-68)	51 (33-69)
Stage IV	-	40 (13-70)	42 (17-69)	NA
120-Day Mortality	10%	9%	7%	4%

Keywords: Lung Cancer Surgery, Surgical Quality Improvement, NSCLC Survival Outcomes

EP.07.21 The Efficacy of the 'Lung Partial Resection Prior to Lobectomy Method' as a No-Touch Isolation Technique in Lung Cancer Surge

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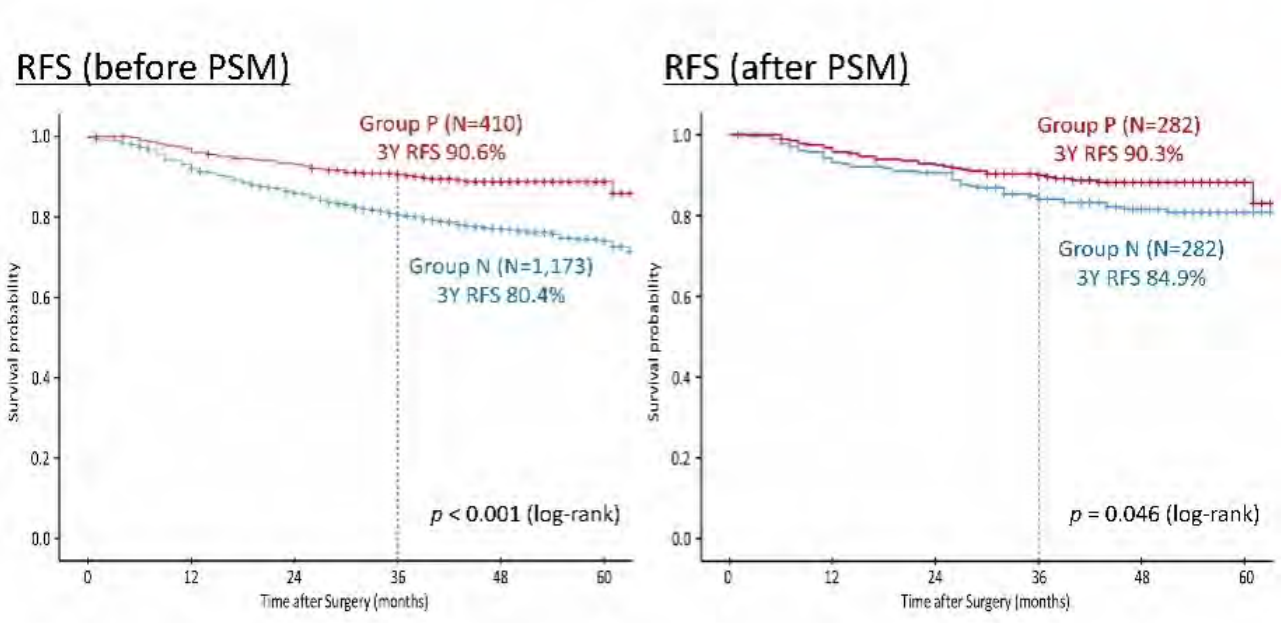
Introduction: Although "no-touch isolation technique (NTIT)", which will theoretically prevent intraoperative release of circulating tumor cells (CTCs) from primary tumor, has been reported, its efficacy for the treatment for non-small cell lung cancer (NSCLC) is uncertain. We evaluated the efficacy of the 'lung partial resection prior to lobectomy method' as a NTIT in surgery for patients with c-stage IA-IB NSCLC.

Methods: We retrospectively reviewed the data of 1,825 patients with c-stage IA-IB (8th) NSCLC who underwent lobectomy + mediastinal lymph node (LN) dissection at 25 Japanese institutes in 2017-2018. Among them, we excluded patients who received neoadjuvant therapy or whose pathological diagnosis was adenocarcinoma in situ or minimally invasive adenocarcinoma, we enrolled and analyzed 1,583 patients in this study. We classified patients into 2 group according to the presence of undergoing lung partial resection (e.g. for intraoperative pathological diagnosis) prior to lobectomy (Group P; who underwent, and Group N; who did not) and compared the postoperative relapse-free survival (RFS) of both groups.

Results: The 410 and 1,173 patients were classified into Group P and Group N. The median follow-up periods were 48 months in both groups. Patients in Group P showed significantly better RFS than those in Group N (3-year RFS 90.6% vs. 80.4%, respectively, p <0.001). However, much confounding factors existed between groups, we performed propensity-score (PS) matching method with use of 17 confounding factors (type of institute, age, sex, smoking history, laterality, tumor location, primary lobe, cT factor, maximum tumor diameter, consolidation-to-tumor ratio, tumor appearance on CT, presence of conducting preoperative PET, SUVmax value, presence of pathological diagnosis before surgery, presence of conducting preoperative TBLB, presence of conducting preoperative percutaneous CT-guided biopsy, and surgical approach) and re-evaluated among 282 matched pairs. Even after PS matching, significantly better RFS was found in Group P than in Group N (3-year RFS 90.3% vs. 84.9%, respectively, p =0.046). Subset analyses among PS matched cohort revealed that the RFS in Group P showed tendency to be better than in Group N among patients without pathologically proven LN metastasis (3-year RFS 92.1% vs. 87.3%, p =0.081), whereas no intergroup difference was shown among patients with pathologically proven LN metastases (3-year RFS 65.6% vs. 52.4%, p =0.418).

Conclusions: For the patients with NSCLC without LN metastases, lung partial resection prior to lobectomy method can be the NTIT that prevents the intraoperative release of CTCs and improves postoperative RFS.



RFS, relapse-free survival; PSM, propensity score matching

Keywords: non-small cell lung cancer, surgery, no-touch isolation technique

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.22 Major Lung Resections for Non-Small Cell Lung Cancer: Does Postoperative Pneumonia Remain a Life-Threatening Complication?

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Introduction: Despite advancements in medical technology and surgical techniques, pneumonia remains the most common postoperative complication. This study aimed to evaluate the incidence and outcome of postoperative pneumonia in non-small cell lung cancer (NSCLC) patients undergoing major lung resections, and identify key risk factors.

Methods: A retrospective analysis was performed on prospectively collected data of patients undergoing major pulmonary resections for NSCLC at an university medical center from 2016 to 2023. Postoperative pneumonia was diagnosed based on the European Perioperative Clinical Outcome (EPCO) criteria, which include new pulmonary infiltrates, leukocytosis, fever, purulent sputum, antibiotic therapy, and increased oxygen demand. Empiric antibiotic therapy was initiated in all cases and adjusted according to antibiogram findings. Major resections included anatomical lobe resections (lobectomies) and pneumonectomies. The study was approved by the institutional ethics comittee (23-11306-BO).

Results: Data from 1,802 patients were analyzed. Lobectomy was the most common procedure (89.2%), followed by bilobectomy (4%) and pneumonectomy (6.8%). Stage I disease was present in 44.3% of patients, and stage II in 22.1%. Postoperative pneumonia occurred in 4.5% of cases. Patients with pneumonia had higher rates of unplanned ICU admission (0.9% vs. 16.1%, p=0.01) and 30-day mortality (0.7% vs. 20.5%, p=0.01). The extent of resection did not significantly influence pneumonia rates (p=0.14). Risk factors included advanced age (age >70 years: 0.8% vs. 1.9%, p=0.05), reduced preoperative diffusing capacity of the lungs for carbon monoxide (DLCO <60%: 0.7% vs. 1.9%, p=0.02), and revision surgery (1.1% vs. 4.4%, p=0.03). Multivariate analysis identified delirium (HR: 13.659, 95% CI: 2.214-84.275, p=0.01), postoperative renal failure (HR: 7.308, 95% CI: 1.334-40.047, p=0.02), and ECOG PS 3 (HR: 2.111, 95% CI: 0.812-5.487, p=0.03) as significant predictors of pneumonia.

Conclusions: Pneumonia after major lung resections remains a significant cause of mortality. Efforts to mitigate modifiable risk factors and to identify and manage postoperative complications hold promise to improve patient outcomes.

Keywords: postoperative pneumonia, lung surgery, lung cancer

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.23 Single Port Robot and Navigational Bronchoscopy During Single Episode of Anesthesia: Less Is More

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Introduction: Robotic lung resection with the multiport robot has been reported to improve perioperative metrics and may influence long term oncologic outcomes. Navigational bronchoscopy has emerged as an excellent platform to diagnose pulmonary nodules in any region of the lung. In our four-year experience, combining robotic bronchoscopy with multiport robotic surgery under single episode of anesthesia enhances the patient experience; diagnosis and definitive therapy are completed on the same day. We are evaluating the value of the Single Port (SP) robot on our Minimally Invasive Diagnosis and Surgery (MIDAS) program.

Methods: We reviewed the records of all patients having MIDASP (single port robot) operations between November 2024 and March 2025. Perioperative outcomes as well as short term follow up were collected. Robotic bronchoscopy was performed with Ion navigational bronchoscope and indocyanine green (ICG - 0.2cc) was used to mark nodules for sub lobar resections. We used the DaVinci Single Port (SP) robot; operations were performed through a 3 - 4 cm subcostal incision docking the robot through an access port. Double lumen endotracheal tube and CO2 insufflation were used in all procedures. Stapling was performed at the bedside for SP patients. Node dissection was completed on all patients. We used our MIDAS postoperative pathway for pain medications, chest drain management, and discharge criteria.

Results: Thirteen patients had MIDASP. Demographics include: Gender - Female 8, Male 5; Age - Mean 70 years, Range 56 - 81 years. All Single Port cases were completed without conversion to another surgical approach. Resections included lobectomy (3) and sub lobar (11). All patients were extubated in the operating room and there were no reintubations or ICU admissions. Chest drains were removed before discharge. Length of stay was 1.1 days; 12 of 13 patients were discharged on post op day 1. Final pathology confirmed: NSCLC (7), Carcinoid (2), Metastatic Urothelial Carcinoma (1), Benign Metastasizing Leiomyoma (1), Solitary Fibrous Tumor of the Pleura (2). NSCLC stages were: 1a (4), 1b (2), 4 (1). There were no mortalities or complications.

Conclusions: The Single Port (SP) robot has added a new dimension to minimally invasive thoracic surgery. Our initial experience with the single port robot has documented safety, decreased length of stay, equivalent node dissection, and similar perioperative morbidity/mortality. Subjectively the patients experience less pain, and we are evaluating this quantitatively. A single episode of anesthesia approach to managing lung nodules adds value to the patient's journey. Since a single subcostal incision may have less impact on the patient's physiology, incorporating the single port robot into this surgical pathway may enhance short- and long-term outcomes.

Keywords: robotic surgery, early lung cancer, navigational bronchoscopy

EP.07.24 Study on Complex Segmentectomy Cases at Our Institution

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Introduction: The effectiveness of segmentectomy for early-stage lung cancer has been demonstrated, and the number of segmentectomy cases is increasing. However, segmentectomy often involves more complex procedures compared to lobectomy. Among these, complex segmentectomy (other than simple segmentectomy), which involves multiple segmental border resections, tends to be even more complex than simple segmentectomy (such as left upper segmentectomy, left lingular segmentectomy, bilateral S6 segmentectomy, and bilateral basal segmentectomy). On the other hand, from the perspective of tumor localization and margin control, there are many cases where complex segmentectomy, including subsegments, should be selected. This study examined the perioperative outcomes of complex segmentectomy cases at our hospital and compared the prognosis of early-stage lung cancer cases.

Methods: From January 2017 to December 2024, 777 cases of lung cancer or metastatic lung tumors that underwent video-assisted thoracoscopic surgery (VATS) segmentectomy at our institution were included. The cases were divided into a simple segmentectomy group and a complex segmentectomy group, and perioperative outcomes were compared. For early-stage lung cancer cases, recurrence rates were also compared.

Results: There were 309 cases (40%) of simple segmentectomy and 468 cases (60%) of complex segmentectomy. Complex segmentectomy was performed in 60.9% of lung cancer cases and 57.6% of metastatic lung tumor cases. The proportion of complex segmentectomies showed an increasing trend over the years. The complex segmentectomy group had smaller tumors compared to the simple segmentectomy group (1.8 cm vs. 2.0 cm, p=0.033), but there were no significant differences in age, smoking index, or respiratory function. The operation time was approximately 10 minutes longer (160 minutes vs. 150 minutes, p=0.001), and the duration of drain placement was shorter (2.4 days vs. 2.6 days, p=0.030) in the complex segmentectomy group. There were no significant differences in the incidence of postoperative complications (≧GIII), persistent pneumothorax (≧7 days), or the need for pleurodesis. In lung cancer cases (cT1N0, R0: n=569), there was no significant difference in the cumulative recurrence-free survival rate (p=0.885).

Conclusions: Although complex segmentectomy was associated with a slight increase in operation time, no significant differences were observed in postoperative complications. Furthermore, there was no difference in the prognosis of lung cancer cases. It seems acceptable to select complex segmentectomy when necessary.

Keywords: complex segmentectomy, early lung cancer, sublober resection

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.25 Real-World Treatment Patterns and Outcomes of Stage I-III Resectable Non-Small Cell Lung Cancer (NSCLC) in Portugal

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Introduction: Lung cancer remains the leading cause of cancer-related deaths, with non-small cell lung cancer (NSCLC) accounting for over 80% of cases. The five-year survival rate of resectable NSCLC is highly dependent on the stage and resectability status, ranging from 92% for stage IA to 26% for stage IIIB. Understanding real-world data on Portuguese patients is crucial to measuring the impact of the disease and identifying potential gaps in care. Therefore, this study aimed to describe the characteristics, treatment patterns, and overall survival (OS) of patients diagnosed with resectable stage I-III NSCLC in Portugal by stage at diagnosis.

Methods: Retrospective, multicenter, observational study that included patients diagnosed with potentially resectable stage I-III NSCLC between July 2016 and December 2017, with follow-up until June 2022.

Results: Of the 401 patients included, 237 (59%) had stage I, 83 (21%) stage II, and 81 (20%) stage III NSCLC. Most patients were males (61%), aged 60 years or older (78%), and were mainly past or current smokers (71%). Additionally, 82% had at least one comorbidity at diagnosis. Most cases were adenocarcinomas (54%). PD-L1 testing was performed in 40% of cases, with 56% expressing less than 1% of PD-L1 positive cells. Genomic testing was conducted on 41% of tumors, of which 39% underwent NGS analysis. Specific alterations were reported in 48% of samples, particularly EGFR mutations (30%). Symptomatic patients had a mean time of 16 weeks from symptoms onset to referral. The mean time from diagnosis to treatment initiation was significantly longer for stage I and II patients than those in stage III (11, 10, and 7 weeks, respectively, p<0.001). Among stage I patients, 84% underwent surgery, either alone (56%) or combined with neoadjuvant systemic therapy (NAT) (1%), adjuvant systemic therapy (AT) (26%), or both (1%). Most stage II patients underwent surgery (83%), 58% received AT, and only 8% received NAT. In stage III patients, 80% underwent surgery, 22% of which in combination with NAT, 38% with AT, and 7% with both NAT and AT. Most patients who received NAT or AT were treated with a two-drug combination including cisplatin. A total of 17 patients underwent both surgery and radiotherapy (RT), including 2 with stage I, 4 with stage II, and 11 with stage III disease. Among non-surgical patients, 74% received only RT (97% stage I, 79% stage II, and 13% stage III patients) and 22% received RT and systemic therapy (0% stage I, 21% stage II, and 75% stage III patients), with stereotactic body radiation therapy (SBRT) being the preferred approach. Median OS was significantly higher for stage I (73 months) than for stage II patients (68 months, p<0.001). The median OS for stage III patients was not reached.

Conclusions: This study provided a comprehensive characterization of clinical and demographic characteristics of patients and treatment patterns for potentially resectable stage I-III NSCLC in Portugal from July 2016 to December 2017. Results highlight stage-specific differences in management and OS. However, ongoing evaluation of real-world treatment patterns is essential to further optimize patient outcomes in NSCLC.

Keywords: Real-World, Treatment Patterns and Outcomes, Resectable NSCLC

EP.07.26 A Novel Thoracic Localization Technique: Combining Intracorporeal Radiopaque Marker Suturing and Intraoperative Cone-Beam CT

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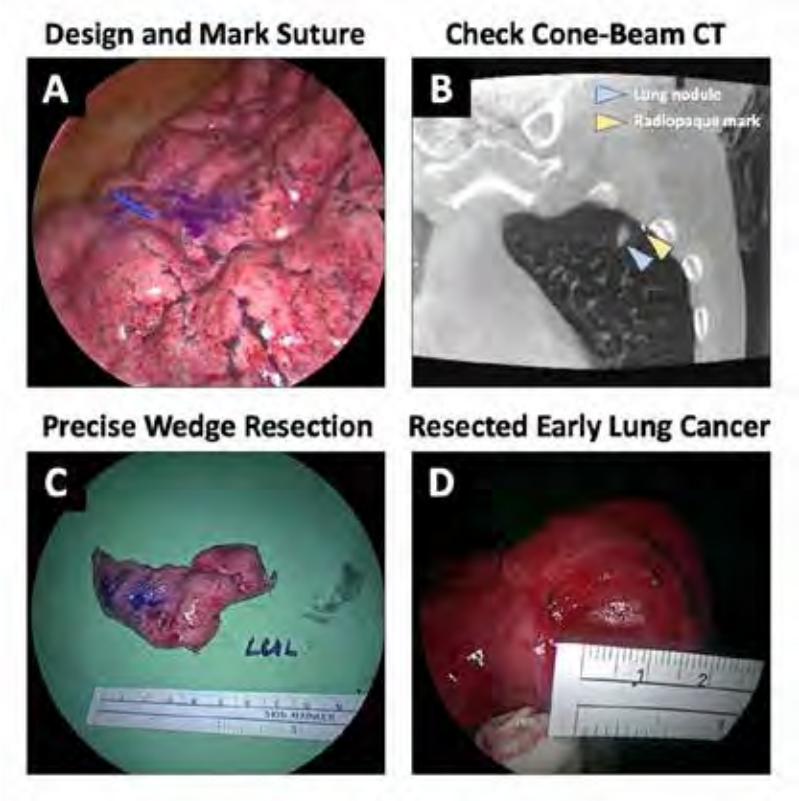
Introduction: Lung cancer remains a major cause of mortality, and early detection of small lung nodules via low-dose CT screening is increasing. Video-assisted thoracoscopic surgery (VATS) is a primary treatment, but the non-palpable nature of these nodules necessitates precise localization. Current CT-guided percutaneous methods using dye, wires, or coils, while accurate, suffer from drawbacks including patient discomfort, psychological distress, and risks of pneumothorax, hemothorax, and air embolism. To address these limitations, we introduce a novel localization technique combining intracorporeal radiopaque marker suturing and intraoperative cone-beam CT in the hybrid operating room.

Methods: We retrospectively reviewed patients undergoing VATS single wedge resection for lung nodules requiring localization. An intracorporeal radiopaque marker suturing technique, guided by intraoperative cone-beam CT, was employed. No preoperative invasive procedures were performed. Following general anesthesia and standard thoracic access, the lung nodule's approximate surface location was marked. A radiopaque marker thread was then intracorporeally sutured to the visceral pleura at this site. Intraoperative cone-beam CT scanning precisely determined the distance between the marker and the nodule, enabling accurate nodule identification and wedge resection.



Results: From May 2022 to March 2025, a total of 241 patients underwent VATS single wedge resection for lung nodules requiring localization using the described intracorporeal radiopaque marker suturing technique with intraoperative cone-beam CT guidance. Notably, this technique proved particularly beneficial for localizing lung nodules deemed difficult for traditional percutaneous methods due to their proximity to the diaphragm or mediastinal structures (including the aorta, heart, and other vital structures), their location beneath bony structures (ribs, scapula, spine, sternum), or their presence within lung fissures. The average localization time per patient was 12 minutes, and the average number of total CT scans during the entire surgery was 2. Importantly, no instances of hemothorax, pneumothorax, air embolism, or procedure-related postoperative pain were observed.

Conclusions: This novel intracorporeal suturing localization technique effectively avoids the pain associated with preoperative percutaneous puncture and eliminates major risks such as hemothorax, pneumothorax, and air embolism. Its utility is particularly pronounced for challenging-to-access lung nodules. Furthermore, the total number of CT scans was lower than reported with traditional localization methods, potentially reducing radiation exposure to medical staff. This approach demonstrates a safe and feasible technique for early lung cancer localization, achieving rapid, precise, and non-percutaneous localization while mitigating risks and patient discomfort.

Keywords: Lung nodule localization, Hybrid OR

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.27 Unravelling Sublobar Resections: Real-World Outcomes after Wedge vs Segmentectomy and Recurrence Risk Factors

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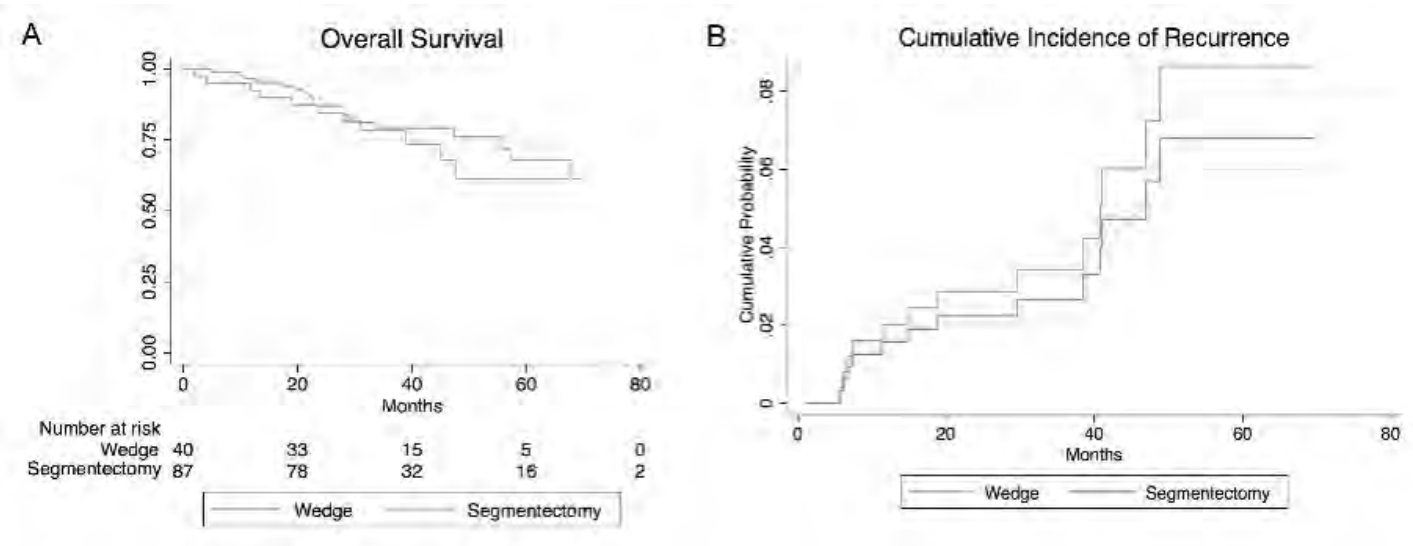
Introduction: Although post-hoc analysis of the CALGB study found no differences in oncological outcomes between anatomic segmentectomy (S) and wedge (W), doubts remain about whether they are truly equivalent in real world settings. In addition, most of the current literature haven't analyzed the association of genetic mutations and detailed pathologic features with recurrence after sublobar resections. The aim of our study is to compare long-term outcomes of S and W and investigate risk factors of recurrence.

Methods: We retrospectively analyzed patients diagnosed with c0-IA non-small cell lung cancer (NSCLC) that underwent S or W with curative intent between 01/01/2018 and 31/12/2022 (follow-up until 01/12/2024). Carcinoid tumors and large cell carcinomas were excluded. Survival was estimated using Kaplan-Meier and compared using log-rank test. Cumulative incidence of recurrence was modeled with death as a competing risk for recurrence. Competing risk analysis with a Fine-Gray's test was used to analyze recurrence. Multivariable analysis using backwards strategy was performed.

Results: The study included 87 patients in the S group and 40 in the W group. Median follow-up was 34 months. Regarding clinical and pathologic features, younger age (p=0.018), higher DLCO (p=0.001), higher nodule-pleura distance on CT (p=0.001), greater proportion of vascular (p=0.004) and lymphatic invasion (p=0.049), and greater number of resected nodes (p=0.000) and biopsied N2 stations (p=0.000) were observed in S compared to W. All procedures were performed by VATS, with only one conversion to thoracotomy in the S group (1.14%).No significant differences were observed in OS (p= 0.507)(Figure1A). Although the difference was not statistically significant, the segmentectomy group showed a trend towards lower recurrence risk (SDHR=0.77; 95% CI: 0.21-2.89; p=0.709)(Figure1B), after adjusting for age and vascular/lymphatic invasion. Recurrence was observed in 21 patients (16.53%): 14 (11.02%) locoregional and 7 (5.51%) distal. In multivariable analysis, lymphatic invasion (SDHR=10.56;CI95%:3.81-29.26;p=0.000), positive PDL-1 expression (SDHR=5.94;CI95%:1.78-19.75;p=0.004) and ALK translocation (SDHR=10.96;CI95%:4.21-28.49;p=0.000) were associated with increased risk of recurrence (locoregional or distal). Age (SDHR=1.07;CI95%:1.02-1.14;p=0.014), micropapillary (SDHR=4.32;CI95%:1.29-14.41;p=0.017) and solid (SDHR=5.85;CI95%:1.57-21.77;p=0.008) adenocarcinoma patterns, and KRAS mutation (SDHR=5.12;CI95%:1.65-15.87;p=0.005) were associated with increased risk of locoregional recurrence.

Conclusions: Although not statistically significant, in our study segmentectomy was associated with lower risk of recurrence. After sublobar resections, special attention should be paid to lymphatic invasion, PD-L1 positive expression, micropapillary and solid adenocarcinoma patterns, and ALK and KRAS mutations in order to guide follow-up and future studies regarding potential adjuvant therapies in early-stage NSCLC patients.



Keywords: Sublobar, NSCLC, Recurrence

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.28 Real-Time Image-Guided Indocyanine Green Fluorescencedual-Visualization Technique Forthoracoscopic Segmentectomy

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Introduction: The primary goal of thoracoscopic segmentectomy is the complete resection of early pulmonary carcinoma while sparing as much of the normal pulmonary parenchyma as possible, but an obvious trade-off exists between the pulmonary parenchymal preservation and an adequate resection margin. In this clinical trial, we developed and evaluated a real-time image-guided indocyanine green (ICG) fluorescence dual-visualization technique to confirm the resection margin by improving the intraoperative localization of the pulmonary nodule and identification of the intersegmental boundary line (IBL).

Methods: This study was utilized in 35 patients with a screening-detected lung nodule <2 cm to complete thoracoscopic segmentectomy from December 2020 to June 2021. Computed tomography-guided localization of the pulmonary nodule with ICG solution was performed on the day of surgery. During the surgery, after dissecting the targeted pulmonary segmental arteries, ICG at 5mg/body was injected into the systemic vein.

Results: We observed no toxicity. The dual-visualization technique was successfullyimplemented in all 35 patients to achieve a negative resection margin, which was more than 2 (mean 2.71 ± 0.59) cm, or the size of the tumor based on the final pathological examinations. No intraoperative complications occurred and only one patient had postoperative prolonged air leaks, which was ceased 8 days later after conservative management without reoperation.

Conclusions: This technique demonstrated safety and efficacy in achievingoncologically adequate resection margins while preserving pulmonary parenchyma during thoracoscopic anatomical segmentectomy. Comparative studies are warranted to evaluate long-term outcomes against conventional techniques.

Keywords: Segmentectomy, resection margin, dual-visualization technique

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.29 Single-Port Robotic Anatomical Lung Resection Using the Novel Chinese SP1000 Robotic System: Initial Experience

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Introduction: RATS, first introduced in 2002 by Melfi et al., has rapidly become the preferred technique in many thoracic centers worldwide due to its enhanced visualization, precision, maneuverability, and tremor filtration advantages. While multi-port robotic-assisted thoracic surgery (mRATS), involving 3 to 4 ports, remains the standard, the drive towards further minimizing invasiveness has paved the way for the exploration of single-port robotic surgery (uRATS). The evolution of robotic-assisted thoracoscopic surgery (RATS) has been revolutionized by single-port platforms (uRATS), offering superior triangulation flexibility and reduced intercostal nerve compression. However, evidence comparing these access strategies remains absent in the uRATS literature. This study aims to compare the clinical outcomes of subcostal and intercostal access routes using the single-port robotic surgery platform SP1000.

Methods: From January to July 2024, a total of 15 patients were enrolled, undergoing either subcostal uRATS (6 cases) or intercostal uRATS (9 cases) anatomical lung resection surgeries. The anatomic sequence of the robotic Edge SP1000 (Figure 1A-B) subcostal and intercostal lobectomy/segmentectomy is similar to the conventional intercostal robotic technique. For the subcostal uRATS group, a 4-cm utility incision is made in the subcostal margin at the mid-clavicular line during the operation (Figure 1C-D) and a 12-mm assistant port was initially created in the fifth intercostal space (ICS) along the midaxillary line (MAL) (Figure 1C-D).for intercostal uRATS group, A 4 cm utility incision was made in the fifth ICS along the posterior axillary line (PAL) during the operation (Figure 1E, F). The study involved a detailed comparison of operative times, blood loss, number of lymph nodes dissected, and postoperative complications.

Results: All surgeries were completed successfully. The intercostal group had shorter surgery times (156.0±33.4 minutes vs. 209.2±33.6 minutes, P=0.010), more lymph nodes dissected (21.3±5.7 vs. 13.5±4.5, P=0.014), and less intraoperative blood loss (17.2±13.7 mL vs. 70.0±34.6 mL, P=0.001). There were no significant differences between the two groups in terms of postoperative complication rates, hospital stay duration, drainage volume, and there were no infections or deaths within 30 days post-surgery in either group.

Conclusions: The study demonstrates that both subcostal and intercostal uRATS approaches are feasible and effective for anatomical lung resection. Despite the subcostal approach's longer operative times and greater blood loss, it remains a viable option under specific surgical conditions. Future research should focus on optimizing these techniques to enhance their clinical efficacy.

Keywords: Robotic-assisted thoracoscopic surgery, uRATS, SP1000 single-port robotic surgical system

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.30 Preop-Intraop Consistency in Thoracic Surgery: MRMC Reanalysis of Surgical Planning Accuracy

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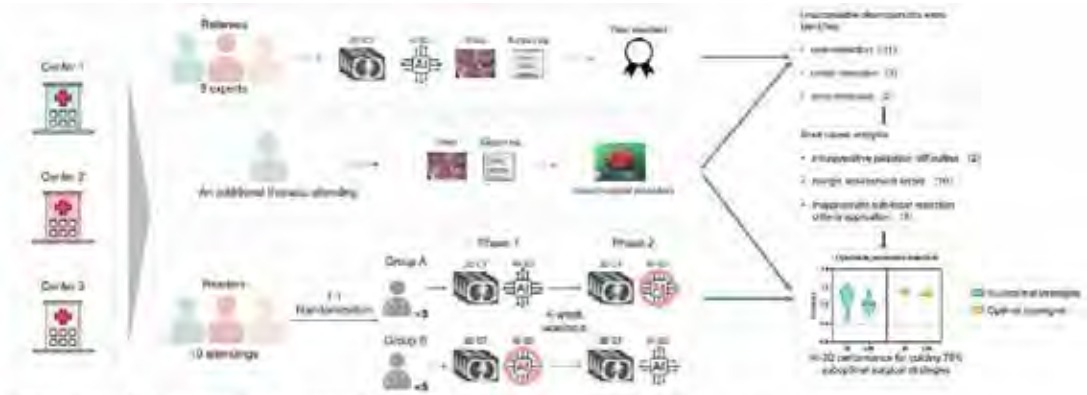
Introduction: Three-dimensional (3D) reconstruction enhances spatial awareness to improve anatomical variant identification, with demonstrated surgical benefits in urological surgery and other specialties, though its impact on pulmonary surgical planning remains unsubstantiated. Building upon our prior multi-center, multi-reader, multi-case (MRMC) retrospective study, we employed gold-standard surgical planning panels and AI-driven 3D reconstruction to systematically evaluate the performed surgical procedures and identify cases amenable to procedural optimization through 3D guidance.

Methods: The MRMC study assessed an artificial intelligence (AI) system for preoperative planning. Three expert surgeons from three centers established the gold standard using surgical logs, videos, CT scans, and manual 3D reconstructions. Ten surgeons as readers were randomized into two groups for two rounds of fully crossed pre-operative planning simulations (4-week interval) with or without AI-derived 3D pulmonary vessel reconstructions. Surgical videos and anesthesia/surgical records from all patients were independently reviewed by an additional senior thoracic surgeon unaffiliated with the original procedures to determine actual procedures. Discrepancies between executed surgical procedure and gold-standard plans were classified into three categories: over-resection (exceeding planned resection margins), under-resection (insufficient anatomical coverage), and error-resection (fundamentally altered surgical approaches).

Results: A total of 140 patients were consecutively enrolled across three tertiary centers. Surgical video analysis identified 62 lobectomies and 78 segmentectomies. Comparison with gold-standard plans revealed 21 discrepancies (15.0%): 5 clinically justified (2 multifocal cancers requiring extended resection, 1 compromised sub-lobar resection in an octogenarian, 2 sub-segmental resections exceeding anatomical resolution standards) and 16 protocol deviations (11.4%). Deviations included: 11 over-resections (5 conversions to lobectomy, 6 extended segmentectomies), 3 under-resections (lobectomy-to-segmentectomy conversions), and 2 error-resections (adjacent-segment substitutions). Root cause analysis attributed discrepancies to intraoperative palpation difficulties (2 cases), margin assessment errors (10), and inappropriate sub-lobar resection criteria application (4). Among 12 cases involving palpation or margin errors, preoperative planning accuracy improved from 52% (2D CT) to 76% with AI-3D across 10 readers.

Conclusions: Our study demonstrates that even at leading Chinese tertiary hospitals, surgical plans relying solely on 2D CT exhibit optimization potential in 11.4% (16/140) of pulmonary resections, primarily due to spatial misinterpretations of complex anatomy. Cases with non-palpable nodules or ambiguous margins—representing 75% (12/16) of suboptimal strategies—were identified as prime candidates for 3D reconstruction-guided refinement. These findings underscore AI-3D's critical role in enhancing precision for thoracic surgical planning, particularly in anatomically challenging scenarios requiring enhanced intraoperative decision support.



The workflow of the MRMC study and Consistency Analysis of Surgical Procedures.
The multi-center, multi-reader, multi-case (MRMC) study was conducted as a novel two-phase crossover design. In the initial phase, half of the readers utilized standard 2D CT imaging, while the remainder utilized both 2D CT images and AI-enhanced 3D reconstructions. Following a 28-day washout period, the groups switched methodologies. Each reader was tasked with determining the extent of resection. Three expert surgeons from three centers established the golden standard based on collected surgical logs, videos, CT scans, and manually constructed 3D reconstructions. Surgical videos and anesthesia/surgical records were reviewed by an additional senior thoracic to determine actual procedures. Through comparison with gold-standard surgical plans, clinically unacceptable discrepancies were identified and yielding quantitative discrepancy profiles and root cause. At last, Subgroup analysis was conducted in Readers group, the performance of AI-3D to guide surgical strategy was shown.

Inclusion criteria for readers and golden standard referee
1.Certified attending physician in thoracic surgery department.
2.Practicing thoracoscopic surgery independently for at least one year.
3.Physicians with national license for clinical practicing.
4.Physicians with a good clinical practice certificate.
5.The expert group consists of thoracic surgeons with associate senior clinical titles or above, and their professional directions lobectomy and segmentectomy.

Keywords: lung surgery, 3D reconstruction, artificial intelligence

EP.07.31 A Comparative Analysis of Sublobar Versus Lobar Resection for Early-Stage Non-Small Cell Lung Cancer in Octogenarian Patients

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[1]Seoul National University, Seoul/KR ,[2]Seoul National University Hospital, Seoul/KR ,[3]Seoul National University College of Medicine, Seoul/KR

Introduction: In octogenarian patients with early-stage non-small cell lung cancer (NSCLC), careful consideration of the extent of pulmonary resection is crucial due to increased operative risks associated with age-related functional decline and comorbidities. This study aimed to compare the outcomes of sublobar resection and lobectomy in this demographic.

Methods: A retrospective analysis was conducted on patients aged 80 years or older who underwent curative surgery for clinical stage II or less NSCLC between 2011 and 2022. The primary endpoint was overall survival (OS), while secondary endpoints included recurrence-free survival (RFS), and cumulative incidence of lung cancer-related mortality and noncancer-related mortality.

Results: Among 220 patients, 48 (22%) underwent sublobar resection (wedge resection - 30, segmentectomy - 18), and 172 underwent lobectomy. No significant differences were observed in performance status or pulmonary function between the two groups. However, clinical (P < 0.001) and pathological stage (P < 0.001) were significantly higher in the lobectomy group. The postoperative complication rate was significantly higher after lobectomy (18.8% vs 38.4%, P = 0.047). At a median follow-up of 4.1 years, the 5-year OS indicated a trend towards better survival following sublobar resection, though not statistically significant (80.4% vs 64.6%, P = 0.35). The 5-year RFS were not different significantly between the two groups (81.5% vs 72.7%, P = 0.32). The 5-year cumulative incidence of lung cancer-related mortality (0% vs 12.5%, P = 0.47), and noncancer-related mortality (9.3% vs 18.6%, P = 0.75) did not differ significantly between the groups (Figure 1). Sublobar resection was not a prognostic factor for OS, lung cancer-related mortality and noncancer-related mortality (Table 1).

Conclusions: Sublobar resection demonstrated long-term oncologic outcomes comparable to those of lobectomy. Given the higher complication rate after lobectomy, sublobar resection may be considered the preferred surgical option for octogenarians with early-stage NSCLC.

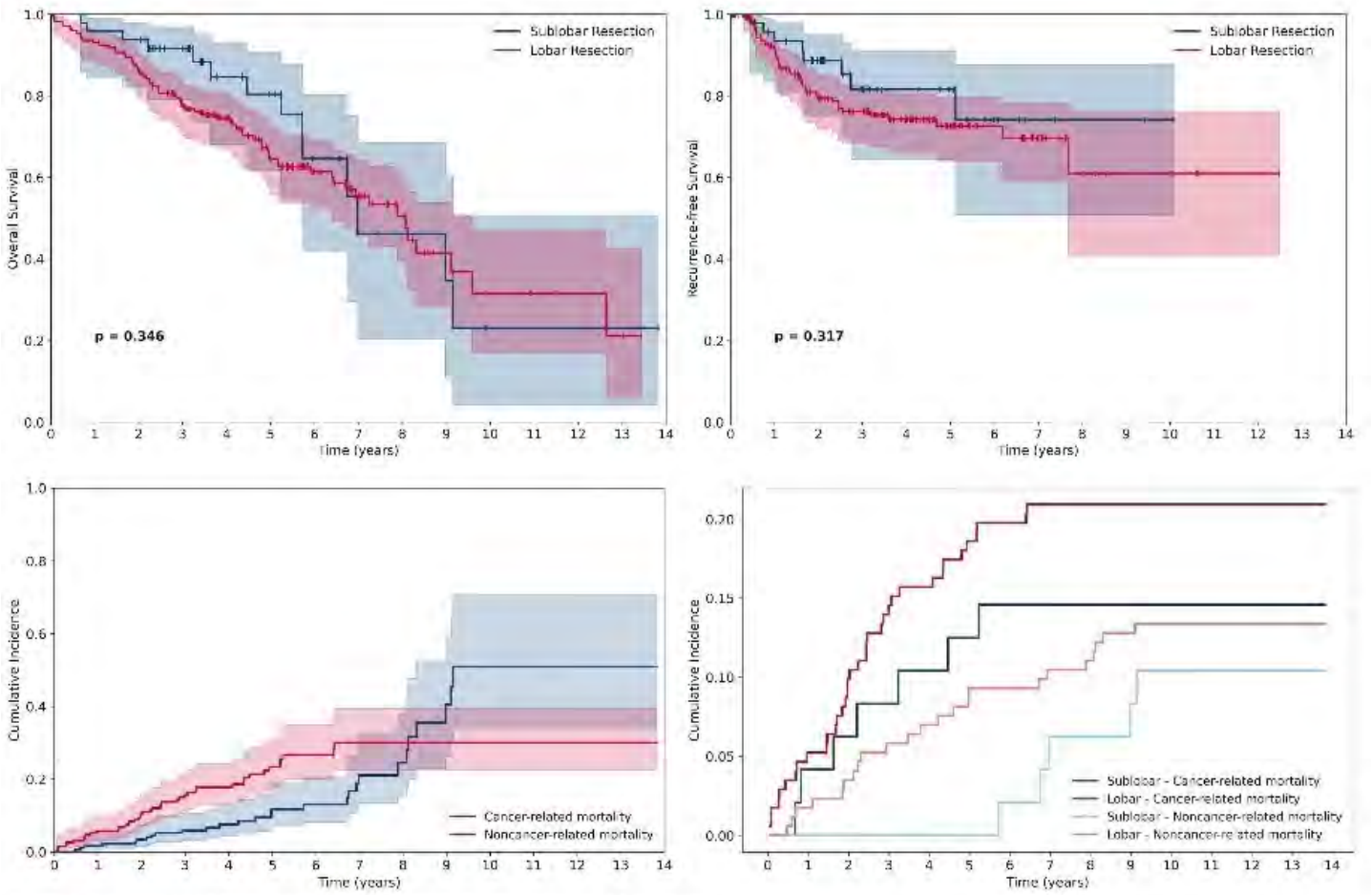

Figure 1. Comparison of Clinical Outcomes after Sublobar Resection and Lobectomy
(A) Overall survival. (B) Recurrence-free survival. Cumulative incidence of lung cancer-related mortality and noncancer-related mortality in the entire cohort (C) and in each group (D).

	All-cause mortality						Cancer-related mortality						Noncancer-related mortality					
	Univariable			Multivariable			Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.1	1.0 – 1.3	0.04	0.7	0.5 – 1.0	0.06	1.2	1.0 – 1.3	0.04				1.0	0.9 – 1.2	0.63			
Sex (female)	0.5	0.3 – 0.9	0.02				0.6	0.3 – 1.2	0.15	0.2	0.1 – 0.6	0.03	0.3	0.1 – 0.9	0.04			
ECOG-PS	1.7	1.1 – 2.5	< 0.01	3.9	1.8 – 8.5	< 0.01	1.4	0.8 – 2.6	0.25				1.2	0.7 – 2.4	0.49			
BMI	0.9	0.8 – 1.0	< 0.01				1.0	0.9 – 1.1	0.53				0.9	0.7 – 1.0	0.01	0.9	0.7 – 1.0	< 0.01
CCI	1.5	1.2 – 1.9	< 0.01	3.6	2.0 – 6.2	< 0.01	1.4	1.0 – 2.0	0.05				1.3	0.8 – 2.1	0.21			
Other cancer hx	2.2	1.3 – 3.5	< 0.01	7.7	3.1 – 19.5	< 0.01	2.2	1.2 – 4.1	0.02	3.8	1.9 – 10.0	< 0.01	1.9	0.9 – 3.9	0.10			
Renal disease	2.2	1.3 – 3.8	< 0.01	5.9	1.9 – 17.7	< 0.01	1.9	1.0 – 3.9	0.07				2.3	1.0 – 5.0	0.04	2.2	1.1 – 4.3	0.03
FVC, %	1.0	1.0 – 1.0	0.05				1.0	1.0 – 1.0	0.09				1.0	1.0 – 1.0	0.24			
FEV1, %	1.0	1.0 – 1.0	0.05				1.0	1.0 – 1.0	0.15				1.0	1.0 – 1.0	0.15			
DLCO, %	1.0	1.0 – 1.0	0.14				1.0	1.0 – 1.0	0.05				1.0	1.0 – 1.0	0.14			
Smoking 1	1.5	1.3 – 1.7	< 0.01				1.4	1.1 – 1.8	< 0.01				1.5	1.1 – 1.9	< 0.01	2.2	1.3 – 4.1	< 0.01
Smoking 2	1.4	1.2 – 1.6	< 0.01				1.3	1.1 – 1.6	< 0.01				1.4	1.2 – 1.7	< 0.01			
STS operative mortality	3.8	2.6 – 5.7	< 0.01				2.9	1.7 – 5.0	< 0.01				1.9	1.0 – 3.8	0.06			
c Stage	2.3	1.5 – 3.5	< 0.01				3.8	2.1 – 7.0	< 0.01				0.8	0.4 – 1.9	0.68			
p Stage	2.0	1.5 – 2.7	< 0.01				1.8	1.3 – 2.6	< 0.01				1.4	0.8 – 2.4	0.18	2.7	2.0 – 7.3	0.04
pT Stage	1.8	1.5 – 2.3	< 0.01	1.8	1.1 – 3.1	0.02	2.1	1.5 – 2.8	< 0.01	3.9	1.7 – 9.0	< 0.01	0.9	0.5 – 1.8	0.77			
pN Stage	1.5	1.1 – 1.6	< 0.01				1.4	1.1 – 1.9	0.01	3.7	1.6 – 8.1	< 0.01	1.2	0.8 – 1.6	0.37			
Thoracotomy	2.0	1.1 – 3.7	0.02				2.5	1.2 – 5.1	0.01				1.1	0.4 – 3.6	0.84			
Sublobar resection	**0.8**	**0.4 – 1.3**	**0.35**				**0.8**	**0.3 – 1.7**	**0.50**				**0.9**	**0.4 – 2.2**	**0.81**			
LN dissection (vs sampling)	0.9	0.6 – 1.3	0.56				1.0	0.6 – 1.9	0.93				0.7	0.4 – 1.1	0.13			
Complication	1.5	1.0 – 2.2	0.06	0.5	0.2 – 1.0	0.06	2.1	1.2 – 3.9	0.02				1.2	0.6 – 2.5	0.62			
Postop Pneumonia	1.2	0.8 – 1.6	0.34				2.8	1.1 – 7.0	0.03				1.0	0.3 – 3.3	0.94			
Postop Atrial fibrillation	1.0	0.4 – 2.3	0.96				0.8	0.2 – 2.9	0.63				2.6	1.0 – 6.7	0.05			

Table 1. Univariable and Multivariable Regression Analysis for All-Cause Mortality, Lung Cancer-Related Mortality, and Noncancer-Related Mortality

- All-cause mortality was analyzed using Cox regression analysis.
- Lung cancer-related death and non-lung cancer-related death were analyzed using the Fine-Gray subdistribution method to account for competing risks.
- For multivariable regression, variables with $P < 0.2$ in the univariable analysis were included in the model. Backward selection was performed by sequentially removing variables with $P \geq 0.1$ until only those with $P < 0.10$ remained.

Keywords: Octogenarian, Sublobar resection, Early-stage NSCLC

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.32 Initial Experience With Robot-Assisted Thoracic Surgery for Anatomical Lung Resection: A Case Series of 40 Patients From a Japanese Regional Hospital

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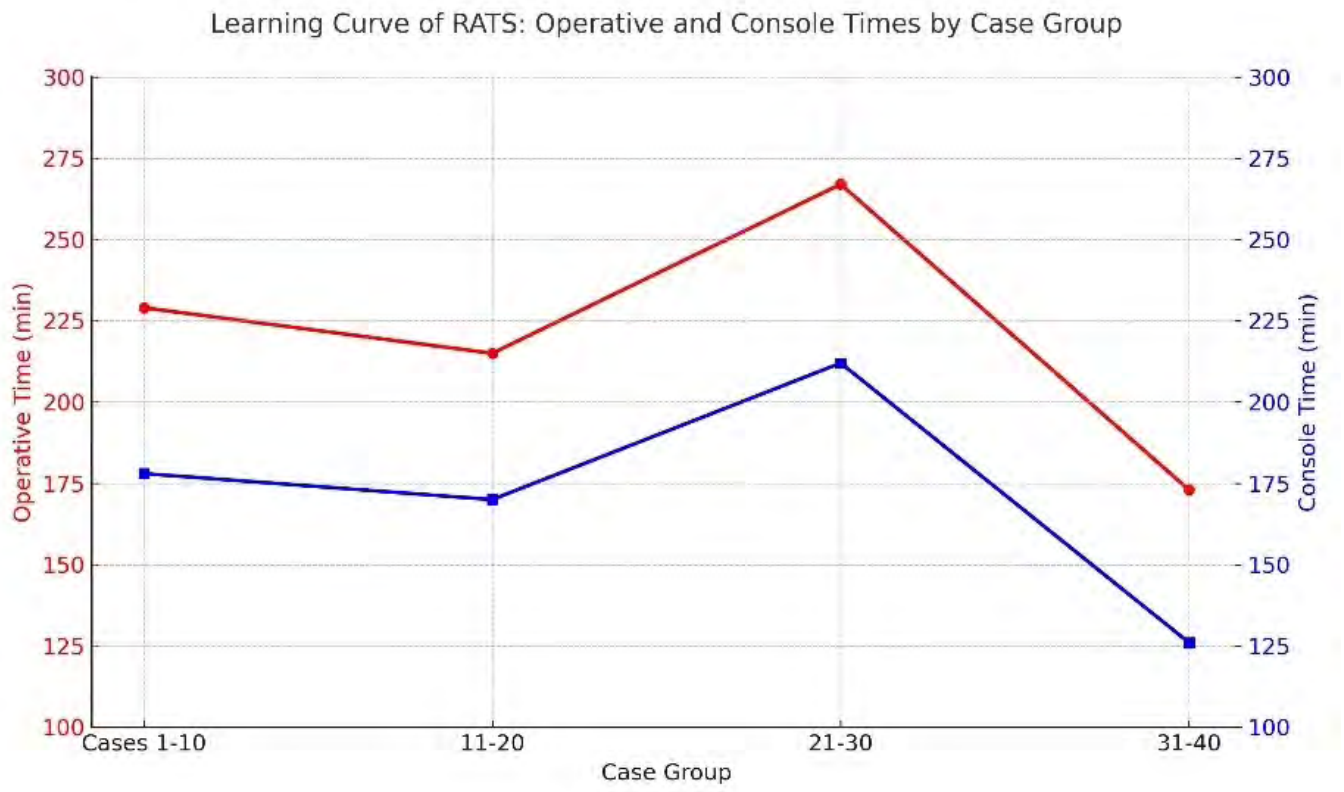
Introduction: Robot-assisted thoracic surgery (RATS) has become an increasingly utilized minimally invasive option for anatomical lung resection. However, evidence regarding the early-phase implementation of RATS in regional Japanese hospitals remains scarce. We aimed to report our institutional experience with the first 40 RATS cases, focusing on perioperative outcomes and learning curve analysis.

Methods: This retrospective case series was conducted at Ashikaga Red Cross Hospital, a 555-bed regional hospital in Japan. The institution had existing robotic surgery programs in urology and gastrointestinal surgery. A RATS program was launched in November 2023 using the da Vinci Xi system. All procedures were performed by a single board-certified thoracic surgeon. The first 10 cases were proctored by an external thoracic surgeon certified as a robotic surgery proctor; subsequent cases were performed independently with institutional staff. Forty patients (18 male, 22 female) underwent RATS anatomical lung resections for clinical stage 0-IIB primary lung cancer between November 2023 and March 2025. The median age was 73 years (range: 49-85). Surgical procedures included 29 lobectomies and 11 segmentectomies. Outcomes evaluated included operative time, console time, blood loss, complications, and hospital stay. Median values were analyzed across four consecutive 10-case groups.

Results: No conversions to thoracotomy were observed. The overall median operative time was 220 minutes, and console time was 162 minutes. The median estimated blood loss was 6 mL (range: 0-1111 mL). Postoperative complications classified as Clavien-Dindo grade ≥ IIIa occurred in 2 patients (5%), and no 30-day mortality was observed. Median operative times by group were 229, 215, 267, and 173 minutes, respectively. Median console times were 178, 170, 212, and 126 minutes. A significant reduction in both operative and console times was noted in the final group, indicating procedural optimization. Figure 1 illustrates this trend.



Conclusions: Our findings suggest that RATS for anatomical lung resection across clinical stages 0 to IIB can be safely introduced in a regional hospital setting with structured support and multidisciplinary collaboration. The data support a moderate learning curve with clear efficiency gains after 30 cases.

Figure 1: Learning curve analysis showing median operative and console times in consecutive 10-case groups.

AI Disclosure: This abstract was written with the assistance of ChatGPT (OpenAI, 2024) for language refinement. All clinical data and interpretations were provided by the authors.

Keywords: Robot-assisted thoracic surgery, Anatomical lung resection, Learning cureve

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.33 The Pictorial Fit Frail Scale as a Preoperative Risk Stratification Tool in Lung Resection Patients

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Introduction: Pictorial Fit Frail Scale (PFFS) is a validated, self-administered, and easy frailty assessment tool that is understudied in thoracic surgery. Our objective was to evaluate whether PFFS can be used to risk-stratify patients undergoing lung resection.

Methods: All patients evaluated for lung surgery between October 2020 and February 2025 were given PFFS for preoperative frailty assessment. Patients who underwent lung resection were divided into 'fit' (PFFS score: 0-0.2) or 'frail' cohorts (PFFS score:0.21-1) based on validated scores. Surgeons were not provided with PFFS scores for surgical decision-making. Descriptive and parametric analysis was used to compare the perioperative characteristics and outcomes between the two groups. P-value <0.05 was considered statistically significant.

Results: During the study period, 272 patients underwent lung resection and completed a PFFS preoperatively. Within the cohort, 201(74%) patients were classified as 'fit' and 71(26%) as 'frail' by PFFS. The median age was 71 and 74 years in the 'fit' and 'frail' cohort, respectively (P=0.006). 'Fit' patients had a higher preoperative FEV1% (93% vs. 83%, P=0.05) compared to 'frail' patients; 'frail' patients had a higher rate of wedge resections (53% vs. 44%, p=0.4). Postoperative adverse events were more frequently noted in the 'frail' group (23% vs. 17%, P=0.3). Major adverse events were comparable between the two groups (Table 1). The median length of stay for both groups was 2 days, however, there was more variability amongst the 'frail' cohort reflected in the higher interquartile range. In addition, frail patients were more frequently discharged to a rehab facility compared to fit peers (1% vs. 4.2%), although this was not statistically significant. Intrahospital mortality was observed in 1/201 fit patients and 1/71 frail patients. The 30- and 90-day mortality was comparable between the two groups. One-year overall survival was 96.5% and 97.2% in 'fit' and 'frail' patients, respectively. Although statistically insignificant, increasing PFFS scores (indicating increased frailty) were associated with longer hospitalizations (β:2.12[95%CI:-2.9-7.1], p=0.4).

Conclusions: Frailty assessment tools such as PFFS have the potential to identify subclinical frailty and improve risk stratification for patients undergoing lung surgery. Although surgical decision-making was not based on PFFS, 'frail' cohort had higher rates of wedge resection compared to 'fit' peers. Hospital length of stay was similar between the groups; however, 'frail' patients were more likely to be discharged to a facility postoperatively. Future work will focus on performing analyses with larger sample sizes to identify significant associations with PFFS scores and postoperative outcomes.

Table 1. Characteristics of the overall cohort were categorized by patients who were classified as fit (PFFS score 0 – 0.2) and frail (PFFS score 0.21 – 1).

Variables; median [IQR] or n (%)	Total N=272	Non-frail (PFFS≤0.2) N=201(73.9%)	Frail (PFFS>0.2) N=71(26.1%)	P value*
Age(years)	72.2[66.9-77]	71.4[66.6-75.9]	74.6[69.1-79.5]	0.006
Sex				0.4
Female	170(62.5)	129(64.2)	41(57.7)	
Male	102(37.5)	72(35.8)	30(42.3)	
FEV1%	91[75-105]	93.5[75-107]	83[71-102]	0.05
Charlson comorbidity index	5[3-6]	5[3-6]	5[4-7]	0.009
Body mass index	27.3[24.1-30.2]	27.2[23.5-30]	27.8[24.6-31.1]	0.1
4-m gait speed(m/s)	0.98[0.85-1.1]	1.04[0.89-1.18]	0.82[0.64-0.99]	<0.001
Type of surgery				0.4
Wedge resection	127(46.7)	89(44.3)	38(53.5)	
Segmentectomy	56(20.6)	45(22.4)	11(15.5)	
Lobectomy	86(31.6)	65(32.3)	21(29.6)	
Pneumonectomy	3(1.1)	2(1)	1(1.4)	
Unplanned ICU admission	4(1.5)	3(1.5)	1(1.4)	1
Return to OR	7(2.6)	6(3)	1(1.4)	0.7
Any postop adverse events (grade II and above)[1]	50(18.5)	34(16.9)	16(22.9)	0.3
Major postop adverse events (Grade III and above)[1]	18(6.6)	14(7)	4(5.6)	1
Length of stay(days)	2[1-3]	2[1-3]	2[2-5]	0.05
Discharge disposition				0.2
Home±services	265(97.4)	198(98.5)	67(94.4)	
Rehab/nursing facilities	5(1.8)	2(1)	3(4.2)	
Death	2(0.7)	1(0.5)	1(1.4)	
30-day readmission	12(4.4)	8(4)	4(5.6)	0.5
30-day mortality	1(0.4)	0(0)	1(1.4)	0.3
90-day mortality	3(1.1)	2(1)	1(1.4)	1
1-year overall survival	263(96.7)	1096(96.5)	69(97.8)	1

1-postop adverse events are classified based on the Clavien-Dindo scale.

*Bold values indicate significant P values.

Keywords: Pictorial Fit Frail Scale, Frailty, Lung resection

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.34 A Study of Lung Cancer Patients Who Survived for More Than 5 Years After Incomplete Resection

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Introduction: Complete resection is important for long-term survival in lung cancer. The development of imaging equipment such as thin slice CT and PET decreased the number of cases deemed unresectable during surgery. Even so, there are a certain number of cases of incomplete resection. On the other hand, advances in drug therapy have allowed some cases to survive for longer periods after incomplete resection.

Methods: To explore the pathological and clinical trends of long-term survivors who have undergone incomplete resection.We retrospectively examined 33 patients who survived for more than 5 years after incomplete resection of lung cancer at our hospital between January 2000 and December 2017, inclusive.

Results: Of the 33 cases, 21 were male and 12 were female, with an average age of 69 years. Twenty-five cases of histology were adenocarcinoma, four cases of squamous cell carcinoma, one case of large cell carcinoma, one case of pleomorphic carcinoma, and two cases of small cell carcinoma. The causes of incomplete resection were pleural dissemination in 7 cases, metastatic lymph node remnant in 4 cases, chest wall invasion in 1 case, bronchial stump positive in 1 case, malignant pleural effusion in 4 cases, and pleural lavage cytology positive in 15 cases. Twenty-nine patients underwent lobectomy, three underwent partial resection, and only one was limited to exploratory thoracotomy.

Conclusions: Long-term survivors had a higher percentage of females and positive effusion-positive cases. In addition, there are many driver mutation-positive cases, suggesting that drug therapy with TKIs facilitates long-term survival.

Keywords: Incomplete resection, NSCLC, Surgery

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.35 Comparative Analysis of Anterior and Posterior Approaches in Robotic Pulmonary Resection

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Introduction: Robotic pulmonary resection (RPR) is generally performed via either an anterior or a posterior approach, with institutional preferences varying. Our institution employs both approaches, and this study aims to compare their outcomes.

Methods: We retrospectively analyzed 85 consecutive cases of RPR performed between November 2020 and February 2025. The da Vinci system was used, with the Si model utilized until August 2023 and the Xi model thereafter. The median patient age was 71 years (range, 25-86 years); there were 35 males, and procedures included 75 lobectomies and 10 segmentectomies. Clinical staging was as follows: IA in 71 cases, IB in 4, IIB in 6, IIIA in 1, with 3 cases of metastatic lung tumors. Four console surgeons performed the procedures, with 39 cases employing the anterior approach and 46 using the posterior approach. We compared console time, number of stapler firings, blood loss, and postoperative complications between the two groups using the Mann-Whitney test. The learning curve was evaluated using the cumulative sum (CUSUM) method.

Results: The posterior approach group had a significantly higher median age (72.5 vs. 67 years, p=0.01) and a greater proportion of segmentectomies. There were no significant differences in operative time, console time, blood loss, or postoperative complications between the groups. However, the number of stapler firings was significantly higher in the posterior approach group (median of 7 vs. 5, p<0.001). Among the three surgeons who performed at least 10 cases, proficiency was achieved by the third to fourth case, with no differences noted between the two approaches.

Conclusions: Short-term outcomes, learning curves, and complication rates did not differ significantly between the anterior and posterior approaches in RPR. The increased use of staplers in the posterior approach is likely attributable to the utilization of the da Vinci stapler.

Keywords: Robot-assisted thoracic surgery, Minimally invasive surgery, early-stage lung cancer

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.36 Introduction of Dural-Port Robot Assisted Thoracoscopic Lung Disection - Aiming for Reduce-Port RATS That Anyone Can Do

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Introduction: Reduce-port surgery always attracts many surgeons, however a surgical operation needs to be ensured safety and curability. We develop the "Dual-port Robot assisted thoracoscopic (RATS) lung dissection for lung cancer" as a minimally invasive and easy operation. In this study, we introduce Dual-port RATS (DRATS) lung dissection to confirm safety.

Methods: Under general anesthesia with single-lung ventilation, the patients were placed in the lateral decubitus position. The da Vinci Xi Surgical SystemR was positioned at the patient's head side. The cross of the laser was placed at the camera port and conventional targeting was not necessary. From 4 to 4.5 cm diameter working port was created in the sixth intercostal space (ICS) along the middle axillary line as a main window. A camera port was placed at the anterior edge of the window, and an instrument port was placed at the posterior edge. To avoid collisions, we did not use all four arms. The assistant inserted two devices between the ports of the main window. A 12mm diameter port was inserted at the anterior end of the 8th ICS for the stapler. We used the only four devices: a curved dissector, a fenestrated bipolar, SynchrosealR, and SureformR.

Results: Four operations were performed using the DRATS lung dissection for 3 months. The mean operation time was 200.8 min. The mean console time was 149.8 min. The blood loss was 27.5 g. The duration of chest tube drainage was 2.75 days, and mean postoperative stay was 4.5 days.

Conclusions: Our method is safe and easy to perform. This is because an assistant can easily operate two devices and provide appropriate support. We will increase the number of cases to evaluate safety and oncological outcomes.

Keywords: Robotic-assisted thoracic surgery (RATS), dual-portal RATS (DRATS) lung dissection, reduce-port RATS

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.37 An Initial Experience of Resectable Non Small Cell Lung Cancer From a Tertiary Care Center

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Introduction: Lung cancer is the second most common malignancy and the leading cause of cancer death for both sexes worldwide. In western Rajasthan people face the exposure of mines, marbles and stones as a major risk factor for lung and thoracic malignancies . Here, we present an initial experience of managing patients with a resectable lung cancer at our center. The main goal was to see the surgical outcomes and compare them to the guidelines as per the best standard of care.

Methods: This is a Retrospective analysis of a prospectively maintained data base from January 2020 to December 2024.

Results: A total of 12 patients underwent thoracic surgery for a resectable lung cancer.The median age was 52.5 years (Range 24 to70 years). A male predominance was seen with eight male and four female patients. Patients had a median duration of symptoms of seven months (range 4-8 months) before presentation. Cigarette smoking in synergism with occupational exposure to mines and marbles was a major risk factor. All the females were non smoker.The upper lobe was the most common subsite with six patients having disease in right upper (03) and left upper lobe (03), followed by lower lobe (04) and two involving fissure.All the pre operative core biopsies revealed Non Small Cell on histology and molecular profile including five squamous cell, four adenocarcinoma, two carcinoids and one alveolar rhabdomyosarcoma. Ten patients underwent upfront surgery. Two patients were operated after 4# of neoadjuvant chemotherapy (paclitaxel +carboplatin). Surgical approach included a thoracotomy followed by resection with mediastinal node dissection. Ten patients underwent Lobectomy. A bi lobectomy and an apical segmentectomy were done in one patients each. Mean blood loss was 250ml. The median duration of hospital stay was 10 days. Major post operative complications were pneumonia (02) and seroma(03). One mortality was seen on postoperative day five. The post surgery pathological staging revealed median tumor size to be 4cm (range 2 to 11cm) with eight patients in early stage and node negative status and four patients with a locally advanced disease. Three patients were given adjuvant radiation of (55 Gy in 20# over 5 weeks) and one was put on targeted therapy.At a median follow up of 18 months two patients had developed locoregional relapse.

Conclusions: The end result of the present study demonstrated a relatively high overall survival in two years after multimodal treatment. The ability to perform surgery with R0 resection in all cases with a low complication rate, represents the importance of a dedicated thoracic oncology team. Encompassing all possible modalities to extend patients 'survival and quality of life is the ultimate goal of our team in future.

Keywords: Non small cell lung cancer, Thoracic Surgical oncology, Experience from a tertiary care center

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.38 Immune Checkpoint Inhibitors May Not Fully Mitigate the Adverse Prognostic Impact of PD-L1 Expression in Early Lung Cance

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Introduction: PD-L1 expression is thought to correlate with the grade of malignancy in lung cancer. On the other hand, immune checkpoint inhibitors have emerged as an option for recurrence after lung resection and are expected to be highly effective in patients of lung cancers with PD-L1 expression. In this study, we investigated the impact of treatment with immune checkpoint inhibitors after recurrence on postoperative prognosis in early stage lung cancer patients.

Methods: We analyzed 141 patients with stage pI non-small cell lung cancer who underwent complete resection at Tohoku University Hospital from January 2017 to December 2018. We retrospectively evaluated pathological factors and the treatment after recurrence and examined recurrence-free and overall survival rates according to PD-L1 expression.

Results: PD-L1 expression was classified as high (≧50%) in 19 patients, low (1-49%) in 50 patients, and negative in 72 patients; with increasing PD-L1 expression, the rates of pleural invasion, vascular invasion, and lymphatic invasion increased. Recurrence patterns included local recurrence in 8 patients, distant recurrence in 5 patients, and both local and distant recurrence in 4. Patients with negative PD-L1 expression had better OS and RFS than those with positive expression. Patients who bared lung cancer with PD-L1 expression and without driver mutations were predominantly treated with immune checkpoint inhibitors after relapse, but two of the five patients were untreatable after recurrence.

Conclusions: PD-L1 expression in early-stage lung cancer appears to be associated with the grade of oncological malignancy. Treatment with immune checkpoint inhibitors may not sufficiently mitigate the adverse prognostic implications of PD-L1 expression despite its high efficacy for lung cancers with PD-L1 expression.

Keywords: PD-L1, early-stage lung cancer

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.39 Simply the Best: Analysis Of 1000+ Patients Comparing Single-Fraction to Three-Fraction Lung SBRT for Early-Stage Inoperable Lung Cancer

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Introduction: A never-realized cooperative group phase III trial had planned to compare single fraction (SF) to three fraction (TF) lung stereotactic body radiotherapy (SBRT) for inoperable early-stage lung cancer (ESLC) patients (pts), with a primary endpoint of overall survival (OS). We analyzed our large single institution database to investigate this question and other relevant cancer- and treatment-related outcomes.

Methods: We surveyed our institutional review board-approved prospective lung SBRT data registry from 2003 to 2024 for ESLC pts treated with SF and TF SBRT, on and off protocols. Rates of local failure (LF), distant failure (DF) and toxicity were assessed, as well as OS. Prognostic factors for LF and DF were identified with competing risk regression with all-cause mortality defined as a competing event. Factors associated with OS were identified with Cox proportional hazards regression.

Results: For the 21-year interval, 1094 pts met study criteria for this retrospective analysis, with the SF cohort having 676 pts (61.8%) and the TF 418 pts (38.2%). 37.2% pts were alive at analysis. Median follow up for all, SF, and TF pts was 29.3, 24.4 and 39.8 months, respectively (p= <0.0001). Patient characteristics included: female (51%); median age 73.9 years, median KPS 80; 25% still smoking; inoperability by lung co-morbidities in 53.1%; with no differences by fractionation (Fx). Tumor characteristics included: median size 1.8 cm; median PET SUVmax 6.6; 64.2% with biopsy proven cancer and the majority adenocarcinoma at 44.1%; with no differences by Fx. SF SBRT consisted of 34 Gy for 88.2% and 30 Gy [with homogeneous planning (HP)] 11.8%. TF SBRT consisted of 60 Gy [with HP] for 82.3% and 54 Gy 17.7%. Grade 3 and higher toxicity was reported in 2.4% pts, with no significant difference by Fx (p=0.40). Grade 3 and higher chest wall toxicity was: SF 0.3% and TF 1%. Each Fx cohort had grade 5 in 1 pt (both as pneumonitis). At 5 years, failure patterns by SF and TF were: LF 5.2% vs. 3.1% (p=0.05) and DF 20.1% vs. 24.1% (p=0.16), respectively. Median and 5-year OS by SF and TF were: 43.6 months and 37.5%; 44.7 months and 41.3%, respectively(p=0.27). Multivariate analysis (MVA) for LF revealed no pt, tumor or treatment associations. DF was associated with histology on MVA (p=0.0039). MVA for OS was significantly associated with age at SBRT (p=0.0015), KPS (p=<0.0001), gender (p=<0.0001) and tumor size (p=0.0002).

Conclusions: In this analysis of over 1000 pts treated in a single center, there were no differences seen in OS between SF and TF lung SBRT pts. Rates of high-grade toxicity including of the chest wall were similar between Fx schedules, as were LF and DM rates. These results suggests that SF may be the preferred lung SBRT option for ESLC, potentially offering logistical and resource advantages.

Keywords: inoperable early stage lung cancer, SBRT, fractionation

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.40 Efficacy of Re-Irradiation With SABR of Lung Cancer After Primary SABR: A Single Centre Experience

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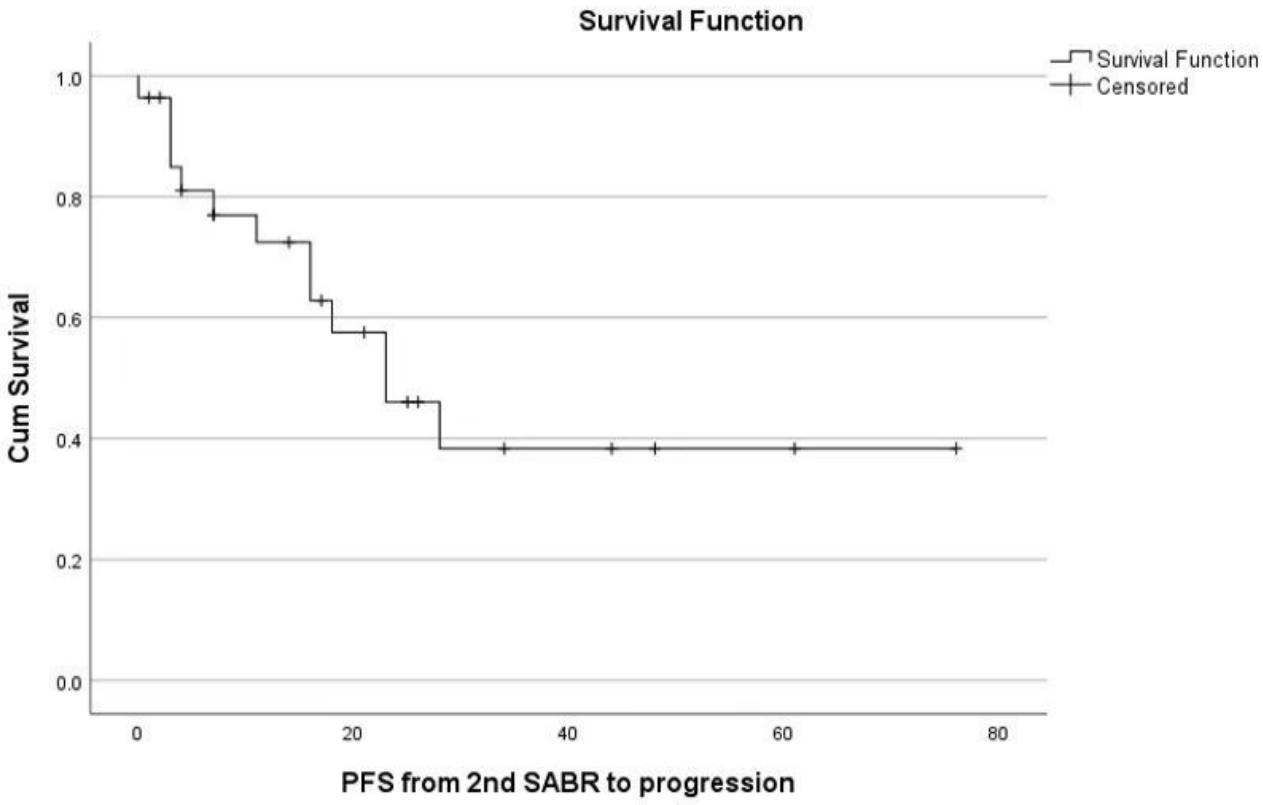
Introduction: While incidents of second primary lung cancers (SPLC) are on the rise, there is a scarcity of data that investigates the effectiveness of re-irradiation with stereotactic ablative body radiotherapy (SABR) following primary SABR. This study evaluates progression-free survival (PFS), local control (LC), and overall survival (OS) following re-irradiation with SABR.

Methods: An ongoing retrospective review of 1033 distinct patients with SABR to the lung from January 2015 to December 2020 examined demographics, radiotherapy data, and outcomes from the electronic patient record. Patients were considered for analysis if they had a SABR re-irradiation for SPLC after 2 years following primary SABR. 28 patients were identified for analysis.

Results: The median age was 72.7, and 46.5% of the patients had a Charlson Comorbidity Index (CCI) of 5 or more. While 75% of patients included in the final analysis were diagnosed with Stage 1 lung cancer, all of the patients had active or past tobacco use. The median time interval between both SABR treatments is 33.5 months, with all treatments delivering BED (10) of 81Gy and more. 55Gy in 5 fractions was the most commonly used fractionation regimen in both primary & re-irradiation settings. The median OS from the 2nd SABR is 30 months (14.0 - 46.0 CI 95%), while the median PFS from the 2nd SABR is 23.0 months (11.7 - 34.3 CI 95%). SABR re-irradiation shows a 92.9% LC rate, comparable to 92.7% LC at 1-year in the primary SABR setting [1].

Conclusions: This study demonstrates the effectiveness of SABR re-irradiation following primary SABR. Further analysis is planned on a larger cohort and will investigate treatment failure patterns, radiation dosimetry & toxicities.



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Keywords: SABR, Re-Irradiation, Local Control

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
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EP.07.41 Individualized SBRT for Ultra-Central NSCLC Achieves Optimal Tumor Control With Minimal Toxicity

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Introduction: Stereotactic body radiation therapy (SBRT) provides excellent outcomes for early-stage non-small cell lung cancer (NSCLC). However, treating ultra-central NSCLC (UCNLC)-tumors adjacent to critical organs at risk (OARs)-remains challenging due to potential toxicities. Advances in personalized radiotherapy planning may help overcome these challenges. This study evaluates the efficacy and safety of tailored SBRT approaches for UCNLC.

Methods: We reviewed 66 patients with stage I-II unresectable UCNLC treated with SBRT at Shanghai Pulmonary Hospital (January 2020-December 2023). UCNLC was defined as a planning target volume (PTV) abutting or overlapping the proximal bronchial tree, esophagus, heart, great vessels, or pulmonary vessels, or within 1 cm of these structures. Rigorous OAR constraints (maximum dose and volumetric thresholds) were used to protect critical structures. Individualized SBRT plans incorporated non-uniform PTV modifications (e.g., PTV_crop and PTV_high/low) to meet these stringent constraints. Primary endpoints were local control (LC) and progression-free survival (PFS), while secondary endpoints included regional control (RC), distant control (DC), overall survival (OS), and treatment-related toxicity.

Results: Non-uniform PTV modifications were employed in 45.5% of patients, enabling 53.3% to achieve a biologically effective dose (BED10) of 100 Gy while adhering to strict OAR constraints. After a median follow-up of 23.7 months, median PFS was 42.9 months (95% CI: 34.5-51.3), with 1- and 3-year PFS rates of 93.9% and 67.0%, respectively. LC rates reached 98.5% at 1 year and 81.4% at 3 years; corresponding OS rates were 98.5% at 1 year and 92.8% at 3 years. Toxicities were minimal, with grade 1 and 2 radiation pneumonitis in 28.8% and 7.6% of patients, respectively, and only one grade 3 pneumonitis case (1.5%). Long-term toxicities were also mild, including grade 1 pulmonary fibrosis in 9% and one case of grade 2 fibrosis. No severe toxicities (> grade 3) were observed. Importantly, non-uniform PTV modifications did not compromise survival outcomes.

Conclusions: Tailored SBRT that incorporates non-uniform PTV modifications alongside rigorous OAR constraints achieved excellent tumor control with minimal toxicity in UCNLC. These findings underscore the feasibility and effectiveness of personalized radiotherapy planning, affirming SBRT as a safe and viable treatment option for challenging ultra-central tumors.

Keywords: stereotactic radiotherapy, ultra-central, non-small cell lung caner

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.42 Stereotactic Body Radiation Therapy Versus Surgery in Early-Stage Non-Small Cell Lung Cancer. How Does Comorbidity Impact?

Lung Cancer. How Does Comorbidity Impact?
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Introduction: Surgery remains the standard treatment for early-stage non-small cell lung cancer (ES-NSCLC). For patients unfit for surgery, stereotactic body radiation therapy (SBRT) offers high local control with low toxicity. This study aimed to compare overall survival (OS) between surgery and SBRT in early-stage NSCLC, considering comorbid burden.

Methods: A cohort study of patients with clinical ES-NSCLC diagnosed between 2019 and 2021, identified through Tumor Registry Database was made. Patients were stratified by age (<75, ≥75), treatment (surgery, SBRT), and comorbidity by Charlson Comorbidity Index (CCI), categorized as no, low or high comorbidity. Variables: age, sex, histology, hospital admissions before NSCLC diagnosis, follow-up and survival. Kaplan-Meier and hazard ratios were used for survival analysis.

Results: 713 patients were included (mean age 68y, 70.7% male). Most patients were diagnosed at stage I (79.1%), and 83.6% received surgery while 16.4% were treated with SBRT. Based on the CCI, 40.5% had no comorbidity, 35.2% low and 24.3% high. Median follow-up was 28 months. In patients without comorbidity, OS did not significantly differ between surgery and SBRT. However, in those with comorbidities, surgery was associated with improved OS. In the high-comorbidity subgroup, 1-year OS for <75y was 95.7% for surgery vs 84.6% for SBRT, and 80.0% vs 73.3% respectively in ≥75y. SBRT patients had significantly more hospital admissions related to comorbidities prior to cancer diagnosis, suggesting greater baseline fragility.

Conclusions: SBRT provides comparable OS to surgery in early-stage NSCLC patients without comorbidities. In patients with comorbidity, surgery was associated with better outcomes. The higher pre-diagnosis healthcare utilization in SBRT patients suggests a degree of frailty not fully captured by conventional comorbidity indices. The CCI may therefore be insufficient in differentiating surgical from non-surgical candidates. These results highlight the need for more nuanced and clinically meaningful tools to guide treatment individualized decisions in ES-NSCLC

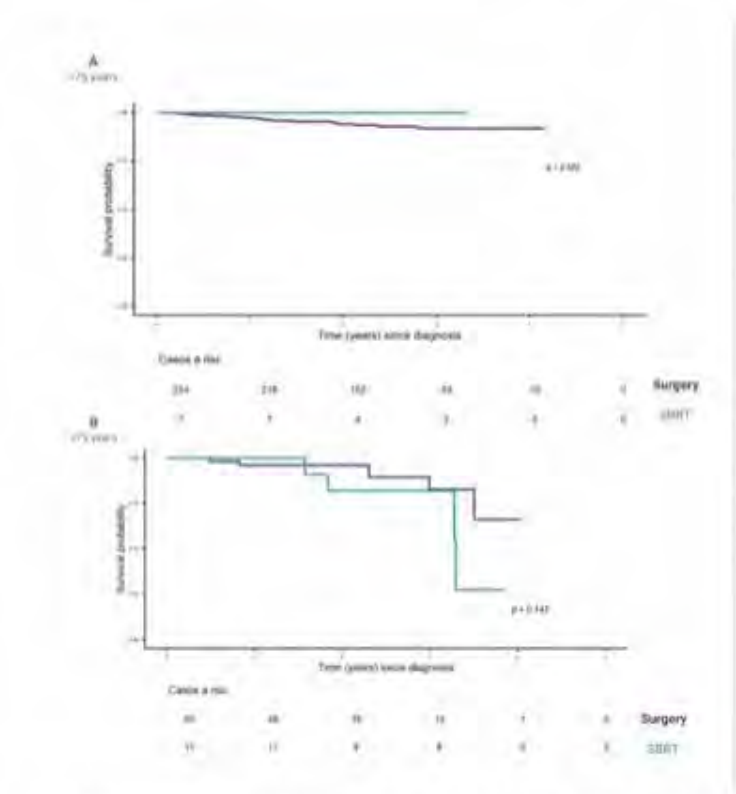

Figure 1. OS according to treatment (surgery vs SBRT) for each group of patients [<75 years (A) and ≥75 years (B)] with **no-comorbidity** by CCI.

Table 1

	Surgery	SBRT
Chronic pulmonary disease	0.7 (0.62-0.75)	1.4 (1.2-1.63)
Diabetes	0.4 (0.38-0.49)	0.9 (0.77-1.12)
Peripheral vascular disease	0.3 (0.21-0.29)	0.4 (0.31-0.55)
Mild liver disease	0.1 (0.11-0.17)	0.1 (0.07-0.2)
Myocardial infarction	0.2 (0.13-0.2)	0.4 (0.28-0.51)

Table 1. Hospital admissions per patient (mean, CI95%) by the five most popular comorbid condition in our patients represented by CCI in surgery and SBRT groups.

Keywords: SBRT, SABR, Comorbidity

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.07.43 The Role of FDG-PET/CT SUVmax in Predicting Treatment Outcomes and Progression Risk in SBRT for ES-NSCLC

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Introduction: Stereotactic body radiation therapy (SBRT) is the standard of care for medically inoperable early-stage non-small cell lung cancer (ES-NSCLC). FDG-PET/CT, widely used for pre-treatment staging, provides critical metabolic information and is employed as a diagnostic tool for managing pulmonary lesions without histological confirmation. This study investigates the predictive value of pre-treatment FDG-PET/CT, specifically the relationship between lesion SUVmax and the risk of disease progression, as well as treatment response to SBRT.

Methods: Retrospective study included ES-NSCLC patients treated with SBRT between 2016 and 2023 who underwent pre-treatment FDG-PET/CT imaging. Tumor characteristics and FDG-PET/CT SUVmax of the primary lesion were recorded. Radiological response at three months of SBRT, and progression (type and timing) were also collected. The relationship between FDG-PET/CT variables and treatment response/progression was analyzed with statistical significance set at $p < 0.05$.

Results: A total of 49 patients were included in the study, of whom 91.6% were male. Former smokers comprised 73.5% of the cohort, and 69.4% had a history of emphysema or pulmonary obstructive disease (EPOD). Histological confirmation was available for 57.1% of lesions. Tumor location was central in 34.7% and peripheral in 65.3% of cases. The median SUVmax of the primary lesion was 9.94 (SD 7.2). The most common treatment regimen was 8×750 cGy (32.7%), followed by 5×1000 cGy (22.4%) and 5×1100 cGy (20.4%). At the first post-SBRT assessment, 40.8% of patients had a stable primary lesion response and 44.9% had a partial response. Median follow-up time was 1.5 years. Median progression-free survival was 1 year. A total of 23 patients experienced disease progression; among them, 52.2% had local and/or nodal progression, while the remainder developed distant metastases. The SUVmax values in primary lesions were not associated with increased risk of progression ($p = 0.3$). Interestingly, patients with stability of the primary lesion at first follow-up had significantly lower baseline SUVmax values (mean 7.6 SD 6.9), with statistical significance ($p = 0.04$). Of these patients, 60% lacked histological confirmation of malignancy. No significant differences were observed in progression patterns or treatment fractionation schedules.

Conclusions: We not found relationship between SUVmax values and an increased risk of progression of ES-NSCLC, although further studies specifically addressing this question are needed. The finding that most patients with stable disease at the first follow-up had low SUVmax values and lacked histological confirmation may suggest potential overtreatment of these lesions.

Keywords: FDG-PET/TC, SBRT, Early lung cancer

EP.07.44 Perioperative Treatment Patterns and Clinical Outcomes in Early-Stage NSCLC: A Real-World Study (Peri-R-02)

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Introduction: The perioperative management of resectable non-small cell lung cancer (NSCLC) has evolved significantly with the integration of immunotherapy. However, perioperative treatment patterns and clinical outcomes in real-world clinical practice remain inadequately characterized.

Methods: The Peri-R-02 study (NCT06610240) was a real-world study in patients with stage I-III NSCLC who underwent radical surgery and received neoadjuvant therapy from two medical centers in China between January 2020 and Feb 2025. The primary endpoint was pathologic complete response (pCR), and the secondary endpoints were objective response rate (ORR), major pathologic response (MPR) and event-free survival (EFS).

Results: In the Peri-R-02 study, a total of 609 patients were analyzed and divided into the immunotherapy checkpoints inhibitor based neoadjuvant cohort (ICI, n=507) and EGFR/ALK tyrosine kinase inhibitor-based neoadjuvant cohort (TKI, n=57) and chemotherapy alone neoadjuvant cohort (Chemo, n=45). After neoadjuvant therapy, surgical outcomes showed comparable R0 resection rates (ICI:97.6%, TKI:96.5%, Chemo:88.9%) and adjuvant therapy administration rates (ICI:79.3%, TKI:86.4%, Chemo:73.3%). Baseline characteristics revealed distinct cohort profiles, ICI and Chemo cohort were predominantly male (ICI, 93.5%; Chemo, 75.6%) and squamous histology (ICI, 70.2%; Chemo, 63.1%), TKI cohort have higher female proportion (57.9%), non-squamous histology (98.2%) and driver gene mutations (EGFR:77.2%, ALK:15.8%). Disease stage (stage III: ICI, 86.4%; TKI, 78.9%; Chemo, 91.1%) and age (>65%: ICI, 43.2%; TKI, 42.1%; Chemo, 42.2%) showed comparable distributions across all three cohorts. ICI cohort demonstrated significant benefits in pCR rate (36.5% vs 7.0% vs 6.7%; P<.001) and MPR (61.4% vs 26.1% vs 12.9%; P<.001) compared to TKI cohort or chemo cohort. ICI cohort and TKI cohort showed significant higher ORR (60.5% vs 60.1% vs 25.5%; P<.001) compared to Chemo cohort. With a median follow-up time of 16.2 months, an EFS benefit trend favoring ICI cohort (HR= 0.44 [95% CI: 0.26, 0.74]; P=0 0.002) and TKI cohort (HR=0.42 [95% CI: 0.20, 0.90]; P=0.025) was observed compared to Chemo cohort.

	ICI cohort N=507	TKI cohort N=57	Chemo cohort N=45
Neoadjuvant therapy regimens, %	ICIs+Chemo, 96.6% ICIs + Anlotinib/Beva, 2.6% ICIs mono, 0.8%	EGFR/ALK TKI + chemo, 42.1% EGFR/ALK TKI, 57.9%	Chemotherapy, 88.9% Chemo+beva, 11.1%
Neoadjuvant Treatment cycles/time, median(range)	3 cycles (1-9)	2 months (1-13)	2cycles (1-6)
R0 resection rate, n (%)	495 (97.6%)	55 (96. 55%)	40 (88.9%)
Adjuvant Treatment Rate, n (%)	402(79.3%)	49(86.0%)	33(73.3%)
pCR, n (%)	185(36.5%)	4(7.0%)	3(6.7%)
ORR	325(60.6%)	36(63.2%)	9(20.0%)

ICI, immunotherapy checkpoints inhibitor; TKI, tyrosine kinase inhibitor; Chemotherapy, chemo; pCR, pathologic complete response; ORR, objective response rate.

Conclusions: In real-world practice, ICI-based neoadjuvant therapy showed greater utilization frequency than TKI or chemo regimens, achieving significantly higher pathological response rates versus both TKI or chemo regimens, while demonstrating EFS benefit trend over conventional chemotherapy. Continued follow-up is being conducted to assess long-term efficacy and safety.

Keywords: Immunotherapy, Neoadjuvant Therapy, Non-small Cell Lung Cancer

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
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EP.07.45 Single-Cell Analysis Revealed the Characteristics of Tumors With Different Responses to Neoadjuvant Chemo Immunotherapy in Stage II-IIIB NSCLC

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Introduction: Neoadjuvant chemo-immunotherapy (NCIT) has shown promising results in patients with non-small cell lung cancer (NSCLC). However, resistance to treatment remains a constraint to fully understanding treatment responsiveness.

Methods: In this study (ChiCTR2300069552), patients diagnosed with stage II-IIIB NSCLC without EGFR/ALK/ROS1 gene variations were enrolled. Neoadjuvant tislelizumab plus platinum-based doublet chemotherapy for up to 4 cycles was administered. We comprehensively characterized the tumor and immune cell states within the tumor microenvironment (TME) across multiple sequential single-cell samples grouped by pathological complete remission (pCR) and non-pCR based on pathology results. This was achieved by analyzing the single-cell transcriptomes of a total of 473,192 cells from 20 patients, both pre- and post-NCIT, along with their corresponding paracancerous tissues.

Results: From February 2023 to September 2024, 30 patients were enrolled. The overall response rate was 83.3%, and the disease control rate was 100%. Among patients who underwent surgery, the major pathological remission (MPR) rate was 66.7%, and pCR was 50%. We first observed a significantly higher proportion of cytotoxic T cells, TH17 cells, and type II alveolar cells in the pCR group compared to the non-pCR group. In contrast, the proportion of T regulatory cells and exhausted T cells in the non-pCR group was significantly higher than in the pCR group. Secondly, we found that while the proportion of cytotoxic T cells in the pCR group decreased, the proportion of NKT cells significantly increased after NCIT, suggesting that NKT cells may be associated with treatment efficacy. Tumor-associated fibroblasts increased significantly after treatment in the non-pCR group, which may be associated with poor efficacy. Finally, tumor cell trajectory analysis showed that the pCR and non-pCR groups exhibit different evolutionary trajectories.

Conclusions: Our study provides novel insights into the different cellular and molecular components that correspond to NSCLC NCIT responsiveness, which will benefit future personalized chemo-immunotherapy.

Keywords: chemo-immunotherapy, Single-cell analysis, tumor microenvironment

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.46 Clinical and Radiologic Factors Associated With Surgical Eligibility After Neoadjuvant Chemoimmunotherapy in Stage II-III NSCLC

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Introduction: Neoadjuvant chemoimmunotherapy (NCIT) has demonstrated improved resectability and survival in patients with stage II-III non-small cell lung cancer (NSCLC). However, some patients are not eligible for surgery after NCIT. This study evaluates real-world data to identify baseline clinical and radiologic characteristics associated with surgical eligibility following NCIT.

Methods: We retrospectively analyzed 100 patients with stage II-III NSCLC who received NCIT at Samsung Medical Center between November 2022 and December 2023. Clinical variables included performance status, pulmonary function (DLCO, FEV1), and comorbidities. Radiologic parameters—assessed by experienced thoracic radiologists using CT and PET/CT scans before and after NCIT—included tumor location, bronchial or vascular abutment, necrosis, cavitation, extranodal extension, and metabolic activity. Multivariable logistic regression identified independent predictors of non-surgical treatment decisions.

Results: The mean age of the study population was 64.8 years, with 86% male and 87% ever-smokers. NCIT was completed in 98% of patients. Surgery was performed in 82% of patients. Among those who did not undergo surgery, the main reasons included impaired cardiopulmonary function (n = 9), disease progression (n = 3), and patient refusal (n = 3). Among those who performed surgery, clinical downstaging occurred in 56.1% (n = 46), no change in 40.2% (n = 33), and upstaging in 3.7% (n = 3). Multivariable analysis revealed that ECOG ≥1 (OR 10.89, p = 0.027), DLCO <60% (OR 13.65, p = 0.035), tumor abutment to the main bronchus (OR 10.20, p = 0.035), and incomplete NCIT (OR 0.01, p = 0.013) were significantly associated with a shift away from surgery.

Conclusions: Pre-treatment clinical, imaging, and pulmonary function parameters are key predictors of surgical eligibility following NCIT in stage II-III NSCLC. Identifying these factors may help guide individualized treatment planning in real-world practice. Further validation and development of predictive models across different cohort may improve treatment strategies and outcomes.

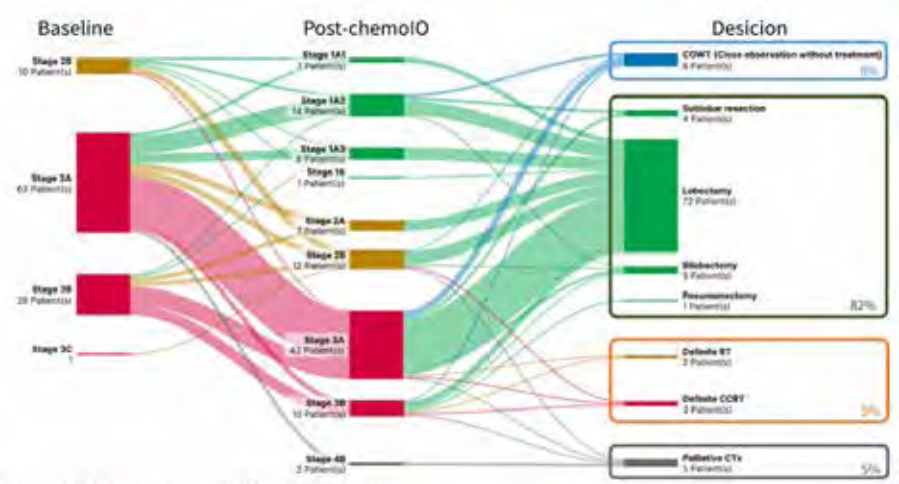

Figure 1. Sankey diagram of the study cohort

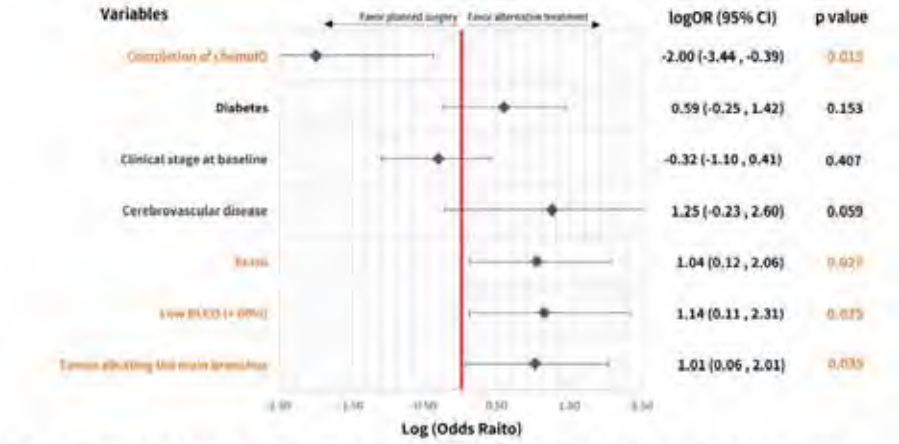

Figure 2. Forest plot from the multivariate analysis of factors associated with changes in the treatment plan, excluding cases of close observation without treatment.

Keywords: neoadjuvant, chemoimmunotherapy, predictor

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.47 Real-World Implementation of Neoadjuvant Chemo-Immunotherapy in Resectable Non-Small Cell Lung Cancer

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Introduction: In alignment with the recommendation of National Institute of Health and Care Excellence (NICE), nivolumab combined with chemotherapy is currently used for selected patients with resectable non-small cell lung cancer (NSCLC). However, real-world data on outcomes and implementation are limited. Therefore, we aimed to capture real-world data on safety, efficacy and feasibility of chemoimmunotherapy in resectable NSCLC.

Methods: Between 22 March 2023 and 29 October 2024, we retrospectively reviewed patients referred for neoadjuvant chemo-immunotherapy at Liverpool Heart and Chest Hospital, following publication of the NICE guidance. Data collected included demographics, treatment adherence, adverse events, surgical outcomes, pathological response, peri-operative complications and mortality.

Results: During this period, 978 patients underwent surgery for primary lung cancer. Of 184 patients referred to neoadjuvant treatment, 145 patients commenced neoadjuvant treatment and 136 underwent surgery (attrition rate 6%). Adherence to chemoimmunotherapy was excellent;133 patients (92%) completed three cycles. Minimally invasive surgery was performed in 113 patients (83%) with 12 conversions (10%). Standard lobectomy was performed in 92% of cases and pneumonectomy rate was 2%. Complete pathological response was achieved in 41 (30%) and major pathological response in 21 patients (15%). The 90-day mortality in the surgical cohort was 4%.

Conclusions: Neoadjuvant chemo-immunotherapy is feasible and well tolerated in a real-world setting, with low attrition and encouraging pathological response rates. The high utilisation of minimally invasive surgery and low peri-operative complications, along with low mortality, support its integration into the standard care for selected patients with resectable NSCLC.

Keywords: immunotherapy, Chemotherapy, lung cancer

EP.07.48 The Impact of Sarcopenia on Neoadjuvant Chemoimmunotherapy in Earlier Stage Resectable NSCLC

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Introduction: Immunotherapy (IO) targeting programmed death (PD) 1 and PD ligand(L)-1 has been recently introduced in the neoadjuvant [combined with chemotherapy (CT)] and adjuvant setting to enhance outcomes in resectable NSCLC and improve the chances of achieving a cure. The interplay between nutritional status and anticancer immunity represents an emerging and intriguing area of research. This study explored the influence of sarcopenia on the pathological response to the neoadjuvant CT-IO in resectable non-small-cell lung cancer (NSCLC).

Methods: A retrospective analysis was performed of patients with earlier stage resectable NSCLC receiving neoadjuvant CT-IO at our institution from August 2021 to August 2024. Body composition parameters at third lumbar level were assessed by applying an arti artificial intelligence (AI)-powered-software to computed tomography (CT) performed at baseline and before surgery (T1). Sarcopenia was defined according to Skeletal Muscle Index (SMI) sex-based cut-offs of the International definition. Primary endpoint was the pathological complete response (pCR) rate; secondary endpoints were Major Pathological Response (MPR) rate and event-free-survival (EFS).

Results: Data from 34 patients were collected, including 20 (58%) females and 14 (42%) males. The median age was 65.5 years (range 45-80). The median Body Mass Index (BMI) was 24.6 kg/m2. At baseline, 16 (47%) patients were sarcopenic and the majority of them (10/16, 63%) were classified as normal-weight by BMI. The PCR rate was significantly higher in patients without sarcopenia compared with sarcopenic patients (66.7 vs 31.3%, OR 4.4, 95%CI 1.04-18.59; p=0.039). Also PD-L1 high-expression (≥50%) was significantly associated with pCR rate (p=0.021). No significant differences in term of pCR and MPR were observed according to SMI and fat tissue indices. Multivariate regression analysis confirmed significantly higher likelihood of pCR rate with non-sarcopenia status (OR 4.2 , 95% CI.0.83-21.14, p=0.081) and PD-L1 high-expression (OR 7.48, 95% CI 1.16-48.19, p=0.034). Out the 29 evaluable patients at T1, sarcopenia was present in 18 (62%) cases, including 2 patients who were non-sarcopenic at baseline. Difference of SMI and fat tissue-related indices between T1 and baseline were not significantly associated with pCR and MPR. After a median follow-up 12.6 months (mo), a better EFS trend was observed in patients without sarcopenia at baseline (not reached vs 23.7 mo, HR 0.23, 95%CI 0.04-1.37, p=0.106).

Conclusions: Non-sarcopenic status may represent an intriguing predictive markers of pathological response to CT-IO in the potentially-curative setting of resectable NSCLC. Prospective data on larger population are needed to validate this easy-assessable clinical biomarker.

Keywords: Neoadjuvant chemoimmunotherapy, Sarcopenia in Earlier Stage NSCLC, Predictor of pCR

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER
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EP.07.49 Neoadjuvant Sunvozertinib for Early-Stage NSCLC Patients With EGFR Exon 20 Insertion Mutation: A Case Series

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Introduction: Sunvozertinib is an oral, potent, highly selective EGFR-TKI approved in China for the treatment of advanced NSCLC with EGFR exon 20 insertion (exon20ins) mutation. Few reports describe the advantages of this therapeutic strategy in a neoadjuvant setting. Here, we firstly report a real-world series showing the encouraging clinical activity of sunvozertinib as neoadjuvant therapy in early-stage NSCLC patients harboring EGFR exon20ins mutation.

Methods: We retrospectively collected profiles of NSCLC patients with EGFR exon20ins mutation receiving sunvozertinib as neoadjuvant treatment. TNM staging was based on AJCC 9th Edition. The data analyzed by investigators included response assessment by RECIST 1.1 and safety outcomes. The data cutoff was March 21, 2025.

Results: At data cutoff, three NSCLC patients with EGFR exon20ins mutation were retrospectively collected. All the patients received sunvozertinib as neoadjuvant treatment and achieved obvious partial response (PR) before surgery. Then all the patients underwent surgery successfully. Patient 1, a 67-year-old male patient was diagnosed with stage IIIB lung adenocarcinoma. The patient received a therapy of sunvozertinib 300 mg QD for 3 months then 150mg QD for another 3 months as neoadjuvant treatment. The preoperative CT scan showed significant reduction by about 80%. At data cutoff, the patient has undergone surgery successfully. No intolerable adverse event was observed. Patient 2, A 54-year-old female patient was diagnosed with stage IIIA lung adenocarcinoma. The patient received sunvozertinib 300 mg QD as neoadjuvant treatment for 3 months. The preoperative CT scan showed that the primary lesion achieved obvious PR and then the patient underwent surgery successfully. There were no drug-related adverse events during the neoadjuvant treatment. Patient 3, A 78-year-old male patient was diagnosed with stage IIB lung adenocarcinoma. The patient received sunvozertinib 300 mg QD orally for 3 months. The preoperative CT scan showed obvious tumor shrinkage by about 50%. Then the patient underwent surgery successfully. The safety profile of sunvozertinib in this patient was good.

Conclusions: In this real-world case series, neoadjuvant sunvozertinib showed encouraging clinical benefit in early-stage NSCLC patients with EGFR exon20ins mutation and all the three patients achieved obvious PR before surgery. In addition, the safety profile was acceptable. Prospective studies with larger sample sizes of sunvozertinib in early-stage NSCLC patients are worth further investigation.

Keywords: EGFR exon20ins, Sunvozertinib, Neoadjuvant treatment

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.50 Real-World Treatment Strategy and Postoperative Prognosis for Clinical Stage II/III NSCLC: A Multicenter Study

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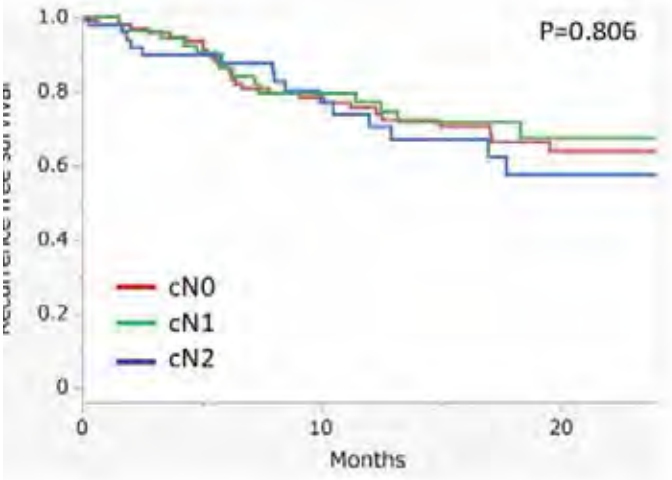
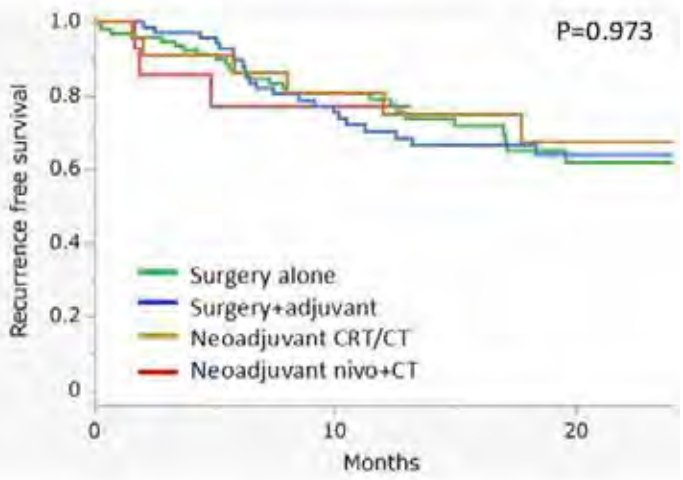
Introduction: For stage II/III non-small cell lung cancer (NSCLC), postoperative tyrosine kinase inhibitors, postoperative immune checkpoint inhibitors (ICIs), and recently, neoadjuvant ICI have become standard treatment options. We conducted a multicenter retrospective observational study to investigate the real-world treatment patterns and prognostic outcome for clinical stage II/III NSCLC in this era of perioperative personalized medicine.

Methods: We retrospectively analyzed 201 cases of clinical stage II/III NSCLC (based on the 9th edition of the TNM classification) who underwent surgery at 5 institutions in Japan between March 2022 and August 2024. The primary endpoint was the treatment strategy based on clinical factors (N status or clinical stage). Postoperative prognosis was also examined.

Results: The median age was 72 years, and 68% of the patients were male. The distribution of clinical N stages was cN0/1/2 in 48%, 27%, and 25% of cases, respectively, and cStage II/III in 61% and 39%, respectively. Among all cases, 82% underwent upfront surgery, while 18% received neoadjuvant therapy (11% were chemoradiotherapy (CRT) or chemotherapy (CT), and 7% received nivolumab+CT). Among the upfront surgery cases, 70 patients (42%) received adjuvant therapy. The rate of neoadjuvant therapy increased from 10% to 24% (P=0.0154) following neoadjuvant first approval of neoadjuvant nivolumab+CT regimen in Japan (from 6% to 24% in cN1 cases, from 33% to 50% in cN2 cases). Finally, we analyzed recurrence-free survival (RFS). No significant difference in RFS was observed based on clinical stage, N status, or treatment modality. The 1-year RFS rates for clinical stage II and III were 76% and 73%, respectively (P=0.866). The 1-year RFS rates for cN0, cN1, and cN2 were 76%, 77%, and 71%, respectively (P=0.806). Based on treatment modality, the 1-year RFS rates were 79% for surgery alone, 70% for surgery plus adjuvant therapy, 75% for the neoadjuvant CRT/CT group, and 77% for the neoadjuvant nivo+chemo (P=0.973).

Conclusions: The introduction of neoadjuvant therapy has increased for cN1/N2 cases following neoadjuvant nivolumab+chemotherapy regimen approval . Due to the impact of neoadjuvant therapy, the short-term prognosis of cN1/N2 cases was comparable to that of cN0 cases. Further follow-up is needed to assess long-term outcomes by treatment modality.





EP.07.51 Long-Term Egfr-Tki as Neoadjuvant Therapy Effectively Achieved Depth of Pathological Response

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Introduction: Emerging evidence suggest that neoadjuvant therapy is capable of improving R0 resection rate, controlling regional recurrence and distant metastasis in NSCLC. Nevertheless, the NEOS trial reported limited pathological response (MPR 15%, PCR 0%) with 6-week third-generation EGFR-TKI in EGFR-mutant NSCLC. Given EGFR-TKI exerts its effect by inhibiting the growth of tumor cells instead of inducing cytotoxic effects, we assumed that prolonged duration of neoadjuvant therapy may be a promising approach to improve the depth pathological response for EGFR-mtated NSCLC patients.

Methods: We retrospectively analyzed stage IA-IVA(AJCC 9th) NSCLC patients harboring EGFR mutations without prior anti-tumor treatment from 2022 to 2024 in Xiangya hospital. All the patients were treated with regular dose of third-generation EGFR-TKI at least 3 months as neoadjuvant therapy. The primary endpoint was pDepOR (pathologically depth of response). Secondary endpoints included PFS, ORR, DCR and safety.

Results: In total, 13 patients were enrolled and analyzed with the median age of 60 years old (range 53-76). Among them, two patients were clinically diagnosed as stage IVA due to possible lesions localized in contralateral lung reported by PET-CT. Eight patients received neoadjuvant therapy over half year. 84.6% of candidates reached pDepOR to varying degrees. The pDepOR distribution: >95% (30.8%), 50-95% (53.8%), 26-50% (15.4%). The ORR was 46.2% and the DCR was 100%. No grade ≥3 AEs occurred before surgery. As for surgery, long-term EGFR-TKI as neoadjuvant therapy did not increased the difficulty nor complications. The operation time of 11 patients was within 2 hours and all the patients were discharged within 5 days. The majority of patients (84.6%) had intraoperative blood loss was no more than 50ml. The post-op drainage was around 200-400ml and the drainage tube can be pulled off within 4 days.

Conclusions: Long-term 3rd-generation EGFR-TKI as neoadjuvant therapy can effectively shrink the depth of tumor without making surgery more complicated. Enrollment will continue for further analyses.

Keywords: EGFR-mutant NSCLC, Long-term neoadjuvant therapy, targeted therapy

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.52 PD-L1 Tumor Expression Changes in Non-Small Cell Lung Cancer After Neoadjuvant Chemoimmunotherapy and the Relation With Pathologic Response

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Introduction: Programmed death-ligand 1 (PD-L1) expression on cancer cells remains the most important predictive factor for checkpoint inhibitors in non-small cell lung cancer (NSCLC). The use of PD-1/PD-L1 antibodies in combination with chemotherapy as neoadjuvant or perioperative treatment for NSCLC is not dependant on PD-L1 expression level and PD-L1 does not correlate so strong with treatment outcomes as it does in the palliative setting. Chemotherapy was believed to increase the level of PD-L1 expression and to boost the mechanisms of response to checkpoint inhibitors. The effects of neoadjuvant chemoimmunotherapy on the PD-L1 expression on tumour cells and the correlation between pathological response and the PD-L1 status-change remain unknown.

Methods: We investigated 18 cases of patients diagnosed with locally advanced NSCLC and found resectable, who were treated with neoadjuvant chemoimmunotherapy in routine clinical practice. We retrospectively recorded demographics, initial stage, histology, regimen used, baseline PD-L1 (bPD-L1) expression and pathological response with percentage of vital cancer cells in the resected specimen. We also conducted prospective PD-L1 expression assessment in the resected specimen (yPD-L1), with the initial results blinded from the pathologist, we excluded cases with pathological complete response (pCR). We used SP263 clone for PD-L1 stain. Collected data was analysed, change is presented in percentage points (p.p.) and numbers are rounded to two decimal places. All patients consent to study participation.

Results: Our cohort included 9 females and 9 males; the median age was 67 years at the day of treatment introduction. There were 10 cases of squamous cell carcinoma and 8 cases of adenocarcinoma. Median bPD-L1 expression was 73% (average 54%, SD=0.42, range 0-100%). Clinical stage IIIA was predominant, with N2 positive in 9 cases. Most patients received nivolumab (13/18), the rest got durvalumab and pembrolizumab (3 and 2 accordingly) in combination with histology specific chemotherapy. 16 patients completed the whole planned neoadjuvant treatment. Major pathological response (MPR) rate was 61% (11/18) and the median percetage of remaining living cancer cells in resection specimen (LCCSp) was only 10% (average 23%). 17 cases were node-positive (N+) at baseline, only 6 remained N+ after neoadjuvant phase. LCCSp had very low negative linear correlation with bPD-L1 (r= -0.249), but median bPD-L1 in pCR group was 80%. Median yPD-L1 expression was 10% (average 25%, change from baseline (-)63 p.p.for median value and (-)31 p.p. for average value) and change from baseline in the evaluable-only group was (-)14 p.p. The potency of-PD-L1 stain was decreased in resection specimens and in cases when living cancer cells proportion was low the assessment was less reliable.

Conclusions: Very high PD-L1 expression is a good predictive factor to complete pathologic response after neoadjuvant treatment with chemoimmunotherapy of NSCLC. PD-L1 expression decreases after neoadjuvant chemoimmunotherapy for NSCLC which may explain smaller (or uncertain) benefit from adjuvant phase of perioperative treatment observed in recent registration trials. Further investigation is needed.

Keywords: PD-L1, neoadjuvant, chemoimmunotherapy

EP.07.53 Impact of Subcutaneous Fat on the Relative Dose Intensity of Adjuvant Chemotherapy in Patients With Non-Small Cell Lung Cancer

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Introduction: Maintaining a high relative dose intensity (RDI) is important for enhancing the efficacy of chemotherapy in various cancers. Reduced or delayed administration of anticancer drugs may result in poor prognosis. This study examined the effect of subcutaneous fat on the RDI of platinum-based agents during postoperative adjuvant chemotherapy in patients with pathological stage II-III non-small cell lung cancer (NSCLC).

Methods: Toward this, 101 patients subjected to adjuvant platinum chemotherapy after complete resection of pathological stage II-III NSCLC at our institution between 2017-2019 were included in this study. RDI was defined as the ratio of the actual dose (mg/m2/week) to the planned dose (mg/m2/week) of platinum agents (cisplatin and carboplatin) used in adjuvant chemotherapy. The area of subcutaneous fat (SFA) was measured with a Synapse Vincent (FUJIFILM, Tokyo, Japan) using preoperative CT at the level of the third lumbar vertebra. Cutoff values of subcutaneous fat area were determined using receiver operating characteristic (ROC) analysis to predict the completion of four courses of adjuvant chemotherapy. A logistic regression model was used to perform multivariable analysis of factors related to the RDI, including SFA, as a variable.

Results: Median age was 64 (35-78) years, median BMI 22.9 (16.9-29.7) kg/m2, 72 patients had adenocarcinoma, and 51 (50.1%) had pathological stage III NSCLC; 75 patients received four courses of adjuvant chemotherapy and 83 received cisplatin, and the median RDI was 75 (range 23-100) %. There were 34 patients (33.7%) with low RDI (RDI < 70 %). There were no significant differences in clinicopathological factors, including age (62.8 vs 62.3, p=0.773), BMI (23.5 vs 22.8, p=0.269), and gender (male: 67.6% vs. 76.1%, p=0.476), between the low- and high-RDI groups. The number of patients with high SFA (>137 cm2) was significantly higher in the low-RDI group than in the high-RDI group (32.4% vs. 10.4%, p=0.012). The 5-year RFS rates were 42.5% and 60.4% in the low- and high-RDI groups, respectively (p=0.084). Multivariable analysis revealed SFA as an independent predictive factor associated with low RDI (HR 4.120, 95%CI 1.39-12.2, p=0.01).

Conclusions: High subcutaneous fat area was associated with low RDI in platinum-based adjuvant therapy in patients with pathologic stage II-III NSCLC.

Keywords: Adjuvant chemotherapy, relative dose intensity, subcutaneous fat

EP.07.54 Lymphatic Permeation as a Key Risk Factor for Recurrence in Pathological Stage IIA NSCLC Under the 9Th TNM Classification

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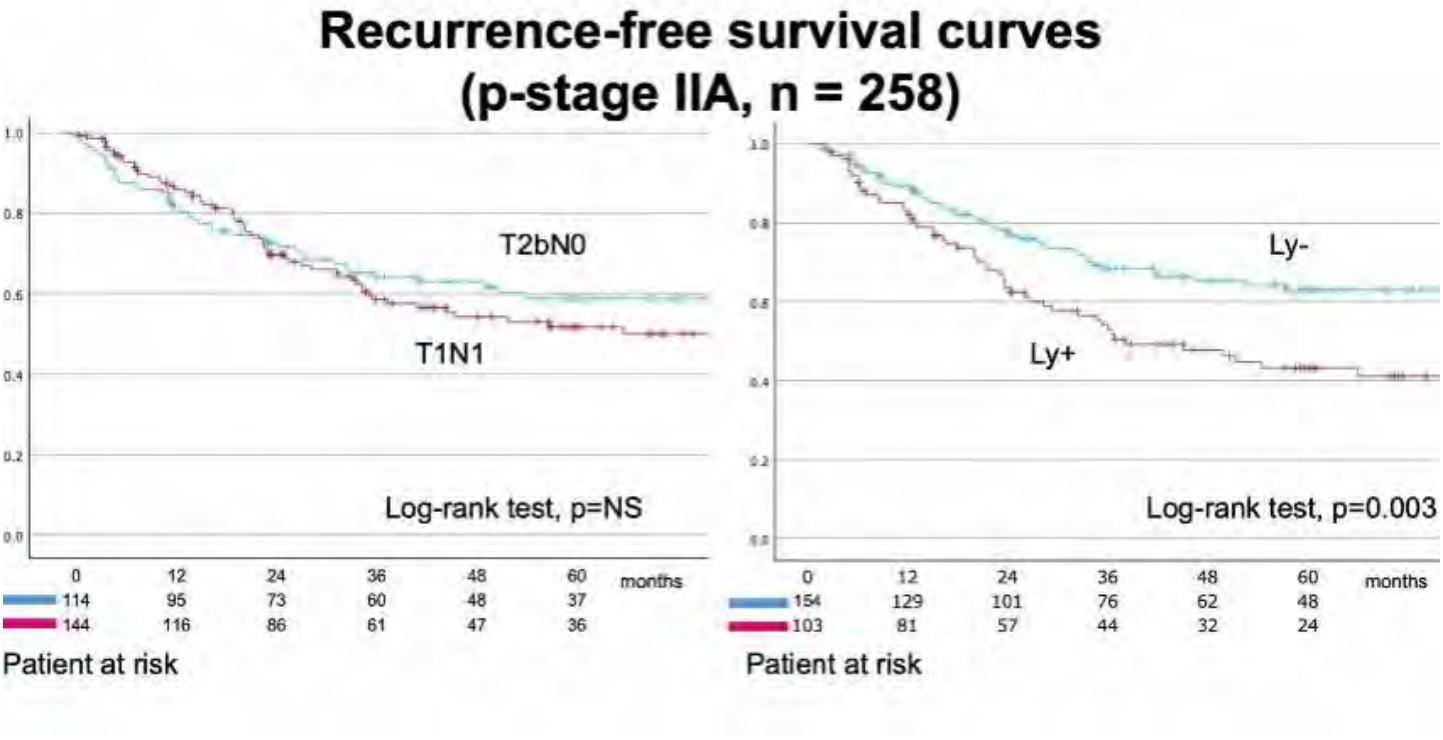
Introduction: In the 9th edition of the TNM classification, T1N1 non-small cell lung cancer (NSCLC), previously classified as stage IIB, has been redefined as stage IIA. This stage, which originally included only T2bN0 tumors, now comprises both node-negative and node-positive disease, resulting in a more heterogeneous population. While some clinical guidelines recommend adjuvant therapy for all patients with stage IIA, others limit its use to those with high-risk features, which remain inconsistently defined. Thus, identifying robust pathological risk factors for recurrence is essential to inform appropriate postoperative management.

Methods: We retrospectively analyzed 724 patients with pathological stage II NSCLC (based on the 9th edition TNM classification) who underwent curative resection between 2010 and 2022. The data were collected from the HITOKA3 database, which comprises cases from three institutions: Hiroshima University, Tokyo Medical University, and Kanagawa Cancer Center. Clinicopathological characteristics and survival outcomes were evaluated.

Results: Among the 724 patients (men:women = 508:216; median age 64), 672 underwent lobectomy, 46 segmentectomy, and 6 pneumonectomy. Stage IIA and IIB included 258 and 466 patients, respectively. Within stage IIA, 144 were T1N1 and 114 were T2bN0. The 5-year overall survival (5yOS) was 73.4% for IIA and 64.2% for IIB. The 5-year recurrence-free survival (5yRFS) was 54.2% (IIA) and 47.2% (IIB), showing no significant difference. In stage IIA, 5yRFS was 50.0% in T1N1 and 58.8% in T2bN0 (p = NS). Multivariate analysis was performed including postoperative TNM factors and pathological invasive features such as tumor size, lymph node metastasis status, vascular invasion, pleural invasion, and histology. Among these, lymphatic permeation (ly) was identified as the only independent risk factor for recurrence (p = 0.009), with 5-year recurrence-free survival (5yRFS) of 41.2% in ly-positive and 63.0% in ly-negative cases.

Conclusions: Lymphatic permeation represents a significant prognostic factor for recurrence in patients with pathological stage IIA NSCLC. It may serve as a valuable criterion for stratifying patients who are likely to benefit from adjuvant therapy within the framework of the revised TNM classification.



Keywords: Lymphatic permeation, TNM classification 9th Edition, Non-small cell lung cancer

EP.07.55 Adjuvant Sunvozertinib for Early-Stage NSCLC Patients With EGFR Exon 20 Insertion Mutation: A Case Series

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Introduction: Disease recurrence in early-stage non-small cell lung cancer (NSCLC) often peaks around one year post-surgery, with poorly differentiated tumors and other high-risk factors increasing recurrence likelihood. Notably, NSCLC patients harboring EGFR exon 20 insertion (EGFR exon20ins) mutations exhibit higher malignancy, underscoring the importance of adjuvant treatment for these patients. Sunvozertinib is an oral, potent, highly selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) approved in China for the treatment of advanced NSCLC with EGFR exon20ins mutations. Here, we firstly present a real-world case series highlighting the clinical efficacy and safety of sunvozertinib as adjuvant treatment in early-stage NSCLC patients with poorly-differentiated pathological type harboring EGFR exon20ins mutation.

Methods: A retrospective review was conducted on medical records from January 2024 to January 2025, identifying patients with poorly-differentiated NSCLC harboring EGFR exon20ins mutation detected through postoperative next-generation sequencing (NGS) and subsequently treated with sunvozertinib as adjuvant therapy. TNM staging was based on IASLC 9th Edition. The data analyzed by investigators mainly included disease-free survival (DFS) and safety outcomes. The data cutoff was March 20, 2025.

Results: Three poorly-differentiated NSCLC patients with EGFR exon20ins mutation were retrospectively collected and the detailed information were in Table 1. All the patients underwent complete tumor resection, followed by six months of adjuvant treatment with sunvozertinib 150 mg once daily. Patient 1, a 56-year-old male patient was diagnosed with stage IA1 poorly-differentiated lung adenocarcinoma. At the data cutoff, the patient did not relapse and the DFS reached 13 months. Only grade 1 oral mucositis occurred during treatment which improved after symptomatic treatment. Patient 2, a 72-year-old male patient was diagnosed with stage IA2 poorly-differentiated lung adenocarcinoma. This patient did not experience a relapse at data cut off with a DFS of 12 months. No intolerable adverse event was observed. Patient 3, a 55-year-old female patient was diagnosed with stage IIB poorly-differentiated lung adenocarcinoma. At the data cutoff, the DFS of this patient reached 10 months with no disease recurrence. The patient developed a mild rash during treatment which improved after applying hormone ointment.

Table 1. Case summary (Data cutoff: March 20, 2025)

Patient case	Sex	Age	Stage	EGFR exon20ins mutation subtype	Concurrent mutation	Pathological type	High-risk factors	Adjuvant treatment	Adverse events	Recurrence	DFS (months)
1	Male	56	IA1	p.S768_D770dup	PTEN	Poorly-differentiated adenocarcinoma	Airway spread	Sunvozertinib monotherapy	Oral mucositis	None	13
2	Male	72	IA2	p.D770_N771insG	TP53	Poorly-differentiated adenocarcinoma	Micropapillary component	Sunvozertinib monotherapy	None	None	12
3	Female	55	IIB	p.A763_Y764insFQEA	TP53; MGMT	Poorly-differentiated adenocarcinoma	Vascular invasion, airway spread	Sunvozertinib monotherapy	Rash	None	10

Conclusions: For NSCLC patients with EGFR exon20ins mutation, sunvozertinib showed sustained efficacy and safety benefits as adjuvant treatment after surgery. Adjuvant treatment with sunvozertinib helped these patients pass the 1-year peak period of disease recurrence successfully. Prospective studies of sunvozertinib in early-stage NSCLC patients are worth further investigation.

Keywords: EGFR exon20ins, Sunvozertinib, Adjuvant treatment

EP.07 EARLY-STAGE NON-SMALL CELL LUNG CANCER

EP.07.56 Efficacy and Safety of Postoperative Adjuvant Chemotherapy and Atezolizumab and Osimertinib Maintenance Therapy for NSCLC at Our Hospital

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Introduction: Atezolizumab was shown to be effective in the IMpower010 trial and osimertinib in the ADAURA trial as maintenance therapy after adjuvant chemotherapy for non-small cell lung cancer, and they are now available in clinical practice.

Methods: Patients who underwent surgery at our hospital and received postoperative adjuvant chemotherapy and subsequent atezolizumab maintenance or osimertinib maintenance by March 2025 at our department and affiliated hospitals were retrospectively reviewed.

Results: A total of 24 patients were included, 11 were negative for EGFR mutations and 13 were positive for EGFR mutations. Of the 11 EGFR mutation-negative patients, 10 were men and 1 was a woman, with a median age of 68 years (58-78). 8 of the 11 patients were switched to atezolizumab maintenance therapy, including 1 case of early relapse after 3 courses of maintenance therapy, 1 case of discontinuation due to irAE liver damage (Grede2) after 1 course of maintenance therapy, 3 cases of completion of treatment after 1 year and 3 cases of ongoing treatment. Of the 13 EGFR mutation-positive patients, 2 were men and 11 were women, with a median age of 72 years (60-77). 2 of the 13 patients could not start osimertinib maintenance therapy after CDDP+VNR therapy due to recurrence of brain metastasis or AKI during CDDP+VNR therapy, 1 patient was on CDDP+VNR therapy and the remaining 10 patients started osimertinib maintenance therapy. 2 of the 10 patients started osimertinib maintenance therapy without CDDP+VNR. 1 of the 10 patients on osimertinib maintenance therapy had a recurrence of bone metastasis, but was judged to be oligo-metastasis and continued on osimertinib maintenance therapy.

Conclusions: Atezolizumab maintenance and osimertinib maintenance also resulted in one recurrence each, and in cases of early recurrence during atezolizumab maintenance, MAPK gene deletion/amplification and TP53 gene mutation were found in the cancer gene panel test, suggesting that these gene mutations may be involved in early recurrence. These mutations may have contributed to early recurrence. If comprehensive gene analysis can be carried out in each group in the future to investigate the characteristics of gene expression in recurrent and non-recurrent cases, this may contribute to the development of superior adjuvant therapy.

Keywords: adjuvant chemotherapy, atezolizumab, osimertinib

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.08.01 Surgery for Resectable Lung Cancer With Radiographic Disease Control After Chemoimmunotherapy: A Retrospective Cohort Study

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Introduction: Immune checkpoint inhibitors have achieved breakthrough progresses in perioperative treatment for non-small cell lung cancer (NSCLC) and have become one of the standard regimens for patients with resectable NSCLC. However, whether surgery is needed for patients with resectable NSCLC who achieve radiographic disease control after chemoimmunotherapy remains controversial.

Methods: We retrospectively collected medical records of patients with stage IIB-IIIB (AJCC 8th edition) resectable NSCLC who received 2-6 cycles tislelizumab plus platinum-based doublet chemotherapy and achieved radiographic disease control in the Affiliated Hospital of Zunyi Medical University from November 2021 to January 2024. The radiographic disease control was defined as patients achieved complete remission, partial remission, or stable disease after chemoimmunotherapy per RECIST v1.1. Based on whether surgery, patients were divided into surgery group or non-surgery group. The surgery group and non-surgery group were both received tislelizumab monotherapy as maintenance therapy until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). The secondary endpoints included objective response rate (ORR) and overall survival (OS).

Results: A total of 56 patients (28 in each group) were enrolled, with a median age of 59.0 years (IQR: 56.0-66.75). As of February 2025, the median follow-up duration was 19.67 months (IQR: 15.54-27.79). Neither group reached the median PFS. The surgery group improved average PFS versus the non-surgery group (37.2 months vs. 27.4 months; stratified hazard ratio 0.16 [95% CI: 0.03-0.77]; one-sided p = 0.02). The 12-month PFS rates were 100% vs. 85.7%, respectively. The ORR was 85.7% in the surgery group and 67.9% in the non-surgery group. The surgery group demonstrated a better OS benefit trend than the non-surgery group (HR = 0.096 [95% CI: 0.012-0.79]; one-sided p = 0.029). The surgical group showed superior 12-month OS rates compared to the non-surgical group (100% vs. 88.9%). No grade 3-4 adverse events were observed in either group. The data are still being followed up.

Conclusions: For patients with resectable stage IIB-IIIB NSCLC who achieved radiographic disease control after tislelizumab combined with chemotherapy, surgical intervention may provide additional survival benefits. The long-term follow-up data and large sample prospective studies are required for further validation.

Keywords: non-small-cell lung cancer, surgery, chemoimmunotherapy

EP.08.02 A Study of Patients With Lung Cancer Complicated With Ipf Who Underwent Partial Pulmonary Resection

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Introduction: Wedge resection is often the only feasible option for the surgical treatment of lung cancer that has been complicated by idiopathic pulmonary fibrosis (IPF). In this study, we investigated the prognosis of patients with lung cancer and concurrent IPF who underwent wedge resection.

Methods: We conducted a retrospective analysis of six patients with lung cancer and IPF that underwent wedge resection at our institution between January 2015 and December 2017. Postoperative acute exacerbation (AE) of IPF was defined as occurring within 30 days after surgery.

Results: Among these six patients, five were male, with a median age of 73.5 years. Five patients had a history of smoking, with a median Brinkman Index (BI) of 1,147.5. All cases had a performance status (PS) of 0. The rationale for choosing partial resection included: hypoxemia in four cases, a history of contralateral lower lobectomy in one case, and history of AE in one case. Patients underwent Video-Assisted Thoracoscopic Surgery (VATS) with automatic staplers. Intraoperative frozen section analysis confirmed negative surgical margins in all resected specimens. Histological findings included five cases of squamous cell carcinoma and one large cell neuroendocrine carcinoma. Pathologic assessment of the resected specimens revealed tumor invasion diameters of ≤20 mm in one case, ≤30 mm in four cases, and ≤70 mm in one case. Among these, two cases had positive surgical margins, and four had negative margins. At follow up, one patient remained alive with recurrence of the disease, four died from lung cancer progression, and one developed local recurrence but ultimately died from IPF exacerbation. Median recurrence-free survival (RFS) was 11.2 months, and median overall survival (OS) was 22.2 months. All four lung cancer-related deaths involved metastases: one patient developed liver metastasis, two developed intrapulmonary metastasis, and one exhibited both local margin recurrence and intrapulmonary metastases. The only long-term survivor experienced recurrence at the surgical margin but achieved long-term survival of 97.5 months postoperatively with chemotherapy. This patient later developed metachronous lung cancer in the subpleural area of the ipsilateral lung, which was successfully treated with another wedge resection, and remains recurrence-free. None of the patients experienced postoperative AE.

Conclusions: There is little literature related to research involving the prognosis of lung cancer patients complicated with IPF who were deemed unsuitable for lobectomy and underwent wedge resection. Currently, there are no established guidelines regarding surgical procedures for lung cancer in patients with IPF. At our institution, the surgical resection strategy is determined through multidisciplinary board discussions involving thoracic surgeons and pulmonologists. The balance between oncological radicality and parenchymal preservation remains a therapeutic challenge. Our findings demonstrate elevated recurrence rates, particularly in cases with multifocal intrapulmonary metastases, suggests wedge resection may provide inadequate oncological radicality. Nevertheless, the absence of postoperative AE and presence of a long-term survivor in our cohort indicate that wedge resection remains a viable treatment option for patients with IPF and lung cancer when radical surgery is contraindicated. When choosing a surgical approach, close collaboration with IPF-specialized pulmonologists is essential for optimal outcomes.

Keywords: lung cancer, wedge resection, idiopathic pulmonary fibrosis

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.03 Surgical Outcomes in Induction and Perioperative Chemoimmunotherapy Trials: A Meta Analysis

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Introduction: Immunotherapy (IO) has revolutionized the treatment landscape for non-small cell lung cancer (NSCLC). However, its influence on surgical outcomes remains uncertain. This study aimed to evaluate surgical outcomes in patients undergoing neoadjuvant or perioperative (chemo)-IO protocols.

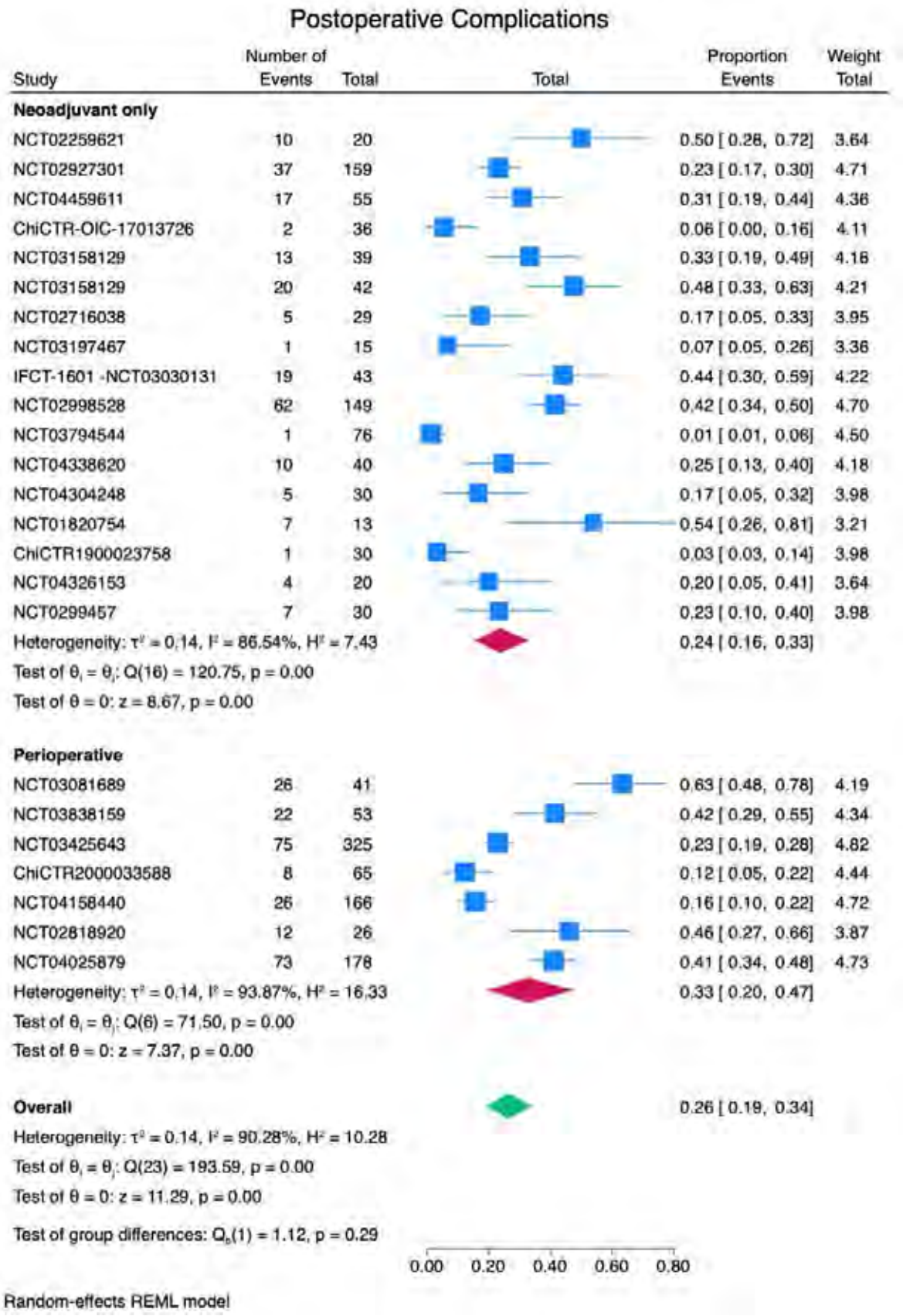
Methods: A systematic review and meta-analysis were conducted using PubMed and Embase up to December 2024. Prospective trials investigating preoperative IO, with or without chemotherapy, in neoadjuvant or perioperative settings were included. Two independent reviewers (P.B. and F.G.) screened studies and extracted data.

Primary outcomes included postoperative complications, minimally invasive surgery (MIS), and pneumonectomy rate.

Results: Twenty-seven studies involving 4,505 patients were analyzed; 2,691 patients in experimental arms were included. Ten studies used perioperative protocols, 17 used neoadjuvant protocols. The pooled proportion of surgery delayed beyond protocol-defined timeframes was 0.09 (95% CI 0.05-0.14). The use of MIS and conversion rates varied significantly among the studies; the pooled proportion of MIS was 0.47 (CI 0.32-0.62), with a conversion pooled proportion of 0.18 (CI 0.10-0.26). MIS use was higher in perioperative trials, though not significantly. However, conversion was less frequent in the perioperative group, although not significantly (p=0.08). Comparing IO vs. chemo-IO (CTIO), MIS use was significantly higher with IO alone (40.1%, CI 35-45%) versus CTIO (31.9%, CI 28.0-37.0; p=0.017), while conversion rates were similar (9.0% vs. 6.6%; p=0.208).The pooled pneumonectomy proportion was 0.11 (95% CI 0.09-0.13), with no significant difference between neoadjuvant and perioperative protocols (p=0.180), although slightly higher in IO trials (p=0.054). Pooled proportion for intraoperative and postoperative complications was 0.04 (CI 0.01-0.08) and 0.26 (CI 0.19-0.34), respectively. Both were significantly higher in CTIO vs. IO (p<0.001 and p=0.021, respectively). The pooled postoperative mortality rate was consistently low at 0.01 (CI 0.00-0.01) with no significant difference according to protocol (p=0.170) or treatment (p=0.150).

Conclusions: Surgical outcomes among (chemo)-IO trials vary widely. While MIS is increasingly adopted, conversion rates remain notable. Chemo-immunotherapy is associated with higher complication rates.

Greater adoption of IO-based strategies may improve surgical feasibility and reduce morbidity by enabling wider MIS implementation.



Keywords: Chemo immunotherapy, Surgery, Neoadjuvant

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.04 Reducing Medication Burden and Accelerating Recovery Through Tubeless Thoracic Surgery: A Large-Scale Real-World Study

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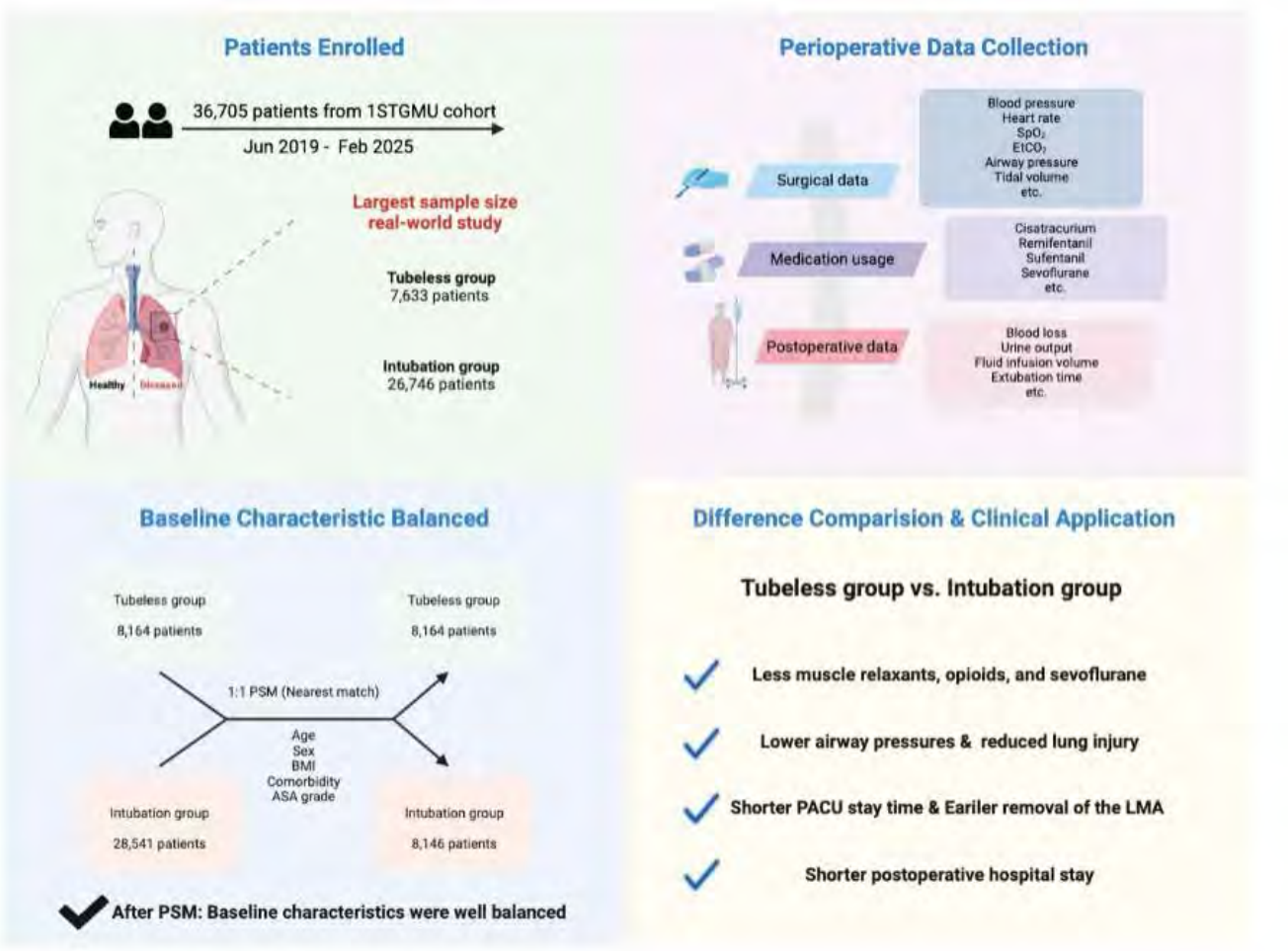
Introduction: Thoracic surgery has evolved from open procedures to minimally invasive approaches, with video-assisted thoracoscopic surgery (VATS) becoming the preferable care for early-stage non-small cell lung cancer and other thoracic conditions. Tubeless thoracic surgery represents a paradigm shift in surgical and anesthetic management, eliminating the need for endotracheal intubation while potentially enabling faster recovery, though evidence remains limited. We conducted a large-scale real-world cohort to validate its impact on perioperative outcomes.

Methods: We collected data from patients who underwent VATS for lung cancer between June 2019 and January 2025. Patients were divided into tubeless or intubated VATS groups and matched 1:1 using propensity score matching (PSM). Surgical outcomes, anesthesia medication use, and ventilatory parameters were compared to evaluate their roles in this approach.

Results: 45,619 patients were screened for eligibility, and 36,705 patients were included. After PSM, each group contains 8,146 patients. The tubeless approach demonstrated remarkable reduction in medication use (standardized mean dosages), including muscle relaxants (rocuronium: 256.81 vs 931.12; cisatrocurium: 47.13 vs 204.02), opioids (sulfentanil: 163.08 vs 258.57; remifentanil: 6076.43 vs 7873.43), and sevoflurane used (335 vs 4119 patients) (all P<0.001). Recovery was faster, with shorter time to airway device removal (33.40 vs 36.88 min), Post Anesthesia Care Unit (PACU) stay (83.07 vs 90.46 min), and postoperative hospital stay (3.11 vs 3.84 days) (all P<0.001). Ventilatory parameters were also more favorable in the tubeless group, with lower plateau pressure (8.58 vs 17.24 cmH2O) and minute volume (3.64 vs 4.80 L/min) (all P<0.001).

Conclusions: Based on the largest dataset to date, our findings demonstrate that tubeless VATS enables dramatically faster recovery through substantial reductions in medication use and ventilation pressures, while promoting remarkable resource efficiency. This study provides new evidence for the tubeless approach.



Keywords: Tubeless, thoracic surgery, VATS surgery

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.08.05 Minimally Invasive Approaches for Pancoast Tumor Resection: A Comparative Analysis of Surgical Techniques and Outcomes

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Introduction: Pancoast tumors arise from within the superior sulcus, with most clinical manifestations occurring due to mass effect on surrounding structures. Symptoms include shoulder and arm musculoskeletal pain, Horner's syndrome, and various neurological complications. Although these tumors often mimic musculoskeletal conditions, they originate from lung tissue. Due to their location, surgical treatment frequently necessitates extensive chest wall resection and intercostal dissection, which can lead to decreased respiratory function and postoperative morbidity. Advances in minimally invasive techniques, including robot-assisted thoracic surgery (RATS) and uniportal video-assisted thoracic surgery (U-VATS), have been explored as potential alternatives to traditional open thoracotomy to reduce surgical trauma and preserve lung function.

Methods: We conducted a retrospective analysis of nine patients with Pancoast tumors who underwent surgical resection between 2018 and 2024, using data from the Mie Thoracic Surgery Database (MiTSD), a multi-center registry. The surgical approaches included open thoracotomy (n=7), robot-assisted thoracic surgery (RATS) with a lateral incision (n=2), and uniportal video-assisted thoracic surgery (U-VATS) with a high lateral incision (n=1). Eight cases involved lobectomy, while one underwent left upper division segmentectomy. Preoperative chemoradiation therapy was administered in both the RATS and U-VATS groups to reduce tumor burden and facilitate resection.

Results: Of the nine cases, eight patients were male and one was female. Surgical procedures included six right upper lobectomy two left upper lobectomy and one left upper division segmentectomy. The mean operative time and blood loss for each approach were as follows: open thoracotomy (n=6): 370 minutes, 660 mL; RATS (n=2): 524 minutes, 719.5 mL; and U-VATS (n=1): 402 minutes, 734 mL. The operative time was longer in the RATS group due to revascularization; however, blood loss did not differ significantly among the three groups. Postoperative complications in the open thoracotomy group included neuropathy (n=2), pleural effusion reaccumulation (n=2), and upper extremity elevation failure (n=1). In the RATS group, one patient developed an infection requiring reoperation. The U-VATS had postoperative infection necessitating drain reinsertion. In a segmentectomy case, the predicted postoperative FEV1.0 was calculated as follows: left lobectomy vs. left upper division segmentectomy = 971 mL / 1100 mL. Similarly, the predicted postoperative DLCO was 46.1% / 52.3%, indicating a potential advantage in preserving lung function with segmentectomy.

Conclusions: Due to the typical midline-to-posterior location of Pancoast tumors, the posterior approach is frequently utilized. When lesions are located dorsally, a high posterolateral or posterior transaxillary (hook) approach is often preferred. The hook approach provides clear visualization of the subclavian artery, facilitating resection and reconstruction with minimal technical difficulty. In contrast, the posterior approach offers dorsal visualization but limits anterior access, making direct observation of critical structures more challenging.The use of RATS and U-VATS enables enhanced visualization within the thoracic cavity and minimizes muscle dissection, which may help preserve respiratory function. In the method described here, dorsal dissection was limited to the rhomboid and vastus lateralis muscles, reducing trauma to surrounding tissues. Incorporating RATS and U-VATS techniques into Pancoast tumor surgery may provide a less invasive alternative while maintaining oncologic efficacy and improving postoperative recovery.

Keywords: Pancoast tumor, Minimmary invasive approach, Complication

EP.08.06 Survival Analysis and Nomogram for Postoperative Pulmonary Sarcomatoid Carcinoma Patients: SEER Database Analysis and External Validation

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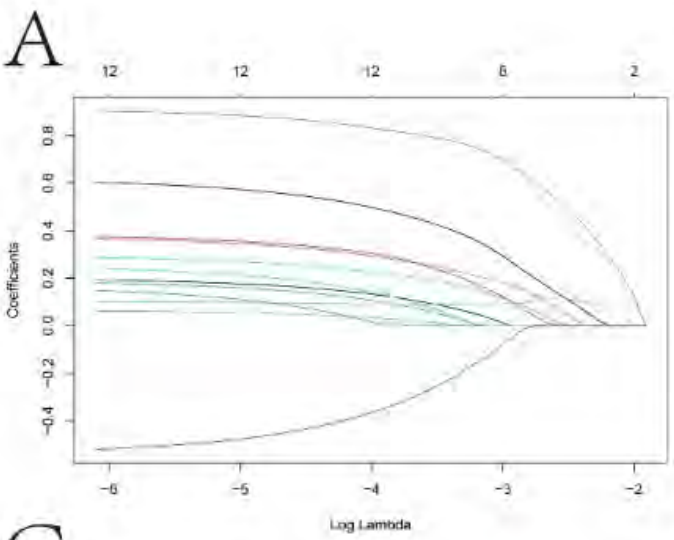
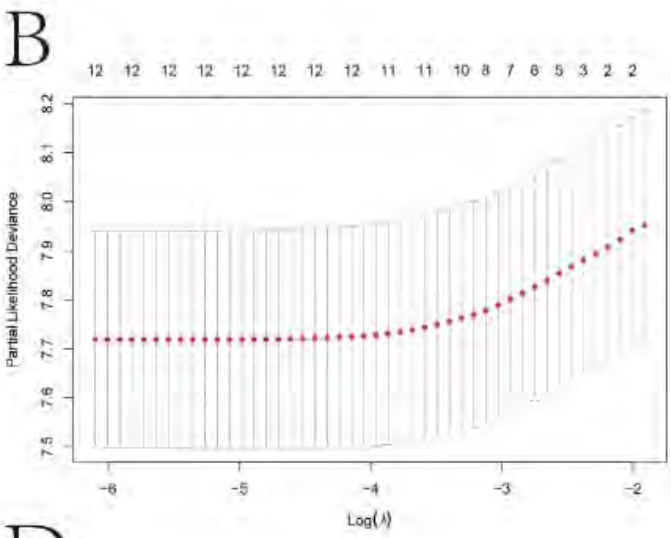
Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare and deadly form of aggressive lung cancer. This study aims to develop a nomogram to predict the overall survival (OS) of PSC patients undergoing surgery.

Methods: The model was developed using 481 PSC patients from the SEER database (training cohort) and 45 surgical cases from Tianjin Medical University (external validation). Twelve standardized clinical factors were analyzed. Discrimination was assessed via time-dependent ROC curves (AUC), C-index, and calibration. DCA compared prognostic performance between the nomogram and 9th AJCC-TNM staging. Cox regression identified independent prognostic factors.

Results: LASSO regression was used to identify potential clinical variables for inclusion in the nomogram (Figure 1.A/B). Then univariate (Figure 1.C) and multivariate (Figure 1.D) Cox regression analyses were used to assess the impact of clinical factors on patient outcomes. The multivariate analysis identified age, pathological subtype, T stage, lymph node metastasis, and distant metastasis as independent prognostic factors for patient outcomes. Then, a nomogram were constructed with the relevant variables (Figure 1E). The concordance index (C-index) of the nomogram was 0.657 (95% CI, 0.638 to 0.676) in the training cohort and 0.716 (95% CI, 0.671 to 0.761) in the external validation cohort. In the training cohort, the AUC values for the 1-year, 3-year, and 5-year survival rates were 0.696, 0.710, and 0.663. In the external validation cohort, the AUC values for the 1-year, 3-year, and 5-year survival rates were 0.809, 0.765, and 0.785. Both the C-index and AUC indicate strong discriminatory ability of the nomogram. DCA suggested that the nomogram outperforms the 9th AJCC-TNM staging system in predicting OS, indicating its potential clinical utility.

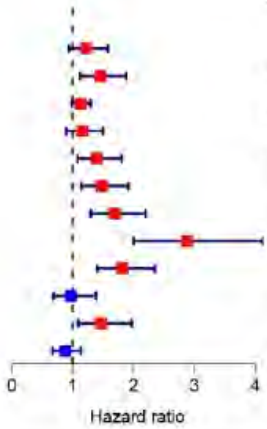
Conclusions: A survival analysis and a nomogram with robust C-index and AUC values was developed and the validated model demonstrates certain clinical value.





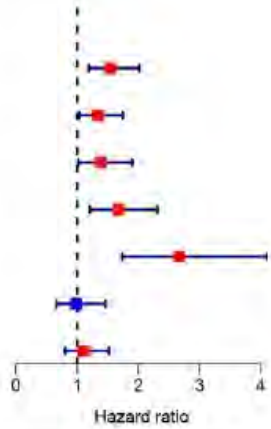
C

	pvalue	Hazard radio
Sex	0.137	1.216(0.939−1.580)
Age	0.004	1.453(1.123−1.879)
Primary_Site	0.070	1.132(0.990−1.295)
Laterality	0.264	1.158(0.895−1.497)
Pathology	0.011	1.397(1.080−1.808)
T_stage	0.003	1.480(1.144−1.913)
Lymphatic metastasis	<0.001	1.689(1.297−2.199)
Distant metastasis	<0.001	2.873(2.001−4.126)
TNM_Stage	<0.001	1.816(1.404−2.350)
Surgery	0.882	0.973(0.682−1.389)
Radiation	0.011	1.467(1.093−1.969)
Chemotherapy	0.316	0.875(0.673−1.136)



D

	pvalue	Hazard radio
Age	0.001	1.546(1.187−2.015)
Pathology	0.027	1.344(1.034−1.746)
T_stage	0.039	1.391(1.017−1.902)
Lymphatic metastasis	0.002	1.670(1.209−2.308)
Distant metastasis	<0.001	2.672(1.739−4.105)
TNM_Stage	0.940	0.985(0.662−1.464)
Radiation	0.556	1.102(0.798−1.521)



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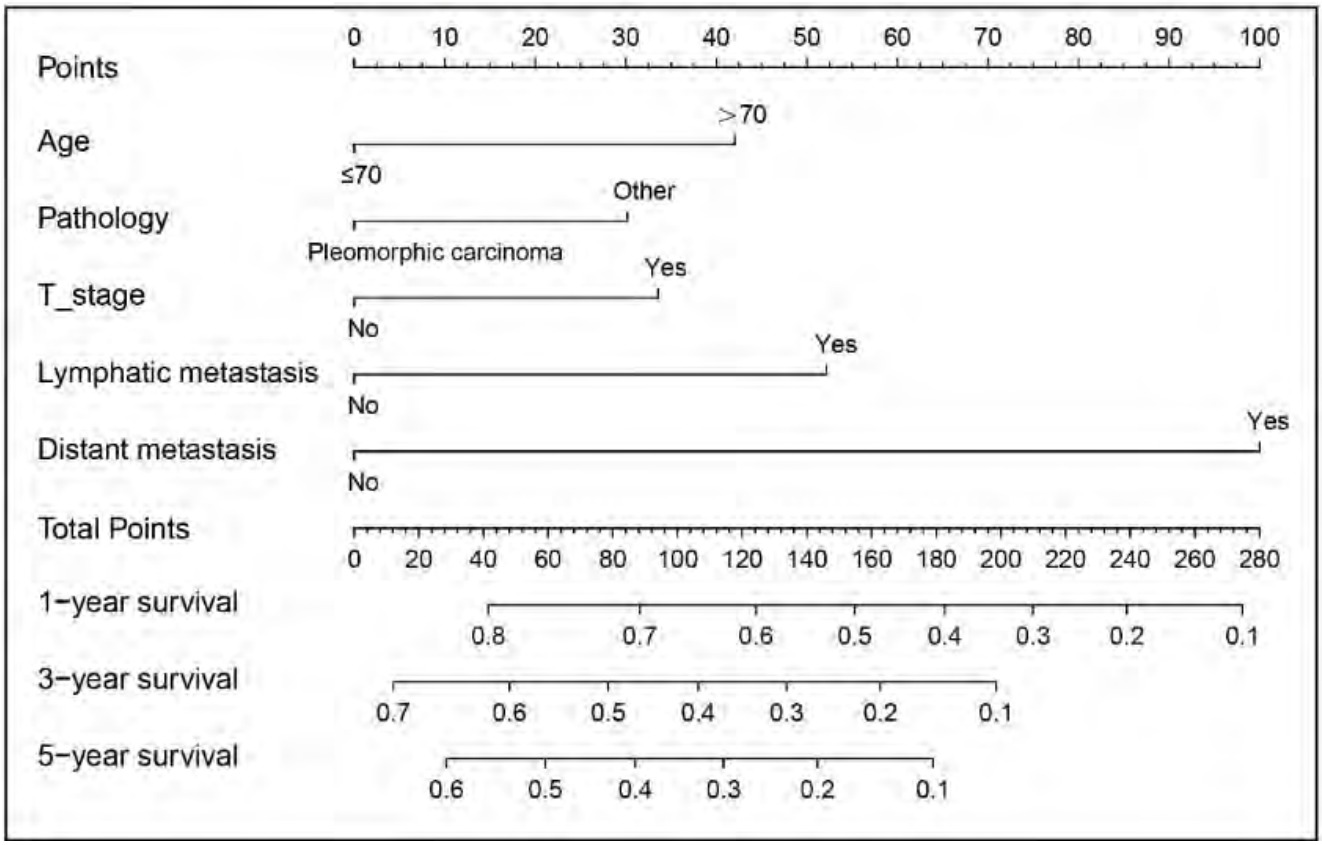

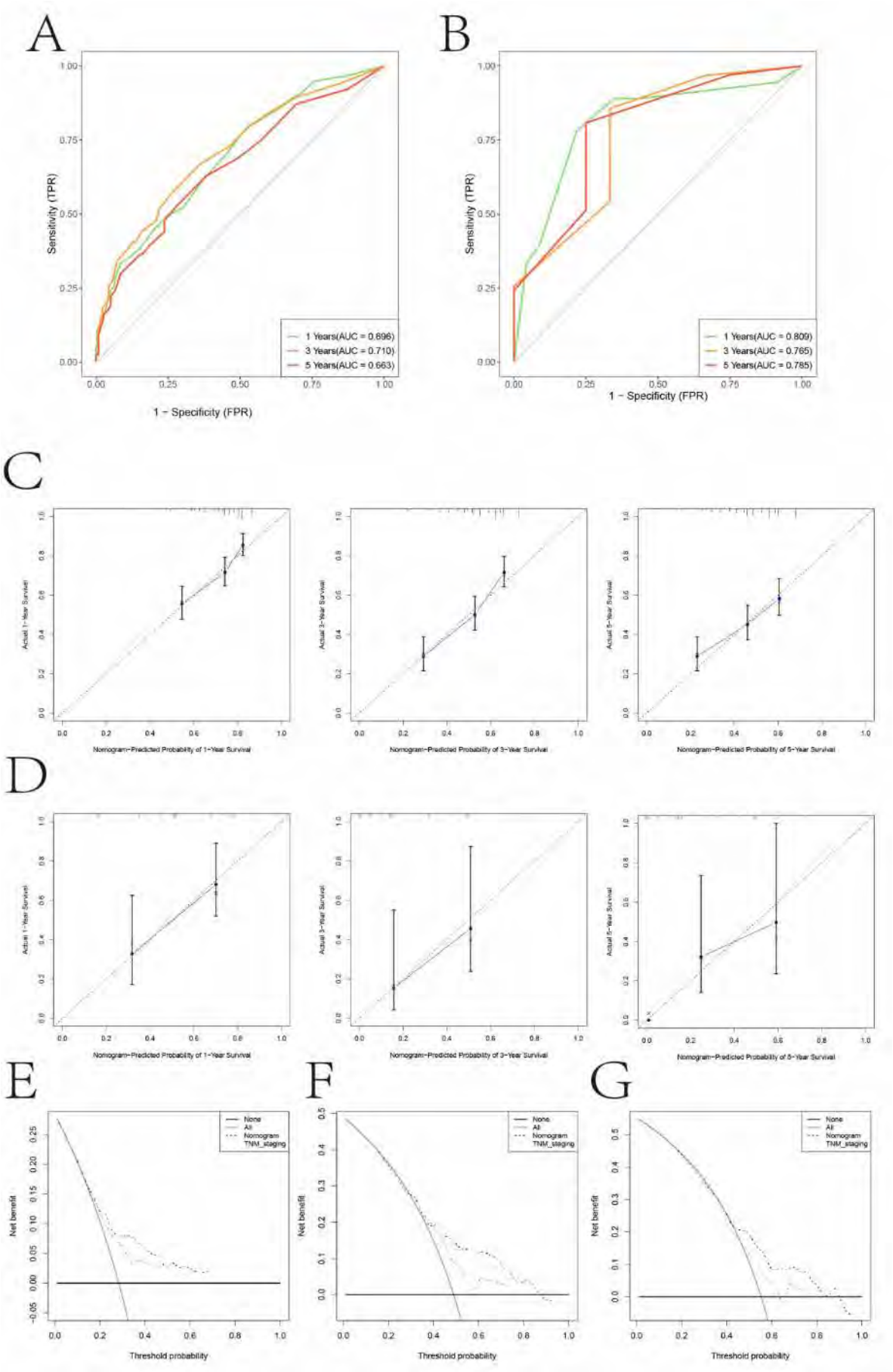

Keywords: SEER, Pulmonary Sarcomatoid Carcinoma, Nomogram

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.07 The Role of Surgery After Neoadjuvant Immunotherapy in NSCLC : Refining the Multimodal Paradigm

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Introduction: Neoadjuvant immunotherapy (IO) has emerged as a promising therapeutic approach for selected patients with resectable non-small cell lung cancer (NSCLC). This study evaluates the outcomes of induction IO followed by surgical resection in patients with resectable or potentially resectable NSCLC.

Methods: We conducted a retrospective analysis of patients with resectable or potentially resectable NSCLC who underwent induction chemotherapy (CT) plus IO, followed by surgical resection between January 2017 and January 2025.Collected data included demographics, surgical details, pathological response, postoperative complications, overall survival (OS), local recurrence-free survival (LRFS), and distant recurrence-free survival (DRFS).Continuous variables were reported as mean ± SD, and categorical variables as absolute numbers and percentages. Survival analysis was performed using the Kaplan-Meier method.

Results: Among 37 patients, 10 were excluded due disease progression prior surgery, incomplete treatment, or enrollment in placebo arms.The final cohort included 27 patients (63% male; median age: 64).Histology was predominantly squamous cell carcinoma (48%) and adenocarcinoma (41%).PD-L1 was >1% in 19 cases, with PD-L1 >50% in six; two had concurrent KRAS mutations.Neoadjuvant IO included nivolumab (n=15), pembrolizumab (n=9), and durvalumab (n=3).Clinical staging included cIIA (4%), cIIB (7%), cIIIA (70%), and cIIIB (19%); all cN2 cases (37%) were pathologically confirmed.

Restaging was performed using CT (48%), PET/CT (37%), PET/CT + EBUS (7.5%), and PET/CT + mediastinoscopy (7.5%). Post-induction clinical staging showed ycIA (22%), ycIB (19%), ycIIA (4%), ycIIB (22%), ycIIIA (33%); with downstaging observed in 92% (n=25). Surgical procedures included 23 lobectomies (85%), 3 lobectomies with wedge resections (11%), and 1 bilobectomy (4%). A minimally invasive approach was used in 70% of cases (Video-Assisted Thoracoscopic Surgery 63%, Robotic-Assisted Thoracic Surgery 7%). The mean operative time was 240 ± 97 minutes, and the mean drainage duration was 7 ± 4 days.The mean number of biopsied lymph nodes was 9 ±5, and mean of biopsied lymph node stations was 4 ± 1. Postoperative complications occurred in 11 patients (41%), mainly respiratory (37%), including persistent air leak (19%), respiratory infection (7%), pleural effusion (4%), hemothorax (4%), and empyema (4%). One patient required reoperation for hemothorax. Pathologic stging was yp0 (41%), ypI (41%), and ypII (18%). Pathologic complete response (pCR) was achieved in 41%, major pathologic response (MPR) in 41%, and partial response in 18%.Among cN2 patients (n=10), 80% (n=8) were downstaged to ypN0. Adjuvant therapy was administered in 74% of cases (IO 75%, CT+IO 20%, RT 5%). At follow-up, one patient developed both local and distant recurrence (at 8 and 20 months, respectively). There was no 90-day mortality. All patients who underwent CT+IO+R0 resection (without adjuvant treatment) remained alive and recurrence-free at one year.

Conclusions: - Surgery following induction immunotherapy in resectable NSCLC is safe and associated with excellent pathological response rates and early survival outcomes. - These findings support its integration as a key component of the multimodal strategy in the management of resectable or potentially resectable NSCLC - Additionally, it is crucial to standardize and homogenize the definition of resectability in this setting to ensure consistent patient selection, optimize outcomes, and facilitate comparisons across studies.

Keywords: Non-small cell lung cancer (NSCLC), Neoadjuvant immunotherapy, Surgical resection

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.08 Complex Tracheobronchial Reconstruction for Locally Advanced T4N2M0 Non-Small Cell Lung Cancer Using Three-Dimensional Models

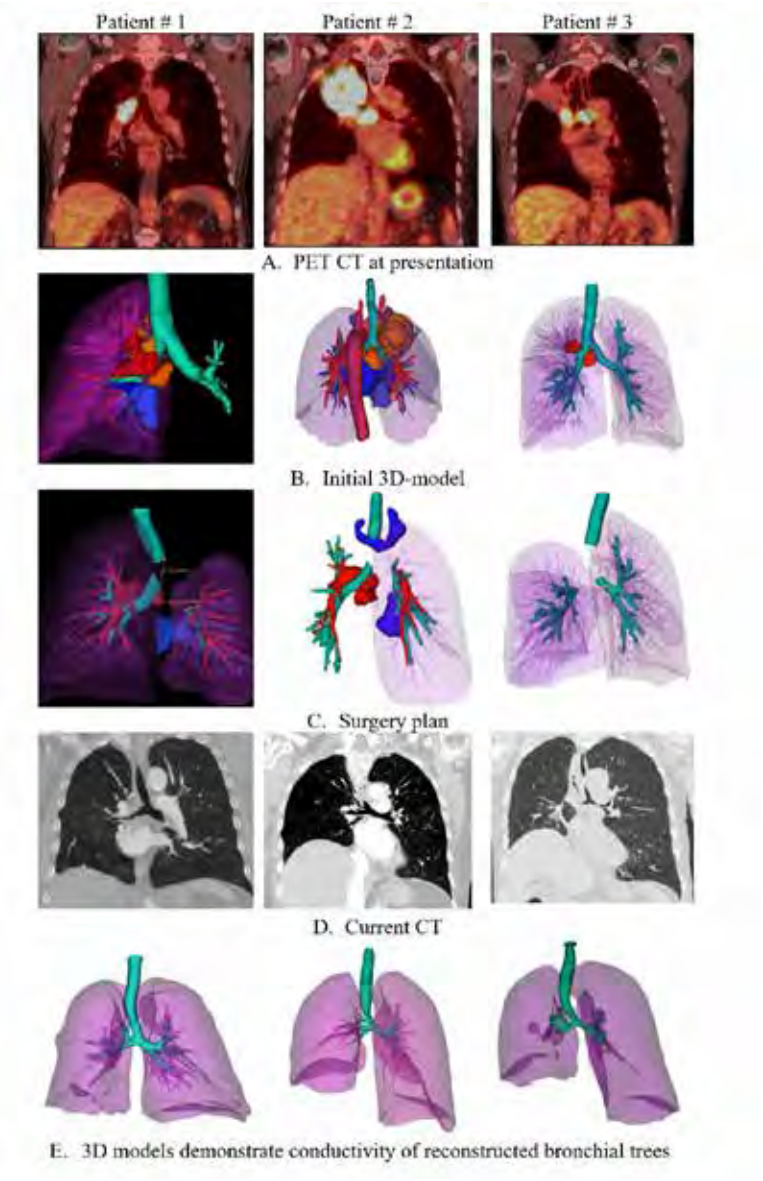
S. Yeskov[1], S. Krasny[1], A. Sukalinskaya[1], T. Filipava[1], A. Hulenka[1], S. Kremeneuski[1], N. Paramonava[1], Y. Tsarkouskaya[1], P. Famianok[1], V. Fiankevich[2], I. Yeskov[3]
[1]N.N. Alexandrov National Cancer Centre of Belarus, Minsk/BY ,[2]Belarussian State University, Minsk/BY ,[3]Gymnasium No. [12], Minsk/BY

Introduction: Organ-preserving surgery for centrally located lung cancer is a proven approach, even in cases involving trachea or superior vena cava. Success depends on perioperative therapy and completeness of surgery.

Methods: We present three cases of T4N2M0 non-small cell lung cancer treated with preoperative platinum-based chemotherapy or chemoimmunotherapy. 3D-modeling, utilizing the open-source 3D Slicer software, was employed for precise surgical planning based on pretreatment tumor borders. Detailed data is provided in Table 1 and Figure 1.

Results: All patients underwent R0 resection. One patient underwent coronary artery bypass surgery before lung cancer surgery, achieving 39 months of relapse-free survival without adjuvant therapy. Another patient with EGFR mutant adenocarcinoma developed pleural dissemination nearly three years after surgery despite osimertinib treatment. Pathology revealed a pathological complete response of the primary tumor following chemoimmunotherapy in the third patient, though residual subcarinal lymph node metastasis was detected. Planned treatment includes two cycles of carboplatin and paclitaxel, followed by 12 months of atezolizumab.

Conclusions: Despite significant progress in drug therapy, surgery remains vital for achieving tumor elimination. Preoperative chemoimmunotherapy shows promise as a treatment option for locally advanced T4 NSCLC. Accurate 3D-modeled planning is an essential tool for surgeon, helping to ensure the resection line is correctly positioned outside pretreatment tumor borders, minimizing errors and maximizing surgical success.



	Patient # 1	Patient # 2	Patient # 3
Sex, Age	**Male, 67 y.o.**	**Female, 60 y.o.**	**Male, 68 y.o.**
Histology; extension; stations of affected lymph nodes; pTNM/ypTNM;	Squamous cell carcinoma, GII; right upper lobe bronchus, bronchus intermedius, right mainstem bronchus, trachea (5 mm from tracheal bifurcation (TBA)); 10, 7, 4R (EBUS FNAB); pT4N2M0/ypT4N1M0	Adenocarcinoma, GIII, EGFR exon 19 deletion; right upper lobe, right upper lobe bronchus, right mainstem bronchus, trachea (15 mm from TBA), vena cava superior; 2R, 4R, 7, 9R, 10; pT4N2M0/ypT4N2M0	Squamous cell carcinoma, GII; right upper lobe bronchus, right mainstem bronchus, trachea (25 mm from TBA), left main stem bronchus 15 mm; 7; pT4N2M0/ypT0N2M0
Neoadjuvant treatment	2 cycles of cisplatin and vinorelbine	4 cycles of cisplatin and vinorelbine	4 cycles of carboplatin, paclitaxel and atezolizumab
Neoadjuvant treatment effect	Partial response	Partial response	Primary tumor – pCR, subcarinal lymph node – partial response
Surgery; R	Sequential surgical treatment. Left ventricle aneurism plasty, coronary artery bypass surgery. Two months later – sleeve carinal resection combined with right upper double sleeve bilobectomy; R0	Sleeve carinal resection combined with right upper double sleeve bilobectomy, vena cava superior prosthetic replacement; R0	Sleeve carinal resection combined with right upper sleeve lobectomy; R0
Adjuvant treatment	No	35 months of osimertinib	The treatment plan of two cycles of carboplatin and paclitaxel, followed by 12 months of atezolizumab
Complications; follow up time; recurrence, time; outcome	No; 39 months; no; alive	No, 39 months; locoregional recurrence (pleural dissemination), 35 months (VATS biopsy: adenocarcinoma, EGFR exon 19 deletion, MET amplification, CDK4 amplification, MDM2 amplification); alive	Right laryngeal nerve palsy; 2 months; No; alive.

Keywords: T4 locally advanced lung cancer, surgery, 3D modelling

EP.08.09 Aggravation of Tumor Necrosis After Transbronchial Biopsy in Lung Cancer: A Fatal Complication Despite Rescue Surgery

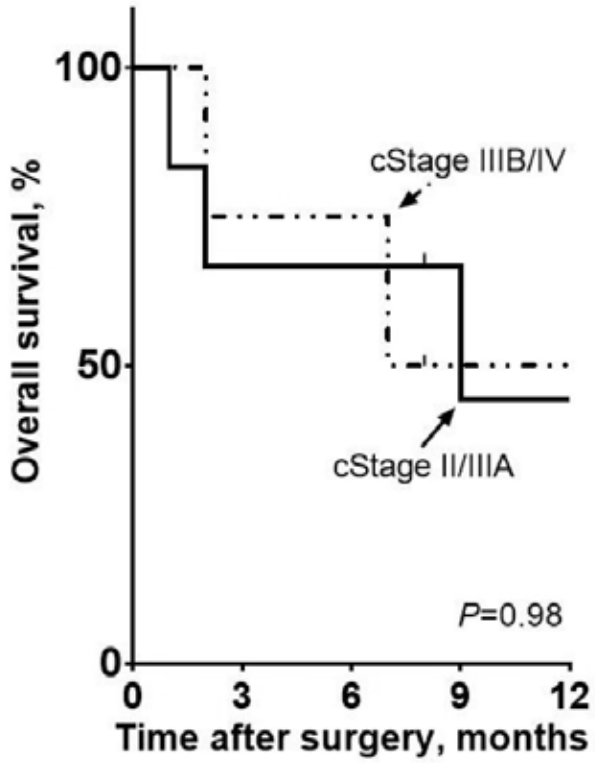
S. Hattori, T. Saito, Y. Takeyasu, N. Makihara, T. Utsumi, N. Maru, A.K. Kobayashi, K.J. Fukumoto, H. Matsui, Y. Taniguchi, T. Kurata, T. Murakawa
Kansai Medical University Hospital, Hirakata, Osaka/JP

Introduction: Infectious complications following transbronchial biopsy (TBB), often linked to the aggravation of preexisting tumor necrosis, can delay lung cancer treatment and worsen survival outcomes. While emergency surgery may be required in severe cases, data on its clinical outcomes remain unclear. This study aims to evaluate the clinical characteristics and prognosis of patients undergoing emergency rescue surgery for post-TBB complications associated with aggravated tumor necrosis.

Methods: A retrospective review was conducted on 2,717 patients who underwent bronchoscopic procedures at Kansai Medical University Hospital between January 2016 and February 2024. Patients included in the study had histologically confirmed lung cancer and required emergency rescue surgery for post-TBB complications, such as lung abscess or hemoptysis, associated with aggravated tumor necrosis.

Results: Nine patients (0.3%) met the inclusion criteria, with complications including lung abscesses (n=7) and hemoptysis (n=2). The median age was 72 years, with clinical stages II/IIIA (n=5) and IIIB/IV (n=4). Tumors had a median diameter of 6.0 cm on CT, all with low-attenuation areas (≤30 Hounsfield units). Median preoperative CRP and albumin levels were 7.0 mg/dL and 2.4 g/dL, respectively. Surgical procedures included lobectomy (n=6), bilobectomy (n=2), and pneumonectomy (n=1), with a median operative time of 123 minutes and blood loss of 940 mL. Pathological staging revealed stage II/IIIA in 6 patients (all R0 resections) and stage IIIB/IVA in 3 patients. Histological subtypes included squamous cell carcinoma (n=4), pleomorphic carcinoma (n=2), adenosquamous carcinoma (n=2), and large cell carcinoma (n=1). Tumor necrosis was observed in all resected specimens, while 55.6% (n=5) of TBB specimens showed necrosis. Additionally, bacterial cultures identified oral commensal bacteria in 7 cases. The 30-day mortality rate was 0%, however, the 90-day mortality rate was 33.3% (n=3). The cause of death included sepsis (n=2) and shock associated with ileus (n=1). One-year survival rates were 44% for stage II/IIIA and 50% for stage IIIB/IV (Figure).

Conclusions: Patients requiring rescue surgery for post-TBB complications were characterized by large tumor size (≥3 cm), low-attenuation CT features, and preexisting necrosis. Despite surgical intervention, the high mortality rate highlights the need for preventive strategies, including upfront surgical resection for high-risk patients. Future studies are necessary to validate these approaches.



Keywords: Tumor necrosis, Trasbronchial biopsy, Rescue surgery

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.08.10 N3 Stage May no Longer Be Considered Unresectable in Anaplastic Lymphoma Kinase(ALK)-Positive Non-Small Cell Lung Cancer: A Case Series

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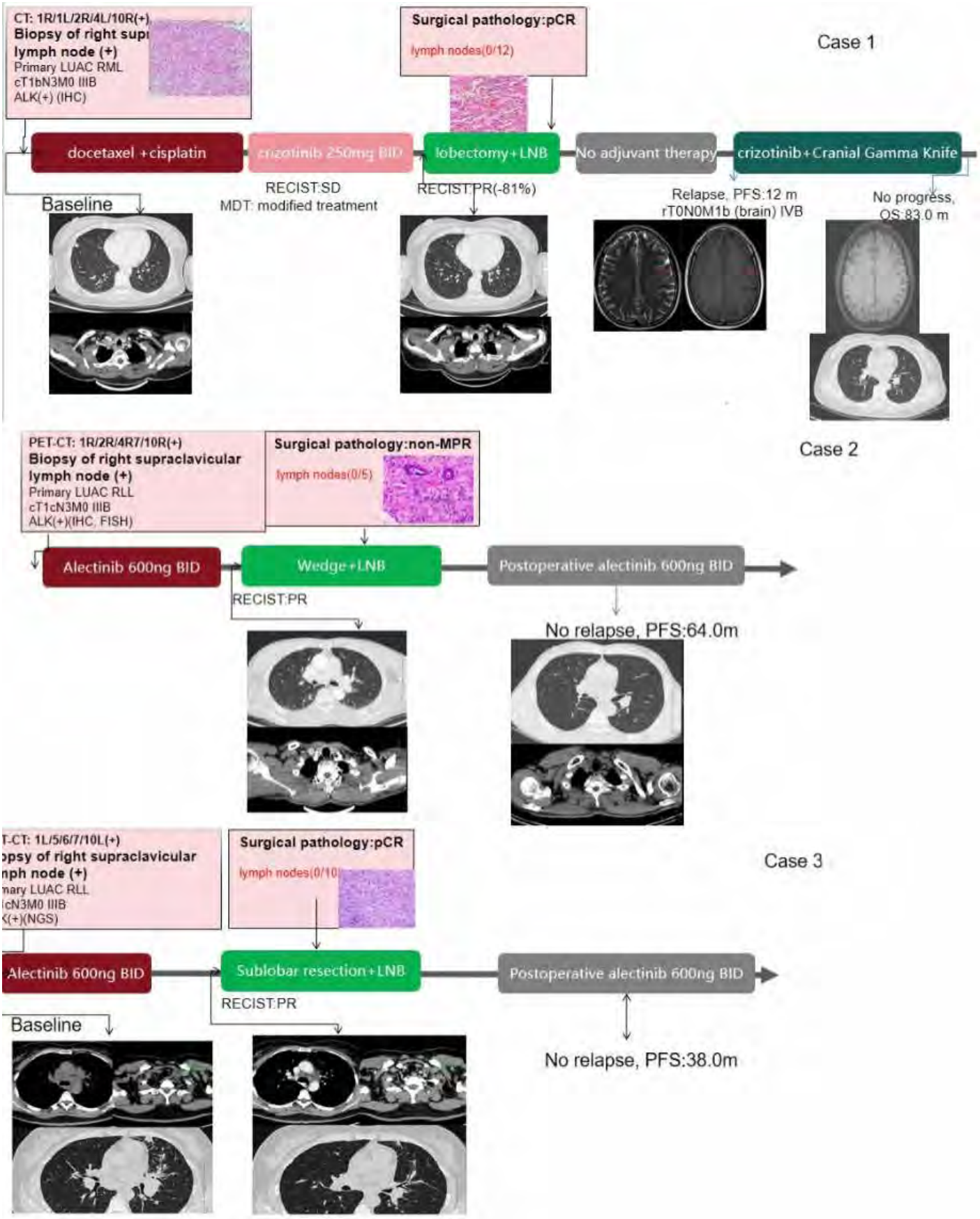
[1]GuangDong Provincial Peoples Hospital, Guang Zhou/CN ,[2]Guangdong Provincial People's Hospital, Guang Zhou/CN

Introduction: In recent years, the development of ALK-tyrosine kinase inhibitors (ALK-TKIs) has significantly improved the survival of patients with unresectable locally advanced ALK-positive disease. Some of these patients may become eligible for surgery after induction targeted therapy. However, whether this treatment paradigm—conversion from unresectable to resectable disease—provides a survival benefit remains uncertain, particularly for patients with N3 disease in whom supraclavicular and contralateral lymph nodes are not dissected during surgery.

Methods: N3 stage NSCLC patients with ALK detected by next-generation sequencing (NGS) received concomitant oral crizotinib or alectinib.

Results: Three patients were retrospectively reviewed: 1) a 45-year-old female patient was diagnosed with stage T1bN3M0 IIIB lung adenocarcinoma. The patient first received three cycles of docetaxel plus cisplatin, and the treatment response was evaluated as stable disease (SD).After multidisciplinary team (MDT) discussion, the treatment regimen was modified to crizotinib. After 150 days of treatment, CT imaging showed a significant reduction in the volume of the primary lesion, and the treatment response was evaluated as partial response (PR). The patient subsequently underwent conversion thoracotomy with lobectomy and mediastinal lymph node dissection. Postoperative pathological evaluation confirmed a pathological complete response (pCR). The patient experienced disease recurrence on March 1, 2020, with a stage rT0N0M1b (brain), IVA. The progression-free survival(PFS) was 12.0 months. By the time of manuscript submission, the overall survival(OS) was 83.0 months. 2)a 57-year-old male patient was diagnosed with stage T1cN3M0 IIIB lung adenocarcinoma. After 225 days of induction targeted therapy with alectinib, the treatment response was evaluated as PR.The patient subsequently underwent pulmonary wedge resection and lymph node biopsy. Postoperative pathological evaluation achieved non-major pathological rsponse(non-MPR). Adjuvant targeted therapy with alectinib was continued postoperatively. By the time of manuscript submission, the patient had not experienced recurrence, with PFS and OS of 64.0 months. 3)a 51-year-old male patient was diagnosed with stage T1cN3M0 IIIB lung adenocarcinoma.NGS revealed an ALK mutation. After 135 days of induction targeted therapy with alectinib, the treatment response was evaluated as PR. The patient subsequently underwent sublobar resection and lymph node dissection. Postoperative pathological evaluation confirmed pCR. Adjuvant targeted therapy with alectinib was continued postoperatively. By the time of manuscript submission, the patient had not experienced recurrence, with PFS and OS of 38 months.

Conclusions: These case sheds light on the feasibility and safety of alectinib and crizotinib as a conservsion treatment and the efficacy of for stage N3 NSCLC patients with ALK rearrangement.



Keywords: Unresectable NSCLC, ALK mutation, conversion therapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.11 Multimodality Approach for Locally Advanced Lung Cancer, When Is Surgery Most Beneficial in a Resource-Constrained Environments

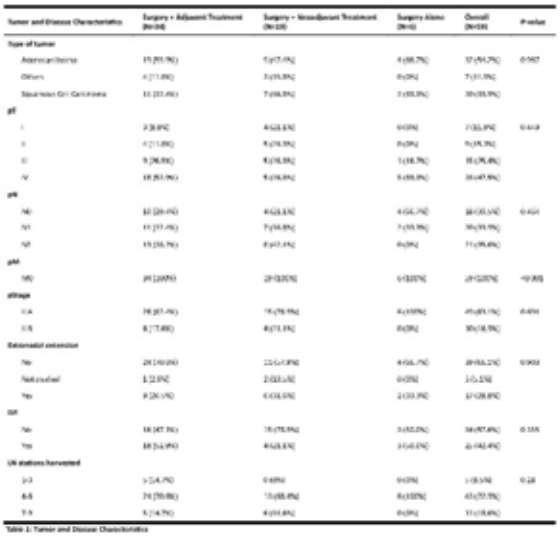
R. Abdel Jalil
King Hussein Cancer Center, AMMAN/JO

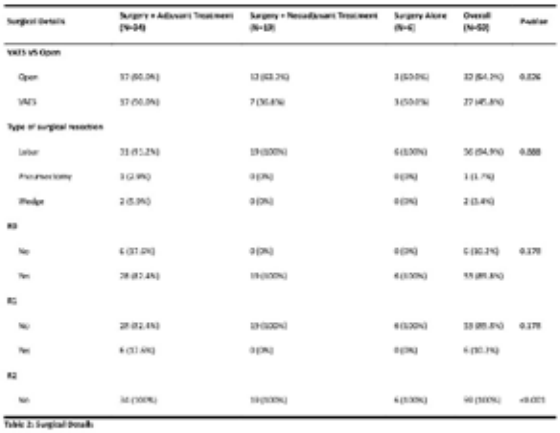
Introduction: Stage III non-small cell lung cancer (NSCLC) is a complex and challenging disease due to its heterogenicity and the absence of standardized treatment protocols. This study aimed to investigate the role of surgical resection as part of a multimodal treatment approach to improve overall survival (OS) and disease-free survival (DFS) in resource-limited settings.

Methods: The medical records of 309 patients who underwent surgery for confirmed primary lung cancer at the King Hussein Cancer Center (KHCC) in Amman, Jordan, between 2016 and 2022 were reviewed. 59 of them diagnosed with Stage III NSCLC underwent curative surgery. Patients were grouped into three categories: surgery alone, neoadjuvant therapy followed by surgery, and surgery combined with adjuvant therapy. Demographic, clinical, and survival data were statistically analyzed to compare the outcomes across these groups.

Results: The study cohort consisted predominantly of males (86.4%), with adenocarcinoma being the most common histological subtype (54.2%). Patients who underwent surgery alone had the lowest recurrence rate (8.8%), whereas those who underwent surgery alone had the highest three-year OS and DFS rates (66.7%). Improved OS and DFS were observed in patients with pN0 status and no evidence of lymphovascular invasion (LVI). Minimally invasive surgical approaches such as VATS were associated with better perioperative outcomes than open surgery.

Conclusions: Surgical resection, particularly when achieving negative margins (R0) in patients with N0 disease, is critical for improving survival in patients with Stage III NSCLC. Multimodal strategies can enhance these benefits further. However, challenges related to healthcare access in resource-limited settings highlight the need for customized treatment protocols and broader access to advanced medical therapies.





Keywords: locally advanced NSCLC, Combined Modality Therapy, Resource Limited Settings

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.12 Occult Lymph Nodal Metastasis in Sub-Centimeter Lung Cancer: A Report of Seven Cases and Review of Literature

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Nanjing Drum Tower Hospital, Medical School of Nanjing University, Nanjing/CN

Introduction: Occult lymph node metastasis (OLNM) after surgery for stage IA sub-centimeter lung cancer is an extremely rare clinical situation, with few reported cases in the literature. Further investigation is warranted into the clinical characteristics of patients and the radiological features of lung nodules. Here, we aim to provide a comprehensive insight into this tumor type.

Methods: We present cases that sub-centimeter non-small cell lung cancer (NSCLC) patients who underwent surgery at our center and were found to have OLNM in postoperative pathology. This is the first time such cases have been reported. We reviewed the existing literature on this rare event and collected detailed clinical, histopathological, and radiological data for analysis.

Results: A total of 7 sub-centimeter lung cancer patients were diagnosed with OLNM based on routine pathology, including 1 male and 6 females, with an average age of 58.7±9.3 years. All patients had no clinical symptoms and were found by physical examination, with follow-up durations ranging from 1 week to 3 years. Among these patients, 4 exhibited mediastinal lymph node metastasis. Preoperative chest CT in all patients showed pure-solid nodules (PSN), and 6 patients changed the surgical procedure based on intraoperative frozen sections results. Routine pathology revealed that all adenocarcinoma patients presented high-risk factors for recurrence, including visceral pleural invasion (VPI), spread through air spaces (STAS), vascular invasion, and poorly differentiated tumor.

Conclusions: Sub-centimeter lung cancers with radiological feature of PSN are at risk for lymph node metastasis. Surgeons should pay close attention to intraoperative rapid pathology results to prevent inadequate surgical treatment. Adenocarcinoma patients often present with one or more high-risk factors for recurrence, active adjuvant treatment and follow-up are necessary.

Keywords: sub-centimeter lung cancer, lymph node metastasis, pathology

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.13 Machine Learning Prediction of Overall Survival in Stage III Unresectable NSCLC: Data Analysis From a Single Center Prospective Cohort

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[1]Fondazione Policlinico Universitario Campus Bio-Medico, Roma/IT

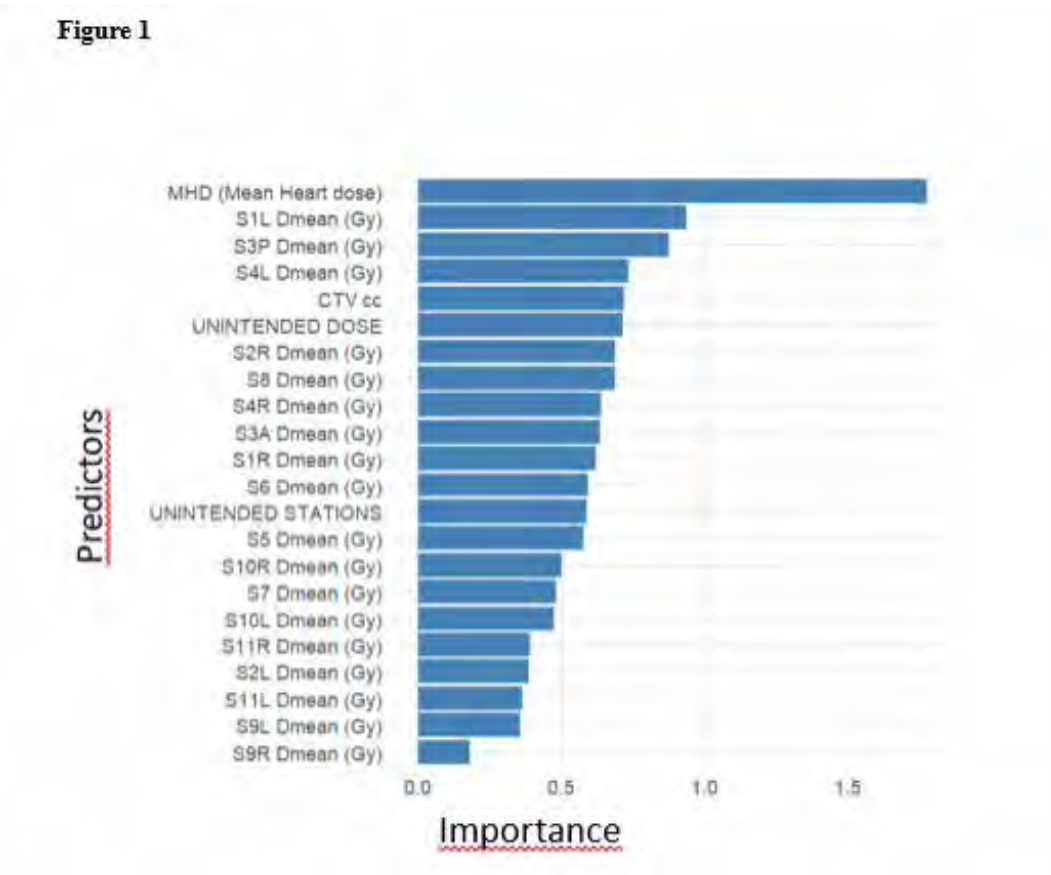
Introduction: The standard treatment for stage III unresectable NSCLC patients, is concurrent chemo-radiotherapy (cCRT) followed by Durvalumab immunotherapy (IT). Radiotherapy to uninvolved mediastinal nodes as well as to lymphocytes in the blood pool can to induce lymphopenia and affect immune response. This study aims to describe the outcome of CRT followed by IT and to explore the ability of a random forest (RF) model to predict overall survival (OS) in these patients including in the model planning data potentially involved in the negative immunologic impact of RT.

Methods: A retrospective analysis of a prospective cohort of 45 patients with stage III locally advanced, non-oncogene-addicted NSCLC (PDL-1 ≥1%) treated since 2019 with cCRT (60 Gy in 30 fractions) followed by Durvalumab IT was conducted.Treatment plans were reviewed by 2 radiation oncologist with > 10 years of experience and mediastinal nodal stations (involved and uninvolved) were contoured according to JLCS-JASTRO CT atlas and the relative received dose collected. OS was evaluated using KM curves. The choice of RF model was related to its reliability in small sized dataset. All patients were divided chronologically into the training (32 patients) and validation (13 patients) groups. Death was defined as the end point. The prediction performance was quantified by the area under the curve (AUC).

Results: The mean age was 77 (range: 52-86); 70% patients were current or former smokers. 53% of patients had adenocarcinoma. Most patients had stage IIIB (47%). All underwent cCRT followed by Durvalumab, completing a median of 15 cycles (range 1-26).Grade 3 pneumonitis occurred in 10.0% of patients, G3 esophagitis in 2.2%, and G3 thrombocytopenia in 11.1%. The median Overall Survival (OS) was 53.5 months (95% CI: 32.85-74.14). 1-2-5 year OS was 94.7%, 80.4% and 39.3% respectively. A Mean Heart Dose (MHD) of <5.2 Gy (predictor of radiation- related lymphopenia), was associated with improved survival (p-value = 0.05). The RF model achieved an AUC of 0.8667 (95%IC: 0.8333-0.9666). The most important predictor variables (figure 1), were represented by MHD, dose to nodal stations S1, S3P, S4L, CTV cc, mean incidental dose to “non target” nodal stations.

Conclusions: Concurrent chemo-radiotherapy followed by Durvalumab shows promising outcomes for stage III locally advanced NSCLC in real life setting. The RF model showed a good performance in predicting OS in these patients, highlighting the importance of the mediastinal RT dose and OARs dose. Optimizing radiotherapy planning is essential for enhancing treatment efficacy.

Figure 1



Keywords: chemoradiation, immunotherapy, lymphocyte sparin

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.14 Adaptive Radiotherapy in Locally Advanced Lung Cancer - a Single-Centre Retrospective Study

A. Tibdewal, P. Adole, G. Maheshwari, K. Prabhash, V. Noronha, N. Menon, M. Shah, G. Khatavkar, S. Pedapathi, S. Yewle, J.P. Agarwal
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Introduction: Concurrent Chemoradiation (CTRT) followed by Durvalumab is the standard of care for unresectable locally advanced lung cancer (LC). During RT, tumor volume and position changes necessitate adapting radiotherapy (ART) planning. ART may offer dosimetric and clinical advantages, however, its clinical utility remains under investigation. This study aimed to evaluate outcome comparison in patients treated with ART and those who did not need ART.

Methods: A retrospective analysis was conducted on patients with LALC treated with CTRT between January 2017 and December 2019. All patients underwent 18F-FDG PET-CT and brain MRI for baseline staging, and treatment decisions were taken after a multidisciplinary tumor board. All patients routinely undergo weekly audit, and the need for ART was identified based on tumor response, resolution of atelectasis, or disease progression. Clinical details were extracted from electronic medical records and the treatment planning system. Progression-free (PFS) and overall survival (OS) were defined from the diagnosis date until progression/death and death, respectively. Loco-regional recurrence-free survival (LRFS) was defined from RT starting till loco-regional recurrence or death, whichever is earlier. Survival comparisons between the ART and non-ART cohorts were performed using the log-rank test, with significance set at a p-value of < 0.05.

Results: A total of 156 patients were included. The median age was 59 years (range: 28-80), males (78%), and smokers (65%). Adenocarcinoma (46.2%), squamous cell carcinoma (40.4%), and small cell carcinoma (13.5%). The median planning target volume (PTV) was 444 cc (IQR: 284-606). Median lung-PTV V20 was 18.5% (IQR: 13.8-23.6), and mean lung dose (MLD) was 11.13 Gy (IQR: 9.75-13.1). ART was required in 35 patients (22.4%), due to tumor shrinkage (74%), resolution of atelectasis (20%), or progression (6%), at a median dose of 26 Gy (range: 14-36). The median time to deliver the ART plan was 5 days (IQR: 3.5-7.5). After a median follow-up of 23 months (range: 11-46), the median OS, PFS, and LRFS for entire cohort was 28 months (IQR: 14-54), 17 months (IQR: 15-50), and 28 months (IQR: 27-51), respectively. Median and 2-yr OS in ART vs non-ART groups were 25m (IQR:15-50) & 54.3% (95%CI: 37.9-70.7) vs 31m (IQR: 13-55) & 58% (95%CI: 49.2-66.8) (p=0.54). Median and 2-yr PFS were 15m (IQR: 6-41) & 38% (95%CI: 21.3-54.5) vs 20m (IQR: 9-54) (p=0.5) & 43.6% (95%CI: 33.8-53.4). Median and 2-yr LRFS were 39m (IQR: 29-52) & 61.6% (95%CI: 44.2-79) vs 27m (IQR: 36-52) & 53.8% (95%CI: 43.6-63.9)(p=0.9), (p=0.9). There was no difference in LRF between ART (45.7%) and non-ART (43%). ART modestly increased lung-PTV V20 (+3.7%) and MLD (+4.5%) (p=0.158), but significantly reduced heart V20 (−18.3%) and spinal cord Dmax (−6.7%), (p=0.005). Grade ≥2 acute toxicities included pneumonitis (5.2%), skin toxicity (11.8%), and esophagitis (16.3%).

Conclusions: One-fourth of patients do require ART during CTRT. Adaptive RT was not associated with inferior loco-regional control or overall survival. While ART demonstrated dosimetric advantages in sparing critical organs, these did not translate into significant clinical benefit. Pre-emptive anticipation of the need for ART through weekly audits may be considered for precision CTRT.

Keywords: Adaptive Radiotherapy, Chemoradiation, Lung Cancer

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.15 Predicting Locations of In-Field Failure Leading to Proton Re-Irradiation for NSCLC

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Introduction: Previous single-institution studies have suggested that in-field disease progression following chemo-radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC) most often occurs at sites with bulky disease. We aimed to validate that finding using a cohort of patients who underwent reirradiation for recurrent NSCLC.

Methods: We reviewed records of consecutive patients with LA-NSCLC treated between 2019 and 2024 at a large proton center with thoracic radiotherapy (RT) for recurrent disease following prior chemotherapy and photon RT. Volumes of pulmonary tumors and lymph nodes initially treated with photon RT were tabulated, and lesions that required reirradiation with protons were identified. Volumes of lesions that required reirradiation were compared with volumes of lesions that did not require reirradiation using Kruskall-Wallis testing. A previously identified volume cutoff (25 cc) was tested as a predictor of in-field disease recurrence using logistic regression.

Results: Twenty-seven patients met selection criteria for this analysis. Fourteen patients (52%) had squamous cell carcinoma, and 13 (48%) had adenocarcinoma. The median initial RT dose was 60Gy (range: 45 to 66 Gy), and the median initial dose per fraction was 2 Gy (range: 1.8 to 3 Gy). The median interval between radiotherapy courses was 23 months (range: 7 to 92 months). Median age at the time of reirradiation was 68 years (range: 49 to 86 years). Twenty-five patients (93%) required reirradiation of a tumor or lymph node region previously treated with RT, and for 24 of those patients (96%), only one tumor or lymph node region required reirradiation. Among those 24 patients who required reirradiation of a single tumor or lymph node, for 22 patients (92%), it was the largest tumor or lymph node at the time of initial treatment that required reirradiation. The median initial volume of targets that required reirradiation was 89 cc (IQR: 49 to 123 cc). The median initial volume of targets that did not require reirradiation was 20 cc (IQR: 8 to 36 cc). Using the a priori volume cutoff of 25 cc , larger tumors and lymph nodes were significantly more likely to require reirradiation than smaller lesions (OR=8.0, p<0.001) (Figure 1).

Conclusions: Sites of local disease recurrence may be predictable, and the benefits of selectively applying local treatment intensification to more bulky sites could warrant investigation.

Figure 1

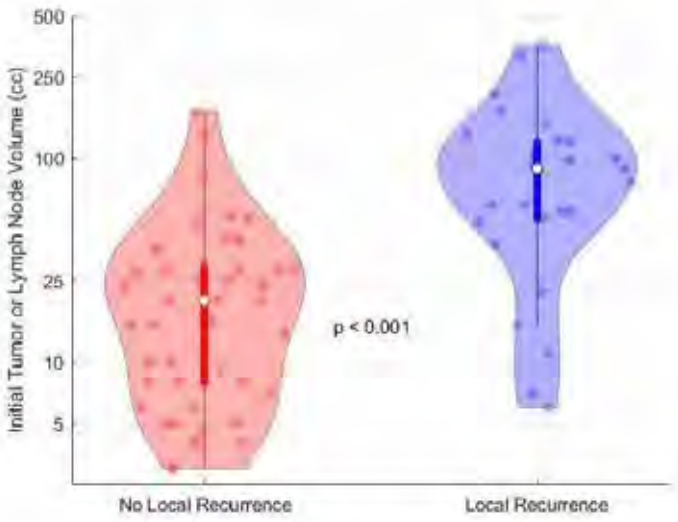

Figure 1: The violin plot: x-axis represents two groups, No local Recurrence and local Recurrence; y-axis represents log scale initial lesion volume (cc). The white dot represents the median lesion volume. P-value <0.001 from Kruskall-Wallis test suggests that the difference in lesion volume between the two groups is statistically significant. Patients in the local Recurrence group tend to have larger lesion volumes compared to those in the No local Recurrence group.

Keywords: Locally Advanced NSCLC, Initial Tumor Volume, Thoracic Radiation therapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.16 Impact of Pathological Subtypes and Radiation Dose on Survival in Lung Cancer: A Retrospective Analysis From a Single Institution

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Introduction: Lung cancer remains the leading cause of cancer-related deaths worldwide. Radiotherapy plays a fundamental role in treatment, and recent studies emphasize the importance of personalized dose escalation strategies based on tumor histology. This study investigates how pathological subtypes and radiation dose escalation impact survival outcomes in lung cancer patients treated at a single institution between 2020 and 2025.

Methods: We conducted a retrospective analysis of 103 lung cancer patients treated with radiotherapy. Patients were classified by histological subtype: adenocarcinoma, squamous cell carcinoma, and other subtypes. Radiation doses ranged from 50 to 70 Gy (mean: 62 Gy). Pulmonary dosimetric parameters, including mean lung dose (MLD), V20, and Dmax, were recorded. Survival outcomes were evaluated using Kaplan-Meier analysis, and independent prognostic factors were identified through Cox proportional hazards models, adjusting for age, disease stage, comorbidities, and smoking history. Treatment-related toxicities (≥grade 3) were assessed following CTCAE v5.0 guidelines.

Results: Patients who received ≥65 Gy had a significantly higher 1-year survival rate (72.5%) compared to those treated with <65 Gy (61.2%; $p<0.05$). The median overall survival (OS) for the entire cohort was 17.8 months, with an overall survival rate of 64.1%. Adenocarcinoma patients had better OS than those with squamous cell carcinoma (median: 20.1 vs. 15.6 months; HR 0.79, 95% CI: 0.63-0.95). Higher MLD and V20 were associated with increased rates of ≥grade 3 pneumonitis (8.1%) and esophagitis (6.3%). Multivariate analysis confirmed that histology and radiation dose were independent predictors of survival.

Conclusions: Personalized radiotherapy strategies that account for tumor histology and optimized dose escalation can significantly improve survival outcomes in lung cancer patients. Notably, adenocarcinoma patients demonstrated a greater survival benefit from higher radiation doses. Additionally, the growing evidence of the synergy between radiotherapy and immunotherapy suggests that combining these approaches may enhance the antitumor response and prolong survival, particularly in selected subgroups. These findings align with recent international studies and reinforce the need for prospective trials incorporating molecular biomarkers, immunotherapy, and advanced radiotherapy techniques to further refine lung cancer treatment strategies.

Keywords: Lung Cancer, Pathological Subtypes, Dose Escalation

EP.08.17 Patterns of Recurrence and Eligibility for Salvage Therapy After Curative Intent Treatment for Unresectable Stage III NSCLC

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Introduction: Definitive chemoradiotherapy (CRT) followed by durvalumab is the standard of care for unresectable stage III non-small cell lung cancer (NSCLC). Patterns of recurrence determine options for salvage therapy. For oligo-recurrence, stereotactic radiosurgery to the brain (SRS) or stereotactic body radiotherapy (SBRT) may be used alone, as an alternative to surgery or in conjunction with systemic treatment. This study aimed to analyze the patterns of recurrence and amenability to salvage SRS/SBRT or surgery following curative intent treatment for patients with unresectable stage III NSCLC.

Methods: Patients with unresectable stage III NSCLC treated at BC Cancer, British Columbia, Canada from January 2018-December 2021 were identified. A retrospective chart review was performed including patient characteristics, surveillance compliance, initial treatment, recurrence patterns (detected on imaging), number of sites of metastases and salvageability. Patients eligible for salvage treatment were determined by multidisciplinary assessment, defined as those amenable to salvage SRS/SBRT or surgery for intrathoracic recurrence, extrathoracic recurrence in the body or recurrence in the central nervous system (CNS).

Results: 433 of 459 patients completed CRT as planned with a median follow up of 31.4 months. Patients were median age 68 years, male 54%, never/ever smoking history 10/90%, adenocarcinoma 61%, stage IIIA/B/C 48/45/7%. Median radiation dose was 60 Gy with 63% receiving platinum/etoposide and 37% receiving carboplatin/paclitaxel. 63% received at least 1 dose of durvalumab consolidation. 271/433 patients had recurrence. There was no difference in pattern or number of sites of recurrence based on durvalumab treatment. Of patients with recurrence, 269 received body imaging while 139 received CNS imaging. Most recurrences were intrathoracic only in 137/269 or 51%, compared to extrathoracic only (excluding CNS) 10%, 31% of patients had both intrathoracic/extrathoracic and 61/139 or 44% of patients had CNS recurrence. 44% of patients had 1-5 body metastatic sites at recurrence compared to >5 sites (47%). Relatively higher proportions of CNS recurrences were limited to 1-5 sites (75%) vs 25% with >5 sites. 51/271 were deemed eligible for salvage therapy.

Conclusions: In this retrospective cohort of patients treated with CRT for unresectable stage III NSCLC, the recurrence rate was 62% after a median duration of 31.4 m of follow up. Intrathoracic only recurrence was noted in 51% of patients and 19% were potentially amenable to salvage therapy with SRS/SBRT or surgery. The possibility of salvage therapy supports the routine surveillance imaging for timely detection of such cases for patients who have completed first-line curative intent chemoradiotherapy.

Pattern of first recurrence	Total	CRT only	CRT followed by durvalumab	P value
BODY	**n=269 with imaging**	**n=109**	**n=160**	
Intrathoracic only	137 (51%)	55 (50%)	82 (51%)	0.89
Extrathoracic only	27 (10%)	10 (9%)	17 (11%)	0.69
Intra/extrathoracic	84 (31%)	37 (34%)	47 (29%)	0.43
Liver	13 (5%)	13 (12%)	26 (16%)	0.33
Adrenal	24 (9%)	10 (9%)	14 (9%)	0.95
Bone	50 (19%)	20 18%)	30 (19%)	0.90
CNS	**n=139 with imaging**	**n=59**	**n=80**	
	61 (44%)	27 (46%)	34 (42%)	0.70

Keywords: SRS/SBRT, Recurrent unresectable stage III NSCLC, Salvage therapy

EP.08.18 Concurrent Chemoradiotherapy (ConCRT) in Locally Advanced (LA) Non-Small Cell Lung Cancer (NSCLC)In the Durvalumab Era

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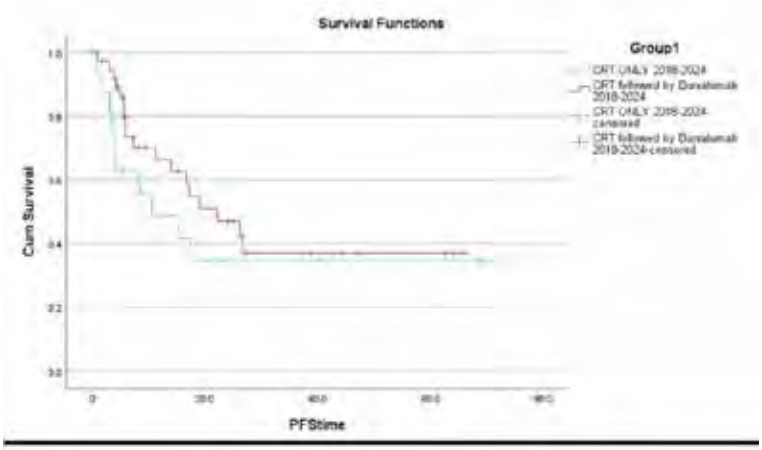
Introduction: Following the presentation of the PACIFIC trial, we adopted ConCRT, followed by Durvalumab maintenance, for patients with unresectable, LA NSCLC without disease progression after CRT and PD-L1 expression >1%, as per the EMA approval. We compare outcomes of this approach with our historical series of conCRT from 2005 to 2017. This analysis examines a register of all patients consecutively assigned to conCRT since 2018, conducted in an intent-to-treat manner.

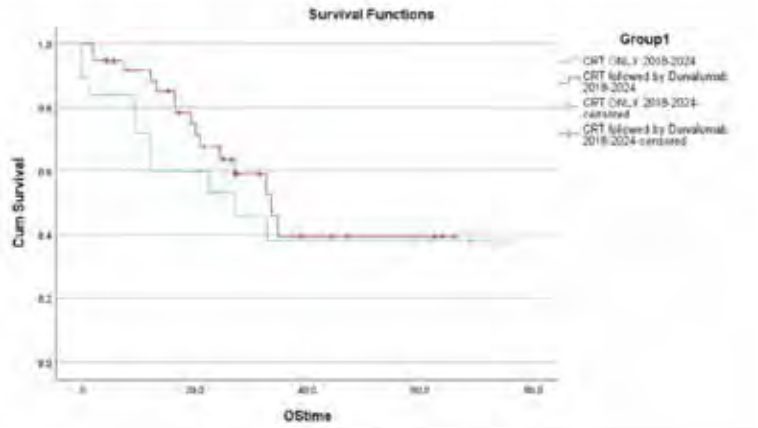
Methods: From March 2018 to May 2024, we assigned ConCRT followed by 1 year Durvalumab maintenance to 37 consecutive patients with LA NSCLC who were deemed unresectable and had PD-L1 expression >1%. 19 patients with PD-L1-negative disease received only conCRT. Patients had ECOG performance status 0-2 and were treated mainly with either weekly carboplatin-paclitaxel or Cisplatin/Carboplatin-Vinorelbine (with dose reduction of Vin to 15mg/m2 during the concurrent phase). We report outcomes for both cohorts of PD-L1 positive and negative patients, and compare to our pre-2018 series (JTO 13(10):S854. DOI:10.1016/j.jtho.2018.08.1533).

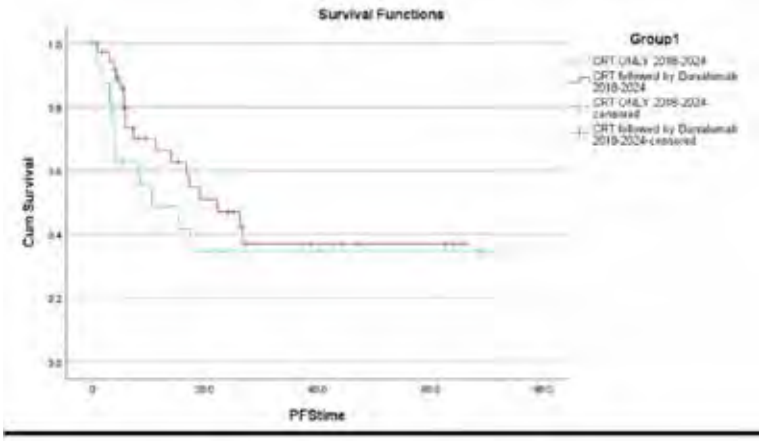
Results: For the conCRT Durva series, 5-year progression-free survival (PFS) and overall survival (OS) rates were 37% (95%CI, 18,8%-55,3%) and 39,3% (95%CI, 18,4%-59,8%), respectively whilst for the conCRT, 5-year PFS and OS rates were 34,7% (95%CI, 12,9%-57,8%) and 38% (95%CI, 15%-61%). 5-year PFS and OS rates for our historical CRT series were 25% and 28,2%, respectively. For the conCRT Durva series, median PFS (mPFS) was 22,3 months and median OS (mOS) was 33,6 months, whilst for the conCRT series, mPFS was 10,7 and mOS 27,2 months. mPFS and mOS for our historical CRT series of 86 patients treated pre-2018, were 14,1 months and 24,8 months, respectively. Further information in table 1 and PFS and OS curves.

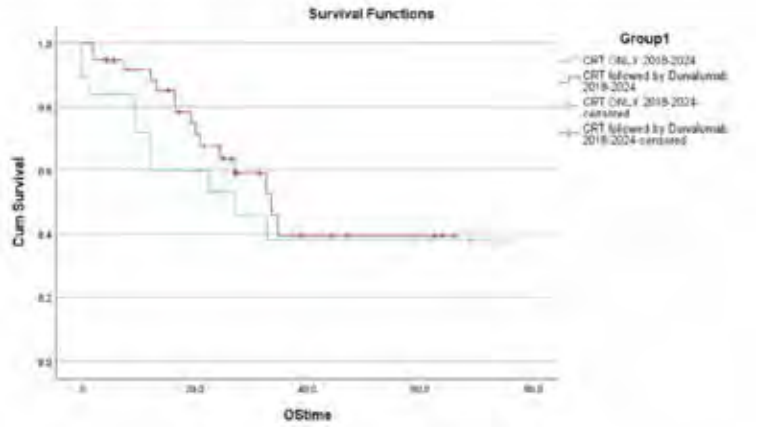
Conclusions: ConCRT with and without Durvalumab produced encouraging results, compatible with the PACIFIC data, and better than our historical series before the introduction of Durvalumab.

Demographics	CRT alone (N=19) (%)	CRT + Durvalumab maintenance (N=37) (%)
Age years (median)	66	70
Male	15 (78,9)	35 (94,6)
Female	4 (21,1)	2 (5,4)
Performance status		
0	12 (63,1)	22 (59,5)
1	7 (36.9)	13 (35,1)
2	-	2 (5,4)
Histology		
Adenocarcinoma	8 (42,1)	12 (32,4)
Squamous	8 (42,1)	21 (56,8)
NOS	1 (5,3)	4 (10,8)
Other	2 (10,5)	-
Stage		
II	2 (10,5)	4 (10,8)
IIIA	9 (47,3)	18 (48,7)
IIIB/IIIC	4 (21,1)	13 (35,1)
Local relapse	4 (21,1)	2 (5,4)
Staging PET scan	17 (89,5)	35 (94,6)
TPS		
< 1%	15 (78,9)	-
1% - 49%	-	18 (48,7)
≥ 50%	3 (15,8)	16 (43,2)
NA	1 (5,3)	3 (8,1)
Type of CRT		
Concurrent chemo-RT	19 (100)	31 (83,8)
Sequential chemo-RT	-	6 (16,2)
Chemotherapy regimen		
Platinum-Vinorelbine	11 (57,9)	15 (40,5)
Platinum-Paclitaxel	8 (42,1)	18 (48,7)
Platinum-Etoposide	-	3 (8,1)
NA	-	1 (2,7)









Keywords: concurrent, chemoradiation, NSCLC

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.19 Timing and Predictors of Lymphopenia in Lung Cancer Patients Undergoing Proton and Photon Chemoradiotherapy

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Introduction: Treatment-induced lymphopenia is a well-known and clinically significant adverse effect observed in patients undergoing proton or photon chemoradiotherapy (PT-CRT or PH-CRT) for lung cancer, especially given the increasing use of adjuvant immune checkpoint inhibitors. Although PT may provide dosimetric advantages by reducing integral body dose, direct comparisons remain limited. This study aimed to assess the timing and identify factors associated with grade 3 lymphopenia (G3L) in patients treated definitively with PT-CRT or PH-CRT.

Methods: We performed a retrospective analysis of patients with locally advanced or recurrent lung cancer who underwent definitive PT-CRT or PH-CRT at a single institution. All patients received conventionally fractionated radiotherapy alongside chemotherapy, and lymphopenia was graded per CTCAE version 5.0. We analyzed the timing of G3L and its association with clinical and dosimetric factors, including age, gender, pre-treatment absolute lymphocyte count (ALC), tumor histology, concurrent chemotherapy regimen, induction chemotherapy (ICT), treatment volume (planning target volume [PTV] or clinical target volume [CTV], lung V5, and mean lung dose (MLD). Group comparisons used Mann-Whitney U and Chi-square tests, Kaplan-Meier estimates assessed time to G3L, and univariate/multivariate Cox regression identified factors associated with G3L.

Results: A total of 68 patients (PT-CRT: 47, PH-CRT: 21) were evaluated. Both groups were comparable in terms of median age (76 years [range, 54-88] vs. 72 years [range, 51-83]), gender (male: 55.3% vs. 71.4%), histological subtype (adenocarcinoma: 55.3% vs. 52.4%), and type of concurrent chemotherapy (paclitaxel/carboplatin: 80.9% vs. 85.7%), in PT-CRT and PH-CRT, respectively, all p>0.05. Median PTV/CTV was similar (292.3 cc PT-CRT vs. 331.2 cc PH-CRT, p>0.05). Across the entire cohort, the median delivered dose was 60 Gy/GyE (range, 59-70 Gy/GyE) in 30 fractions (range, 30-35). Despite the similar target volumes and radiation doses, median MLD was significantly lower in PT-CRT (10.7 Gy vs. 15.0 Gy, p=0.01). Median time to G3L was longer in PT-CRT (31 vs. 21 days, p=0.07). Larger PTV/CTV (p=0.015) and radiotherapy modality (p=0.08) correlated with G3L in univariate cox-regression analysis, but only PTV/CTV remained significant in multivariate analysis (p=0.015).

Conclusions: G3L was common in both PT-CRT and P-CRT, strongly associated with larger PTV. Although PT-CRT showed a trend toward delayed lymphopenia onset, significance of radiation modality was lost in multivariate analysis, likely due to the interplay effect of other variables, such as treatment volume or sample size limitations. Given the expanding use of immune checkpoint inhibitors, optimizing radiation planning and target volume management to minimize lymphopenia is crucial

Keywords: proton therapy, lung cancer, lymphopenia

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER
TUESDAY, SEPTEMBER 9, 2025

EP.08.20 Comparative Survival Post-Radiotherapy in Small Vs. Non-Small Cell Lung Cancer: Revisiting Prognostic and Dosimetric Factors

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Introduction: This study aimed to critically compare survival rates, recurrence patterns, and radiotherapy outcomes between Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), assessing prognostic variables and exploring how radiotherapy dosimetry influences clinical outcomes.

Methods: A retrospective analysis was conducted on lung cancer patients treated with radiation therapy, evaluating demographic characteristics, tumor staging, and key dosimetric parameters. The study focused on identifying differences in survival, recurrence patterns, and potential impacts of radiotherapy planning on clinical outcomes. The dosimetric parameters analyzed included mean total dose and fractions of each different histological type.

Results: A total of 207 patients were analyzed, with a mean age of 66 years (range 29-92) and a balanced gender distribution (50,2% male, 49,8% female). Smoking history was recorded in 81,16% of patients, averaging 55.28 pack-years. The majority presented with advanced-stage disease (86,47% Stage III or IV), and 56,04% were Stage IV. The cohort consisted of 191 NSCLC (92.3%) and 16 SCLC (7.7%) patients. Overall mortality was 24.6% (51 deaths). Notably, SCLC patients exhibited higher survival rates (75.4%) with lower recurrence (37,5%, 6 patients), contrasting with the 74,87% survival and 67,54% recurrence in NSCLC. These results substantially diverge from established literature, which consistently reports poorer outcomes in SCLC, typically characterized by rapid recurrence and low 5-year survival (<10%). Dosimetric analysis revealed that patients with non-small cell lung cancer (NSCLC) received a median dose of 3292.68 cGy administered in 10 fractions, while patients with small cell lung cancer (SCLC) received higher doses (3853.33 cGy) with a median of 9 fractions. Despite receiving higher doses in fewer fractions, patients with SCLC in our cohort demonstrated unexpectedly higher survival rates and lower recurrence compared to patients with NSCLC. The subgroup analysis indicated that the one-year progression-free survival (PFS) rate was 58.3% in SCLC versus 41.2% in NSCLC (p=0.021), suggesting a potential advantage of the therapeutic approach employed in the analyzed cohort. Additionally, NSCLC patients treated with escalated-dose radiotherapy (>4,000 cGy) demonstrated a modest survival benefit, with a median overall survival of 19.8 months vs. 16.2 months (p=0.034), indicating that personalized dosimetry may improve clinical outcomes.

Conclusions: Contrary to existing literature, SCLC patients in this cohort demonstrated higher survival and lower recurrence post-radiotherapy compared to NSCLC. This may reflect earlier diagnosis, intensified multimodal treatment, and higher-dose, hypofractionated radiotherapy in SCLC. In NSCLC, escalated-dose radiotherapy was associated with modest survival gains, supporting personalized dosing strategies. Comparative assessments by histologic subtype are key to refining treatment decisions. Concurrent evaluation of survival, recurrence, and dosimetric data offers critical insight into therapeutic response. These findings challenge conventional prognostic models and suggest that individualized radiotherapy may improve outcomes. Prospective studies with integrated dosimetric analysis are needed to confirm and translate these insights into practice.

Keywords: SCLC NSCLC, Comparative Survival, Radiotherapy Results

EP.08.21 Sequential Radiotherapy Following Induction Immunochemotherapy/Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

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Introduction: The use of immune checkpoint inhibitors (ICIs) during concurrent chemoradiotherapy (CCRT) has been established as the standard of treatment forunresectable stage III non-small cell lung cancer (NSCLC) by previous studies, including the PACIFICtrial. Inductionimmunochemotherapy was addedbefore CCRT in the PACIFIC-BRAZIL study,improving progression-free survival (PFS). However,4% of patients showed disease progression during induction immunochemotherapy, which raises concerns regarding the bestfollow-up treatment. In this research,the safety and efficacy of sequential radiotherapy were retrospectivelyevaluated in patients who didnot establish remission with induction therapies in real-world settings.

Methods: A multicenterretrospective researchwas conducted on 29 patients withunresectable stage III NSCLC who hadsequential radiotherapy after inductiontherapy failed to produce remission.Induction immunochemotherapy wasadministered to 18 patients,while induction chemotherapy wasgiven to 11. Log-rank tests wereused for univariate analysis,and progression-free survival(PFS) and overall survival(OS)were assessed using Kaplan-Meier analysis.Multivariate Cox regression was used to determineprognostic factors.

Results: The disease control rate (DCR) was 96·6%, while the objectiveresponse rate (ORR) was 37·9%. Themedian overall survival (MOS) was 32·7(95%CI 30·1-35·3) months, and the median progression-free survival (MPFS) was 5·1(95%CI 3·9-6·3) months overall, with 6·6 months in the immunochemotherapy group and 3·7months in the chemotherapy group($\chi 2$=7·68,P=0·006).Theone-year survival rate was 82·%(95%CI68·1%-97·4%).Although OS did not vary significantly across subgroups,progression-freesurvival was significantly better in the immunochemotherapy group(immunochemotherapygroup vs. chemotherapy group,HR:0·174,95%CI 0·054-0·566,P=0·004).No patient had any disease progression while receivingradiotherapy.The proportion of patients whoreceived immunotherapymaintenance as a re-challenge after induction immunochemotherapywas 88·9%,with a 12-month survival rate of 87·5%. There were 16(55·2%) cases of radiation pneumonitis and 2(6·9%)cases of radiation pneumonitis that were grade III orhigher. One patient passed away from radiationpneumonitis,although the cause of deathcould not be associatedwith radiation pneumonitis since the patient had a pre-existingPneumocystis infection before receiving radiotherapy.

Conclusions: For unresectable stage IIINSCLC patients who arenot responsive to induction treatments, sequential radiation is a feasibleand effective method that offers better PFS with a manageable safety profile. These results also demonstrate thepossible advantages of immunotherapy re-challengeafter successful radiotherapy.

Keywords: Unresectable stage III NSCLC, Immunochemotherapy, Radiotherapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.22 Treatment Patterns and Clinical Outcomes in South Korean Patients With Unresectable Stage III EGFRm NSCLC Undergoing CRT

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Introduction: In the Phase III LAURA study (NCT03521154), osimertinib demonstrated statistically significant and clinically meaningful progression-free survival (PFS) benefit versus placebo, post-definitive CRT in patients with unresectable stage III EGFRm NSCLC (PFS hazard ratio [HR] 0.16; p<0.001). Real-world treatment patterns and clinical outcomes are important to evaluate the impact of new treatments. Here, we report data from the South Korean cohort of a global, retrospective, real-world study in this setting.

Methods: Data were extracted from medical records of patients (aged ≥19 years) with unresectable stage III EGFRm (Ex19del/L858R) NSCLC diagnosed between Jan 2016 and Dec 2019, who underwent CRT as standard of care at selected sites in South Korea. The primary study outcome was real-world PFS (rwPFS); secondary outcomes included mutation testing and treatment patterns, real-world time to next treatment or death (rwTTNTD) and real-world overall survival (rwOS). Data cut-off: 31 Dec 2022.

Results: In total, 60 patients from South Korea were enrolled across three sites: median age 65 years; 50% female; 93% ECOG PS 0-1; 38% current/former smokers; 68% Ex19del/32% L858R. Most patients (38 [63%]) underwent sequential CRT (sCRT); 22 (37%) patients underwent concurrent CRT (cCRT) (Table). The most common chemotherapy regimen was platinum + paclitaxel: 54/60 (90%) all patients; 34/38 (89%) sCRT; 20/22 (91%) cCRT. Overall, 56 patients (93%) underwent CRT alone, three (5%) received CRT + durvalumab and one patient (2%) received CRT + EGFR-TKI + IO as first treatment. In total, 57 patients received a subsequent treatment upon disease progression, of which EGFR-TKIs were the most commonly used (45/57; 79%). Median (95% CI) rwPFS, rwTTNTD and rwOS were 8.0 months (6.0, 9.0), 9.0 months (7.0, 9.5) and 54.9 months (36.9, 64.9) respectively, in patients who underwent CRT alone. By CRT type, median (95% CI) rwPFS, rwTTNTD and rwOS were 7.5 months (6.0, 9.0), 9.0 months (6.1, 9.4), 54.9 months (36.9, 64.9) and 8.6 months (2.8, 11.0), 8.8 months (3.5, 13.1), 61.5 months (15.5, 69.9) in patients who underwent sCRT or cCRT, respectively.

Conclusions: In this real-world analysis of patients from South Korea with unresectable stage III EGFRm NSCLC, most patients underwent CRT alone as first treatment, most commonly sCRT. The majority of patients received EGFR-TKIs as first subsequent treatment. The rwPFS observed highlights the need for alternative first treatment options in this patient population; the prolonged rwOS observed may be attributed to subsequent use of EGFR-TKIs.

Table: Summary of treatment patterns.

	All patients (N=60)
First treatment, n (%)	
sCRT	**38 (63)**
Cisplatin + paclitaxel*	30 (79)
Carboplatin + paclitaxel*	3 (8)
Cisplatin + etoposide*	2 (5)
Carboplatin + pemetrexed + durvalumab*	1 (3)
Cisplatin + etoposide + durvalumab*	1 (3)
Cisplatin + paclitaxel + durvalumab*	1 (3)
cCRT	**22 (37)**
Carboplatin + paclitaxel†	17 (77)
Cisplatin + paclitaxel†	3 (14)
Carboplatin + pemetrexed†	1 (5)
Cisplatin + gemcitabine + gefitinib + nivolumab†	1 (5)
First subsequent treatment, n (%)	**57 (95)**
EGFR-TKI‡	45 (79)
Radiotherapy only‡	7 (12)
Chemotherapy‡	5 (9)

*Percentages calculated as a proportion of patients who underwent sCRT (n=38). †Percentages calculated as a proportion of patients who underwent cCRT (n= 22). ‡Percentages calculated as a proportion of patients who underwent subsequent treatment post first treatment (n=57). CRT, chemoradiotherapy; cCRT, concurrent chemoradiotherapy; EGFR, epidermal growth factor receptor; sCRT, sequential chemoradiotherapy; TKI, tyrosine kinase inhibitor

Keywords: Non-small cell lung cancer, Epidermal growth factor mutation, Chemoradiotherapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.23 EMS to Lung Cancer Patients Receiving Platinum Doublet Concomitant Chemoradiotherapy

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Introduction: To determine feasibility and effect of electrical muscle stimulation (EMS) to patients with lung cancer receiving platinum doublet concomitant chemoradiotherapy (CCRT).

Methods: After IRB approval, from August 2014 to December 2016, lung cancer patients receiving CCRT were assigned to either EMS group (EG) or control group (CG). Eligibility criteria were histologically proofed lung cancer, CCRT for curative intent, performance status (PS) 2 or better, and age 20 or older. The quadriceps muscle of both legs were stimulated using biphasic pulsed current, constant current impulses with a pulse width of 400 μs and a frequency of 75 Hz for 18 minutes, twice daily every day through the whole CCRT period. For EG, patients were allowed to raise the electrical current of the machine as high as they can endure. However, for CG patients, electrical current was only increased until the patient could feel a tingling sensation and no muscle contraction was visible or palpable. Grade 2 or higher adverse effects were evaluated and compared between the two groups. Regarding the survival, because stage IV patients (after a good response to chemotherapy or gamma knife to the brain) or patients with recurrence after surgery were also included in this study, these patients were excluded to make the population more homogeneous.

Results: Eligible patients were 63. Out of them, 36 agreed to participate (EG, 17; CG, 19). The following parameters were all balanced well between the two groups; gender, age, PS. Concomitant to chemotherapy, all patients with non-small lung cancer received 60 Gy in 30 fractions and all patients with small cell lung cancer received 45 Gy in 25 fractions (two times a day). Statistically significantly ($p=0.02$) fewer patients with grade 2 or higher serum albumin loss were observed in EG and a trend ($p=0.08$) of fewer patients with grade 2 or higher neutropenia were observed in EG. There were no adverse effect caused by the EMS intervention. There were 6 stage IV patients and 5 patients receiving CCRT after recurrence, who were excluded from survival evaluation. These decreased the population to 25 patients. There was no difference in overall survival ($p=0.71$) and progression free survival ($p=0.12$) between the two groups.

Conclusions: EMS is feasible and could be effective in preventing cancer cachexia and may prevent neutropenia in patients receiving CCRT, but no survival benefit was observed in this study.

Keywords: lung cancer, cachexia, neutropenia

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.24 Pattern of Care in Locally Advanced NSCLC in India

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Introduction: Locally advanced NSCLC group requires a multi-disciplinary management. Surgery is the standard of care treatment if resectable otherwise concurrent chemo-radiation (CCRT) is preferred. This audit aims to analyse various treatment strategies in real-world settings and their resultant outcomes.

Methods: Medical records of patients presented to the lung cancer clinic from 2014 to 2018 were retrieved. Stage III NSCLC were included in this retrospective analysis. Demographic and clinical data, treatments with outcomes and side effects were analysed. The PFS and OS were computed using Kaplan- Meier survival curves. Cox proportional hazard model (univariate and multivariate) was used to assess factors affecting PFS and OS.

Results: A total of 396 patients were eligible for demography; 53% were > 60 years of age and male-to-female ratio was 4:1. The proportion of squamous cell carcinoma and adenocarcinoma were 55.8% and 31.3% respectively. Survival analysis was limited to 310 patients who received any form of cancer treatment. The intent of treatment was decided to be curative in 240 of them. Upfront surgical resection was performed in 28 patients (11.6%) with 22 receiving adjuvant chemotherapy. Pre- operative chemotherapy followed by surgery was offered to 20 patients (8.3%). The majority of patients taken for definitive chemo- radiation (CTRT) were treated by induction chemotherapy followed by concurrent CTRT (46 patients= 19.2%). Sequential CTRT (SCRT) was opted for 30 patients (12.5%). Concurrent CTRT (CCRT) was received by only 12 patients (5%). Neoadjuvant chemotherapy (NACT- including preoperative and induction chemotherapy before definitive radiotherapy or CTRT) was administered to 200 patients (83.3%). Of these, 104 patients (43.3%) of NACT were not amenable to curative local treatment later on due to poor performance status(PS), comorbidities, poor cardiopulmonary reserve, or logistic issues. The median follow-up was 30.7 months. Survival was assessed by intention to treat analysis. The median PFS and median OS of the curative intent group were 11.9 months (95%CI= 8.99-14.81), and 30.7 months (95%CI= 24.42-36.98) respectively. Upfront resectable patients had longer survival when compared to NACT followed by surgery. Survival outcomes for NACT followed by CCRT were superior to CCRT or SCRT. Both median OS and PFS were found to be superior with surgery plus adjuvant therapy in comparison to definitive CTRT. Long-term survival outcomes were also better with surgical resection. No significant differences in survival outcomes were observed between CCRT and SCRT approaches, likely due to the limited number of patients in the CCRT group. Overall adherence to treatment protocols was 56.7% and adherence to chemotherapy protocols was 50.4%. PS and reception of intended treatment were significant prognostic factors in multivariate analysis for survival. The median PFS and OS of the patients treated with palliative intent were 6.5 months (95% CI: 4.2- 12.7), and 9.1 months (95% CI: 3.1- 15.7) respectively.

Conclusions: Whenever feasible, curative intent treatment should be offered to fit LA- NSCLC patients. Although stage-wise comparison was not performed, it was seen that survival is longer when tumor is resectable. Homogenous treatment protocols and well-equipped cancer facilities must be in place to avoid deviations from standard recommendations.

Keywords: pattern of care study, developing country, locally advanced NSCLC

EP.08.25 CRT Patterns and Short-Term Outcomes on Unresectable NSCLC in Routine Practices in Russia (PASSAT)

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Introduction: Despite the prevalence of unresectable/inoperable locally advanced Non-Small Cell Lung Cancer (LA NSCLC) and wide use of chemoradiotherapy (CRT) as the gold standard there were no real- world data about patients' characteristics, diagnostics approaches, CRT patterns and outcomes in Russia. The study set out to evaluate patients' characteristics and explore the patterns of routine clinical management of LA NSCLC in Russia.

Methods: This is an ongoing multi-center, non-interventional study set out to enroll patients with unresectable/inoperable LA NSCLC (stage II-III, incl. locoregional recurrence and patient's refusal to undergo surgery) receiving CRT in the largest oncology centers in Russia. The primary endpoint was demographic and clinical characteristics of the population. The secondary endpoint was evaluation of diagnostic, treatment approaches and short-term outcomes.

Results: From 31 March 2023 to 22 August 2024, 504 patients (97,4% primary diagnosed) were enrolled from 35 centers. Median age (Q1, Q3) was 65 (60, 70) years. 83,5% were current/former smokers. 91.9% had 0-1 ECOG performance status. 491 patients (97,4%) had primary unresectable NSCLC. Of the enrolled patients 92.1% were diagnosed with Stage III (IIIA 31,55%; IIIB 48,21%; IIIC 12,3%). 73,0% had squamous NSCLC and 24,8% had adenocarcinoma. PD-L1 expression level was evaluated in 26,8% of patients, EGFR - in 47,2%. Concomitant diseases were diagnosed in 79.96% of patients with cardiac (62.5%) and vascular (23.4%) disorders being the most common. CT (94,8%) with further additional PET-CT (61,7%) and fibrobronchoscopy with biopsy/puncture (95,8%) and pathomorphological examination (99%) were the commonly used methods for diagnosis and identification of lymph node involvement. Among 265 (52.6%) patients with N2 invasive staging was performed in 21.5% while 14,3% of patients used both PET-CT and invasive methods. 12,7% of patients with N2 stage whom diagnosis was based only on the CT had bulky or conglomerate lymph nodes. Brain MRI was performed on 49,6% patients. Of the 82,9% of patients without PD, 1.8% had CR, 45.6% - PR, 35.5% - SD. Only 6.4% had PD during or immediately after CRT, and 10.7% patients were unevaluable for response. ORR was reached in 239/504 (47.4%) patients and was higher in the cCRT group (53,1%) than in the sCRT group.

Conclusions: Obtained results will make an important contribution to the necessity of wider use of invasive staging for more precise local disease control and extend cCRT (vs sCRT) use in the routine clinical practice to achieve greater OS in unresectable/inoperable LA NSCLC.

Table 1. CRT Characteristics

CRT Characteristics		
Type of CRT (n = 473), n (%)	Concurrent (cCRT)	309 (65.3)
	Sequential (sCRT)	164 (34.7)
Type of CT (n = 473), n (%)	Induction	80 (15.9)
	Induction + Consolidation	6 (1.2)
	Consolidaion	22 (4.4)
	Not applicable	365 (72.4)
Total number of CT, median (Q1 - Q3)		4 (3–5)
Total RT Dose, n (%)	<54 Gy	45 (9.1)
	54-66 Gy	452 (91.0)
Completed the full course of RT, %		98,6
Interruptions (N = 497), %	Radiotherapy	17,3
	Chemoterapy	9,7

Keywords: Locally Advanced Non-Small Cell Lung Cancer, Chemoradiotherapy

EP.08.26 Blood Inflammatory Biomarkers Dynamics in Neoadjuvant Chemoimmunotherapy vs Chemotherapy Alone in Non-Small Cell Lung Cancer

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Introduction: Immunotherapy can modulate the tumor microenvironment, activating T lymphocytes and reversing immunosuppression, but it can also generate resistance mechanisms and adverse immune-mediated responses by regulating cells such as neutrophils, monocytes, and lymphocytes. Inflammatory response in cancer is also closely related to tumor genesis, disease progression, and patient prognosis. Different inflammatory biomarkers have been proposed as predictors of response to immunotherapy, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and the immune inflammation index (SII). The objective of this study is to explore the evolution of inflammatory markers in patients undergoing neoadjuvant treatment followed by surgery and to determine whether there are differences depending on the addition of immunotherapy.

Methods: A retrospective cohort study was performed in a single center setting between January 2018 to December 2024. Fifty-two patients who were diagnosed with resectable stage IIB-IIIB NSCLC treated with neoadjuvant treatment followed by radical resection were included. Groups were formed between patients treated with chemotherapy alone (ChT) or chemotherapy plus immunotherapy (ChIT). Differences in perioperative characteristics and treatment response were compared. Baseline, post-neoadjuvant treatment and post-surgery neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and systemic immune-inflammation index (SII) were calculated and analyzed for correlation with neoadjuvant treatment groups and level of response.

Results: Both groups had similar percentages of comorbidities, pulmonary function tests, and tumor size. The ChIT group had a higher frequency of squamous cell carcinoma (43% vs. 13%, p=0.023) and a higher frequency of N0 and N1 tumors (25% and 12.5% vs. 0%, p=0.002). Neoadjuvant chemoimmunotherapy was associated with an increased major pathologic response (MPR) and complete pathologic response (cPR) compared to chemotherapy alone (65.6% vs 17.4%, p<0.001; 50% vs 13%, p=0.009). No significant differences were shown after neoadjuvant treatment. No differences were observed in the evolution of inflammatory markers according to the neoadjuvant regimen. Besides, no differences were reported in the progression of markers based on the presence of response to treatment. After surgery, significantly elevated levels of PLR, NLR and SII, and decreased levels of LMR were observed in both groups.

Conclusions: Our study shows no differences in the evolution of inflammatory markers associated with neoadjuvant treatment, regardless of the systemic treatment regimen or the degree of response to it. A significant increase in inflammatory status was observed exclusively associated with surgery as published in previous studies.

Table 1

	Q, N = 18			**Q + I**, N = 29			p-value		
	Before neoadjuvancy	**Before surgery**	**After surgery**	**Before neoadjuvancy**	**Before surgery**	**After surgery**	time	group	interaction
PLR	105.3 (65.8, 151.3)	142.3 (101.5, 378.8)	184 (139.1, 262.7)	135 (73.4, 160.5)	118 (87.5, 168.6)	146.3 (103.6, 203.6)	0.004	0.382	0.090
NLR	2.82 (2.06, 4.06)	2.68 (1.94, 5.85)	8.70 (4.70, 11.40)	3.00 (2.38, 3.39)	1.93 (1.52, 3.24)	5.59 (3.14, 6.75)	<0.001	0.088	0.110
LMR	3.48 (2.87, 4.83)	3.31 (1.33, 4.45)	2.00 (0.91, 3.09)	3.60 (3.00, 4.75)	4.20 (3.25, 4.80)	2.10 (1.50, 3.00)	<0.001	0.332	0.328
SI	726 (465.3, 950.7)	610.4 (407.6, 1344.7)	1685.5 (824.6, 2545.8)	734.9 (577.9, 1056.1)	428.2 (302.3, 616)	910 (716.1, 1358.6)	<0.001	0.194	0.186

	MPR (No), N = 24			**MPR (Yes)**, N = 23			p-value		
	Before neoadjuvancy	**Before surgery**	**After surgery**	**Before neoadjuvancy**	**Before surgery**	**After surgery**	time	group	interaction
PLR	112.9 (76.1, 152.8)	138.2 (98.1, 202.7)	156.8 (106.9, 200.5)	138.2 (72.2, 173.2)	118 (100.3, 180)	161 (114.9, 227.2)	0.017	0.828	0.417
NLR	2.91 (2.54, 3.38)	2.73 (1.91, 3.61)	5.94 (2.93, 112)	37 (2.20, 3.56)	1.93 (1.52, 2.51)	6.18 (4.78, 79)	<0.001	0.453	0.349
LMR	3.83 (2.96, 5.13)	3.98 (3.14, 4.61)	2.33 (1.92, 3.63)	3.40 (2.92, 4.36)	3.50 (2.54, 50)	1.91 (1.24, 2.83)	<0.001	0.204	0.531
SI	671.8 (443.3, 893.4)	545.9 (353, 1142.1)	1087.9 (699.2, 2203)	763.2 (645.8, 1094.7)	449.2 (319.7, 577.7)	1112.3 (868.3, 1608.7)	<0.001	0.628	0.088

Keywords: Neoadjuvant, Immunotherapy, Inflammation

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.27 Exploration of Targeted Sequential Surgery Combined Therapy for ROS1-Rearranged Non-Small Cell Lung Cancer

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Introduction: With advances in molecular subtype-guided precision therapy, the clinical management of ROS1-rearranged non-small cell lung cancer (NSCLC) (incidence: 2.6%) faces new challenges. Approximately 50% of newly diagnosed ROS1-rearranged patients present with stage IV disease. Current research primarily focuses on systemic therapy for advanced stages, while the transformative potential of targeted therapy followed by surgery remains underexplored.

Methods: This retrospective study enrolled 20 ROS1-rearranged NSCLC patients (confirmed by next-generation sequencing, NGS) from Guangdong Provincial People's Hospital (2020-2024) who received first-line tyrosine kinase inhibitors (TKIs) followed by surgery. The median preoperative TKI treatment duration was 5.6 months, with 7 patients undergoing dynamic circulating tumor DNA (ctDNA) monitoring for minimal residual disease (MRD). Primary endpoints included pathological response (major pathological response [MPR]: viable tumor ≤10%), while secondary endpoints were event-free survival (EFS) and safety.

Results: Among 20 patients (10 male, 10 female; median age 41.5 years [range 28-67]), initial staging was I/II/III/IV in 1/4/7/8 cases, respectively. Baseline characteristics were balanced between the crizotinib and entrectinib treatment groups(crizotinib 250mg bid, entrectinib 600mg qd). By RECIST 1.1 criteria, the objective response rate (ORR) reached 100% (17 partial responses [PR], 3 stable disease [SD]). R0 resection under video-assisted thoracoscopic surgery (VATS) was achieved in 19 patients (95%; 1 converted to thoracotomy). Postoperative pathology revealed a pathological complete response (pCR) rate of 20% (4/20) and MPR rate of 50% (10/20). Notably, 70% (14/20) exhibited nodal downstaging, with 40% (8/20) achieving Nx→N0 conversion. Regarding safety, 5 patients experienced treatment-related adverse events during preoperative TKI therapy, including 1 case of grade 3 hepatic impairment, with no surgery delays. Kaplan-Meier analysis (median follow-up: 24.6 months) showed median EFS was not reached. Among 7 patients with MRD monitoring, 3 were MRD-positive preoperatively, but all turned negative 1 month post-surgery. Importantly, the MPR rate was significantly higher in patients receiving ≥3 months of TKI therapy versus <3 months (66.7% vs. 0%, P=0.032), and 75% (3/4) of pCR patients received ≥6 months of treatment. No significant difference in MPR rates was observed between TKI agents (P=1.0).

Conclusions: This study is the first to demonstrate that ROS1-TKI induction therapy enables R0 resection in early-to-intermediate-stage NSCLC patients deemed initially unresectable or potentially resectable in advanced stages, with favorable tolerability and no impact on subsequent TKI sequencing. Dynamic ctDNA monitoring effectively guides therapeutic decisions, recommending preoperative TKI therapy for ≥3 months to optimize pathological response. These findings provide novel evidence for multidisciplinary management of ROS1-positive NSCLC.

Keywords: ROS1 fusion, NSCLC, Inductive treatment

EP.08.28 Referral Rates to Medical Oncology Before Lung Cancer Surgery: A Quality Improvement Study in the Era of Perioperative Chemoimmunotherapy

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Introduction: Fifty percent of all patients with non-small cell lung cancer (NSCLC) are diagnosed with localized (20%) or loco-regional disease (30%). Immunotherapy with checkpoint inhibitors along with chemotherapy administered in the perioperative setting has been shown to decrease the risk of distant relapse and surgical outcomes. A meta-analysis of eight phase 2 and 3 randomized clinical trials demonstrated that neoadjuvant chemo-immunotherapy improves pathologic complete response and two-year event-free survival, regardless of treatment-related factors such as chemotherapy type and PD-L1 status. We present a quality improvement project aimed at increasing rates of referral to medical oncology at Northwell Health/Zuckerberg Cancer Center prior to surgical resection in patients with resectable NSCLC.

Methods: The study included 50 patients with pathologically confirmed stage of IB-IIIB NSCLC who underwent surgical resection January - May 2024. Patient charts were retrospectively reviewed for referral to medical oncology prior to surgery for discussions on neoadjuvant chemo-immunotherapy and whether they were presented at the thoracic tumor board. Pre-intervention findings are presented here. We intend to distribute questionnaires and hold multidisciplinary focus groups to identify the reasons for not referring. Through use of Pareto charts, we aim to identify key factors affecting the referral process and create fishbone diagrams to analyze root causes, and then implement se Pareto charts to identify key factors affecting referrals and fishbone diagrams to analyze root causes, then implement Plan, Do, Study, and Act (PDSA) cycles to test and refine improvements.

Results: Among the 50 patients with stage IB-IIIB NSCLC, 11 (22%) were referred to medical oncology for evaluation of neoadjuvant chemotherapy, and 12 (24%) were presented at the tumor board prior to resection. Table 1 provides a breakdown of each stage of NSCLC. Most of the patients referred to medical oncology pre-operatively had stages IIB-IIIB where the referral rates were up to 40% and even amongst those referred to medical oncology, <55% received neoadjuvant chemoimmunotherapy.

Conclusions: Our study found a reduced rate of medical oncology referrals for stage IB-IIIB NSCLC at a major academic center. Suboptimal utilization of perioperative approach was also reflected in a recent real-world study which reported <3% use of stage I and 40% use at stage III. Our findings highlight the need for quality initiatives to identify potential barriers to optimal management of resectable lung cancer to homogenize with evolving standards. These initiatives may also be appropriate for other institutions given global underutilization of perioperative therapies for resectable lung cancer.

Table 1. Rates of medical oncology and tumor board referral in all patients with pathologic stage of IB to IIIB non-small cell lung cancer.

TNM stage	Med Onc Referral (%)	Tumor Board Present (%)	Neoadjuvant (%)
stage 1b (n=15)	0	0	0
stage 2a (n=2)	0	50	50
stage 2b (n=11)	27	36	36
stage 3a (n=17)	47	52	47
stage 3b (n=1)	0	0	0

Keywords: neoadjuvant, non small cell lung cancer

EP.08.29 Pathologic Response After Neoadjuvant Chemoradiotherapy Versus Chemoimmunotherapy in Resected Stage III-N2 Non-Small Cell Lung Cancer

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Introduction: Neoadjuvant chemoimmunotherapy has shown promising activity in locally advanced non-small cell lung cancer (NSCLC). However, data comparing it with conventional neoadjuvant chemoradiotherapy (nCCRT) in resectable stage III-N2 disease remain limited. This study aimed to evaluate clinicopathologic characteristics and pathologic response following neoadjuvant treatment.

Methods: We retrospectively reviewed patients with clinical stage III-N2 NSCLC confirmed to be EGFR-wild type and ALK-negative, treated between November 2021 and December 2024 at a single institution. Patients received either nCCRT or neoadjuvant chemoimmunotherapy (nCIT), followed by multidisciplinary evaluation for curative-intent surgery. Clinicopathologic variables were compared using t-test or chi-square test. Major pathologic response (MPR) was defined as ≤10% viable tumor, and pathologic complete response (pCR) as no residual viable tumor.

Results: Among the 279 patients included, 229 (82.1%) underwent surgery while 50 (17.9%) did not. Of the 171 patients treated with nCCRT, 146 (85.4%) proceeded to surgery, compared to 83 out of 108 (76.9%) in the nCIT group. In the surgical cohort, baseline characteristics were comparable between groups. PD-L1 high expression (≥50%) was more frequent in the nCIT group (p = 0.009). Minimally invasive surgery (VATS or robotic) was performed in 81.9% of nCIT patients and 35.6% of nCCRT patients (p < 0.001). Lobectomy was the predominant resection type in both groups, and pneumonectomy was rare (p = 0.122). R0 resection was achieved in all patients in the nCCRT group and in 97.6% of the nCIT group (p = 0.091). MPR was observed in 68.7% versus 48.1% (p = 0.034), and pCR in 17.8% versus 28.3% (p = 0.041), for nCCRT and nCIT groups, respectively.

Table 1 . Patients' clinicopathologic characteristics comparing neoadjuvant CCRT group with neoadjuvant chemoimmunotherapy

	Neoadjuvant CCRT (n=146)	Neoadjuvant ChemoIO (n=83)	p-value
Age (yr)	62.7 ± 8.8	63.9 ± 10.2	0.44
Male	123 (84.2%)	67 (79.2%)	0.388
Current smoker	118 (92.6%)	67 (91.8%)	0.91
ECOG (+0)	118 (82.5%)	76 (92.8%)	0.213
Neoadjuvant Duration (days)	27.2 ± 4.5	44.2 ± 8.5	<0.001
Cycle of Neoadjuvant therapy	4.3 ± 1.3	2.9 ± 0.6	<0.001
Total dose of Radiotherapy (Gy)	44	-	
Interval to surgery (days)	38.7 ± 9.5	35.9 ± 11.4	0.118
PD-L1 status			0.277
≥50%	43 (30.8%)	25 (30.1%)	
1-49%	31 (21.2%)	24 (28.9%)	
<1%	70 (47.9%)	34 (41%)	
Histology			0.1
Adenocarcinoma	78 (53.4%)	45 (54.2%)	
Squamous cell carcinoma	57 (39.0%)	33 (39.8%)	
Others	11 (7.5%)	5 (6%)	
Clinical T classification			0.51
T1b	14 (10.3%)	3 (10.3%)	
T1c	25 (18.4%)	10 (34.5%)	
T2a	30 (22.1%)	6 (20.7%)	
T2b	16 (11.8%)	3 (10.3%)	
T3	41 (30.1%)	6 (20.7%)	
T4	10 (7.4%)	1 (3.4%)	
Surgical Approach			<0.001
Minimal Invasive Surgery	52 (25.6%)	68 (81.9%)	
Thoracotomy	94 (64.4%)	15 (18.1%)	
Extent of resection			0.001
Pneumonectomy	6 (4.1%)	1 (1.2%)	
Lobectomy	138 (96.5%)	73 (88%)	
Sublobar resection	2 (1.4%)	9 (10.8%)	
Resection margin (R0)	141 (98.6%)	81 (97.6%)	1
ypT classification			0.329
T0	31 (21.8%)	10 (33.3%)	
T1a	33 (23.2%)	2 (6.7%)	
T1b	22 (15.5%)	2 (6.7%)	
T1c	21 (14.8%)	5 (16.7%)	
T2a	12 (8.5%)	4 (13.3%)	
T2b	8 (5.6%)	2 (6.7%)	
T3	11 (7.8%)	3 (10.0%)	
T4	4 (2.8%)	2 (6.7%)	
ypN classification			0.84
N0	74 (52.1%)	38 (46.3%)	
N1	10 (7.0%)	4 (6.7%)	
N2	58 (40.8%)	38 (46.7%)	
ypM classification			0.808
M0	140 (98.6%)	30 (100.0%)	
M1a	1 (0.7%)	0	
M1c	1 (0.7%)	0	
MPR	92 (68.7%)	37 (51.4%)	0.022
pCR	26 (17.8%)	22 (36.1%)	0.008

Conclusions: Distinct patterns of pathologic response were observed between treatment groups. Neoadjuvant chemoimmunotherapy was associated with a higher rate of pathologic complete response, whereas concurrent chemoradiotherapy led to more frequent major pathologic response. These findings highlight differing biological effects of induction strategies in resectable stage III-N2 NSCLC without targetable mutations. Further follow-up is warranted to evaluate long-term survival outcomes associated with each strategy.

Keywords: neoadjuvant, chemoimmunotherapy, concurrent chemoradiation

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.30 The Outcome of Preoprerative Therapy for Resectable NSCLC Patients With EGFR PACC Mutations

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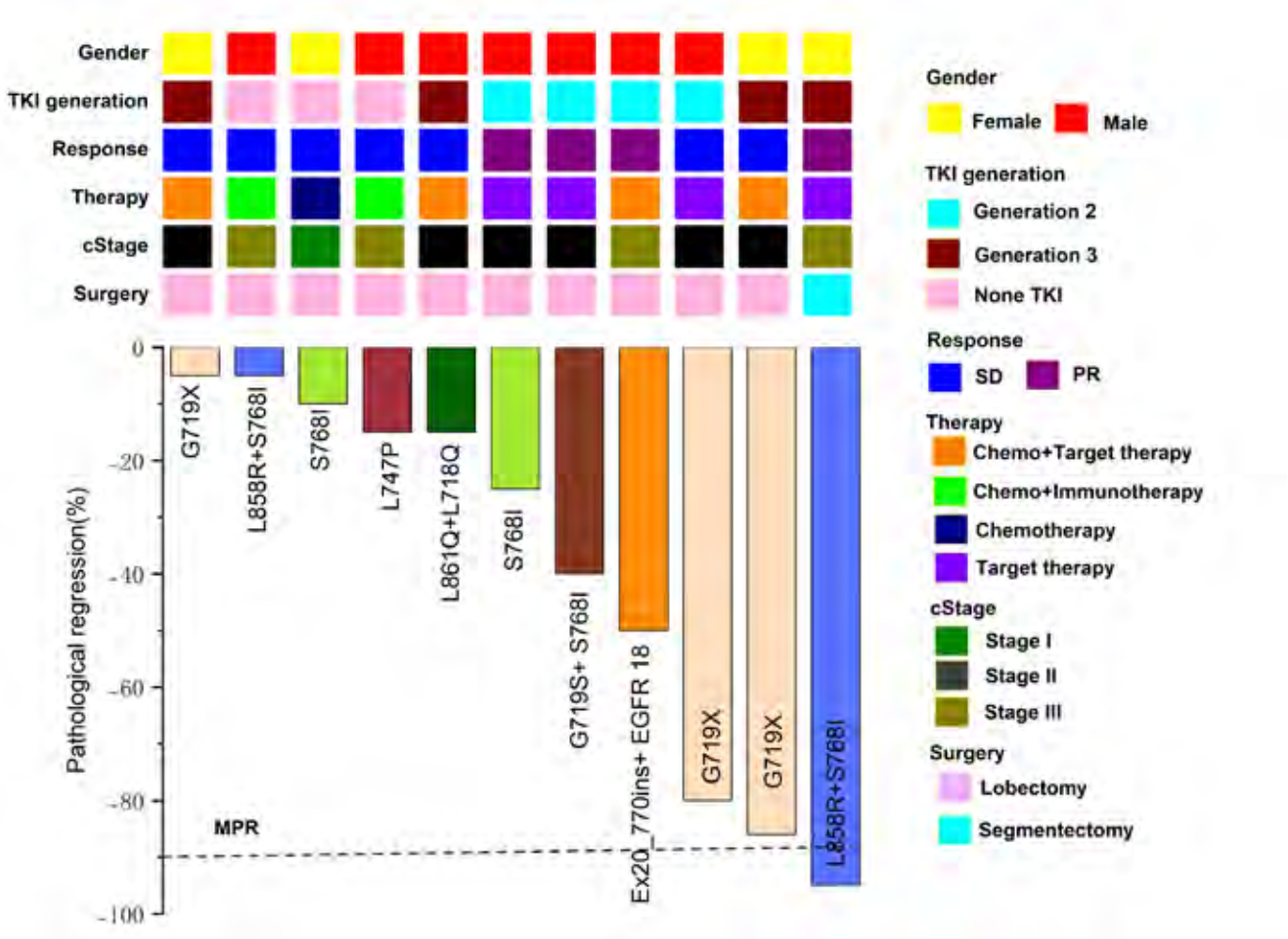
Introduction: The PACC mutation represents a rare subtype among the driver gene EGFR mutations in NSCLC. Second-generation TKIs, such as afatinib, are recommended for treating advanced lung cancer patients harboring this specific mutation. However, there is currently no data regarding preoperative treatment for resectable patients with PACC mutation. This study retrospectively reviewed cases of patients with PACC mutations who underwent preoperative treatment.

Methods: Consecutive patients with EGFR PACC mutations who underwent preoperative treatment and radical resection between 2017 and 2024 were selected from the prospective database of the Department of Thoracic Surgery at Peking University Cancer Hospital. The rates of major pathological response (MPR), pathologic complete response (pCR), and the safety of perioperative treatment in this cohort following neoadjuvant therapy were analyzed.

Results: A total of 11 patients participated in this study, including 7 males (63.6%) with an average age of 61 years; among them, 6 were smokers (54.5%). The clinical stages included stage I in one case (multiple primary lung cancer), stage II in six cases, and stage III in four cases. The specific EGFR mutation sites identified for G719X in three cases, S786I alone in two cases, L858R combined with S786I in two cases, G719S combined with S768I in one case, L747P in one case, and L861Q combined with L718Q in one case. Neoadjuvant treatment primarily consisted of targeted therapy: four patients received targeted therapy alone, four underwent a combination of targeted therapy and chemotherapy, two received chemotherapy combined with immunotherapy, and one was treated with chemotherapy alone. The overall response rate (ORR) for the entire cohort was 36.4% (4/11), while five patients (45.5%) achieved downstaging. The R0 resection rate reached 100% (11/11), as all patients underwent video-assisted thoracoscopic surgery (VATS) for radical lung cancer resection. Assessment results indicated that there was no pathological complete response (pCR) across the group; however, the major pathological response (MPR) rate stood at 9.1% (1/11). Notably, no grade 3 or higher adverse events occurred within the cohort.

Conclusions: The preoperative management of patients harboring EGFR PACC mutations presents a formidable challenge in clinical practice, necessitating the development of innovative treatment regimens to enhance therapeutic efficacy.



Keywords: EGFR PACC Mutation, Preoperative Therapy, Resectable

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.31 Phase II Trial and Correlative Genomic Analysis of Neoadjuvant Sintilimab Plus Chemotherapy in EGFR-Mutant Non-Small Cell Cancer

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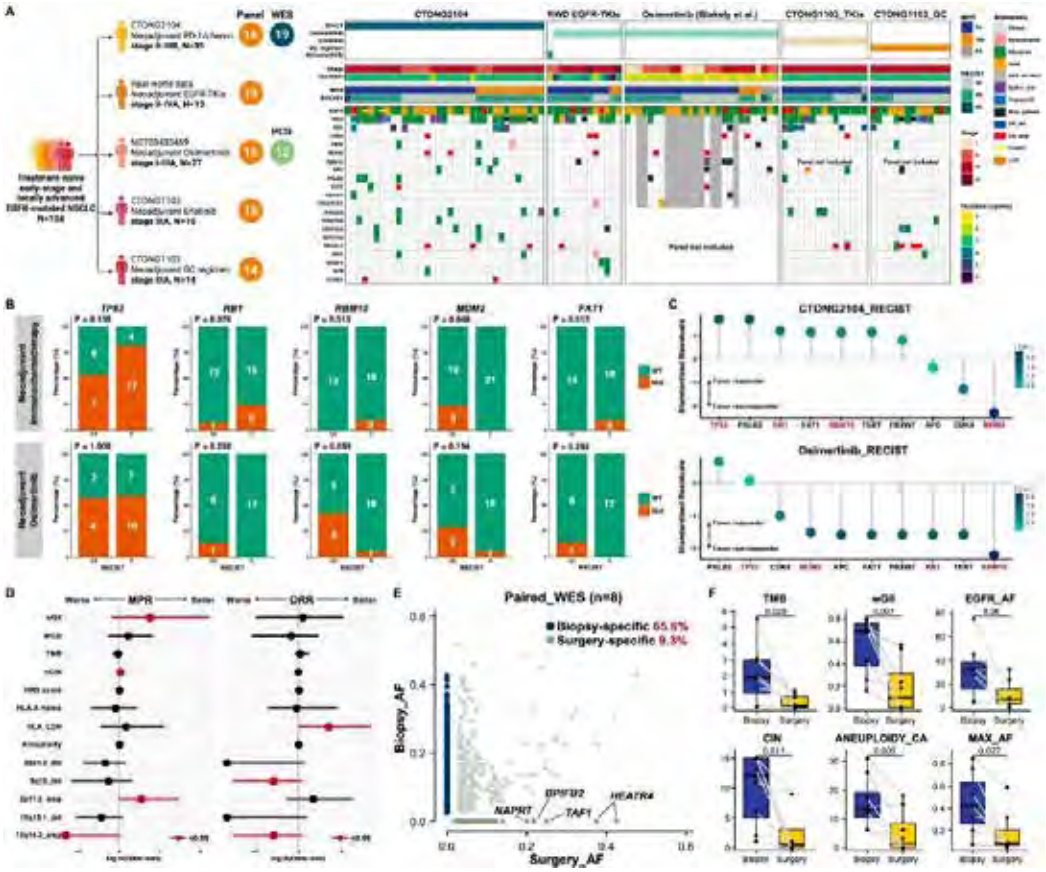
Introduction: We have previously reported the encouraging short-term outcome of the phase 2 prospective trial (NCT05244213). Herein, we report the updated survival analysis as well as an integrated comprehensive genomic analysis with multi-cohorts involved.

Methods: This is an open-label, phase 2 prospective trial with Simon two-stage design. 35 patients with stage IIB-IIIB (N2) and EGFR mutation including non-sensitive mutations were enrolled, and up to 3 cycles sintilimab plus chemotherapy would be provided followed by surgery and observation for stage I cohort or adjuvant osimertinib for stage II cohort. Comprehensive genomic profile of this cohort and other cohorts upon different neoadjuvant treatment modalities were included for subsequent analysis (N=104).

Results: With a median follow-up of 22.5 months for the two-stage cohorts, 12 out of 35 (25.7%) patients experienced disease relapse/progression. The most common relapsed sites were brain (50.0%) and intrapulmonary metastasis (33.3%). The median event-free survival (EFS) was 25.3 months, with 12-month and 24-month EFS rates of 88.6% and 60.0%, respectively. Although there was no significant difference in EFS based on pathological response status, patients who achieved pCR showed a favorable trend in EFS (p=0.27). Specifically, patients with EGFR L858R exhibited better pathological and radiological response as well as survival benefit compared to EGFR 19del and other uncommon subtypes. No overall survival (OS) events were observed so far in this study. For patients who received adjuvant osimertinib or first-line osimertinib after disease relapse, no severe immune-related toxicities were observed with numerically higher incidence of paronychia and ALT/AST elevation when compared with ADAURA. The ORR for those patients who received first-line osimertinib was 87.5%. The most common co-mutations among four EGFR-mutated cohorts were TP53 (60.9%), RB1 (15.2%), RBM10 (9.5%), CDK4 (6.5%) and MDM2 (5.4%). By comparing the radiological response among CTONG2104 cohort, neoadjuvant osimertinib and neoadjuvant erlotinib cohorts, patients with co-mutated RB1 (p=0.29), RBM10 (p=0.06) and MDM2 (p=0.19) tended to not respond well to neoadjuvant EGFR-TKIs while patients with TP53 (p=0.13), RB1 (p=0.37) and RBM10 (p=0.51) co-mutation tended to response well to neoadjuvant immunochemotherapy. Pre-treatment genomic and chromosomal instability could help identify beneficiaries while patients with 12q amplification might not benefit from immunochemotherapy.

Conclusions: Neoadjuvant sintilimab plus chemotherapy yielded encouraging clinical activity in patients with localized EGFR-mutant NSCLC. Comprehensive genomic testing might help inform personalized neoadjuvant treatment strategy. Upfront immunochemotherapy for localized EGFR-mutant NSCLC did not add sever immune toxicity or impact clinical response to adjuvant or first-line osimertinib.



Keywords: NSCLC, Neoadjuvant, EGFR

EP.08.32 Real-World Outcome of Neoadjuvant-Intent Therapy vs Concurrent Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer

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Introduction: Increasingly in real-world practice, some patients with localized or locally advanced non-small cell lung cancer (NSCLC) who would have historically been offered upfront concurrent chemoradiation (CCRT) followed with consolidation immunotherapy are now being treated with a neoadjuvant intent approach (NAI). In clinical trials, rates of not proceeding to surgery after NAI therapy range from 17-22%, and in clinical practice rates will likely be higher.In this retrospective analysis of patients recently treated at a high-volume comprehensive cancer center, we assessed survival outcomes for patients treated with NAI who did not proceed to surgery with those who received upfront CCRT.

Methods: Patients diagnosed with locally advanced NSCLC from 2019 onward were identified through the bioinformatics shared resource at Roswell Park Cancer Institute. Manual chart reviews were conducted to verify demographics, tumor characteristics, treatments, and survival outcomes. Survival outcomes were defined from start of first treatment to progression, death, or last known follow up. Group comparisons were conducted using an unpaired t-test and chi-squared/Fisher's exact test with statistical significance set at $p < 0.05$. Survival outcomes were analyzed using the Kaplan-Meier method.

Results: A cohort of 309 patients with localized or locally advanced NSCLC were identified, of whom 133 received NAI therapy and 95 underwent upfront CCRT. Baseline characteristics are reported in table 1. Within the NAI group, 36 patients (26.5%) did not proceed to surgery, with 18 ultimately completing CCRT. At the time of data lock, with average follow up time of 685 days, median overall survival (OS) was 535 days for NAI patients who did not undergo surgery versus 1177 days for patients receiving upfront CCRT(p = 0.53). Median progression-free survival (PFS) was 449 days in the NAI group versus 843 days in the CCRT group (p = 0.22) (figure 1).

Table 1. characteristics of patients

Characteristic	Neoadjuvant without surgery (N=36)	CCRT (N=95)	P value
Mean Age at diagnosis- yr	65.61	69.30	0.0505
Sex- no %			
Male	16(44.44)	54(56.84)	0.2413
Female	20 (55.56)	41(43.16)	
Smoking status- no (%)			
patient who smokes	19(52.78)	35(36.84)	0.225
Patient with smoking history	17(47.22)	58(61.05)	
Patient who never smoked	0	2(2.10)	
Race-no (%)			
Black	3(8.33)	10(10.53)	0.786
White	33(91.67)	82(86.31)	
Other	0	3(3.16)	
ECOG at baseline- no (%)			
0	12(35.29)	33(36.67)	0.613
1	17(50.0)	51(56.43)	
2	5(14.70)	8(8.70)	
Histology of tumor – no (%)			
Squamous cell carcinoma	19(52.78)	51(53.68)	p>0.99
Non squamous cell carcinoma	17(47.22)	44(46.32)	
Multi-station N2 status -no (%)			
Y	4(23.53)	18(40.0)	0.10
N	13(76.47)	22(59.0)	
PD-L1 expression level-no (%)			
<1%	9(28.12)	25(30.49)	0.93
1-49%	10(31.25)	23(28.05)	
≥50%	13(40.62)	34(41.46)¶	
MDC* discussion occurred-no (%)			
Y	27(75.0)	38(40.0)	0.0005
N	9(25.0)	57(60.0)	
Patients who completed Bronchoscopic Staging -no (%)			
Y	27(75.0)	68 (73.91)	>0.99
N	9(25.0)	24 (26.09)‡	
Patients with salvage CCRT following Neoadjuvant treatment- no(%)			
Y	18(50)		
N	18(50)		

¶17 patients with unknown PD-L1 status

*Multidisciplinary Conference: Weekly Thoracic Oncology "tumor board" consisting of thoracic surgery, thoracic medical oncology, pathology, radiology, radiation oncology, pulmonology and interventional pulmonology representatives.

‡3 patients with unknown bronchoscopic staging

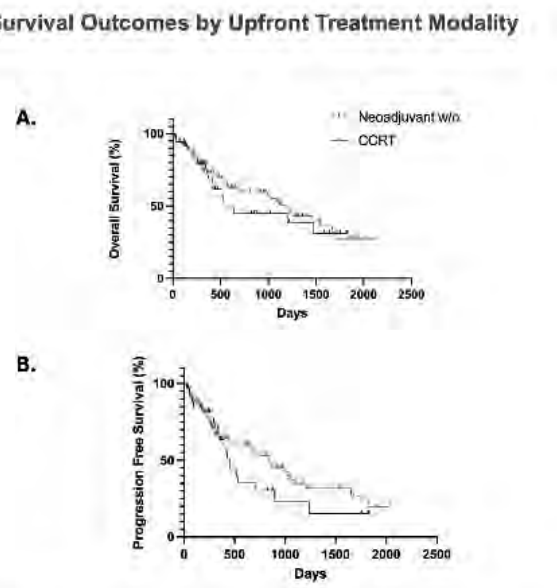

Figure 1: Survival outcomes among upfront neoadjuvant chemoimmunotherapy w/o surgery group vs CCRT. Median Overall survival (OS) (A), was 535 days in the neoadjuvant group vs 1177 days in the upfront CCRT group (p=0.53). Median PFS (B) in the upfront neoadjuvant group was 449 days vs 843 days in the CCRT group(p= 0.22).

Conclusions: Compared to large clinical trials, our institutional experience demonstrates a higher proportion of patients receiving neoadjuvant therapy who ultimately did not proceed to surgery (26.5%), possibly related to high levels of multistation N2 disease in this cohort. There was a numerical trend towards improved survival with CCRT that did not meet threshold for statistical significance. 75% of patients treated with NAI without surgery had at least one case presentation at a multidisciplinary conference (MDC), underlining the importance of close multidisciplinary collaboration in these patients. Our cohort is limited by its retrospective nature and limited follow up time; continuing assessment at our institution is ongoing.

Keywords: neoadjuvant therapy, concurrent chemoradiation

EP.08.33 A Real-World Study of Resectable NSCLC Following Neoadjuvant Immunotherapy: Should Postoperative Adjuvant Immunotherapy Be Recommended?

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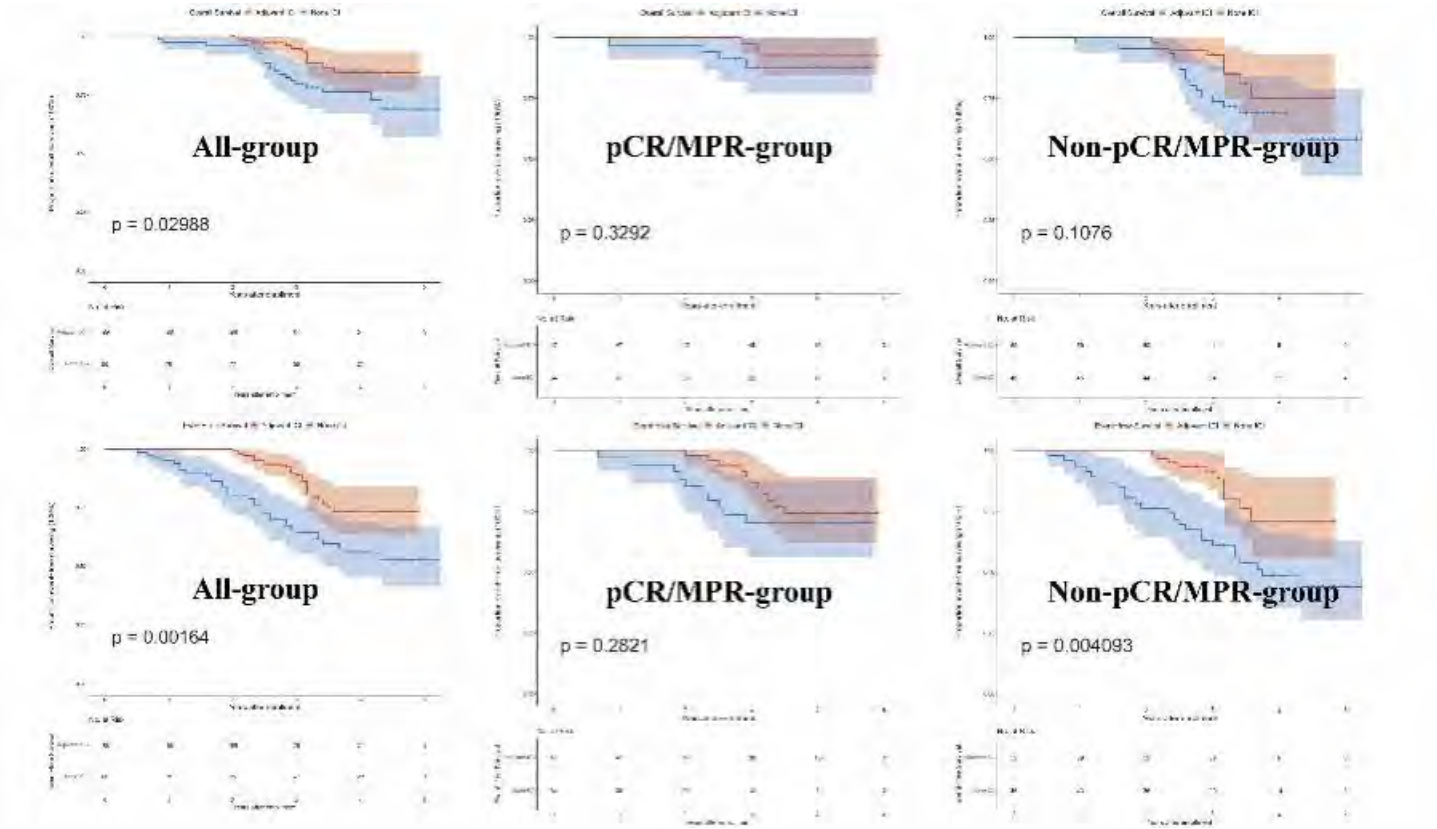
Introduction: This study aims to evaluate the impact of postoperative adjuvant immunotherapy in resectable NSCLC patients who received neoadjuvant chemotherapy combined with immune checkpoint inhibitors (ICIs), focusing on whether extending immune checkpoint inhibition beyond the perioperative period improves survival outcomes.

Methods: A retrospective cohort study was conducted on resectable NSCLC patients treated with NAC combined with ICIs at Zhongshan Hospital, Fudan University, from January 2019 to June 2024. Pathological responses (pCR, MPR, or partial response) were assessed, and event-free survival (EFS) and overall survival (OS) were compared between those receiving postoperative adjuvant ICI therapy and those who did not.

Results: Of 186 patients, 106 received adjuvant ICI therapy and 80 did not. Patients who achieved pCR or MPR showed no significant difference in EFS or OS between the two groups (EFS: p=0.282, OS: p=0.330). In contrast, patients without pCR or MPR experienced significantly improved EFS (p=0.004) with adjuvant ICI therapy, though no clear OS benefit was observed (p=0.108). Multivariable analysis identified age, smoking history, advanced clinical stage, PD-L1 expression, and pathological response as independent predictors of survival. An AI-based decision tree model developed to predict the need for postoperative adjuvant immunotherapy showed strong performance (accuracy: 85%, AUC: 0.82), with key predictors including pathological response, age, clinical stage, and PD-L1 expression. The model suggested that patients with incomplete responses (non-pCR/MPR) were more likely to benefit from adjuvant ICI therapy, and younger patients were more likely to tolerate and benefit from it.

Conclusions: Postoperative adjuvant ICI therapy significantly improves EFS in resectable NSCLC patients, particularly in those without pCR or MPR. However, its impact on OS remains uncertain. These findings suggest the need for personalized treatment strategies, with adjuvant ICI offering greater benefit in patients with incomplete responses. Further prospective studies are needed to clarify its role and optimize treatment sequencing.



Keywords: Resectable NSCLC, Neoadjuvant chemo-immunotherapy, Adjuvant immunotherapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.34 To Resect or Not to Resect: The Evolving Landscape of Definitive Therapy for Stage III NSCLC: Implications for Service Demand in Ireland

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Introduction: Lung cancer is the leading cause of cancer-related mortality in Ireland. Non-small cell lung cancer (NSCLC) constitutes 80-85% of cases, with approximately one quarter presenting with stage III (locally advanced) disease at diagnosis. Traditionally, surgery followed by adjuvant platinum-based chemotherapy was the standard approach for resectable stage III NSCLC, with definitive chemoradiotherapy (dCRT) +/- maintenance immunotherapy. In recent years, several phase III trials have demonstrated a benefit for perioperative chemoimmunotherapy in a subset of patients with stage III NSCLC (EGFR-WT, ALK-WT, PD-L1>1%), based on improved pathologic complete response rates, event-free survival, and overall survival. These advances potentially expand the pool of patients eligible for surgery. In this study, we aim to identify the proportion of stage III NSCLC patients considered eligible for perioperative therapy and surgery, in a tertiary referral centre in Ireland.

Methods: We retrospectively reviewed patients with stage III NSCLC discussed at the Beaumont RCSI Cancer Centre lung cancer tumour board (2012-2023). Patient features, diagnostic testing, treatment and survival (OS) were analysed. Stage was assessed by IASLC TNM version 8, and resectability defined by EORTC consensus criteria and ECOG PS 0-1. Differences in patient features, treatment, and outcome were analysed across three time periods (2012-2015; 2016-2019; 2020-2023).

Results: A total of 422 patients with stage III NSCLC (209 male, 213 female) were identified. Patients with stage IIIA NSCLC accounted for 48% (203/422), stage IIIB 41% (173/422), and stage IIIC for 11% (46/422) of cases. Median OS was 17.4 months for stage IIIA, 13.4 months for stage IIIB, and 7.9 months for stage IIIC NSCLC. There was an increasing proportion of stage IIIA disease over time, rising from 42.7% in 2012-2015 to 50.8% in 2020-2023. Histologically, the majority of patients had non-squamous NSCLC at 54.4% (204/422) followed by squamous NSCLC at 45.6% (171/422). EGFR/ALK/ROS1 were available in 80% of patients with non-squamous NSCLC across all time periods, while PD-L1 was obtained in 69.2% from 2020-2023. dCRT was the primary treatment recommendation for 38.2% (161/422) of patients, with 8.5% (36/422) recommended palliative radiation alone, 20.9% (88/422) palliative chemotherapy alone, and 10.9% (46/422) best supportive care. Surgical resection was recommended for 34% (n=69) of stage IIIA and 9.2% (n=16) of stage IIIB NSCLCs. Applying the 2024 EORTC resectability criteria, would have meant that 66% (n=134) of stage IIIA and 26.6% (n=46) of stage IIIB cases with an ECOG PS of 0-1 could have been considered for surgery.

Conclusions: In this study, we identify that in a large tertiary cancer centre, more than half of historical patients with stage IIIA NSCLC and a quarter of patients with stage IIIB NSCLC patients may have been eligible for perioperative chemoimmunotherapy and curative surgery based on 2024 international recommendations and regulatory approvals. This change in treatment approach will require investment in rapid biomarker and related diagnostic testing, and surgical services. Next steps include conducting an analysis based on National Cancer Registry of Ireland (NCRI) data on stage III NSCLC incidence projections, to evaluate anticipated service demands nationally.

Keywords: Stage III NSCLC, Perioperative Immunotherapy, Resectability

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.35 Accurate Pathologic Response Assessment of Lung Squamous Cell Carcinomatreated With Neoadjuvant Immunochemotherapy therapy

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Introduction: The pathological response assessment system in lung cancer surgical specimens post-neoadjuvant therapy includes the cPRC method recommended by IASLC for all treatment regimens and the immune-related pathologic response criteria (irPRC) for immunotherapy. However, there is a lack of sufficient comparative research data on the application value of these two assessment systems in the pathologic response assessment.

Methods: A total of 83 LSCC patients who received neoadjuvant immunochemotherapy and underwent complete resection at Shanghai Pulmonary Hospital between 2019 and 2023 were enrolled. All surgical specimen H&E sections (778 sections) were digitized using Motic scanning software, and the Aperio ImageScope ×64 software was used to manually annotate the tumor bed, residual viable tumor (RVT), and necrotic areas in the H&E-stained sections. We compared the consistency of the IASLC-recommended calculation method (cPRC method, RVT% = viable tumor cell area / tumor bed area) and the irPRC assessment calculation method (RVT% =A1*S1/S+A2*S2/S+A3*S3/S+·····+An* Sn/S) in evaluating the pathological response.

Results: Using the IASLC multidisciplinary-recommended cPRC and irPRC methods, we assessed the pathological response in 83 LSCC patients treated with neoadjuvant immunochemotherapy. The results revealed that 28 cases (33.7%) achieved complete pathological response (CPR), 28 cases (33.7%) achieved major pathological response (MPR), and 27 cases (32.5%) were classified as non-MPR. For these non-CPR cases, the average absolute difference in RVT% calculated by the two assessment methods was 0.95% (range: 0% to 7.90%). Specifically, 41 cases (74.5%) showed a difference of 0% ≤ |RVT% difference| ≤ 2%, eight cases (14.5%) had a difference of 2% < |RVT% difference| ≤ 4%, and six cases (10.9%) exhibited a difference of |RVT% difference| > 4%. Among the cases with |RVT% difference| > 4%, five were non-MPR patients and one was an MPR patient. The consistency between the two methods in pathological response assessment grouping was excellent, with a Kappa coefficient of one indicating strong agreement.

Conclusions: Both the cPRC and irPRC methods are suitable for assessing pathological response in surgical specimens following neoadjuvant immunotherapy. However, when significant discrepancies in RVT% values exist across different wax blocks, the cPRC method is more significantly impacted in pathological response assessment compared to the irPRC method. Additionally, the irPRC method provides enhanced precision in pathological response evaluation when RVT% approaches the 10% threshold.

Keywords: Manually annotate, Pathologic response, cPRC; irPRC

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.36 Vebreltinib as Neoadjuvant Therapy in Three Cases of MET Exon 14 Skipping Mutation-Positive NSCLC: A Case Series

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Introduction: MET exon 14 skipping mutation were discovered in non-small cell lung cancer (NSCLC) and the efficacy of MET-targeted treatment in these patients has been established. However, neoadjuvant therapy in these patients has limited treatment options.

Methods: Clinical data were obtained from the Shanghai Pulmonary Hospital. Reverse transcription-polymerase chain reaction (RT-PCR) was performed to detect gene mutation. Tumor and adjacent normal tissue were collected during surgery for postoperative pathological assessment.

Results: Three patients were prospectively enrolled. Case 1: A 70-year-old female patient was diagnosed with stage T3N1M0 (IIIA) NSCLC, CT scan revealed a 56.76mm tumor tissue mass in the basal segment of the upper lobe of the left lung with left hilar lymph nodes metastasis. RT-PCR identified a MET exon 14 skipping mutation. The patient was administered Vebreltinib 200mg twice daily. After 4 cycles of treatment, the CT scan showed a 48.4% reduction in the primary lesion volume, shrinking to 29.31mm, and the clinical evaluation was partial response (PR) according to RECIST 1.1. Video-assisted thoracoscopic surgery (VATS) left upper lobectomy was planned following neoadjuvant treatment, but transformed to open thoracotomy due to tissue adhesion during operation. Postoperative pathological examination revealed the residual tumor was 8%, achieving a major pathological response without lymph node invasion, and the postoperative pathological stage was ypT1cN0Mx. The treatment-related adverse events (AE) were decreased leucocyte count, decreased neutrophil count, peripheral edema and rash, which all for grade 2 according to CTCAE 5.0. Case 2: A 61-year-old male patient was diagnosed with stage T4N0M0 (IIIA) NSCLC. CT scan revealed a 57.06mm tumor tissue in the right upper lobe of lung with invasion of the mediastinum. RT-PCR identified MET exon 14 skipping mutation. After administering 4 cycles of Vebreltinib 200mg twice daily, the CT scan revealed tumor shrinkage of 26.4%, and the clinical evaluation indicated stable disease (SD). The patient underwent VATS right upper lobectomy. Postoperative pathological examination revealed a stage of T1cN1Mx with 75% residual tumor cells. There were no other AE except Grade 1 anemia. Case 3: A 62-year-old male patient was diagnosed with stage T4N2M0 (IIIB) NSCLC. PT-PCR revealed MET exon 14 skipping mutation. The patient received Vebreltinib treatment (200 mg bid po) 4 cycles for neoadjuvant treatment. CT images on C4 of the treatment showed 34% shrinkage of the primary tumor, assessed as PR. There were no other drug-related side effects except Grade 2 peripheral edema. This patient is undergoing preoperative evaluation.

Conclusions: These cases highlight the potential therapeutic benefit of MET-targeted therapy as neoadjuvant treatment for MET exon 14 skipping mutation-positive IIIA-IIIB NSCLC. Our findings suggest that highly sensitive MET-TKI may confer clinical benefits for these patients and the toxicity profile is tolerable. However, tissue adhesion should be noted during surgery.

Keywords: Met exon 14 skipping mutation, neoadjuvant, non-small cell lung cancer

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.37 Treatment Strategies for Unresectable Stage IIIA Lung Cancer After Neoadjuvant Therapy

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Introduction: Stage III non-small cell lung cancer (NSCLC) is a heterogeneousdisease and accounts for 22% of all cases of NSCLC. Neoadjuvant treatment in patients with resectable stage IIIA is changing the paradigm of locally advanced disease and is recommended in the major treatment guidelines. However, among patients undergoing neoadjuvant treatment, 7-17% are unable to undergo subsequent surgical treatment. In these patients, management is uncertain.

Methods: This case report highlights three cases of stage IIIA lung adenocarcinoma candidates for neoadjuvant therapy and surgical treatment, in which surgery could not be performed due to patient contraindications, and radical chemoradiotherapy was proposed. Patient data were reviewed confidentially and anonymized for presentation.

Results: Patient A: 73-year-old woman diagnosed in March 2023 with stage IIIA squamous cell lung adenocarcinoma (cT4N1M0). PD-L1 <1%. Neoadjuvant treatment with Cisplatin - Gemcitabine and nivolumab, according to CheckMate 816 trial regimen. Partial response after 3 cycles. Thoracic surgery was proposed, but the patient declined. Finally, sequential radiotherapy was chosen. Carboplatin (AUC 5) and Paclitaxel (175 mg/m^2), followed by 66 Gy of sequential radiotherapy. Partial response after treatment. Last follow-up in February 2025 with maintained partial response. Patient B: 49-year-old woman, diagnosed in May 2023 with stage IIIA lung adenocarcinoma (cT2N2M0). PD-L1 80%. KRAS G12V mutation. Neoadjuvant treatment with Carboplatin - Paclitaxel - Nivolumab, according NADIM II regimen. Stable disease after 4 cycles. Proposed for pneumonectomy but inoperable patient due to cardiac pathology. As an alternative, concomitant chemoradiotherapy (Carboplatino (AUC5) -Paclitaxel (175mg/m^2) plus sequential radiotherapy, 56 Gy total doce) followed by Durvalumab as maintainance treatment, leading to a complete response. Finished Durvalumab in October 2024 maintaining complete response until the most recent follow-up in February 2025.Patient C: 70-year-old man diagnosed in March 2023 with stage IIIA lung adenocarcinoma (cT3N1M0). PD-L1 5%. Neoadyuvant treatment with Cisplatino-pemetrexed- Nivolumab according Checkmate 816 regimen. Partial metabolic response in PET-TC after 3 cycles. Surgical contraindication due to high probability of pneumonectomy and patient comorbidity. Given PD-L1 5%, Pemetrexed - Pembrolizumab was proposed as maintenance. After 3 cycles, complete metabolic response in PET-TC. Proposed for sequential radiotherapy, total dose of 66 Gy. Sustained partial response with Pemetrexed-Pembrolizumab until February 2025.

Conclusions: Neoadjuvant chemoimmunotherapy has demonstrated significant benefits, with nearly 20- 40% of patients achieving complete responses and between 80-90% of patients reaching curative surgery. There is no established evidence regarding the management of patients who remain inoperable after neoadyuvant treatment. Concurrent or sequential chemoradiotherapy followed by consolidation immunotherapy could be a beneficial approach, as evidenced by the clinical cases reported earlier. However, both this approach and other concerns, such as the selection of the appropiate immunotherapy for consolidation (same immunotherapy as in neoadjuvant therapy or different) remain uncertain. Further studies are needed in this area.

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.38 Real-World Data of Adjuvant Therapy With Aumolertinib for EGFR-Mutated NSCLC Patients

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Introduction: Aumolertinib is the first innovative third-generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) in China. In previous clinical trials, it has shown excellent efficacy and safety in advanced NSCLC patients (pts), especially with central nervous system (CNS) metastases. However, there is still lack of research on the adjuvant therapy of pts after radical surgery. Here, we conducted a retrospective real-world study to investigated the efficacy and safety of aumolertinib for stage IA2-IIIB NSCLC after R0 resectiona with EGFR mutations.

Methods: Pts who underwent radical surgery with EGFR-mutant were enrolled and received a daily dose of aumolertinib 110 mg up to 3 years, depended on the pts's pathologic stage and physical conditions. The disease-free survival (DFS), overall survival (OS), safety and tolerability were evaluated.

Results: The study retrospectively analyzed 62 pts with stage IA2-IIIB who underwent radical surgery and were pathologically confirmed to have EGFR mutation (mostly exon 19 deletion or L858R, 6.4% rare mutation; 24% pts with EGFR co-mutations and 16% with TP53 co-mutation). Among them, 21 pts (33.9%) were accompanied by multiple pulmonary nodules.As of October 2024, the median follow-up time was 33.3 months. The 1-year DFS rate was 100%, the 2-year DFS rate was 93.5%, and the 3-year DFS rate was similar to the results of ADAURA study, reaching 84.2%. However, it is important to note that our study included 2 pts (3.2%) with stage IIIB, whereas the AUAURA study excluded this population. In terms of overall survival (OS), both 1-year and 2-year OS rates in this study were 100%. The 3-year OS rate of aumolertinib was 98.3% (2 pts died, one from COVID-19 and the other died in a car accident, both unrelated to lung cancer treatment), compared with 85% for Osimertinib in the ADAURA study. Notably, in further analysis, there was no statistical difference in DFS rates among multiple important subgroups(preoperative multiple nodules vs. Single lesions, p=0.99; Ex19del vs. L858R, p=0.246; with or without TP53 mutations, p=0.38). We observed a total of 33 pts (53.2%) with high-risk factors in postoperative pathology, including poorly differentiated carcinoma, Vascular invasion, pleural invasion, and with micropapillary and solid components, etc. There was no statistically significant difference in DFS rate (p=0.313) and OS rate (p=0.90) among pts with or without high-risk pathological factors after surgery.No grade≥3 adverse events occurred during aumolertinib treatment. The most common side effects were rash and mouth ulceration. No pts withdrew from therapy due to adverse drug reactions.

Conclusions: Our real-world study data reinforces the remarkable effectiveness of aumolertinib as a postoperative adjuvant treatment for NSCLC with an excellent safety profile. Although 5-year OS data were not available in this study, the findings suggest that aumolertinib has the potential to improve pts outcomes.

Keywords: EGFR mutant NSCLC, adjuvant therapy, Aumolertinib

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.39 Adjuvant Therapy With Furmonertinib Significantly Reduces the Recurrence Rate in Lung Cancer Patients With Exon 20 Insertion Mutations

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Introduction: Exon 20 insertion mutations in the EGFR gene are a rare subtype of non-small cell lung cancer (NSCLC) with limited treatment options and poor prognosis. Postoperative recurrence remains a significant challenge in these patients. Furmonertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), has shown promise in targeting exon 20 insertion mutations. We report a series of cases evaluating the efficacy of Furmonertinib as adjuvant therapy in reducing recurrence rates in NSCLC patients with exon 20 insertion mutations.

Methods: We retrospectively identified 5 patients from Shanghai General Hospital who underwent curative surgery for NSCLC with confirmed exon 20 insertion mutations and received Furmonertinib as adjuvant therapy between 2020 and 2024.

Results: The 5 patients had a median age of 73 (range, 41-75) years, with 4 (80%) being female. All patients received adjuvant therapy with Furmonertinib after surgery(One of the patients switched to Sunvozertinib after one year of Furmonertinib treatment). During a median follow-up of 24 months, 1 (20%) patients experienced disease recurrence(the patient who discontinued Furmonertinib midway and switched to Sunvozertinib). The most common adverse events were mild diarrhea (40%) and leukopenia (20%), with no grade 3 or higher toxicities reported. Disease-free survival (DFS) at 2 years was 80%, significantly higher than expected for this mutation subtype.

Conclusions: This case series highlights the potential of Furmonertinib as an effective adjuvant therapy in reducing recurrence rates in NSCLC patients with exon 20 insertion mutations. Further prospective studies are warranted to confirm these findings and to better understand the long-term efficacy and safety of Furmonertinib in this population.

Keywords: exon 20 insertion mutation, Furmonertinib, adjuvant therapy

EP.08.40 Immunotherapy Extended Survival in Patients With Recurrent Pulmonary Pleomorphic Carcinoma Following Surgery

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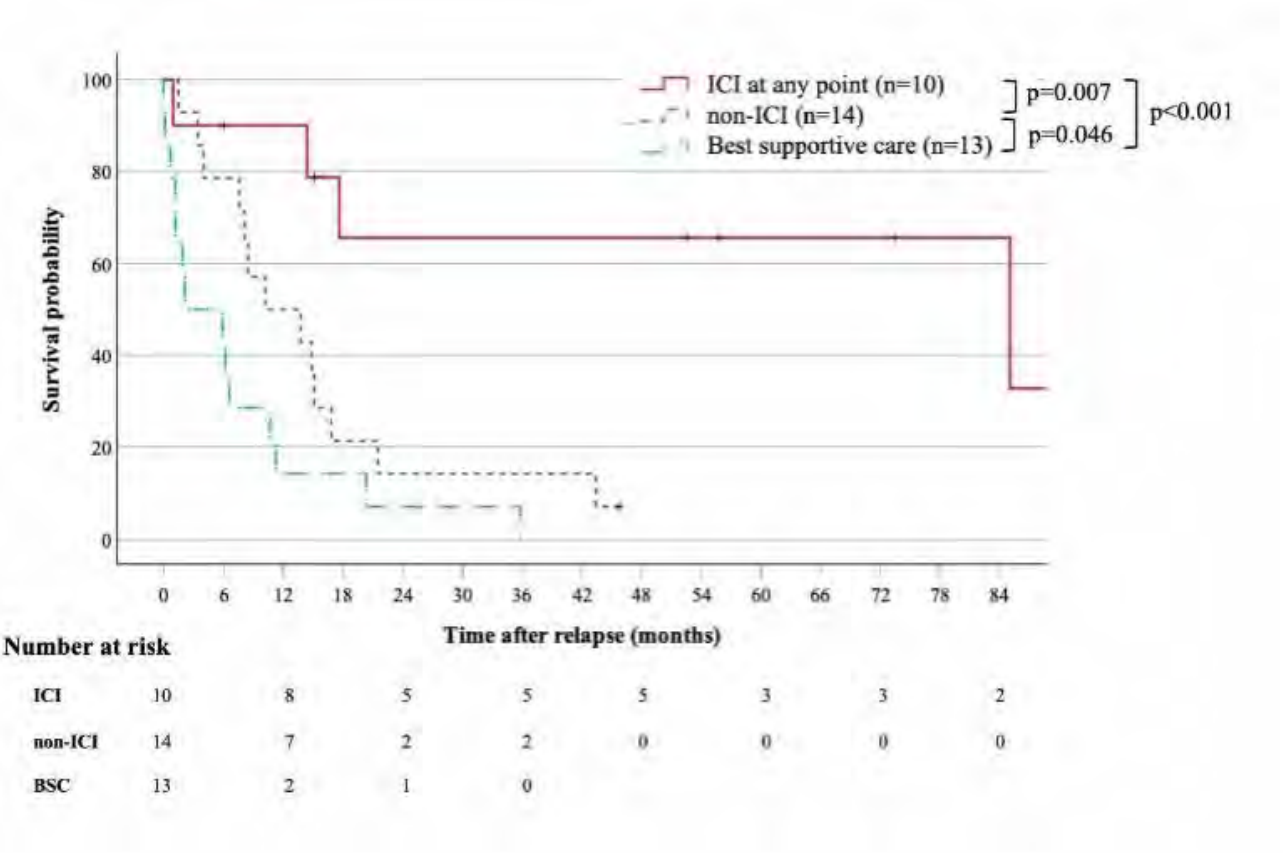
Introduction: Pulmonary pleomorphic carcinoma (PC) is a rare histological type of lung cancer, accounting for approximately 0.4% of all cases, and is known for its aggressive nature. PC is resistant to conventional treatment however, programmed death-ligand 1 (PD-L1) expression in PC is reported to be high in most cases. This study aims to investigate factors associated with recurrence and evaluate the efficacy of ICIs after recurrence in patients with surgically resected PC.

Methods: A total of 71 patients with PC who underwent pulmonary resection at Tokyo Medical University Hospital between 2008 and 2022 were retrospectively analyzed.

Results: The median age at the time of surgery was 71 years (range: 43-85), and the majority of patients were male (59 patients, 83%). 64 patients (90%) had smoking history. The median pathological tumor size was 4.2 (range: 0.4-12.0) cm and pathological stage I/II/III/IV (8th edition) was 17 (24%), 28 (39%), 25 (35%), and 1 (1%), respectively. PD-L1 expression (28-8 clones) was positive in 62 patients (87%), of which 22 patients (33%) showed PD-L1 expression levels of ≥50%. The 5-year overall survival rate was 48.6%.Postoperative recurrence occurred in 38 patients (54%), with a median recurrence-free survival of 19.4 months. Treatment after recurrence was administered to 24 patients (63%), and ICIs were administered to 10 patients (26%). Thirteen patients (34%) did not receive any treatment and 7 of them, due to poor PS by progressive disease.The overall response rate of patients treated with ICIs was significantly higher (5 out of 10 patients, 50%) than that of patients treated without ICIs (1 out of 14 patients, 7%). Among the 5 patients with high responses to ICIs (complete response or partial response), 4 patients showed high PD-L1 expression (≥50%). The 3-year survival rate after relapse was significantly higher in patients treated with ICIs compared to those without ICIs (65.6% vs. 14.3%, Log-rank p = 0.007) (Figure 1).

Conclusions: Recurrence in the early postoperative period and rapid progress of PC were observed and conventional systemic treatment was in effective. ICIs after recurrence in PC improved prognosis compared to other treatment, and favorable outcomes were observed in cases with high PD-L1 expression. Careful postoperative follow-up, and early intervention at the time of recurrence, are crucial for this aggressive type of lung cancer.



Keywords: Pulmonary pleomorphic carcinoma, non-small cell lung cancer, immunotherapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.41 Tislelizumab Combined With Chemotherapy for Conversion Therapy in Stage III-N3 Non-Small Cell Lung Cancer: A Phase 2, Single-Arm Trial

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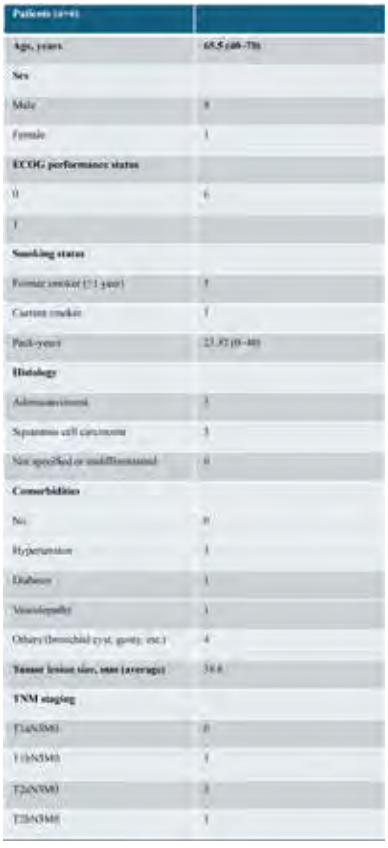
Introduction: Stage III non-small cell lung cancer (NSCLC) is a disease with significant heterogeneity, and selecting an effective treatment strategy is a challenge faced by clinicians. There are already some studies exploring whether surgical treatment is suitable for N3 patients. In recent years, immunotherapy has achieved continuous success in the perioperative treatment of early-stage resectable NSCLC, demonstrating significant tumor shrinkage effects and Event-Free Survival (EFS) benefits. This study is designed to investigate whether technically resectable Stage III-N3 NSCLC patients can be converted to surgically resectable after treatment with tislelizumab (PD-1 inhibitor) in combination with chemotherapy.

Methods: This was an open-label, single-arm, phase 2 trial. Eligible patients were aged 18 years or older with histologically or cytologically documented, untreated Stage III-N3 NSCLC. N3 lymph node metastasis is diagnosed through pathological examination using EBUS (endobronchial ultrasound), EUS (endoscopic ultrasound), thoracoscopy, mediastinoscopy, or fine-needle aspiration biopsy. Patients received conversion treatment with nab-paclitaxel (260mg/m^2) and Cisplatin (75 mg/m^2) or Carboplatin (AUC 5) plus Tislelizumab (200 mg) on day 1 of each 21-day cycle, for 3-4 cycles before surgical resection, followed by standard adjuvant therapy. The primary endpoints were R0 rate, assessed in the intention-to-treat population, and MPR, evaluated in the surgical patients. The Secondary endpoints were pCR, TTDM, EFS, OS, and Surgical-related outcomes. Safety was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov under the registration number: ChiCTR2400081493, and is ongoing.

Results: Between February 2024 to February 2025, we screened 7 patients for eligibility, of whom 6 patients were enrolled and received conversion treatment (Fig 1). Among them, 5 patients completed 4 cycles of conversion treatment, and 4 patients underwent surgery. one case recently completed conversion therapy and evaluated for surgery 4-6 weeks later. All surgical patients achieved R0 resection, and 3/4 achieved MPR, 1/4 achieved pCR. The downstaging rate of T classification after conversion therapy reached 100%, and the downstaging rate of pathological N classification reached 3/4. During the conversion therapy, any treatment-related adverse events were Grade 1-2.

Conclusions: This ongoing clinical study has shown exciting preliminary efficacy. As more data to be collected, surgery following conversion therapy with immunotherapy combined with chemotherapy is becoming a new direction in the clinical research of N3 locally advanced lung cancer.



Keywords: Conversion Therapy, Stage III-N3 NSCLC, Tislelizumab

EP.08.42 A Prognostic Marker for Consolidation Therapy With Durvalumab After Concurrent Chemoradiotherapy in NSCLC: The Utility of Serum CYFRA 21-1

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Introduction: Following concurrent chemoradiotherapy (cCRT), consolidation therapy with durvalumab has become a standard treatment for locally advanced non-small cell lung cancer (NSCLC). However, potential risks associate with durvalumab necessitate the identification of biomarkers to predict patient outcomes. Serum CYFRA 21-1, recognized for its high sensitivity and specificity in detecting squamous cell carcinoma, has been highlighted as an indicator of treatment response and prognosis in advanced NSCLC treated with immune checkpoint inhibitors. However, effectiveness as a prognostic biomarker for consolidation therapy with durvalumab after cCRT in locally advanced NSCLC remains unclear.

Methods: We conducted a retrospective study of patients with locally advanced NSCLC who underwent durvalumab consolidation therapy following cCRT with curative intent, between July 2018 and November 2024. Patients without serum CYFRA 21-1 measurements were excluded. For comparison, serum CEA levels were also measured. The threshold values were established at CYFRA 21-1 ≥3.5 ng/mL and CEA ≥5.0 ng/mL. To assess the overall survival (OS) and progression-free survival (PFS), Kaplan-Meier curves were utilized, and comparisons were made using the log-rank test. Both univariate and multivariate analyses were conducted using Cox proportional hazards models, with statistical significance determined at $p < 0.05$.

Results: A total of 124 patients were analyzed, with a median age of 69 years (range: 40-86). Of these, 95 were male and 29 female. Regarding performance status (PS), 67 patients had a PS of 0, while 57 had a PS ≥1. The histological analyses revealed 47 cases of squamous cell carcinoma and 77 cases of non-squamous cell carcinoma. 66 patients were at stage IIA-IIIA, while 58 were at stage IIIB-IIIC. 9 patients had EGFR mutations. Elevated levels of CYFRA 21-1 were found in 34 patients, and CEA levels were elevated in 59 patients. Patients with elevated CYFRA 21-1 levels had significantly shorter OS compared to those with normal levels (median OS: 45.5 months vs. not reached, $p < 0.05$, hazard ratio (HR) 2.12). No significant difference in OS was observed between patients with elevated and normal CEA levels (median OS: not reached vs. not reached, $p = 0.74$, HR 1.11). Furthermore, the analysis restricted to patients with non-squamous cell carcinoma demonstrated a similar trend (median OS: 45.5 month vs. not reached, $p = 0.104$, HR 2.15). Multivariate analysis which included tumor stage, which represents tumor volume, histological type and CYFRA 21-1 levels showed CYFRA 21-1 emerged as an independent prognostic factor (HR = 2.07, $p < 0.05$). Regarding PFS, the CYFRA 21-1 high group was shorter than that of the normal group (median PFS: 15.7 vs. 31.5 months, $p = 0.08$, HR1.55). PFS was similar between patients with high and normal CEA levels (median PFS: 24.6 vs. 27.6 months, $p = 0.37$, HR1.24).

Conclusions: Serum CYFRA 21-1 levels may be a useful prognostic biomarker for patients with locally advanced NSCLC treated with durvalumab consolidation therapy following cCRT. Considering the analysis restricted to non-squamous NSCLC and results of multivariate analysis, serum CYFRA 21-1 levels may be a prognostic factor independent of histological type and tumor volume.

Keywords: CYFRA 21-1, durvalumab, chemoradiotherapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.43 Surgical Stress After Lung Cancer Surgery Triggers the Outgrowth of Distant Metastases

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Introduction: Patients with lung cancer have a high incidence of tumor recurrence even after curative surgical resection. Some reports have indicated that immunosuppressive cells induced by surgical stress can contribute to tumor recurrence after surgery. Circulating tumor cells (CTCs) float in the blood and reach metastatic sites not only in advanced lung cancer, but also in early stage lung cancer that can be curatively resected. Usually, most CTCs are eliminated by the host antitumor immune response, and only a few become dormant tumor cells. When dormant tumor cells recruit immunosuppressive cells, they begin to grow and metastasize. However, the specific immunosuppressive cells involved have not been identified and their dynamics after surgery are not fully understood.

Methods: We first investigated which immunosuppressive cells are increased in the blood after surgery and correlated with cancer recurrence in patients with non-small cell lung cancer (NSCLC). Next, we established a mouse model of lung cancer recurrence after tumor resection. We then analyzed the mechanisms of post-operative recurrence via immunosuppressive cells using this model.

Results: Using the mouse model of recurrent lung cancer, we showed that the serum level of monocyte chemoattractant protein-1 (MCP-1) increased immediately after tumor resection, subsequently recruiting monocytes from the bone marrow into the blood. These blood monocytes rapidly migrated into distant micrometastases and became tumor growth-promoting tumor associated macrophages (TAMs). Furthermore, even after blood MCP-1 and monocyte levels decreased after tumor resection, TAMs remained enriched in micrometastases because MCP-1 secreted by the micrometastases continued to recruit monocytes around the tumor. Consequently, tumor resection triggers the outgrowth of distant metastases via the MCP-1-monocyte-TAM axis. When we administered an MCP-1 inhibitor to lung cancer recurrent model mice, blood monocytes and TAMs in micrometastases decreased after tumor resection. Finally, peri- and postoperative treatment of model mice with an MCP-1 inhibitor decreased distant metastases after surgery.

Conclusions: To the best of our knowledge, this is the first study to explore the immunological mechanisms and therapeutic potential of the MCP-1-monocyte-TAM axis in lung cancer recurrence. The findings of this study provide the following insights. First, surgery causes dynamic changes in the immune status of both systemic and local metastatic regions. After surgery, CTCs that adhere to metastatic organs recruit an increasing number of blood monocytes that differentiate into TAMs, resulting in metastatic outgrowth. Second, an MCP-1 inhibitor decreases the number of monocytes and TAMs in micrometastases, leading to reduced metastatic recurrence after surgery. Our results suggest that the risk of metastatic recurrence after surgery can be reduced by developing a therapeutic method targeting the MCP-1-monocyte-TAM axis. These results also suggest that increased post-operative blood monocyte levels are a risk factor for tumor recurrence in patients with NSCLC.

Keywords: Surgical stress, monocyte, recurrence

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.44 The Prognosis of NSCLC Patients Who Received Neoadjuvant Immunotherapy

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Introduction: Immune checkpoint inhibitors (ICIs) have been incorporated into diverse neoadjuvant therapy regimens for the treatment of non-small cell lung cancer (NSCLC). Nevertheless, the efficacy of ICIs as a neoadjuvant treatment remains largely unexplored in real-world clinical data.

Methods: Between April 01, 2018 and June 30, 2022, We have retrospectively enrolled 171 NSCLC patients treated with neoadjuvant immunotherapy and subsequent surgery in this cohort study. We performed Cox proportional hazards regression analysis and Kaplan-Meier survival analysis to evaluate the prognosis of patients in this cohort. Subgroup analysis was conducted to evaluate the efficacy of neoadjuvant immunotherapy between different subgroups.

Results: The median follow-up time of patients in our cohort was 23.4 months. Among patients undergoing neoadjuvant immunotherapy, the 1-year overall survival (OS) and event-free survival (EFS) rates were 98.8% and 95.9%, respectively. And the 2-year OS and EFS rates were 96.5% and 91.8%, respectively. We also screened for the beneficial subpopulation for neoadjuvant immunotherapy via the subgroup analysis. Patients who achieved pathological complete response (pCR) have longer survival time than the others. The survival benefits (OS and EFS) were also observed among patients who did not achieve pCR. In addition, we did not observe significant differences in prognosis for patients receiving different types of ICIs.

Conclusions: Neoadjuvant immunotherapy resulted in a favorable prognosis for NSCLC patients, suggesting the potential value of multiple ICIs in the treatment of NSCLC patients.

Keywords: non-small cell lung cancer, neoadjuvant therapy, immune checkpoint inhibitor

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.45 Real-World Long-Term Outcomes of First-Line Pembrolizumab in Advanced NSCLC and PD-L1 =50%: A Systematic Review and Meta-Analysis

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Introduction: Pembrolizumab has revolutionized first-line treatment for advanced non-small cell lung cancer (NSCLC) with high PD-L1 expression (≥50%), but pivotal trials such as KEYNOTE-024 or KEYNOTE-042 often restrict the population to match randomization. These excluded populations, however, reflect those most commonly seen in our clinical practice. Pooled real-world data and long-term outcomes remain crucial to validate the external validity of clinical trial findings and inform treatment decisions for these broader and more representative patient populations.

Methods: We performed a systematic review and meta-analysis of real-world studies reporting outcomes of pembrolizumab monotherapy in patients with advanced NSCLC (non-EGFR/ALK-mutated) and PD-L1 ≥50%, ECOG 0-2. A comprehensive search was conducted in PubMed, Embase, and the Cochrane Library from inception to February 2025 and identified five eligible studies (n = 2,888) that met our inclusion criteria. Analyses were conducted using R software (random-effects model), and heterogeneity was assessed via the I^2 statistic.

Results: Across studies, the mean age was 70.6 years, with 65.6% male and 77.2% identified as current or former smokers. Our meta-analysis reported a pooled mean overall survival (OS) of 22.56 months (95% CI: 19.13-26.56), with individual study means ranging from 19.10 months (Velcheti 2024) to 29.00 months (Cvijic 2023). Mean progression-free survival (PFS), pooled from four studies (n = 1,593), was 12.22 months (95% CI: 5.75-18.70), with study-level means ranging from 7.90 to 22.00 months. These real-world outcomes are notably consistent with KEYNOTE-024 (median OS: 26.3 months).

Conclusions: This is the first meta-analysis to assess long-term real-world outcomes of pembrolizumab in this high-risk population with advanced NSCLC and PD-L1 ≥50%. Our findings suggest that the survival benefits observed in clinical trials may extend to broader and real-world populations, including those typically excluded from randomized studies. These results provide real-world evidence that may support the use of first-line pembrolizumab as a standard treatment option, reaffirming its potential role as immunotherapy in NSCLC with high PD-L1 expression.

Keywords: Non-Small Cell Lung Cancer, Pembrolizumab, Real-World Evidence

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.46 Neoadjuvant Immunotherapy Improves Recurrence-Free Survival in Resectable Non-Small Cell Lung Cancer - a 10-Year Institutional Experience

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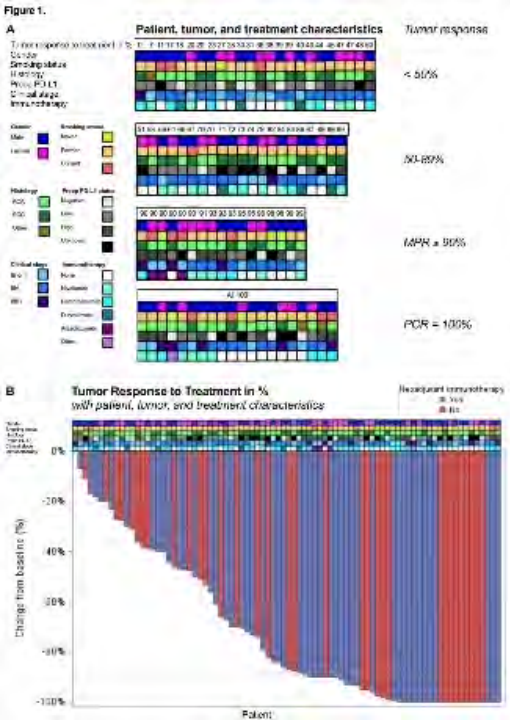
Introduction: Clinical trials have shown improved short-term survival with neoadjuvant immunotherapy + chemotherapy (NAIO) vs platinum-based chemotherapy (CT). Long-term real-world experiences remain understudied.

Methods: Stage IB-IV NSCLC patients who underwent NAIO or NACT and surgical resection at YNHH from October 2015 - January 2025 were included. Demographics, stage, treatment data, pathologic information, and survival outcomes were compared by Chi-square or Fisher's exact test, and Kaplan-Meier survival curves using SAS 9.4.

Results: Among 107 consecutive patents (39 NACT, 68 NAIO), demographics were similar between groups (Table 1). NAIO recipients more often had high PD-L1 expression (30.9 vs 18%, p=0.02). Surgical treatment and pathological outcomes did not differ significantly (Figure 1); however, the NAIO group more frequently received adjuvant immunotherapy (41.2 vs 18%, p=0.01) and the NACT group more frequently received adjuvant radiation (23.1 vs 6%, p=0.01). The difference in overall survival between NAIO and NACT did not reach statistical significance, but the curves diverged notably after 20 months (Figure 2). NAIO patients had a higher likelihood of recurrence-free survival than NACT (0=0.02). PCR was not associated with improved survival.

Conclusions: In this 10-year institutional experience, NAIO recipients had improved recurrence-free but not overall survival compared to NACT recipients, irrespective of pCR.



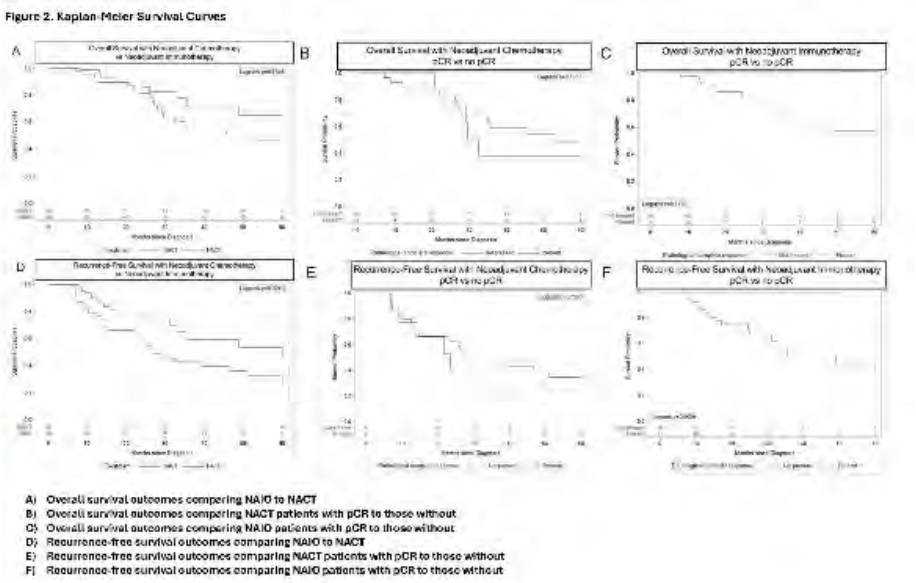


Table 1. Characteristics of Included Patients

Variables	Neoadjuvant chemotherapy (n=39)	Neoadjuvant immunotherapy +/- chemotherapy (n=68)	Total	Chi-square or Fisher's exact test
	n (column %)	n (column %)	n	*p*-value
BASELINE CHARACTERISTICS				
Age				
Median (range) / yrs	64.3 (50-80)	66.5 (38-85)		0.64
<65 yr	23 (59.0)	30 (44.1)	53	
>=65 yr	16 (41.0)	38 (55.9)	54	0.14
Gender				
Male	21 (53.9)	38 (55.9)	59	
Female	18 (46.2)	30 (44.1)	48	0.84
ECOG				
0	16 (41.0)	34 (50.0)	50	
1	19 (48.7)	33 (48.5)	52	
2	4 (10.3)	1 (1.5)	5	0.11
Smoking status				
Never	4 (10.3)	2 (2.9)	6	
Former	28 (71.8)	55 (80.9)	83	
Current	7 (18.0)	11 (16.2)	18	0.27
Pack years				
Median (range) / yrs	30 (0-120)	36 (0-82.5)		0.84
Histology				
ACA	25 (64.1)	36 (52.9)	61	
SCC	13 (33.3)	26 (38.2)	39	0.34
Other	1 (2.6)	6 (8.8)	7	
Pre-op PD-L1 status				
Negative (<1%)	6 (15.4)	17 (25.0)	23	
Low/intermediate (1-49%)	14 (35.9)	24 (35.3)	38	
High (>=50%)	7 (18.0)	21 (30.9)	28	
Unknown	12 (30.8)	6 (8.8)	18	0.02
Clinical stage				
IB or II	10 (25.6)	18 (26.5)	28	
IIIA	22 (56.4)	35 (51.5)	57	
IIIB+	7 (18.0)	15 (22.1)	22	0.85
Platinum-based chemotherapy				
None	0 (0)	8 (11.8)	8	
Carboplatin	16 (41.0)	33 (48.5)	49	
Cisplatin	20 (51.3)	24 (35.3)	44	
Both	3 (7.7)	3 (4.4)	6	0.05
Extent of resection[1]				
Lobectomy or less	28 (71.8)	49 (72.1)	77	
Bilobectomy	6 (15.4)	8 (11.8)	14	
Pneumonectomy	5 (12.8)	11 (16.2)	16	0.80
Sleeve resection[2]	4 (10.3)	8 (11.8)	12	0.81
Surgical approach[3]				
VATS	10 (25.6)	8 (11.8)	18	
RATS	9 (23.1)	24 (35.3)	33	
Open	20 (51.3)	36 (52.9)	56	0.13
Conversion minimally invasive to open[4]	6 (15.4)	5 (7.4)	11	0.19
OUTCOMES				
Positive lymph nodes	12 (30.8)	22 (32.4)	34	0.87
Positive margins	2 (5.1)	2 (2.9)	4	0.62
Pathological response*				
Major	16 (41.0)	23 (36.5)	39	0.56
Complete	9 (23.1)	11 (16.2)	20	0.65
Adjuvant treatment*				
Any	18 (46.2)	34 (50.0)	52	0.70
Immunotherapy	7 (18.0)	28 (41.2)	35	0.01
Chemotherapy	4 (10.3)	7 (10.3)	11	1.00
Radiation	9 (23.1)	4 (6.0)	13	0.01
Other	3 (7.7)	3 (4.5)	6	0.67

1 Lobectomy or less = any type of sublobar lung resection (e.g., wedge, segment) or lobectomy, bilobectomy = either two complete lobes or one complete lobe + sublobar lung resection of an additional lobe
2 Sleeve resection means a more complex lung resection with circumferential excision of involved lung tissue around a bronchus or pulmonary artery branch
3 VATS= video-assisted thoracoscopic surgery, RATS = robotic-assisted thoracoscopic surgery
4 Conversion means that a surgery that was initially started minimally invasively (i.e., VATS or RATS) was converted to an open thoracotomy intraoperatively for any reason. Common reasons include lack of exposure due to scars, or uncontrollable bleeding.
* Percentages do not add up to 100% as variable expressions were analyzed as separate variables.

Keywords: Non-small cell lung cancer, Immunotherapy, Neoadjuvant

EP.08.47 Consolidation Immunotherapy Impact in Non-Small Cell Lung Cancer: A Descriptive Analysis

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Introduction: Consolidative immunotherapy (CIT) after concurrent chemoradiotherapy (CCRT) is the new standard for treating unresectable non-small cell lung cancer (NSCLC) following better outcomes in the Pacific trial. We aim to review our treatment outcomes with this new standard in recent years.

Methods: We have retrospectively analyzed 120 NSCLC patients treated with CCRT between February-2018 and June-2024, all receiving volumetric arc therapy (VMAT) and platin-based chemotherapy. Sixty-seven patients (55.8%) received CIT following Pacific schedule. Toxicity was assessed according to CTCAE 5.0. Overall survival (OS) and progression-free survival (PFS) were analyzed.

Results: With a median follow-up of 27.4 months, median OS (mOS) was 39 months for all patients (95% CI: 28.1 to 49.8). Patients treated with CIT achieved better mOS (46m, 95% CI: 35.7 to 49.4) than those who only received CCRT (34m, 95% CI: 32.1 to 50.3), although not statistically significant (p=0.37). The mPFS was 39 months in CIT group (95% CI: 24.5-53.5), whereas in those who only receive CCRT, it was 13 months (95% CI: 9-17) (p=0.05). Of the 67 patients treated with CIT, 36 (53.7%) couldn´t complete one-year treatment. Eighteen patients prematurely discontinued CIT due to toxicity (50% pneumonitis, 16% hepatitis, 11% nephritis, 11% myopericarditis), 13 due to disease progression, 3 due to intercurrent deaths and 1 due to other causes. Patients who didn't complete 1-year CIT have a mOS of 15 months (95%CI: 10.9 to 19), significantly worse than those who completed it (mOS not reached; OS at 2y: 90.3%) and those treated with CCRT alone (mOS: 34 months; 95%CI: 17.4 to 50.5) (p<0.05). Consolidative immunotherapy administered for 3, 6 or 9 months showed less benefit than completing 1-year treatment.

Conclusions: Consolidative immunotherapy has demonstrated to have a positive impact on survival in NSCLC patients when at least 1-year treatment is completed.

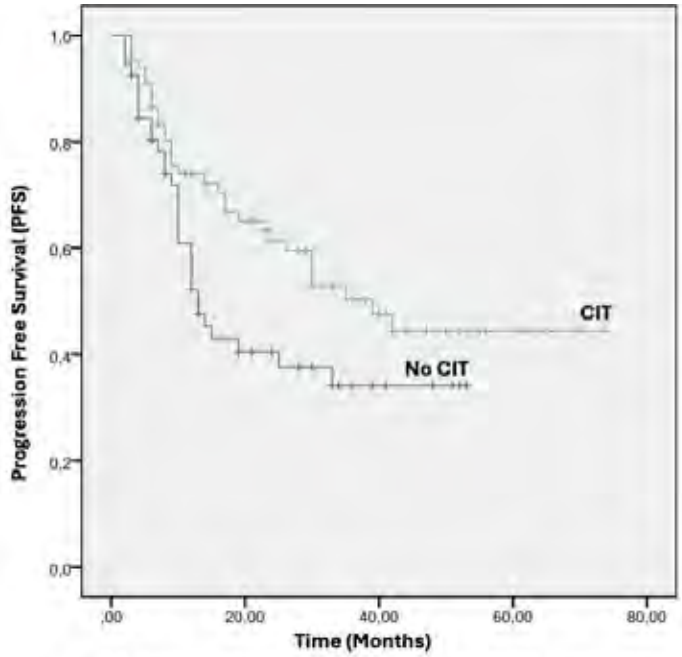

Fig 1. Progression Free Survival (PFS) according to receiving or not receiving CIT.

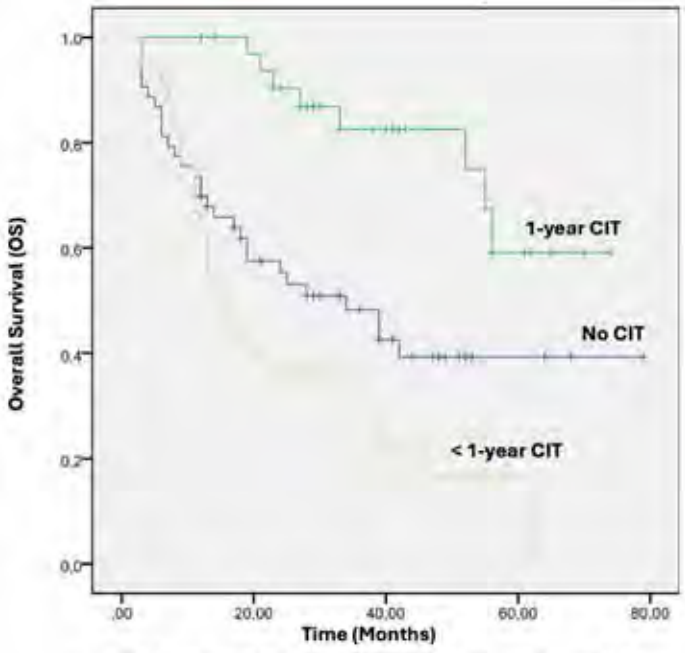

Fig 2. Overall survival (OS) according to receiving 1-year CIT, <1-year CIT or not receiving CIT.

Keywords: Consolidative immunotherapy, Lung cancer, Survival

EP.08.48 PD-L1 Expression and Efficacy of Durvalumab Consolidation in Stage III EGFR-Mutant Non-Small Cell Lung Cancer: A Multicenter Real-World Study

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Introduction: Durvalumab consolidation therapy after concurrent chemoradiotherapy (CCRT) improves outcomes in unresectable stage III non-small cell lung cancer (NSCLC). However, its benefit in patients with epidermal growth factor receptor mutations (EGFR M+) remains controversial, particularly in relation to programmed death-ligand 1 (PD-L1) expression. This study aimed to evaluate the real-world efficacy of durvalumab according to EGFR mutation and PD-L1 expression status.

Methods: This retrospective multicenter study included 249 patients with unresectable stage III NSCLC treated with durvalumab following CCRT across 11 tertiary hospitals in South Korea. Patients were categorized into four cohorts: A (EGFR M-, PD-L1 ≥50%), B (EGFR M-, PD-L1 <50%), C (EGFR M+, PD-L1 ≥50%), and D (EGFR M+, PD-L1 <50%). Progression-free survival (PFS) was the primary endpoint; overall survival (OS) and adverse events were also evaluated.

Results: Among 249 patients, 31 (12.4%) had EGFR M+ NSCLC. Median PFS and OS did not significantly differ between EGFR M+ and M- groups (PFS: 16.6 vs. 18.7 months; OS: 37.4 vs. 35.7 months). Cohort A showed significantly longer PFS compared to cohort D (23.7 vs. 15.2 months; p=0.045). In multivariate analysis, cohort D had a worse PFS than cohort A (adjusted HR=2.27, 95% CI: 1.11-4.66, p=0.025). No significant OS difference was found among the four cohorts. Durvalumab-related adverse events did not differ by EGFR mutation status.

Conclusions: Durvalumab consolidation provided comparable benefit in EGFR-mutant NSCLC patients with high PD-L1 expression (≥50%) to EGFR wild-type patients. However, those with EGFR mutations and low PD-L1 expression showed poorer PFS. These findings suggest PD-L1 may serve as a predictive biomarker for durvalumab efficacy in EGFR-mutant stage III NSCLC, and consolidation therapy should be considered in selected EGFR M+ patients with high PD-L1 expression.

Table 1. Cox regression analyses of progression-free survival in durvalumab-treated patients

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Cohort (Ref: A)				
Cohort B	1.39 (0.92–2.11)	0.117	1.34 (0.88–2.06)	0.173
Cohort C	0.79 (0.28–2.24)	0.664	0.89 (0.3–2.62)	0.834
Cohort D	1.92 (1.00–3.72)	0.052	**2.27 (1.11–4.66)**	**0.025**

The multivariate model was adjusted for age, sex, ECOG PS, smoking status, histology, stage, chemotherapy regimen, and COPD.

COPD, chronic obstructive pulmonary disease; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

Table 2. Cox regression analyses of overall survival in durvalumab-treated patients

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Cohort (Ref: A)				
Cohort B	1.74 (0.99–3.05)	0.055	1.69 (0.95–3.02)	0.074
Cohort C	0.4 (0.05–3.00)	0.372	0.38 (0.05–2.97)	0.358
Cohort D	1.2 (0.44–3.26)	0.72	1.41 (0.48–4.09)	0.53

The multivariate model was adjusted for age, sex, ECOG PS, smoking status, histology, stage, chemotherapy regimen, and COPD.

COPD, chronic obstructive pulmonary disease; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

Keywords: Durvalumab, Lung cancer, Concurrent chemoradiation therapy

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.49 Accurate Pathologic Response Assessment of Lung Adenocarcinoma Treated With Neoadjuvant Targeted Therapy

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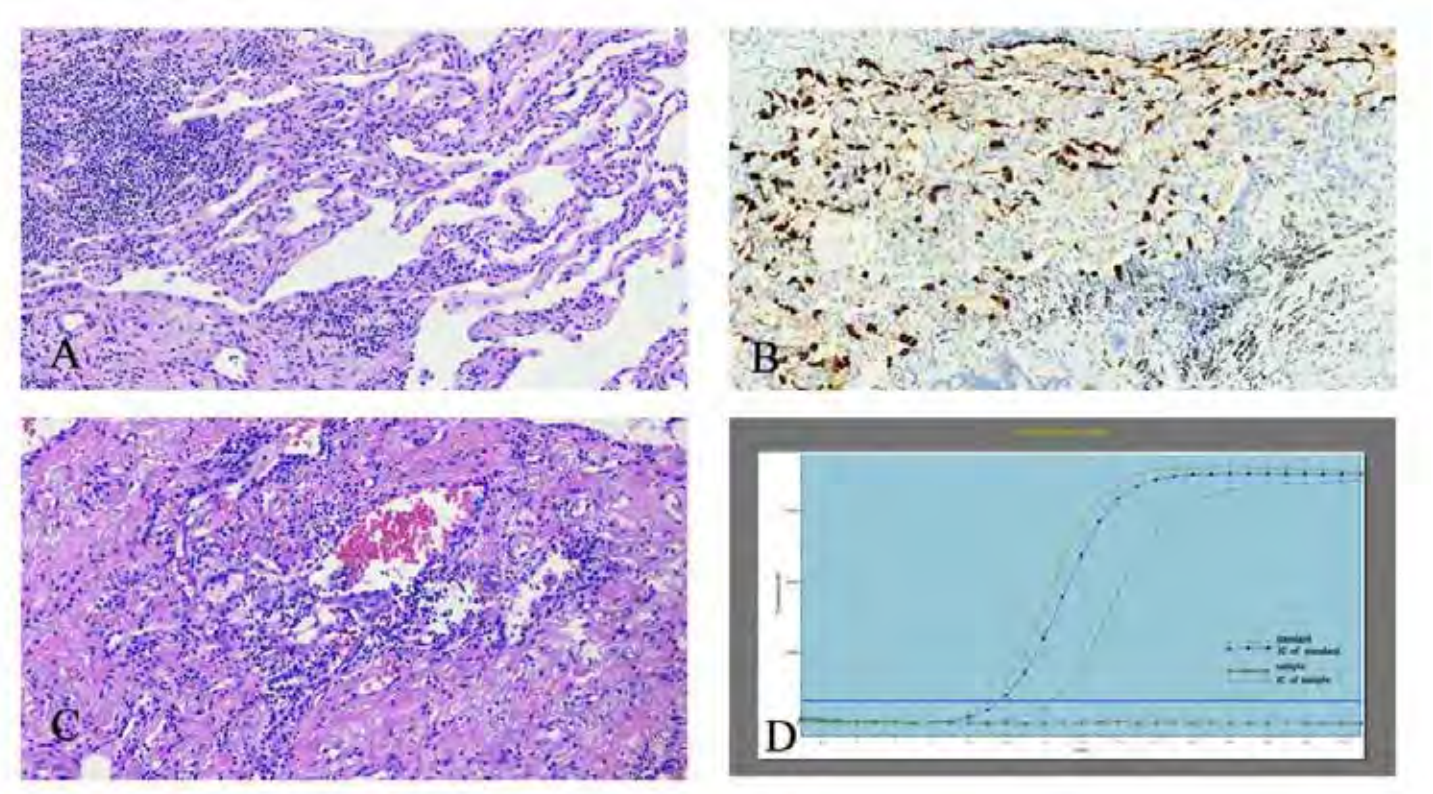
Introduction: Distinguishing the residual viable tumor cells (RVT) from the non-neoplastic reactive proliferative epithelium of neoadjuvant targeted therapy resection specimens is challenging. This study aims to improve the accuracy and reproducibility of assessing residual viable tumor cells (RVT) by integrating H&E staining, immunohistochemical and molecular detection.

Methods: A total of 32 patients who received neoadjuvant targeted therapy and underwent complete resection at Shanghai Pulmonary Hospital between 2018 and 2023 were enrolled. All patients with oncogenic abnormality including ALK rearrangement (n=18), EGFR mutations (n=12), and ROS1 fusions (n=2) were identified pre-treatment. The pathologic response of tumor bed and metastatic lymph nodes (mLN) was evaluated by H&E staining, ALK Ventana-D5F3 immunohistochemistry (for patients with ALK rearrangement) and PCR detection (for patients with EGFR and ROS1 abnormality).

Results: Pathologic response assessment of the 32 patients on H&E images were non-major pathologic response (non-MPR, n=11), major pathologic response (MPR, n=9) and complete pathologic response (CPR, n=12). Among the non-MPR and MPR group, there were 11 patients with ALK rearrangement, eight patients with EGFR mutations, and one patient with ROS1 mutation, respectively. The pathologic response assessment of the tumor bed and mLN was consistent by H&E staining, immunohistochemical staining and molecular detection. In the CPR group on H&E images, there were seven patients with ALK rearrangement, four patients with EGFR mutations, and one patient with ROS1 fusion, respectively. Among the seven patients with ALK rearrangement, four cases showed slightly atypical epithelial cells surrounding the regression tumor bed on H&E images(Figure 1A, 200x), which were confirmed as RVT by ALK(D5F3) immunohistochemistry(Figure 1B, 200x). In the four patients with EGFR mutation, there were two challenging cases where there was controversy as to whether these were neoplastic tumor cells or reactive pneumocyte hyperplasia(Figure 1C, 200x), which were ultimately shown to be reactive changes by PCR detection(Figure 1D, 200x).

Conclusions: In most cases, H&E staining is a simple and time-saving approach to assess the pathologic response of lung adenocarcinoma patients with neoadjuvant targeted therapy. The accuracy and reproducibility of RVT assessment is improved by integrating H&E staining, ALK Ventana-D5F3 immunochemistry or PCR detecting for patients with different oncogenic abnomality.



Keywords: Pathologic response, Targeted therapy, H&E assessment; ALK(D5F3) immunohistochemisty.

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.50 Excellent Response to Osimertinib-Based Regimens in Choroidal Metastasis in Patients With EGFR Exon 19 Deleted Non-Small Cell Lung Cancer a Case Series

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Introduction: Symptomatic choroidal metastasis leading to vision loss is an unusual presentation in metastatic non-small cell lung cancer (NSCLC). Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) approved for first-line treatment for NSCLC patients with exon 19 deletions and L858R epidermal growth factor receptor (EGFR) mutation.

Methods: Here, we describe two cases of patients with EGFR exon 19 deletions and symptomatic choroidal metastasis at baseline who responded to Osimertinib-based regimens.

Results: In case 1, a 66-year-old male presented to the hospital with right-sided vision loss. Visual acuity in the right eye was reduced to 20/200. An ophthalmologic examination revealed a 6 mm x 6mm choroidal mass superior to the optic nerve with an exudative retinal detachment of the right macula. MRI of the brain and orbits with and without contrast demonstrated thickening in the right posterior globe. He was eventually diagnosed with non-small cell lung cancer with liver, bone and choroidal metastasis. A blood-based next-generation sequencing (NGS) panel revealed an exon 19 EGFR deletion. He received systemic therapy with first-line Osimertinib 80 mg once daily with palliative intent. After one month of treatment, his visual acuity improved to 20/30 in the right eye. A detailed eye exam showed complete resolution of subretinal fluid, with shrinkage of the right choroidal mass, consistent with disease response to single agent Osimertinib. In case 2, a 67-year-old female was diagnosed with non-small cell lung cancer with diffuse liver and bone metastasis. While awaiting NGS and PDL-1 results, she received one cycle of chemotherapy. Around the same time, the patient saw an ophthalmologist for worsening vision changes in the left eye for over one month and was diagnosed with choroidal metastasis to the left eye. She could only count her fingers at 1 foot with her left eye. MRI of the orbits showed mild nodular thickening and enhancement of the choroidal layer along the posterior aspect of the left globe, consistent with metastatic involvement. Once NGS results revealed an exon 19 deletion in EGFR, Osimertinib was added to chemotherapy, based on FLAURA-2 trial results. She had a repeat ophthalmologic exam about two weeks after initiation of Osimertinib. By then, her left eye's vision had improved to 20/80. A detailed fundoscopic exam showed resolution of the choroidal metastasis consistent with a quick and excellent disease response.

Conclusions: Osimertinib is a third-generation EGFR TKI currently approved for first-line treatment for patients with EGFR exon 19 deletions and L858R mutation, with and without chemotherapy. Symptomatic choroidal metastasis is an uncommon presentation of non-small cell cancer and represents a therapeutic dilemma. Our above case series provides evidence that osimertinib-based regimens are an effective treatment option for controlling both systemic and intraocular disease burdens, which can replace the need for local therapy.

Keywords: Osimertinib, Choroidal mass

EP.08.51 Impact of KRAS Mutations on Outcomes in Stage III Non-Small Cell Lung Cancer Treated With Chemoradiation and Durvalumab

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[1]Memorial Sloan Kettering Cancer Center, New York/NY/USA ,[2]New York Proton Center, New York/NY/USA

Introduction: KRAS is the most common mutated oncogenic driver in non-small cell lung cancer (NSCLC) of non-squamous histology and is associated with inferior prognosis. Patients with unresectable stage III non-squamous NSCLC harboring KRAS mutations are currently treated with standard concurrent chemoradiation (cCRT) and consolidative durvalumab. Given the association of KRAS mutations with resistance to immunotherapy, we hypothesized that patients with KRAS-mutant non-squamous NSCLC would have inferior progression-free survival (PFS) after cCRT and durvalumab.

Methods: We conducted a retrospective, single-institution analyses of consecutive patients with stage III non-squamous NSCLC who underwent KRAS driver mutation testing with institutional next-generation sequencing (MSK-IMPACT) or other assays. All patients received definitive cCRT and initiated consolidative durvalumab. We estimated PFS and overall survival (OS) from the start of cCRT with the Kaplan-Meier method and compared using the log-rank test. Cumulative incidences of locoregional recurrence (LRR) and distant metastases were estimated for the first progression event with competing risk methodology and compared with Gray's test. For the KRAS-mutant cohort with MSK-IMPACT, top co-mutated genes were summarized.

Results: From 2017-2022, 115 patients met inclusion criteria and 51 were KRAS-mutant (G12C, n=24). The median age was 67 years, 55% were male, and 96% had smoking history. Histology was adenocarcinoma in 102 (89%) patients - 54 (84%) KRAS-wildtype and 48 (94%) KRAS-mutant - and the remaining had unspecified poorly-differentiated carcinomas. Stage was IIIA in 30 (26%), IIIB in 59 (51%), and IIIC in 26 (24%) with more IIIC in KRAS-mutant disease (33% vs 14%, p=0.01). Programmed death ligand 1 (PD-L1) status was high (>50%) in 38 (36%), low (>1-49%) in 24 (23%), negative in 44 (42%), and untested in 9 patients, with no difference by KRAS status. Median PFS was 27 months (95%CI 18-31) overall and 19 months (95%CI 11-30) for KRAS-mutant vs 31 months (95%CI 19-NA) for KRAS-wildtype (p=0.02, Figure 1). There was no difference in OS (p=0.80) or LRR (p=0.34) by KRAS status, but the KRAS-mutant cohort had an increased incidence of distant metastases (2-year: 45% [95%CI 31%-58%]) compared to KRAS-wildtype (2-year: 32%, [95%CI 21%-44%], p=0.03). Of the KRAS-mutant cohort with MSK-IMPACT (n=46), top co-mutations were: TP53 (n=25), TERT (n=10), CDKN2A (n=10), CDKN2B (n=8), and STK11 (n=8).

Conclusions: In stage III non-squamous NSCLC treated with cCRT and consolidative durvalumab, KRAS mutations are associated with inferior PFS and increased incidence of distant metastases. Further research in optimizing treatments for this patient population, including the use of KRAS-targeting therapies, are needed.

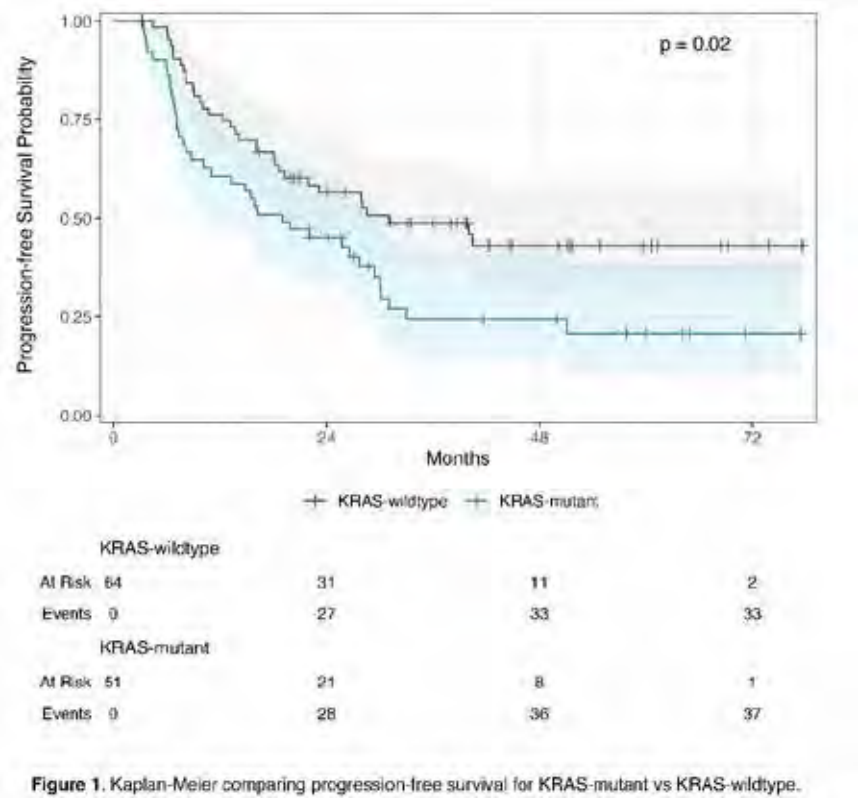

Figure 1. Kaplan-Meier comparing progression-free survival for KRAS-mutant vs KRAS-wildtype.

Keywords: non-small cell lung cancer, KRAS, immunotherapy resistance

EP.08 LOCAL-REGIONAL NON-SMALL CELL LUNG CANCER

EP.08.52 Is Attrition to Surgery Even Less in a Real-World Setting After Neoadjuvant Chemo-Immunotherapy for Non-Small Cell Lung Cancer?

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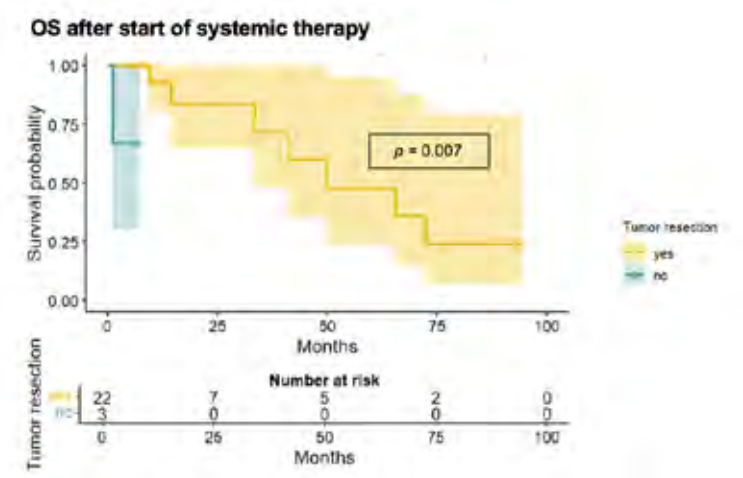
Introduction: Neoadjuvant and perioperative immune checkpoint inhibition (ICI) has been shown to provide excellent outcomes within recently published phase III trials on resectable non-small cell lung cancer (NSCLC). However, high preoperative attrition rates of up to 20% after neoadjuvant ICI remain a central challenge and real-world data that support the treatment protocols are scarce. In this study, we aimed to report real-world data after neoadjuvant and perioperative ICI.

Methods: By review of the prospectively maintained clinical NSCLC database, we identified patients with resectable UICC stage II-III NSCLC of all histologic subtypes who underwent 3-4 cycles of induction ICI (all agents) within a neoadjuvant or perioperative regimen with intended surgical resection between March 2017 and November 2024. Patients treated within ongoing or blinded clinical trials were excluded.

Results: The analyzed cohort of 25 patients included 3 clinical stage IIB, 18 stage IIIA and 4 stage IIIB cases. Clinical T4 disease was present in 12 cases and clinical N2 disease was found in 10 patients. ICI was performed with nivolumab in 15, durvalumab in 6 and pembrolizumab in 4 patients. Attrition to surgery occurred in 12% (progressive disease in 2, cardiac failure in 1 case). 22 patients underwent surgical resection including 14 lobectomies, 3 bilobectomies and 5 pneumonectomies. Surgery was performed minimally invasive in 46% (6 RATS and 4 VATS cases). Surgical complexity was increased due to a high percentage (73%) of patients with hilar fibrosis. R0 resection was achieved in 100% and pathological complete response (pCR) was found in 27%. Among 10 patients with clinical N2 disease who underwent surgery, nodal downstaging to ypN0 occurred in 4 patients (40%). In patients who underwent surgical resection, median EFS was 37 months and median OS was 50 months. Median OS was significantly longer in patients who underwent resection when compared to non-resected patients (50.0 [33.6-72.5] vs. NR [1.2-NR] months; p=0.007).

Conclusions: Our single-center experience, confirms the findings from the phase III trials in a real-world setting and demonstrates R0-resection in 100% of the patients, as well as excellent pCR rates and long-term survival. With a minimally invasive rate of 46%, our results are comparable to the reported MIS rates of the Checkmate 816 trial (39%) and the AEGEAN trial (48%). In our limited sample size, the attrition rate of 12% is lower than the reported rates in clinical trials, nevertheless highlighting the importance of precise patient selection.



Keywords: Immunotherapy, Attrition, Locally advanced

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.01 Feasibility of High Pressure Continuous Positive Airway Pressure to Reduce Respiratory Motion in Thoracic Irradiation

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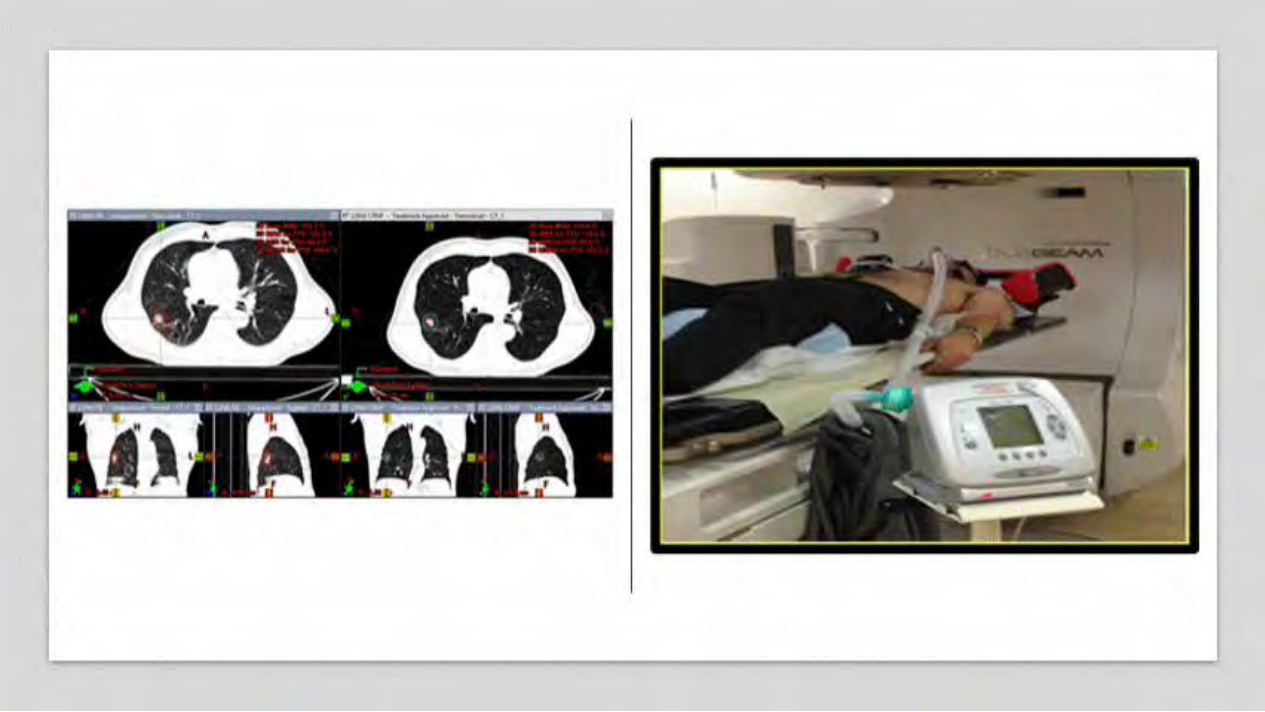
Introduction: Motion management in Lung radiotherapy (RT) can be challenging with no one standard solution. Reducing the tumor motion and reducing the radiation to the lungs are goals of motion management and can improve tumor control and reduce toxicity compared to treating in free breathing. We have previously studied high pressure Continuous Positive Airway Pressure (HP-CPAP) ventilator as a new method for motion management. HP-CPAP increases lung volume in passive manner and reduces tumor motion and thus reduces dose to the lungs and heart in thoracic and breast RT. have shown that using high pressure (HP)-CPAP-ventilator to pressure of 15cm H2O during RT treatment can decrease intrathoracic organ motion and reduce tissue irradiation. Here we study the safety and of compliance regular use of HP-CPAP in patients receiving thorax compared with breast RT.

Methods: Our database included cases treated with RT to lung, mediastinum and breast with HP-CPAP at Sheba Medical Center. Data extracted from electronic medical files included indication for RT, fractionation, compliance and toxicity with HP-CPAP. We grouped patients according to treatment indications and radiation techniques using breast RT as reference.

Results: Between 2014-2024, 404 patients received 512 courses of HP-CPAP RT/SBRT delivered in 4816 fractions. The cohort included 105 breast RT pts., 209 SBRT, pts., and 90 fractionated-RT pts., of them 37 received concomitant-chemotherapy-RT (CCRT). Compliance with breast RT and SBRT was excellent (1-1.9% discontinuation). Most interruptions occurred when receiving fractionated RT to the chest or mediastinum (n=9/90, 10%), particularly in combination with chemotherapy (CCRT) (n= 8/37 21.6%). 13 refused HP-CPAP prior to RT due to discomfort or chest pain. Fourteen patients (3.5%) discontinued CPAP after starting RT due to toxicity that may be related to CPAP including presyncope/weakness (n=3), syncope (n=2), dyspnea (n=2) hypertension (n=2), hoarseness (n=1), or discomfort (n=4).

Conclusions: Compliance of HP-CPAP for respiratory motion management in thoracic and breast RT was excellent, with minimal complication rate. Most interruptions occurred in CCRT group. HP-CPAP can be used as one of the options for motion management.



Keywords: motion manegment, CPAP ventilator, thoracic radiation

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.02 Consolidative Hypofractionated RT for Oligometastatic NSCLC

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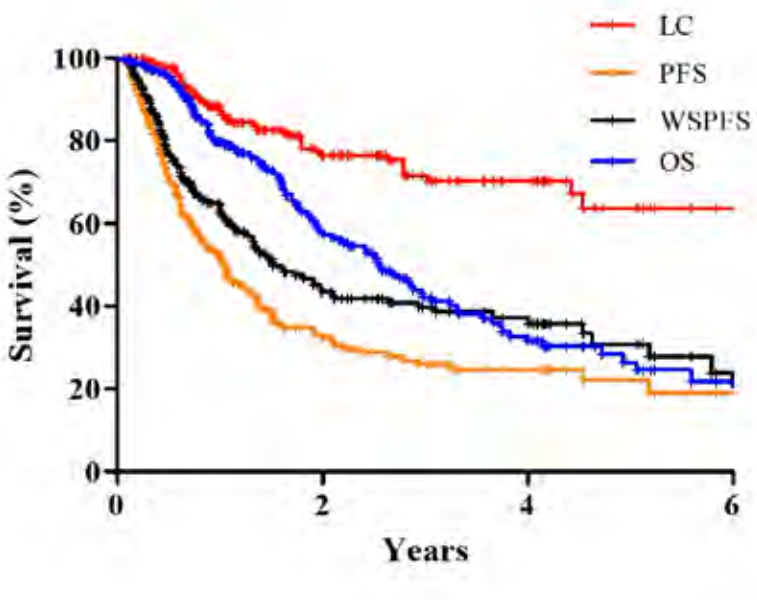
Introduction: This study aimed to evaluate the role of consolidative hypofractionated radiotherapy in the management of oligometastatic non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed patients who received consolidative hypofractionated radiotherapy for oligometastatic NSCLC at Kyungpook National University Chilgok Hospital between 2013 and 2024. Hypofractionated radiotherapy was defined as a biologically effective dose (BED) of ≥ 50 Gy delivered in fewer than 10 fractions. A total of 216 patients (267 radiotherapy sites) met the inclusion criteria. Treatment outcomes, including local control (LC), progression-free survival (PFS), widespread PFS (WSPFS), and overall survival (OS), were analyzed.

Results: The median time to oligometastasis from diagnosis was 1.6 years. Patient disease status was categorized as synchronous (23 patients, 10.6%), metachronous/repeat (118 patients, 54.6%), or induced (75 patients, 34.7%). Oligometastatic sites were predominantly lung (207 lesions, 77.5%) and regional lymph nodes (22 lesions, 8.2%). Various dose fractionation regimens were employed, with 48 Gy in 4 fractions (52 lesions, 19.5%), 50 Gy in 4 fractions (47 lesions, 17.6%), and 60 Gy in 4 fractions (31 lesions, 11.6%) being the most common. The median BED was 105.6 Gy (range, 51.3-151.2 Gy). One-year LC, PFS, WSPFS, and OS rates were 87.3% (median, not reached), 51.2% (median, 1.0 year), 62.6% (median, 1.5 years), and 80.0% (median, 2.6 years), respectively (Figure 1). Grade ≥ 2 radiation pneumonitis occurred in 13 patients (6%) but was safely managed in all cases.

Conclusions: Consolidative hypofractionated radiotherapy for oligometastatic NSCLC can achieve good local control and may offer survival benefits with acceptable toxicity.



Keywords: Consolidative radiotherapy, Oligometastasis, Non-small cell lung cancer

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.03 Survival and Neurotoxicity of WBRT Vs. SRS in Individuals With Brain Metastases From Lung Cancer: Retrospective Study

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[1]RadioSerra Radiation Therapy, Petrópolis - RJ/BR ,[2]Petropolis Medical School - FMP, Petrópolis - RJ/BR ,[3]Centro de Terapia Oncológica, Petrópolis - RJ/BR

Introduction: Brain metastases (BM) in individuals with lung cancer significantly impact prognosis and quality of life. This retrospective study analyzes survival outcomes, treatment patterns, toxicity profiles, and predictive factors influencing treatment efficacy and safety in patients treated at our institution between 2020 and 2025. Additional variables, including detailed dosimetric parameters, tobacco exposure history (pack-years), and extracranial metastasis patterns, were incorporated to enhance predictive modeling.

Methods: A retrospective review of 208 lung cancer patients identified 53 (25%) with BM. Data collected included demographics, ECOG performance status, smoking burden (median 55.3 pack-years), tumor staging, number and volume of brain metastases, extracranial disease burden, and treatment modalities (Whole Brain Radiotherapy [WBRT], Stereotactic Radiosurgery [SRS], and Stereotactic Body Radiotherapy [SBRT]). Dosimetric parameters such as D95% (mean 6307.8 cGy), D98% (mean 1928.4 cGy), heterogeneity index (HI: 0.09), and volume irradiated (V5%: 1.62%, V20%: 0.17%) were analyzed for correlation with outcomes and toxicity (CTCAE v5.0). Kaplan-Meier methods and Cox proportional hazards models were applied for survival and correlation analyses.

Results: The median age was 66.4 years (range: 29-87), with an equal gender distribution. Among BM patients, 27.5% received WBRT, 17.6% underwent SRS, and 54.9% had concurrent extracranial metastases. Metastases outside the CNS were found in 37.4% of patients, while 25% had exclusive BM.Median overall survival (OS) was estimated as 8.0 months (95% CI: 5.6-10.4) for SRS compared to 4.9 months (95% CI: 3.5-6.3) for WBRT (p=0.04). One-year survival rates favored SRS (35%) over WBRT (18%) (p=0.03).Improved OS correlated with:

Higher ECOG performance status (0-1) (HR 0.55, p=0.02)Smaller BM volume (HR 1.45, p=0.01)Lower extracranial metastatic burden (HR 1.62, p=0.005)

Dosimetric analysis revealed that higher HI (mean: 0.09; range: 0.045-0.14) and increased total radiation dose were correlated with higher rates of neurotoxicity (p=0.02). V5% (mean: 1.62%) and V20% (mean: 0.17%) were predictive of increased lung toxicity. Grade 3-4 neurotoxicity occurred in 15% of WBRT patients vs. 5% in SRS patients (p=0.01). Higher cumulative radiation exposure correlated with increased treatment-related toxicity.

Conclusions: SRS provides superior survival benefits and reduced neurotoxicity compared to WBRT in carefully selected lung cancer patients with BM. The inclusion of dosimetric parameters, pack-years, and extracranial disease burden enhances the prognostic model, emphasizing the need for personalized treatment approaches. These findings reinforce the role of SRS as the preferred treatment when clinically feasible. Patient selection based on performance status, lesion volume, smoking burden, and extracranial disease involvement is critical for optimizing outcomes. Further prospective trials are needed to refine treatment decision-making.

Keywords: Brain Metastases, whole brain radiotherapy, stereotactic radiosurgery

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.04 Ablative RT Use and Systemic Therapy Duration in Metastatic EGFR-Mutated NSCLC: A Population-Based Analysis

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Introduction: Advances in systemic therapy have improved survival for patients with EGFR-mutated non-small cell lung cancer (NSCLC). Randomized trials have shown that adding stereotactic body radiation therapy (SBRT) to EGFR-targeted tyrosine kinase inhibitors (TKIs) may improve progression-free survival (PFS) and overall survival (OS). Prospective studies also suggest that SBRT to oligoprogressive sites may prolong the duration of the same line of systemic therapy. This study evaluates these outcomes in a real-world setting using a population-based healthcare administrative database.

Methods: We analyzed data from the provincial Institute for Clinical Evaluative Sciences (ICES), a repository of linked health administrative databases, identifying all patients diagnosed with non-squamous NSCLC between 2002 and 2022, in Ontario, Canada. Eligible patients received EGFR-targeted therapy with Gefitinib or Osimertinib, with treatment start/stop dates and radiotherapy (RT) data recorded. Patients younger than 18 or those with a prior cancer diagnosis within five years of NSCLC diagnosis were excluded. SBRT was defined as any radiotherapy course delivering ≥5Gy per fraction in ≤8 fractions to non-cranial targets, except for single-fraction treatments ≤8Gy. Patients who received SBRT during EGFR-targeted therapy were classified in the SBRT cohort, while all others comprised the palliative RT cohort. The primary outcome was the duration of first-line systemic therapy from time of systemic therapy initiation. Baseline and treatment characteristics were summarized descriptively, and OS was estimated via the Kaplan-Meier method from the date of drug start. Propensity score matching using logistic regression adjusted for baseline factors influencing systemic therapy duration, including age, sex, rurality index, Charlson and Elixhauser comorbidity indices, income quintile, and treatment year. A sensitivity analysis excluded patients treated before 2013, since ~90% of patients were treated after this year.

Results: A total of 898 patients met inclusion criteria, with 185 receiving SBRT and 713 receiving palliative RT. SBRT use increased in later years (2019-2022). The median duration of first-line systemic therapy was 683 days in the SBRT cohort versus 400 days in the palliative RT cohort ($p < 0.001$). Median OS was 35.3 months (95% CI 27.2-77.5) for SBRT and 23.1 months (25.4-32.4) for palliative RT ($p < 0.01$ log rank test). After excluding patients treated before 2013, 797 patients remained (SBRT: 171, palliative RT: 626). Median first-line systemic therapy duration was 692 vs. 393 days, respectively ($p < 0.01$), and median OS was 35.6 (95% CI 31.4-41.2) vs. 23.1 months (95%CI 21.2-24.5) ($p < 0.01$ log rank test). After propensity score matching (n=364, 184 per cohort), standardized mean differences were balanced (<0.1). The SBRT cohort maintained a longer median first-line therapy duration (683 vs. 431 days, $p < 0.01$) and improved median OS (35.3 vs. 23.7 months) ($p < 0.01$ log rank test).

Conclusions: SBRT was associated with prolonged first-line systemic therapy duration and improved OS compared to palliative RT in stage IV EGFR patients treated with targeted therapy. These findings remained consistent after propensity score matching and sensitivity analysis. SBRT may help extend the effective duration of systemic therapy in carefully selected patients.

Keywords: SBRT, Osimertinib, EGFR

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.05 Efficacy and Prognostic Factors of Radiotherapy in Brain Metastases From Non-Small Cell Lung Cancer Patients:A Retrospective Study

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Introduction: To evaluate the efficacy of radiotherapy and prognostic factors in non-small cell lung cancer with brain metastases (NSCLC-BM).

Methods: This retrospective study included 113 NSCLC-BM patients treated with standard cranial radiotherapy at Guangdong Provincial People's Hospital (January 2020-October 2024). Prognostic factors (demographics, KPS score, metastasis features, molecular markers, GPA score, and radiotherapy parameters) were analyzed. Primary and secondary endpoints were intracranial progression-free survival (iPFS) and disease control rate (DCR), respectively. Statistical analyses included Cox regression, Kaplan-Meier, and log-rank tests.

Results: With a median follow-up of 7.7 months, 49 patients (43.4%) experienced endpoint events. Median iPFS was 9.2 months (95% CI: 7.53-16.6), with 6-, 12-, and 18-month iPFS rates of 63.0%, 42.7%, and 38.0%, respectively. Univariate Cox analysis identified brain lesions ≥3 cm (HR=2.632, P=0.016), age ≥60Y (HR=1.921, P=0.028), KPS >2 (HR=6.345, P=0.001), GPA ≤2 (HR=2.070, P=0.020), spinal metastases (HR=22.255, P=0.006), single dose >3 Gy (HR=2.037, P=0.015), total dose <30 Gy (HR=1.757, P=0.049), and biologically effective dose (BED) ≥40 Gy (HR=1.867, P=0.032) as predictors of reduced iPFS. Multivariate Cox analysis confirmed KPS >2 (HR=11.362, P=0.001), lesions ≥3 cm (HR=7.356, P=0.004), spinal metastases (HR=21.957, P=0.036), and BED ≥40 Gy (HR=11.484, P=0.034) as independent risk factors. Increased brain metastases (2-3, ≥4) correlated with reduced iPFS (HR=3.425, P=0.016). Only KPS >2 correlated with reduced DCR (OR=4.727, P=0.027).

Conclusions: KPS >2, brain lesions ≥3 cm, number of brain metastases >1, spinal metastases, and BED ≥40 Gy are independent predictors of worse intracranial control and shortened iPFS post-radiotherapy.

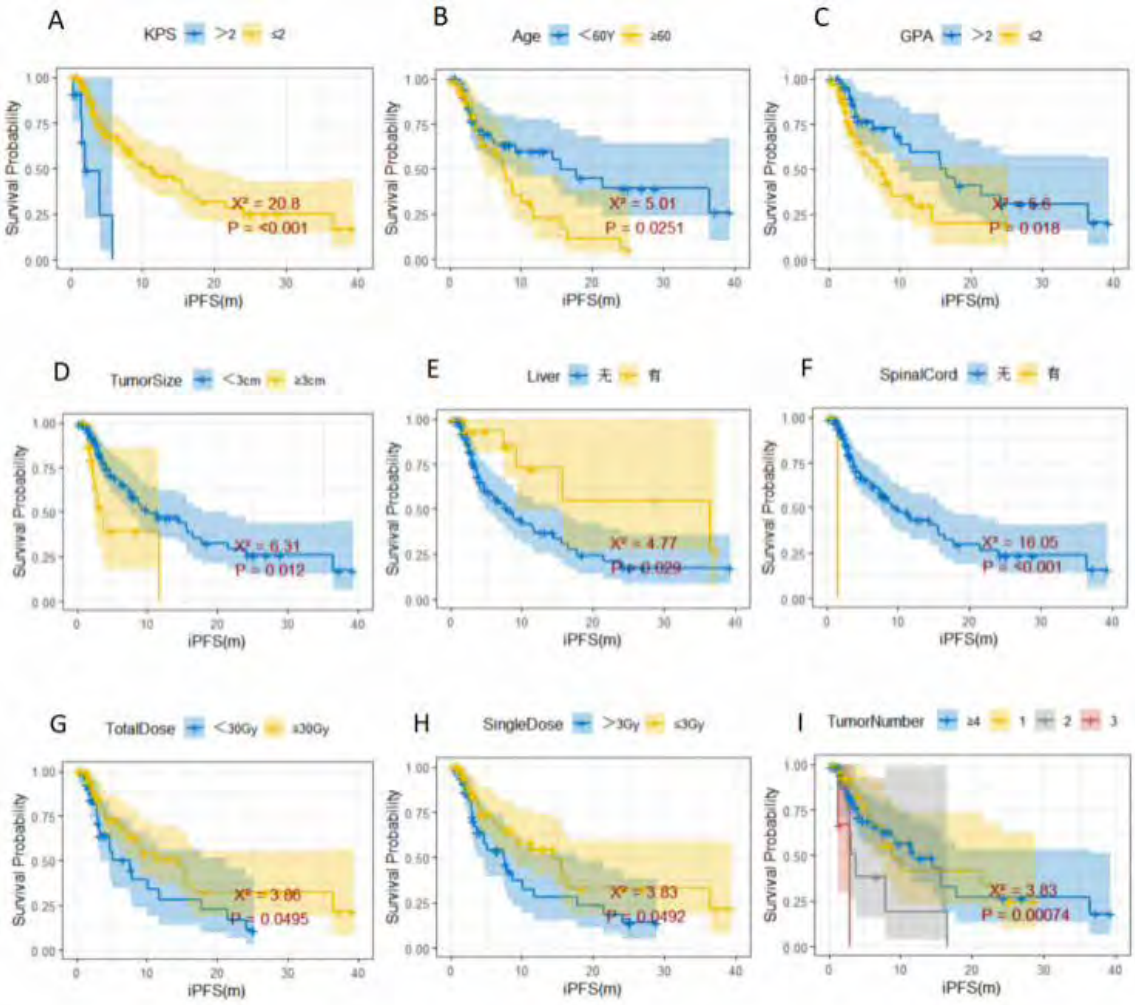

Figure 1 Survival curves of various clinical factors and intracranial progression-free survival of patients with Non-small cell lung cancer with brain metastasis

Table 1 Comparison of intracranial progression-free survival rate between clinic opathological factors groups

Clinical factors	Groups	Median iPFS (m)	95% CI	iPFS			X2	P value
				6 (m)	1 2 (m)	1 8 (m)		
KPS	≤2score	11.43	7.9-17.73	0.684	0.46	0.316	20.8	0.001
	>2score	1.93	1.57-NA	0	0	0		
Age	<60Y	15.53	9.20-NA	0.665	0.599	0.449	5.01	0.0251
	≥60Y	7.67	4.67-11.7	0.597	0.228	0.114		
GPA	>2score	16.6	10.03-NA	0.765	0.593	0.41	5.6	0.018
	≤2score	7.53	4.7-NA	0.544	0.299	0.199		
Tumor Size	<3cm	10.03	7.67-17.73	0.673	0.469	0.322	6.31	0.012
	≥3cm	3.8	2.3-NA	0.394	0	0		
Liver Metastasis	Yes	36.5	9.2-NA	0.933	0.727	0.545	4.77	0.029
	NO	7.9	5.17-15.5	0.572	0.368	0.245		
Spinalcord Metastasis	NO	9.2	7.53-16.6	0.642	0.432	0.297	16.05	0.001
	Yes	1.53	NA-NA	0	0	0		
TotalDose	≥30Gy	14.47	8.67-NA	0.708	0.508	0.323	3.86	0.0495
	<30Gy	7.67	3.4-21.53	0.503	0.283	0.227		
SingleDose	≤3Gy	14.46	8.9-NA	0.713	0.546	0.328	3.83	0.0492
	>3Gy	7.53	4.67-17.7	0.538	0.279	0.232		
TumorNumber	One	8.9	5.8-NA	0.665	0.415	0.415	3.83	0.00074
	Two	3.76	2.96-NA	0.381	0.19	0		
	Three	3	1.3-NA	0	0	0		
	≥Four	11.7	8.67-NA	0.687	0.486	0.27		

Keywords: Non-Small Cell Lung Cancer with Brain Metastases (, Graded Prognostic Assessment (GPA), Biologically effective dose (BED)

EP.09.06 Consolidative High-Dose Thoracic Radiotherapy in NSCLC Without Progression After First-Line Systemic Therapy With ICIs

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Introduction: Consolidative thoracic radiotherapy (CTRT) demonstrated to improve oncological outcomes in patients with advanced and metastatic non-small-cell lung cancer (NSCLC) that did not progress after first-line chemotherapy (CT). However, potential toxicity and clinical benefit of high-dose CTRT in patients treated with prior immune checkpoint inhibitors (ICIs) are yet to be defined. This study aims to investigate clinical results of CTRT in patients with NSCLC and previously treated with (CT-)ICIs.

Methods: Patients treated at our Institution with CTRT after first-line systemic treatment with (CT-)ICIs were retrospectively analyzed. Primary endpoint was acute lung toxicity (≤6 months from CTRT completion). Secondary endpoints were local failure free survival (LFFS), progression free survival (PFS) and overall survival (OS).

Results: A total of 40 patients treated from 2019 to 2024 were included (Table 1).

Table 1. Patients and treatment characteristics

Patients, n		40
Sex, n (%)	Female	11 (27.5)
	Male	29 (72.5)
Age, median (range)		69 (44-84)
BMI, median (range)		25.1 (18.3-33.6)
Performance status, n (%)	ECOG 0	19 (47.5)
	ECOG 1	19 (47.5)
	ECOG 2	2 (5.0)
Stage, n (%)	Locally advanced	18 (45.0)
	Metastatic	22 (55.0)
Histology, n (%)	ADK	32 (80.0)
	SCC	6 (15.0)
	Other	2 (5.0)
COPD, n (%)	Yes	8 (20.0)
	No	32 (80.0)
Smoking history, n (%)	Yes	38 (95.0)
	No	2 (5.0)
Cycles of ICIs before CTRT, median (range)		7 (1-31)
ICI type, n (%)	PD-1 inhibitors	36 (90.0)
	PD-L1 inhibitors	4 (10.0)
Concurrent systemic therapy, n (%)	Yes	20 (50.0)
	No	20 (50.0)
ICIs after CTRT, n (%)	Yes	25 (62.5)
	No	15 (37.5)
Cycles of ICIs after CTRT, median (range)		5 (0-19)
Radiation EQD2 (Gy), median (range) *		51.5 (42.3-70.0)
Radical CTRT schedule, n (%)	54-60 Gy/30 fractions	9 (22.5)
	55 Gy/20 fractions	4 (10.0)
	51 Gy/17 fractions	4 (10.0)
	Others	4 (10.0)
Subradical CTRT schedule, n (%)	45 Gy/15 fractions	15 (37.5)
	Others	4 (10.0)
CTV volume (cc) , median (range)		121 (5.5-560)
PTV volume (cc) , median (range)		243 (24.3-1025)
MLD (Gy), median (IQR) ^		7.5 (0.8-17.4)
V20 (Gy), median (IQR) ^		11.1 (2.4-32.8)
V5 (Gy), median (IQR) ^		33.9 (3.5-77.6)

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group Performance Status; ADK: adenocarcinoma; SCC: squamous cell carcinoma; COPD, chronic obstructive pulmonary disease; ICIs: immune checkpoint inhibitors; PD-1: programmed death 1; PD-L1: programmed death ligand 1; CTRT, consolidative thoracic radiotherapy; EQD2: equivalent dose in 2 Gy fractions; CTV, clinical target volume; PTV, planning target volume; IQR: interquartile range; MLD: mean lung dose; Vx: volume of lung receiving ≥ xGy.
* Assuming an α/β of 10.
^ Following conversion of all dose-fractionation schemes to EQD2 based on the linear-quadratic model, assuming an α/β of 3.

NSCLC presentation was locally advanced not-suitable for definitive radio-chemotherapy and low-burden metastatic in 18 (45%) and 22 (55%) cases, respectively. ICIs were PD-1 inhibitors in 36 (90.0%) patients administered for a median of 7 cycles (range 1-31) prior to CTRT. Radical and subradical CTRT was administered in 21 (52.5%) and 19 (47.5%) patients, respectively, at a median Equivalent Dose in 2 Gy Fractions (EQD2) of 51.5 Gy (58.4 Gy radical and 48.8 Gy subradical CTRT). Acute radiation pneumonitis (aRP) G≥2 rate was 30%, occurring at a median time of 2 months (95% CI 2-4 months) from CTRT, with G3 and G5 aRP observed in 4 (10%) and 1 (2.5%) patients, respectively. aRP G≥2 occurrence correlated with number of pre-CTRT ICIs cycles (7.5 % ≤6 cycles vs 22.5% ≥7 cycles, p = .09), but not with CTRT prescribed dose (15% radical vs 15% subradical, p = .84). Considering all pulmonary acute adverse events (radiation-induced, ICI-induced, infectious, and/or multifactorial pneumonitis), G≥2 rate was 35%, with G3 and G5 toxicities observed in 10% and 7.5% of patients, respectively. At a median estimated follow-up time of 31.6 months (95% CI 23.6-55.0 months), overall local control (LC) was 77.5%, with a 1- and 3-year LFFS rates of 86.1% (95% CI 75.5-98.2%) and 71.9% (95% CI 56.2-92.1%), respectively. Median PFS and OS were 20.2 months (95% CI 9.6 months-NR) and 30.2 months (95% CI 16.1 months-NR), respectively.

Conclusions: In patients with advanced NSCLC that did not progress after first-line systemic therapy with ICIs, high-dose CTRT is associated with promising oncological outcomes and acceptable aRP rate. A careful monitoring of all pulmonary acute adverse events should be recommended.

Keywords: Consolidative high-dose thoracic radiotherapy, Advanced NSCLC, Immune checkpoint inhibitors

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.07 Cardiac Dosimetry and Clinical Outcomes in Individuals With Lung Cancer Undergoing Thoracic Radiotherapy: Retrospective Study

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Introduction: Cardiac radiation exposure has emerged as an independent prognostic factor in thoracic radiotherapy (RT) for individuals with lung cancer. Increased cardiac doses have been associated with higher rates of non-cancer-related mortality and decreased survival. This study investigates the relationship between cardiac dosimetric parameters and clinical outcomes in persons receiving RT for lung cancer.

Methods: A retrospective review was conducted of 211 individuals with lung cancer treated at a single institution between 2020 and 2025. Clinical data included demographics, treatment modality (RT alone, chemoradiotherapy, or RT combined with immunotherapy/targeted therapy), and clinical endpoints: overall survival (OS), progression-free survival (PFS), and metastasis incidence. Cardiac dosimetric parameters collected included V5%, V20%, V35%, V50%, and V60%. Survival analyses were performed using Kaplan-Meier estimates and Cox proportional hazards models. Differences in cardiac dosimetry between individuals who survived and those who did not were assessed using Mann-Whitney U tests.

Results: The median age was 66.4 years (range: 29-90). Treatment modalities included RT alone (58%), concurrent chemoradiotherapy (30%), and RT with immunotherapy or targeted therapy (12%). Among the 35 individuals with available cardiac dosimetric data, the mean cardiac exposures were: V5% 1.62% (±7.02%), V20% 0.17% (±0.13%), V35% 0.15% (±0.19%), V50% 0.093% (±0.14%), and V60% 0.034% (±0.064%). No statistically significant associations were observed between cardiac dose-volume parameters and OS or PFS. However, persons who survived exhibited numerically higher V5% exposure compared to those who did not survive (2.37% vs. 0.54%, p = 0.24). Similar non-significant trends were noted for V20% and V35%. Most individuals were exposed to low cardiac radiation doses, consistent with modern treatment planning standards and the use of cardiac-sparing techniques

Conclusions: Although no statistically significant associations were observed, the data suggest a trend toward improved outcomes with higher V5% exposure—possibly reflecting treatment selection bias or an underpowered subgroup analysis. These findings support further prospective evaluation of cardiac dosimetric thresholds in thoracic RT. Ongoing efforts to minimize cardiac exposure remain essential, and techniques such as IMRT, VMAT, and proton therapy should be considered standard in advanced-stage lung cancer RT planning.

Keywords: Cardiac Dosimetry, thoracic radiotherapy, cardiac toxicity

EP.09.08 Outcomes of SBRT in the Management of Adrenal Metastases From Lung Cancer - Retrospective Data From Tertiary Cancer Centre of India

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Introduction: Adrenal gland metastases (AGM) from lung cancer pose a therapeutic challenge, with optimal management strategies still evolving. Stereotactic Body Radiation Therapy (SBRT) has emerged as a promising non-invasive treatment modality. This study evaluates the clinical outcomes of SBRT in AGM.

Methods: From 2017-2024, all consecutive patients of AGM from lung cancer who were treated with SBRT were included in this retrospective study. The case details were retrieved from the electronic medical records and treatment planning system. All patients underwent either CECT of thorax and abdomen or whole-body PET-CECT. All patients were treated with VMAT technique using motion management strategies. Local control (LC) was defined as the absence of radiological progression from the date of adrenal SBRT till the date of adrenal progression or last follow up. Progression free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier method from SBRT starting date till the date of progression or death, respectively. P-value of <0.05 was considered statistically significant. Toxicities were graded using CTCAE v5.0. Prognostic factors for outcomes were identified using univariate and multivariate analysis (MVA).

Results: A total of 20 patients (16 males, 4 females) with adrenal metastasis from lung primaries (18 NSCLC, 2 SCLC) were included. The median age was 62.5 years (range, 48-71), with synchronous presentation at diagnosis in 70% and oligometastatic (≤3 sites) disease (OM) in 80% of the patients. Nearly 50% had targetable driver mutations. The main indication for SBRT of AGM was oligoprogression (50%), out of which 60% warranted change of systemic therapy. Majority (n=17) received systemic therapy 4 weeks prior to or after SBRT. The median time from lung cancer diagnosis to adrenal SBRT was 9.9 months (range, 1.3-35.6). The median GTV was 12 cc (range, 3.7- 30) and PTV was 33.3 cc (16.4- 75.1). The median total dose and dose per fraction was 38 Gy (30-50 Gy) and 6-10 Gy, respectively with a median biologically effective dose (BED10) of 65.75 Gy (57-100 Gy). At a median follow-up of 13.4 months, 1-year and 2-year LC rates were 90% and 75%, respectively. The median PFS was 11.8 months, with 1-year & 2-year PFS rates of 50% and 12%, respectively. The 1-year & 2-year OS after adrenal SBRT was 61% and 21%. The median OS for metachronous and synchronous AGM was 25.7 and 6.8 months, (p=0.02). Univariate analysis showed a statistical significance favouring metachronous presentation for OS and GTV <12 cc (p=0.02) for PFS. However, MVA did not yield any significance. Grade 1-2 fatigue (10%) and diarrhoea (10%) were observed. No cases of renal injury or any ≥Grade 3 toxicity were reported.

Conclusions: SBRT for adrenal metastases demonstrated excellent local control with minimal toxicity, especially with small tumor size and metachronous OM presentation. However, larger studies will be required for better prognostication of adrenal gland metastases.

Keywords: adrenal metastases, SBRT, oligoprogression

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES
TUESDAY, SEPTEMBER 9, 2025

EP.09.09 Evaluation of Radiotherapy Use in Patients With Metastatic Solid Tumors: An Analysis of Real-World Data

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Introduction: This study aimed to evaluate the use of stereotactic body radiotherapy (SBRT) in treating metastatic lung cancer in the Brazilian population and to analyze different scenarios of its application, with a particular focus on oligometastatic disease. The authors declare no conflicts of interest related to this article.

Methods: This is a retrospective cohort study using medical record data from patients diagnosed and treated with SBRT at Oncologia D'Or between 2019 and 2023. Data were extracted from the electronic medical record system and entered into a form (RedCap). Exploratory data analysis was performed using IBM SPSS 29.0 software.

Results: Among the 85 patients included in the study, 25.9% (n = 22) received treatment with palliative intent, 34.1% (n = 29) for oligoprogression control, 29.4% (n = 25) for oligometastatic control, and 10.6% (n = 9) for oligopersistence control in the setting of the first SBRT. Regarding the best treatment response, 35.8% (n = 29) of patients achieved a complete response, and the median time from the first radiotherapy treatment to systemic therapy change was 5 months. At the time of evaluation, 32.9% (n = 28) of patients had died, with lung cancer being the cause in 85.7% (n = 24) of cases. The median overall survival (OS) of patients who underwent at least one radiotherapy treatment was 12 months (95% CI: 6.004 - 17.996), while the median survival time after the last radiotherapy treatment was 8 months (95% CI: 3.003 - 12.997).

Conclusions: This study provided a comprehensive analysis of different clinical scenarios involving the use of SBRT in lung cancer. Its application was predominantly observed in the context of oligometastatic disease and oligoprogression, where it played a role in sustaining a specific line of treatment. Furthermore, the study assessed SBRT outcomes about distinct driver mutations. Despite the limitation of a small sample size, this represents the first study to evaluate oligometastatic disease in the Brazilian population.

Keywords: lung, radiotherapy, oligometastasis

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.10 Salvage Surgery After Nonoperative Treatment of Initially Unresectable Stage IIIB-IV Non-Small Cell Lung Cancer

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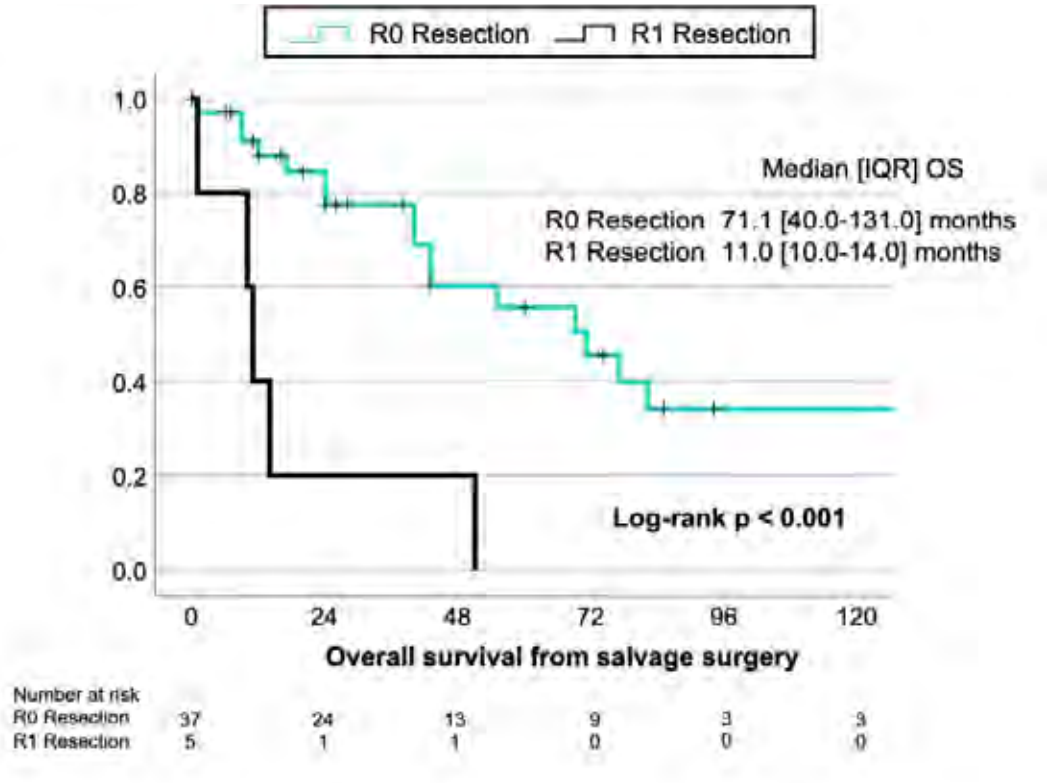
Introduction: Despite the current advancements in systemic treatment, cancer persistence, progression or recurrence remain common after nonoperative treatment of unresectable non-small cell lung cancer (NSCLC). In this situation, lung resection frequently remains among the last options to achieve local cancer control. We aimed to assess the outcomes of salvage lung resection in patients with stage IIIB-IV NSCLC.

Methods: Patients with stage IIIB-IV NSCLC who underwent anatomical lung resection between 2003 and 2024 after initial nonoperative treatment were identified from a prospectively maintained single-center database.

Results: 42 patients were included in the analysis. Median age was 61.5 (IQR 51.8 - 67.5) years and 57.1% were male. The cohort included 9 UICC stage IIIB/C patients and 33 stage IV patients. Nonoperative treatment included definitive chemoradiotherapy in 19 cases (45.2%), immuno- or chemoimmunotherapy in 21 cases (50%) and targeted therapy in 10 cases (23.8%). The indication for lung resection was local recurrence in 4 (9.5%) patients, (oligo) progression under active treatment in 9 (21.4%) patients and (oligo)persistence under active treatment in 29 (69%) patients. Resections included 1 segmentectomy, 14 standard lobectomies, 15 extended lobectomies (incl. sleeve resections, intrapericardial resections, resections of diaphragm, pericardium, large vessels or chest wall), 2 bilobectomies and 10 (extended) pneumonectomies. 66.7% (n=28) of all resections were performed by thoracotomy, 16.7% (n=7) by VATS and 16.7% (n=7) by RATS. Median overall survival was 27.0 months (IQR 11.0-69.5 months), median progression-free survival 22.0 months (IQR 5.0-NR months) and median follow-up was 46.0 months (IQR 29.0-78.5 months). R0-resection was achieved in 88.1% of all cases. Overall survival was significantly improved if R0-resection was achieved (median OS 71.0 [40.0-131.0] months versus 11.0 [10.0-14.0] months, p<0.001).

Conclusions: Salvage surgery remains a valuable option for patients with advanced NSCLC and cancer persistence, progression or recurrence after initial nonoperative treatment and can provide a substantially prolonged long-term survival. In this heavily pretreated population, extended resections with high surgical complexity are common. The achievement of R0-resection is essential as further treatment options are often limited.



Keywords: Salvage Surgery

EP.09.11 Prognostic Impact of Nodal Downstaging After Neoadjuvant Therapy on Survival in Oligometastatic Non-Small Cell Lung Cancer

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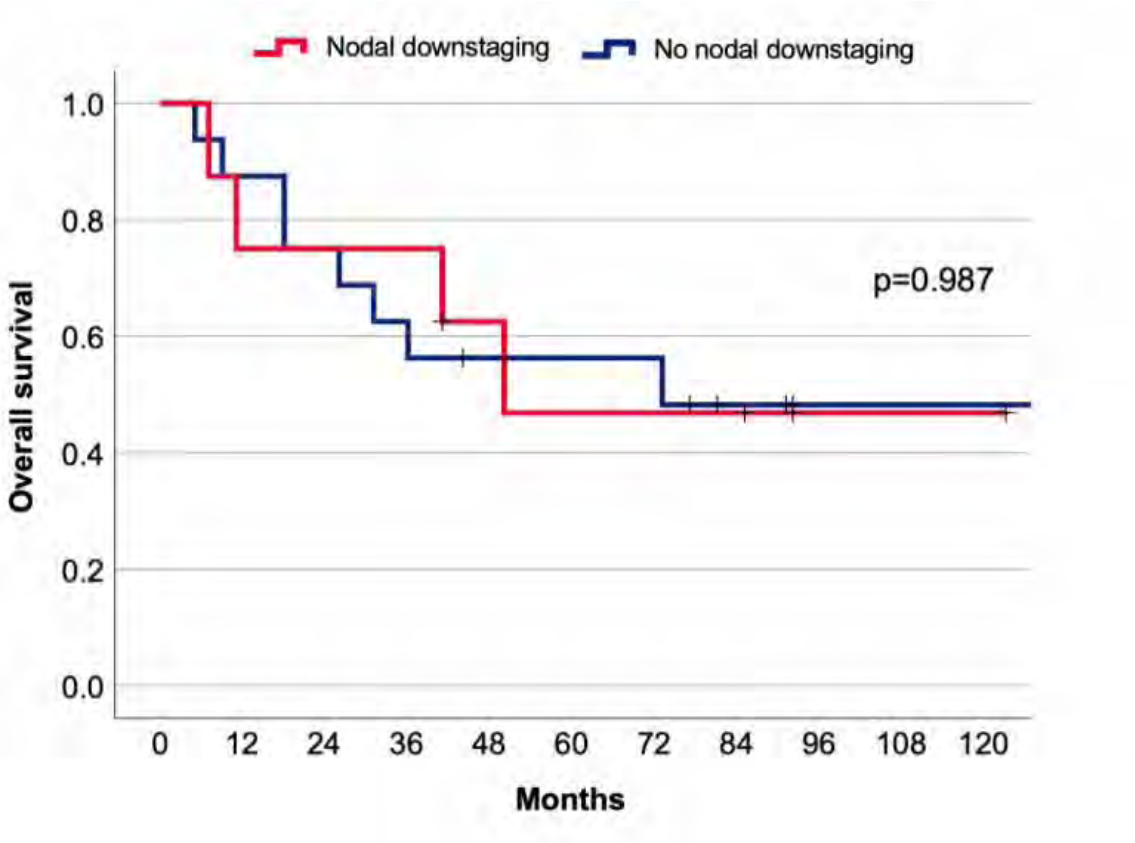
Introduction: At the initial diagnosis of stage IV non-small cell lung cancer (NSCLC), an estimated 25-50% of patients present in an oligometastatic state, characterized by limited metastatic spread and low systemic tumor burden. Multimodal strategies incorporating systemic therapy and local ablative treatment to the primary tumor and all metastatic sites have led to encouraging outcomes. However, patient selection and timing of local ablative treatment remain central challenges. In this study, we retrospectively analyzed a cohort of oligometastatic NSCLC patients with hilar and/or mediastinal nodal involvement who received neoadjuvant systemic therapy before anatomical lung resection as part of a local ablative approach. We investigated the prognostic implications of nodal response on overall survival (OS) following local treatment.

Methods: We retrospectively identified patients with synchronous or metachronous oligometastatic NSCLC who received upfront systemic therapy and subsequently underwent local ablative treatment, including anatomical lung resection, between 2002 and 2020. All patients had hilar and/or mediastinal nodal involvement prior to treatment. Oligometastatic disease was defined as ≤5 distant metastases in ≤3 organs.

Results: Twenty-four patients with oligometastatic NSCLC and nodal involvement were included. The median age at diagnosis was 59 years (IQR: [52.5-66]); 16 patients (67%) were male. Most had an ECOG performance status of 0 (67%) and presented with metachronous metastases (58%). Adenocarcinoma was the predominant subtype (75%). The majority had one metastasis (71%) confined to a single organ (92%), and 88% had ≤3 metastases. Common metastatic sites included the brain (54%), bone (29%), and adrenal gland (13%). All patients received neoadjuvant systemic therapy: 20 (83%) with chemotherapy, 3 (13%) with immunotherapy, and 1 (4%) with targeted therapy. According to RECIST 1.1, 14 (58%) achieved partial response, 8 (33%) had stable disease, and 2 (8%) showed progression. Nodal downstaging, defined as conversion from positive to negative nodal status at surgery, occurred in 8 patients (33%). Among partial responders, 8 (57%) experienced nodal downstaging. OS was comparable between patients with nodal downstaging and those with persistent nodal disease (median OS [95% CI]: 72.8 [37.8-107.9] vs. 116.0 [70.0-162.1] months, p=0.98).

Conclusions: In this cohort, nodal downstaging after neoadjuvant therapy was not associated with OS. Local ablative treatment, including resection, may yield excellent survival even with persistent nodal disease. Further research is needed to identify predictive biomarkers for local therapy in oligometastatic NSCLC.



Keywords: Non-small cell lung cancer, Oligometastatic disease, Nodal downstaging

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.12 Pleurodesis in cM0sM1a Lung Adenocarcinoma With Pleural Metastasis: Impact on Pleural Effusion Control and Survival Outcomes

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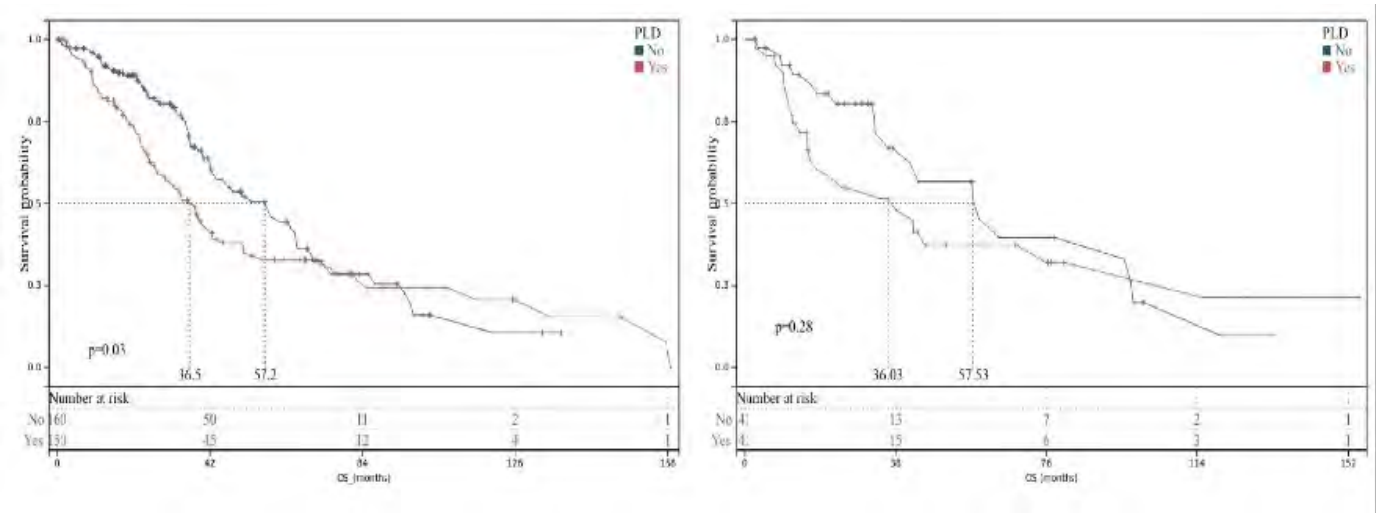
Introduction: Pleurodesis (PLD) is a procedure to treat recurrent malignant pleural effusion (MPE) via pleural adhesion induction. However, its clinical application remains unclear in cM0sM1a lung adenocarcinoma (LUAD) where pleural metastasis is unexpectedly identified during surgery despite negative preoperative imaging. This study aims to assess procedural safety, effusion control efficacy, and survival outcomes of PLD in cM0sM1a LUAD.

Methods: This retrospective study analyzed 310 cM0sM1a LUAD from Sun Yat-sen University Cancer Center (November 2008 to December 2023), categorized into PLD and non-PLD groups. Perioperative outcomes included hospitalization/ICU stay duration, 6-month pleural effusion control efficacy, 30-/90-day mortality and other parameters. Propensity score matching addressed baseline confounders. Perioperative metrics were compared before and after matching; overall survival (OS) was analyzed via Kaplan-Meier methodology and Cox proportional hazards regression.

Results: In 160 non-PLD and 150 PLD surgically treated patients, PLD demonstrated superior malignant pleural effusion control (41.3% vs. 25.6%, p<0.001) but prolonged postoperative hospitalization (6.50 vs. 5.10 days, p<0.001), without differences in fever, ICU readmission, mortality (30-/90-day), repeat thoracentesis, or chest tube duration (p>0.05). Importantly, these findings persisted after 1:1 PSM (n=82), with PLD maintaining superior effusion control (36.59% vs. 9.76%, p=0.008) and longer hospitalization (6.56 vs. 4.78 days, p=0.018). Multivariate Cox regression showed PLD lacked independent prognostic significance (HR=1.02, p=0.93), while intraoperative pleural effusion (HR=2.10, p<0.001) and smoking history (HR=1.49, p=0.028) conferred elevated mortality risk. Pre-matching survival analysis favored non-PLD (median OS 57.2 vs. 36.5 months; p=0.03), but this difference disappeared post-matching (p=0.28).

Conclusions: PLD safely and effectively controls malignant pleural effusion in cM0sM1a LUAD patients despite extended hospitalization. Crucially, PLD exhibited no long-term survival impact. These findings support prophylactic PLD as a viable surgical strategy for alleviating effusion-associated symptoms in M1a disease, while exemplifying the expanding role of surgical interventions in M1a LUAD to complement systemic therapies through symptom control and locoregional management.



EP.09.13 Prognostic Analysis of Patients With Incidentally Diagnosed Pathological Stage IVA Non-Small Cell Lung Cancer After Anatomical Resection

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Introduction: The reported 3-year survival rate of clinical stage IVA non-small cell lung cancer (NSCLC) is approximately 35%. This study aimed to evaluate the prognosis of patients with pathological stage IVA NSCLC who underwent anatomical resection at our institution.

Methods: Among patients who underwent lobectomy with mediastinal lymph node dissection at our institution between January 2010 and December 2021, 13 cases diagnosed with pathological stage IVA NSCLC were retrospectively analyzed for their clinicopathological characteristics and postoperative prognosis.

Results: The median age of the patients was 68 years, and 11 were male. Two cases were preoperatively diagnosed as clinical stage I or earlier. Seven cases were adenocarcinoma. The median PET-SUVmax was 8.8. Lymphatic invasion was observed in 6 cases, vessel invasion in 12 cases, pleural invasion in 13 cases, and nodal metastasis in 13 cases. EGFR mutations were detected in 3 cases. The reasons for pathological stage IVA were pleural dissemination in 8 cases (single pleural lesion in 6 cases, multiple pleural lesion in 2 cases) and malignant pleural effusion (Class V in cytology) in 5 cases. Postoperative systemic therapy was administered in 6 cases, and EGFR-TKI therapy was given in 1 case. The median progression-free survival was 15 months (range: 0-46 months), and the median overall survival was 27 months (range: 9-112 months). The 3-year survival rate was 38.5%. Recurrence or disease progression sites included lung metastases in 5 cases, pleural effusion in 3 cases, brain metastases in 2 cases, mediastinal lymph node metastasis in 1 case, and pericardial metastasis in 1 case. Notably, one patient remained progression-free for 46 months postoperatively. This patient had preoperative clinical stage IIB adenocarcinoma and was diagnosed intraoperatively with malignant pleural effusion.

Conclusions: Overall survival rate after anatomic resection for p-stage IVA NSCLC was similar to that previously reported for c-stage IVA patients. These results suggest that anatomic resection for p-stage IVA NSCLC patients does not appear to improve prognosis.

Keywords: pathological stage IVA, Dissemination or Malignant Pleural Effusion

EP.09.14 Efficacy and Safety of Intrathecal Pemetrexed in NSCLC Patients With Leptomeningeal Metastases: A Retrospective Study

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Introduction: Leptomeningeal metastasis (LM), a devastating complication of advanced non-small cell lung cancer (NSCLC), poses therapeutic challenges due to limited effective interventions. This study aimed to evaluate the efficacy and safety profile of premetrexed-based intrathecal chemotherapy in non-small cell lung cancer (NSCLC) patients with leptomeningeal metastasis (LM), while identifying prognostic biomarkers and evaluating the impact of anti-angiogenic therapy.

Methods: We retrospectively analyzed 133 NSCLC patients with LM who received pemetrexed-based intrathecal chemotherapy at Nanjing Drum Tower Hospital affiliated of Nanjing University Medical School, from January 2017 to June 2024. Clinical parameters (age, Karnofsky Performance Status [KPS], genetic alterations), treatment regimens, and survival outcomes were collected. The overall survival (OS), clinical response rate and adverse events (AEs) were evaluated. Prognostic factors were identified through multivariate Cox regression analysis.

Results: The cohort demonstrated a median OS of 14.2 months with 6-month and 1-year OS rates of 83.5% and 56.6%, respectively. Clinical improvement was observed in 91.7% of patients, accompanied by a 64.3% regression or stabilization in leptomeningeal foci. The most common AEs were myelosuppression (57.9%) and elevation of hepatic aminotransferases (25.6%). 12 (9.0%) patients experienced grade 4 adverse events. Subgroup analyses revealed prolonged OS in patients with EGFR common mutations (19del or L858R) versus rare variants (15.9 vs. 11.7 months, p=0.037) and those with KPS ≥ 60 versus <60 (15.8 vs. 11.7 months, p=0.005). Multivariate Cox analysis identified low levels of baseline serum CEA, Cyfra21-1, and cerebrospinal fluid (CSF) Cyfra21-1, as well as use of combined anti-angiogenic therapy were associated with better prognosis.

Conclusions: Pemetrexed-based intrathecal chemotherapy exhibits promising efficacy and manageable toxicity in NSCLC patients with LM. The integration of anti-angiogenic agents and serum/CSF tumor markers (CEA, Cyfra21-1) may optimize therapeutic strategies. These findings warrant prospective validation to establish personalized treatment paradigms for this aggressive malignancy.

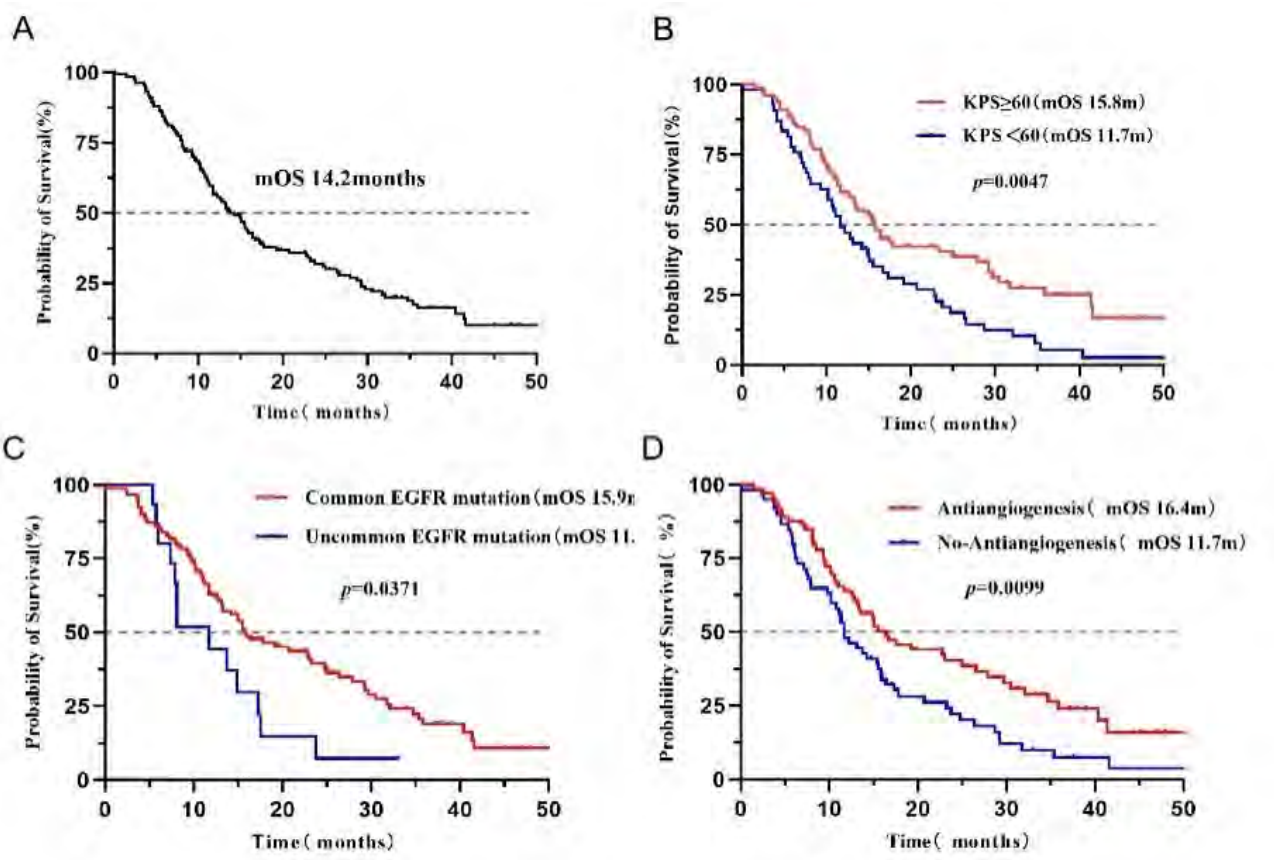

Figure. OS of patients with NSCLC-LM and subgroup analysis

Keywords: Non-small cell lung cancer, Leptomeningeal metastasis, Intrathecal Pemetrexed

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.15 CT-Guided Microwave Ablation as an Alternative Treatment for Non-Surgical Lung Cancer Patients: A Clinical Evaluation of Benefits and Risks

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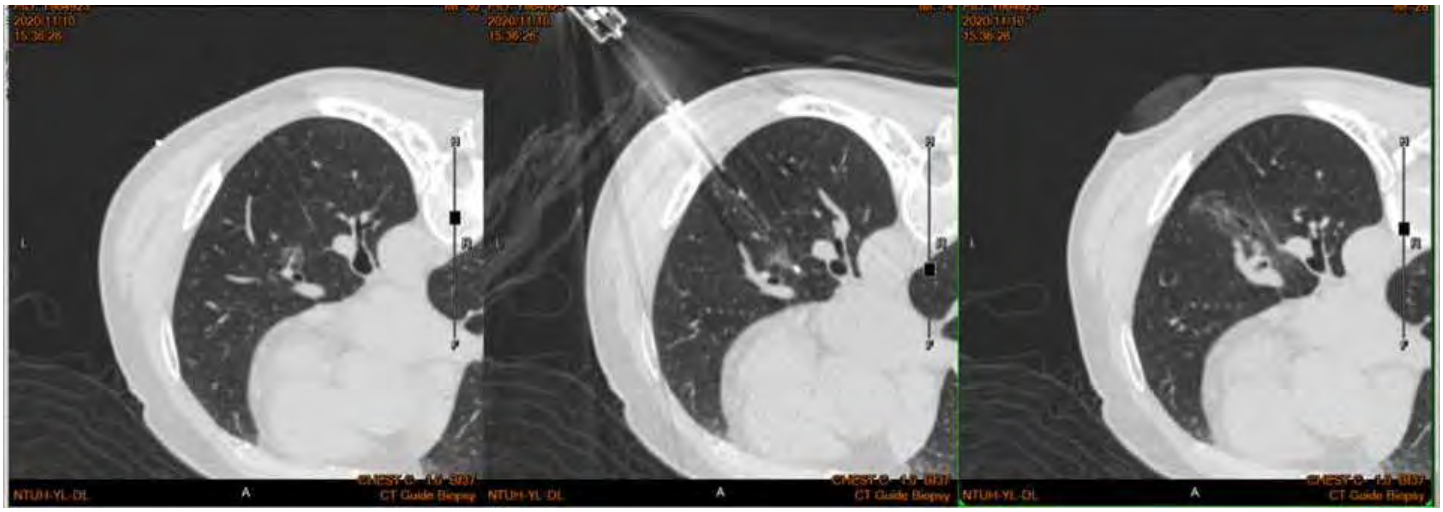
Introduction: For lung cancer patients ineligible for surgical resection, stereotactic radiotherapy and image-guided thermal ablation are alternative treatments. However, the clinical outcomes and risks associated with CT-guided microwave ablation (MWA) require further investigation.

Methods: This prospective cohort study evaluated 23 lung cancer patients who underwent CT-guided MWA between October 2020 and September 2023 using Medtronic's Emprint™ ablation device. Patients had early-stage (I-II) lung cancer or postoperative local recurrence unsuitable for surgery.

Results: The median patient age was 69.5 years (range 46-86), with 43.5% male. Squamous cell carcinoma was observed in 21.7%, while 69.6% had post-treatment recurrence. Tumor size averaged 19.2 mm (range 5-42 mm). Complications included pneumothorax (47.8%), pneumonia (43.5%), chest pain (30.4%), and hemoptysis (8.7%), with severe adverse events in 34.8% of patients. Male gender, right upper lobe tumor location, larger tumor size, and higher energy usage were associated with increased complications. Recurrence occurred in 56.5% of cases, significantly correlated with tumor sizes > 15 mm. Median disease-free survival was 18.4 months, with a 13.0% mortality rate due to severe complications or disease progression.

Conclusions: CT-guided microwave ablation offers a viable treatment option for lung cancer patients who cannot undergo surgery, with promising survival outcomes. However, careful consideration of tumor size and patient-specific risk factors is crucial to minimize complications and optimize results.



Keywords: microwave ablation, complications, survival

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.16 Airway Stenting for the Treatment of Airway Stenosis in Advanced Lung Cancer; a Study of 20 Patients With Advanced Lung Cancer

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Introduction: Advanced lung cancer is often complicated by airway stenosis, fistula formation, and airway hemorrhage, leading to significantly reduced quality of life and lethal situations. Many of these are oncological emergencies that require a rapid treatment. This study aims to clarify the location and type of stents, efficacy, prognosis and complications.

Methods: We retrospectively reviewed patients who underwent airway stenting for central airway stenosis due to advanced lung cancer at our institution between 2005 and 2024.

Results: Twenty patients with advanced lung cancer underwent airway stenting. The mean age was 62.9 (±12.2) years, 19 (95%) were male and 1 (5%) female. 14 (70%) were stage III and 6 (30%) were stage IV. Subjective symptoms were dyspnea in 17 patients (75%) and bloody sputum in 3 patients (15%). All patients had airway stenosis, including 1 (5%) with fistula formation and 4 (20%) with hemorrhage. The stenosis was located in the main bronchus in 12 patients (60%) and in the carina of trachea in 8 patients (40%). Systemic therapy was initiated prior to stenting in 18 patients (90%) and untreated in 2 patients (10%). Four patients (20%) required ventilator management and one patient (5%) required ECMO management prior to stenting. The mean pre-stent PS was 2.95 and the mean MRC breathlessness scale was 4.15. Metallic stents, silicone stents, and both stents were placed under general anesthesia in 13 (65%), 5(25%), and 2 (10%) patients, respectively. Rigid bronchoscope was used only in 5 (25%) patients. After stent placement, both the PS and MRC breathlessness scales showed significant improvement with mean scores of 2.25 and 3.4, respectively ($p<0.01$). Respiratory support was no longer required in all patients after stent placement. Four patients (20%) had sputum retention as an acute complication requiring bronchoscopic clearance. One patient (5%) experienced stent displacement. Median survival for all patients after airway stenting was 198.5 days. Patients who received adjuvant therapy after stenting had a median survival of 418 days, while patients who did not receive adjuvant therapy had a median survival of 88 days, a trend toward longer survival with adjuvant therapy, but not a significant difference ($p=0.179$). There was no difference in survival between metal and silicone stents. Late complications included frequent pneumonia and atelectasis due to granulation in one patient with a metallic stent, which resulted in decreased quality of life and required stent removal.

Conclusions: PS and MRC were improved by airway stenting. In recent years, medical therapy for advanced lung cancer has progressed, and there have been cases of long-term survival after stenting. Because of granulation formation due to long-term implantation, it is necessary to consider the therapeutic intervention after airway stenting when selecting a stent in the future. The risk of complications should also be considered in each case, and the treatment method should be selected on a case-by-case basis.

Keywords: stents, advanced lung cancer, airway stenosis

EP.09 METASTATIC NON-SMALL CELL LUNG CANCER – LOCAL THERAPIES

EP.09.17 Permanent Local Control After Orbital Cryoablation for Ocular Metastasis From Lung Cancer

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Introduction: Choroidal metastases are the most common intraocular malignancies, occurring in approximately 2-7% of patients with metastatic cancer. Lung carcinoma is a major cause of choroidal metastasis, second only to breast cancer. Such lesions frequently threaten vision and significantly affect quality of life. Standard treatment for choroidal metastasis generally combines systemic therapy with local treatments, predominantly external beam radiotherapy, which achieves high tumor regression rates (approximately 85-93%). However, radiotherapy carries risks of ocular complications such as radiation retinopathy and cataracts, and typically requires multiple treatment sessions. Ocular enucleation, involving the complete surgical removal of the eye, is generally reserved as a last-resort intervention for severe, treatment-refractory ocular tumors, including choroidal metastasis from lung cancer. This procedure may result in significant psychological distress due to aesthetic changes and emotional impacts on self-image, as well as rare but possible physical complications such as orbital infection, haemorrhage, or implant extrusion. Consequently, clinicians increasingly prefer conservative, eye-preserving therapies whenever clinically feasible. Cryoablation, a targeted therapy employing tissue-freezing to destroy tumors while preserving healthy ocular structures, offers a promising alternative that potentially avoids enucleation, preserves ocular anatomy, minimizes visual loss, and significantly reduces patient distress. Here, we present two clinical cases of lung cancer patients treated with orbital cryoablation for choroidal metastases, primarily to avoid ocular enucleation.

Methods: Case 1 was a 64-year-old female with active tobacco use diagnosed in 2018 with stage IVA lung adenocarcinoma, featuring molecular mutations (KRAS, TP53, CDKN2A) and PD-L1 expression (40%). She initially underwent systemic treatment following the KEYNOTE-189 phase III study protocol, followed by multiple systemic therapies and stereotactic radiotherapy for orbital metastatic progression leading to visual loss. In April 2021, rapid progression of a right intraorbital metastasis infiltrating the optic nerve and symptomatic exophthalmia prompted orbital cryoablation. Case 2 was a 32-year-old male with active tobacco use diagnosed in May 2021 with a rare NUT carcinoma of the left lower lung lobe (stage IVA), initially presenting with a choroidal metastasis and serous retinal detachment with visual loss. After thoracic surgery, chemo-immunotherapy, and orbital stereotactic radiotherapy, persistent ocular metastatic progression led to orbital cryoablation in November 2021. Both cryoablation procedures utilized targeted orbital freezing through double freeze-thaw cycles directly applied to the metastatic lesions.

Results: Both patients achieved definitive local tumor control after cryoablation. Case 1 demonstrated partial regression of the orbital lesion with symptomatic relief and maintained ocular integrity without significant adverse events. Case 2 achieved a complete local response with no residual enhancement. Neither patient required ocular enucleation. Although both eventually experienced systemic disease progression, local ocular disease control was maintained until their deaths.

Conclusions: These cases represent the first documented use of orbital cryoablation specifically for choroidal metastases from lung cancer, demonstrating effective local tumor control and ocular preservation. Cryoablation emerges as a valuable local therapy alternative in selected ocular metastatic cases, particularly when avoiding enucleation significantly impacts patients' quality of life.

Keywords: Lung cancer, Choroidal metastases, Cryoablation

EP.10 METASTATIC NON-SMALL CELL LUNG CANCER – ANTIBODY-DRUG CONJUGATE AND CYTOTOXIC THERAPY

EP.10.01 Retrospective Study of Pemetrexed Monotherapy for Non-Small Cell Lung Cancer Patients by Renal Function

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Introduction: Pemetrexed (PEM) is one of the commonlyused cytotoxic anticanceragents for non-squamous non-small cell lung cancer (NSCLC). Efficacy of pemetrexed has been shown for non-squamous NSCLC , and PEM is a renally excreted drug and its pharmacokinetics correlate linearly with creatinine clearance (Ccr). Patients whose renal function deteriorated to a Ccr of less than 45 mL/minwere excluded from clinical trials, and the efficacy and safety of PEM have not been established.The purpose of this study is to determine whether the efficacy and safety of PEM in NSCLC patients with reduced renal function differs from that in patients with normal renal function.

Methods: From July 2010 to March 2024, 420 NSCLC patients were treated withpemetrexed at our hospital. Of these, 88 patients were treated with PEM alone, and 72 patients were evaluated retrospectively, excluding 4 patients for whom PEM was administered again and 12 patients for whom the effect of treatment was not evaluated.

Results: 72 patients received PEM monotherapy. Of the 72 patients, 53 had Ccr>45mL/mim and 19 had Ccr<45mL/min, and propensity score matching was performed on these patients. The median progression-free survival estimated at baseline for the Ccr>45 mL/min and Ccr<45 mL/min groups was 71 and 112 days, respectively (p = 0.322), and the median overall survival was 198 and 131 days, respectively (p = 0.912), which were not significantly different. The incidence of febrile neutropenia, an adverse event, was 18.8% and 25.0% (p = 1.000), also not significantly different.

Conclusions: Neither the efficacy nor the safety of PEM for non-squamous NSCLC differed by renal function.Pemetrexed monotherapy may be an option for use as a salvage line even with starting Ccr<45 mL/min, as treatment efficacy and adverse events were similar to those in the group with good renal function.

Keywords: NSCLC, Pemetrexed , reduced renal function

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.01 The Challenge of Immunotherapy in Advanced Lung Cancer Patients With HIV: A Systematic Review of Case Reports

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Introduction: Immunotherapy has significantly revolutionized the treatment landscape for lung cancer, demonstrating both effectiveness and a favourable safety profile. Patients with concurrent HIV and lung cancer face considerable differences in their treatment approaches and clinical outcomes. This specific group has a significantly higher mortality rate. Recent studies have yielded important findings regarding the use of immune checkpoint inhibitors in this patient cohort. However, the available data remains insufficient, and there are recognized barriers and limitations to the use of these therapies in cancer care. Real-world data and clinical practice reports are crucial, as they offer essential perspectives that enhance the sharing of clinical experiences and assist in making complex management decisions. To better assess individual patient management and to analyse the multidisciplinary approach utilized, we have excluded studies and case series, including only case reports in our analysis.

Methods: Following PRISMA guidelines, in March 2025, we searched the MEDLINE, Web of Science, and Scopus databases in the English language. Titles and abstracts were reviewed by 2 independent reviewers; disagreements were resolved by a third. All identified full papers were assessed independently by three researchers. Included studies were required to be case reports and evaluate immunotherapy in advanced lung cancer patients with HIV. The Newcastle Ottawa Scale (NOS) was used to assess the quality of studies included in the systematic review.

Results: The systematic search of the literature identified 8 case reports meeting the selection criteria to analyse in qualitative synthesis.The cases analysed, although limited, illustrate the different settings in which immunotherapy is used. Most notably, there is a clear emphasis on careful infectious disease monitoring throughout the immunotherapy treatment process. The observed heterogeneity in CD4 count variations during treatment underscores the importance of adopting a personalized approach with rigorous multidisciplinary monitoring. The reported responses highlight the need for more appropriate treatments for newly diagnosed HIV-positive patients to enhance prognosis and ensure equitable access to care.

Conclusions: The notable positive outcomes observed in these patients underscore the critical importance of a multidisciplinary strategy and the cooperative efforts of oncologists and HIV specialists.

STUDY	ICI	ANTIRETROVIRAL TREATMENT DURING ICI	CD4 COUNT VARIATION	HIV VIRAL LOAD VARIATION	BEST RESPONSE	irAEs
Hentrich et al., 2017	Second-line nivolumab	Dolutegravir and ritonavir-boosted darunavir	Decrease	Stable (below the limits of detection)	PD	No toxicities reported
Le Garff et al., 2017	Third-line nivolumab	Abacavir, lamivudine and dolutegravir	Increase	Stable	SD	G1 hepatic toxicity
McCullar et al., 2017	Second-line nivolumab	Emtricitabine-tenofovir and lopinavir-ritonavir	Stable	Stable (below the limits of detection)	RC	No toxicities reported
Guihot et al., 2018	Second-line nivolumab	Emtricitabin, tenofovir and dolutegravir	Slight decrease	Increase	SD	No toxicities reported
Guaitoli et al., 2020	Rechallenge pembrolizumab (5th line)	Performed but not better indicated	Decrease	Not reported	PR	No toxicities reported
Kawai et al., 2020	Maintenance durvalumab	Performed but not better indicated	Not reported	Not reported	PD	No toxicities reported
Inno et al., 2023	Chemo-immunotherapy	Emtricitabin, rilpivirine, tenofovir	Slight decrease	Stable	RP	G2 protracted fatigue
Franchina et al., 2025	Chemo-immunotherapy	Bictegravir, emtricitabine, and tenofovir alafenamide	Slight increase	Stable	RP	G2 neutropenia and an increase in transaminases

Keywords: HIV and lung cancer, cancer immunotherapy, antiretroviral therapy and immunotherapy

EP.11.02 Four Year-Experience With Immunotherapy in First Line Treatment of Advanced Lung Cancer in Patients With High and Very High Expression of PD-L1

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Introduction: Immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) or its ligand (PD-L1), have changed the treatment paradigm of metastatic non-small cell lung cancer (NSCLC), specially in tumours with PD-L1 expression ≥50%. This study analyzed demographic and disease-related characteristics, as well as outcomes after first-line ICI treatment in a group of NSCLC patients with PD-L1 ≥50%. We also compared these results between patients with PD-L1 expression 50-89% and those with very high PD-L1 expression (≥90%).

Methods: - Retrospective data from patients with metastatic NSCLC, diagnosed between January 2020 and January 2024. - Objective response rate (ORR) based on iRECIST 1.1 classification. - Survival analysis using Kaplan-Meier method and Cox proportional hazards model.

Results: We present data from 53 patients whose clinical-demographic characteristics are shown in table 1. 44 patients (83%) were treated with Pembrolizumab, 5 with Cemiplimab (9.4%) and 4 with Atezolizumab (7.5%). By the cut-off date, 4 patients were still on treatment. Characteristics between the high PD-L1 expression and very high expression groups, were balanced, except for brain metastasis, which were more prevalent in the PD-L1 ≥90% group. We observed an ORR of 30.19%, a median PFS of 5 months and a median OS of 9 months. In patients with PD-L1 ≥90% (41.5%), median PFS was 6 months and for PD-L1 50-89% (58.5%), 5 months (HR 0.86, 95%CI 0.4-1.5). Median OS was 8.5 and 9 months respectively (HR 0.86, 95%CI 0.4-1.6).

Conclusions: First-line ICI monotherapy for NSCLC in patients with PD-L1 ≥50% has demonstrated a substantial benefit in ORR, PFS and OS in several randomized clinical trials. Our real-world results suggest that there may be a group of patients who don't benefit from this therapy. Therefore, identifying the clinical and biological characteristics of this patients is crucial to seek alternative treatments that achieve better outcomes in this subgroup.

Table 1. Clinical-demographic characteristics of patients with NSCLC

	General population (n=53)	Very high expression of PD-L1 (≥90%) (n=22)	High expression of PD-L1 (50-89%) (n=31)
Sex (n, %)			
Male	37(69.8)	11 (50)	26 (83.9)
Female	16 (30.2)	11 (50)	5 (16.1)
Age (mean, range)	65 (31-44)	62 (31-44)	66 (78-51)
<60	13 (24.5)	7 (31.8)	6 (19.4)
60-80	39 (73.6)	14 (63.6)	25 (80.6)
>80	1 (1.9)	1 (4.5)	0 (0)
Smoking status (n, %)			
Smoker	29 (54.7)	16(72.2)	13(41.9)
Non-smoker	2 (3.8)	1 (4.5)	1 (3.2)
Former smoker	22 (41.5)	5 (22.7)	17 (54.8)
WHO PS (n, %)			
0	22 (41.5)	9 (40.9)	13 (41.9)
1	26 (49.1)	10 (45.5)	16 (51.6)
2	5 (9.4)	3 (13.6)	2 (6.5)
NSCLC disease stage (n, %)			
I	3 (5.7)	1 (4.5)	2 (6.5)
II	4 (7.5)	2 (9)	2 (6.5)
IIIA	1 (1.9)	1 (4.5)	0 (0)
IIIB	3 (5.7)	1 (4.5)	2 (6.5)
IVA	11 (20.8)	2 (9.1)	9 (29.0)
IVB	31 (58.5)	15 (68.2)	16 (51.6)
Tumour histologic type (n, %)			
Adenocarcinoma	32 (60.4)	14 (63.6)	18 (58.1)
Squamous	17 (32.1)	7 (31.8)	10 (32.3)
Other	4 (7.5)	1 (4.5)	3 (9.7)
Brain metastasis (n, %)			
At diagnosis	8 (14.0)	5 (22.7)	3 (9.7)
During evolution of disease	12 (21.1)	8 (36.4)	4 (12.9)
Visceral metastasis (n, %)	41 (71.9)	16 (72.7)	25 (80.6)
Lung	31 (54.4)	11 (50)	20 (64.5)
Nodes	19 (33.3)	8 (36.4)	11 (35.5)
Bone	16 (28.1)	9 (40.9)	7 (22.6)
Adrenal	9 (15.8)	3 (13.6)	6 (19.4)
Liver	10 (17.5)	3 (13.6)	7 (22.6)
Other	4 (7)	4 (18.4)	0 (0)
First line treatment (n, %)			
Pembrolizumab	44 (83)	19 (86.4)	25 (80.6)
Atezolizumab	4 (7.5)	1 (4.5)	3 (9.7)
Cemiplimab	5 (9.4)	2 (9.1)	3 (9.7)
Response in first assessment			
Partial response (PR)	16 (30.2)	6 (27.3)	10 (32.3)
SD (Stable disease)	12 (22.6)	5 (22.7)	7 (22.6)
Pseudo-progressive disease (pPD)	5 (9.4)	2 (9.1)	3 (9.7)
Progressive disease (PD)	20 (37.7)	9 (40.9)	11(35.5)

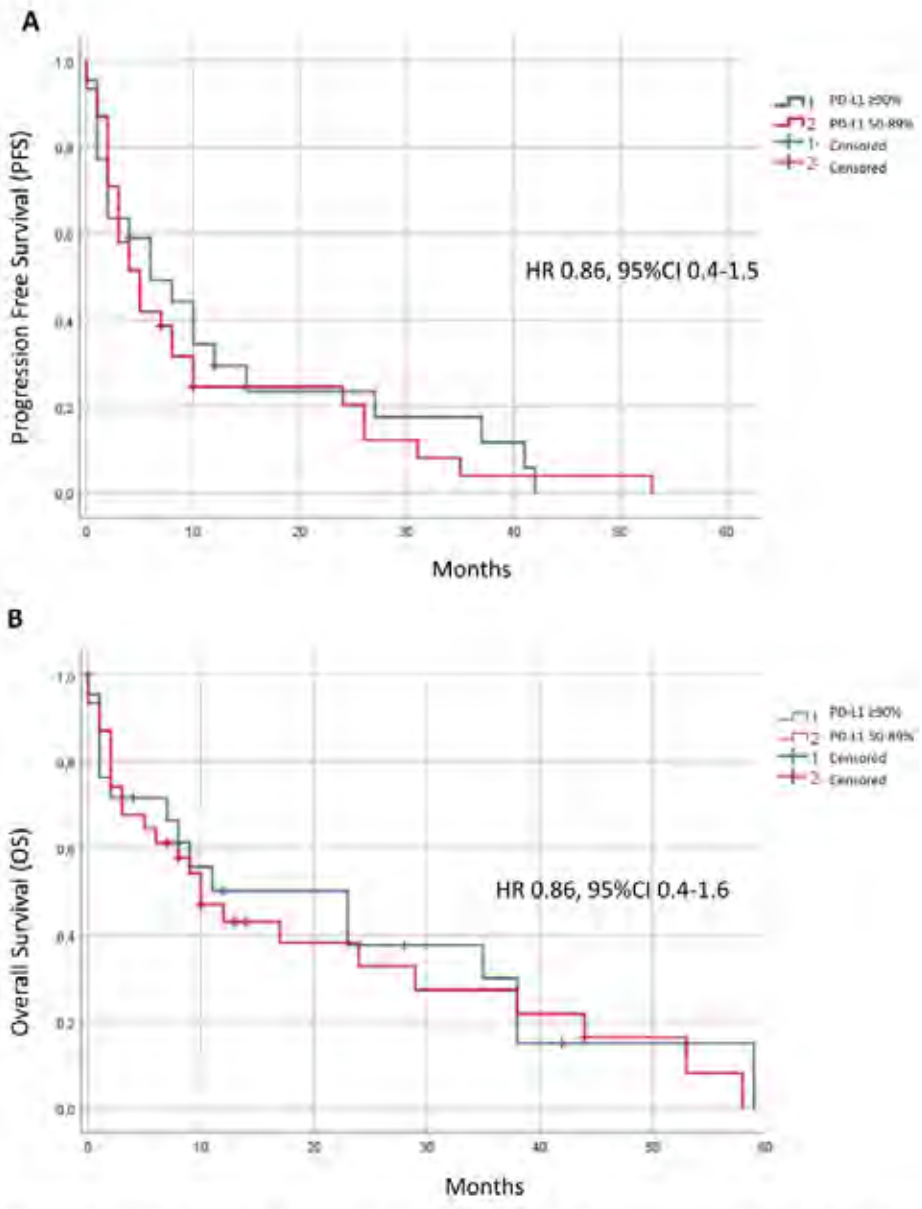

Figure 1. A. Progression free survival in the high PD-L1 expression and very high PD-L1 expression groups. B. Overall survival in the high PD-L1 expression and very high PD-L1 expression groups.

Keywords: Immunotherapy, Real-World Data, PD-L1

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.03 First Line Chemo-Immunotherapy Prognostic Factors Predicting Non Small Cell Lung Cancer Overall Survival

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Introduction: In metastatic NSCLC TPS PDL1<50%, squamous cell carcinoma or non oncogene addicted adeno-carcinoma, chemo-immunotherapy is the first choice of treatment. Currently there are two different therapeutic regimens: platinum based chemotherapy with anti-PD1 Pembrolizumab or with Nivolumab plus anti CTLA4 Ipilimumab. A comparison end to end between these two strategies is lacking. The aim of our multicentric observational study is to identify potential prognostic factors useful in clinical decision making.

Methods: We retrospectively analyzed 363 metastatic NSCLC patients with programmed cell-death ligand (PD-L1) TPS <50%, who received chemo-immunotherapy between march 2022 and october 2023 in the following institutions: A.O.R.N. Cardarelli, A.O.R.N. dei Colli and A.O.R.N. Moscati. We stratified for therapeutic regimens, PD-L1 <1% vs 1-49%, histotypes, distant sites of metastasis, Neutrophils to Lymphocyte Ratio (NLR), presence/absence in NGS of patogenic KRAS mutations, sex and age. We evaluate univariate Kaplan Meier estimated overall survivall and multivariate Cox Regression Hazard Ratio.

Results: At a median follow-up of 12 months, no statistically significant differences were revealed in median OS between patients treated with chemotherapy plus Nivolumab and Ipilimumab or with chemotherapy plus pembrolizumab. A clinically but not statistically significant improvement in median OS has emerged in PD-L1 positive vs negative patients, regardless chemo-immunotherapy regimen. Bone metastasis were associated with a worse prognosis vs no bone metastasis patients (median OS 6.4 vs 13.2 months, log rank test p value = 0.0002). Liver metastasis also resulted in a bad prognosis with a median OS of 4.9 months vs 11.4 months of no liver metastasis patients. (p value = 0.011). NLR from the pretreatment complete blood counts reflected a poor treatment benefits if equal or higher than 3.8. Finally, presence of pathogenetic KRAS gene variants did not have a negative impact on prognosis.

Conclusions: High NLR, Bone and Liver metastasis are associated to significantly shorter overall survival in previously untreated patients with NSCLC with lower or negative expression of PD-L1 and treated in first line with chemo-immunotherapy.

Keywords: First line, chemo-immunotherapy, prognostic factors

EP.11.04 Camrelizumab-Induced Immune-Related Toxic Epidermal Necrolysis in Lung Adenocarcinoma: A Case Report and Literature Review

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Introduction: Immune checkpoint inhibitors (ICIs), such as Camrelizumab, have revolutionized the treatment of non-small cell lung cancer (NSCLC), offering significant improvements in survival outcomes. However, ICIs are associated with immune-related adverse events (irAEs), including rare but severe cutaneous toxicities like toxic epidermal necrolysis (TEN). Here, we report a case of Camrelizumab-induced immune-related TEN in a patient with lung adenocarcinoma (LUAD), highlighting the clinical challenges in diagnosis and management.

Methods: This study presents a case report of a 58-year-old female with stage IV LUAD who developed TEN after receiving Camrelizumab monotherapy. Comprehensive clinical data, including patient history, laboratory results, treatment regimen, and follow-up, were collected and analyzed. A literature review was conducted to contextualize the findings and explore the current understanding of ICI-induced TEN.

Results: The patient developed widespread erythematous rashes, blisters, and epidermal necrosis within 8 days of Camrelizumab treatment. Despite initial management with methylprednisolone, the skin lesions rapidly progressed, involving nearly 70% of the body surface area. The patient was treated with high-dose corticosteroids and intravenous immunoglobulin (IVIg), resulting in gradual improvement. Immunological analysis revealed increased IL-10 levels and reduced T cell, CTL, and NK cell counts after immunotherapy. No significant tumor progression was observed during the treatment period.

Conclusions: Camrelizumab-induced TEN is a life-threatening irAE requiring immediate cessation of ICI therapy and aggressive immunosuppressive treatment. This case emphasizes the need for early recognition of severe cutaneous reactions during ICI treatment. Further research is warranted to understand the underlying mechanisms and develop predictive biomarkers for severe irAEs.

Keywords: Lung adenocarcinoma, Immune-related adverse events, Toxic epidermal necrolysis

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY
TUESDAY, SEPTEMBER 9, 2025

EP.11.05 Prognostic Value of Hb/RDW and Its Correlation With Immune-Inflammatory Profile in NSCLC Receiving First-Line Immunotherapy

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Introduction: The Hemoglobin to Red cell Distribution Width Ratio (Hb/RDW) is a simple and reliable tool directly influenced by factors such as inflammation, nutritional deficiencies, and bone marrow disorders, and a low Hb/RDW seems to be associated with a higher risk of death in patients with cancer. Here, we explored the prognostic role of Hb/RDW and its correlation with blood immunophenotypes and cytokines to provide an easily available non-invasive tool to predict the survival from first-line immune checkpoint inhibitors +/- chemotherapy (ICI+/-CT) in metastatic NSCLC (mNSCLC).

Methods: Clinicopathological data were collected from a monocentric prospective cohort of patients with mNSCLC treated with first-line ICI+/-CT. Baseline blood samples were collected for the assessment of Hb/RDW, relevant immunophenotypes (flow-cytometry) and cytokines (multiplex array). High and low Hb/RDW subgroups were defined according to the median value of Hb/RDW. Correlations of Hb/RDW with survival outcomes in terms of progression-free/overall survival (PFS/OS) and circulating immune-inflammatory benchmarks were analyzed.

Results: Among the 153 patients included, 76% received first-line treatment with ICI + chemotherapy, 31.5% had a PD-L1 tumor proportion score (TPS) ≥ 50%, 71.9% had adenocarcinoma histology, and 43.5% harbored a KRAS mutation. Regarding Hb/RDW, 49.3% of patients had levels equal or below the median (≤0.94). Clinicopathologic characteristics, including age, PD-L1 TPS, performance status, histology, smoking history, and number of metastatic sites, were well balanced between the low and high Hb/RDW subgroups. However, the low Hb/RDW group had a higher proportion of male patients (p = 0.01) and lower median total blood cholesterol levels (p = 0.03), particularly lower median HDL levels (p < 0.001), compared to the high Hb/RDW group. Additionally, patients with low Hb/RDW were more likely to have a baseline concurrent diagnosis of diabetes mellitus (p = 0.02). Hb/RDW did not correlate with baseline derived neutrophil-to-lymphocyte ratio (dNLR) (R = 0.08, p=0.9). At a median follow-up of 27.4 months (95% CI 22.9-32.0), while no meaningful difference regarding median PFS was found, significantly shorter OS was observed in patients with low Hb/RDW compared to patients with high Hb/RDW (11.3 months vs 26.2 months, hazard ratio [HR]: 1.5, p=0.04). The multivariable analysis (adjusting for sex, age, performance status, histology, PD-L1 TPS, metastatic sites, treatment type, dNLR) confirmed the prognostic impact of Hb/RDW in terms of OS (HR 1.6, p=0.03). Compared to patients with high Hb/RDW, patients with low Hb/RDW showed higher baseline blood levels of IL-12 (p=0.04), TNF alpha (p=0.02), IL-6 (p=0.01), and soluble PD-L1 (p= 0.01). In addition, higher baseline immune suppressor cell populations characterized patients with low Hb/RDW, with significantly higher PD-1-positive Natural Killer cells (p=0.05) compared to patients with high Hb/RDW.

Conclusions: In patients with mNSCLC receiving first-line ICI +/- CT, a low Hb/RDW is associated with a higher comorbidity burden, including diabetes mellitus and an unfavorable cholesterol profile, reduced OS and a compromised systemic immune-inflammatory status. As a simple, non-invasive circulating biomarker, Hb/RDW can provide valuable insights into overall patient health, emphasizing its potential role in baseline prognostic stratification.

Keywords: Circulating Biomarkers, Immunotherapy

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.06 First-Line Immunotherapy for PD-L1 =50% Advanced NSCLC vs EGFR-TKIs in EGFR-Mutant NSCLC: A Retrospective Single-Center Study

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Introduction: Immune checkpoint inhibitors (ICIs) have demonstrated durable responses and prolonged survival in some patients with advanced non-small cell lung cancer (NSCLC). We conducted a retrospective single-center analysis to compare the prognostic impact of first-line ICIs and EGFR tyrosine kinase inhibitors (EGFR-TKIs) in patients with advanced NSCLC.

Methods: We collected the following data from patients' medical records: age, sex, ECOG performance status (PS), smoking history, histologic subtype, clinical stage, PD-L1 tumor proportion score (TPS), chemotherapy regimen, and overall survival (OS). The data cutoff was August 31, 2024. OS was defined as the time from the first dose of systemic therapy until death from any cause or the last date of follow-up. Data analyses were performed from January 2017 to December 2022.

Results: A total of 1,368 patients with advanced NSCLC were identified, among whom 979 received systemic chemotherapy. PD-L1 expression was <1% in 263 tumors (26.9%), 1%-49% in 336 (34.3%), ≥50% in 318 (32.5%), and unknown in 62 (6.3%). EGFR mutations were detected in 268 patients (27.4%), all of whom received EGFR-TKIs. The median OS among these 268 patients was 41.9 months (95% CI, 35.7-54.3). Among patients treated with ICI-based regimens, the median OS was: 36.4 months (95% CI, 24.0-48.1) in 128 patients receiving pembrolizumab monotherapy (13.1%), 31.3 months (95% CI, 24.7-46.4) in 111 patients receiving pembrolizumab plus chemotherapy (11.3%), 26.9 months (95% CI, 15.2-NA) in 54 patients receiving ipilimumab plus nivolumab ± chemotherapy (5.5%), 21.5 months (95% CI, 16.2-27.2) in 86 patients receiving atezolizumab plus chemotherapy (8.8%). In the subgroup with PD-L1 ≥50% (n=157) who received pembrolizumab ± chemotherapy, the median OS was 42.15 months (95% CI, 26.7-62.6). Compared with the OS of 41.9 months (95% CI, 35.7-54.3) for the 268 patients who received EGFR-TKIs (hazard ratio [HR], 1.04; 95% CI, 0.80-1.35), there was no significant difference in survival benefit. Restricted mean survival time (RMST) analysis also showed no significant difference.

Conclusions: In this retrospective single-center study, regimens including pembrolizumab for patients with PD-L1 ≥50% advanced NSCLC achieved an OS benefit comparable to that of EGFR-TKIs in patients with EGFR-mutant NSCLC.

Keywords: ICI, EGFR-TKI, OS

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.07 Type2 Diabetes Mellitus Affect Prognosis and Immune Checkpoint Inhibitor Treatment Efficacy for Advanced Non Small Cell Lung Cancer

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Introduction: The effect of type 2 diabetes mellitus (T2DM) on systemic treatments, especially immune check point inhibitor (ICI) for advanced non-small cell lung cancer (NSCLC) remained unclear issue. We conducted retrospective analysis of the effect of T2DM on each type of systemic treatment, ICI, molecular targeted therapy (MTT), and cytotoxic chemotherapy, for advanced NSCLC as multi-cohort retrospective study.

Methods: We reviewed medical charts of patients initiated any systemic treatments after diagnosed advanced NSCLC at Nippon Medical School Chiba-Hokuso hospital from April 2018 to August 2024. Clinicopathological character, treatment effect, and adverse events in these patients were investigated retrospectively

Results: Of 257 patients diagnosed advanced NSCLC and initiated on systemic treatment, 76 (29.6%) patients were diagnosed with T2DM. The numbers of T2DM and non-T2DM patients who initiated immune checkpoint inhibitor (ICI) therapy, molecular targeted therapy (MTT), and cytotoxic chemotherapy were 37 and 78, 30 and 86, 9 and 17, respectively. The overall survival of total patients T2DM patients was significantly worse than total patints without T2DM (34.5 months vs. 19.3 months, hazard ratio [HR] 1.76, P-value 0.0014). Similarly, patients with T2DM in ICI and MTT cohorts was significantly worse than without T2DM (ICI cohort 34.2 months vs. 11.5 months, HR 2.13 [95% CI 1.24-3.66], P-value 0.0049; MTT cohort 43.4 months vs. 27.4 months, HR 1.81 [95% CI: 1.05-3.13], P-value 0.031). Multivariate analysis identified T2DM as an independent poor prognostic factor in the total patients. Median progression-free survival (PFS) was significantly poor for T2DM patients in the ICI cohort (12.5 vs. 5.7 months, hazard ratio [HR] 1.60, P=0.036). However, a significant difference was not found for the MTT cohort (12.7 vs. 13.3 months, HR 1.02, P=0.94). In the ICI cohort, HbA1c was significantly higher in patients with dNLR>3. A similar trend was observed in the NLR in the ICI cohort. In contrast, no association was found between activation of systemic inflammation and glycaemic control in the MTT cohort. However, Multivariate analysis for the PFS in T2DM patients showed specialist consultation was identified as a factor that improved PFS after ICI therapy.

Conclusions: Our research suggests T2DM is one of the prognostic factor for advanced NSCLC and affects ICI treatment efficacy through systemic inflammation acceleration. In addition, our results highlights the importance of strict glycemic control by T2DM specialist intervention.

Keywords: Immune checkpoint inhibitor, Diabetes mellitus, NSCLC

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.08 Comparison of Efficacy and Safety of Combination Therapy With Atezolizumab and Chemotherapy in Non-Small Cell Lung Cancer

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Introduction: Combination therapy with carboplatin, nab-paclitaxel and atezolizumab (ACnP) and combination therapy with carboplatin, paclitaxel, bevacizumab and atezolizumab(ABCP) can be used in patients with renal dysfunction or EGFR-TKI resistance. However, differences in background factors, efficacy, and safety between the two treatment groups are unclear. In this study, we performed a retrospective comparative analysis of the efficacy and safety of the ACnP andABCP in patients with non-small cell lung cancer.

Methods: This study enrolled patients with non-small cell lung cancer (NSCLC) treated withACnP regimen or ABCP regimen from May 2018 through December 2023 in 6hospitals in Japan. The characteristics, the efficacy and the incidence ofadverse events were compared between the two regimens. The hazard ratios of subgroup analysis were analyzed after adjusting for factors including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, histology, EGFR with inverse probability of treatment weighting using propensity score.

Results: Ninety-one patients were enrolled. There were 40 patients in the ACnP group and 51 patients in the ABCP group. There were differences between the two groups in age, gender, smoking history, histology, EGFR status, and TTF-1 status. The objective response rate was 55.0% in the ACnP group and 45.1% in the ABCP group. The median time to treatment failure was 5.5 months and6.6 months, the progression-free survival was 5.5 months and 6.9 months, the median overall survival was 16.2 months and 18.3 months in the ACnP group and ABCP group, respectively. Subgroup analysis after inverse probability weighting adjustment for progression-free survival and overall survival showed patients with brain metastases, liver metastases, EGFR positive, PD-L1 positive, and CCr < 45 significantly favored the ABCP regimen for progression-free survival. For overall survival, patients with brain and liver metastases significantly favored ABCP regimen. Among the adverse events we evaluated, neutropenia, peripheral neuropathy, and skin rash were significantly less frequent with the ACnP group.

Conclusions: In this study, the ABCP regimen was found to be effective in liver metastases,brain metastases, and EGFR-positive cases.

Keywords: Atezolizumab, ABCP, ACnP

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.09 Predictive Value of Markers of Systemic Inflammation in Patients With Advanced NSCLC Treated With First-Line Immune Checkpoint Inhibitors

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionised treatment of NSCLC over the past several years, both in early and advanced stage. Markers of host systemic inflammation, such as neutrophile-to-lymphocyte ratio (NLR), Lung immune Prognostic Index (LIPI) and Glasgow Prognostic Score (GPS) have been proposed as potential predictive markers of ICI response and resistance.

Methods: In this retrospective analysis, we evaluated the relationship of pre-treatment values of NLR, LIPI and GPS on the survival of patients with metastatic NSCLC and PD-L1≥50% treated with first-line pembrolizumab at the Institute for Oncology and Radiology of Serbia. Data from 100 consecutive patients were obtained from hospital medical records. NLR was calculated as the absolute neutrophil/lymphocyte count from complete blood count. LIPI was developed by the association between the derived NLR (dNLR) and the blood level of lactate dehydrogenase (LDH). It is divided into three subsets: good, with dNLR ≤3 and LDH≤ upper limit of normal (ULN); intermediate, with dNLR >3 or LDH >ULN and poor, dNLR >3 and LDH>ULN. GPS is calculated from C-reactive protein (CRP) and serum albumin. GPS is 0 when CRP ≤10 mg/L and albumin ≥3.5 g/dl, 1 when CRP ≤10 and albumin <3.5 or CRP >10 and albumin ≥3.5 and 2 when CRP >10 and albumin <3.5. Cut-off values were determined using ROC curves. Correlation with progression-free survival (PFS) and overall survival (OS) was examined by the Kaplan-Meier method and Cox regression.

Results: Patients with NLR under the cut-off value of 4.46 had a median PFS of 20.70 months (CI 95%, 14.09-27.37), in those with NLR over 4.46 mPFS was 12.45 (CI 95%, 0.0-34.15); p=0.332. Median OS in patients with NLR ≤4.46 was 25.40 months (CI 95%, 9.12-41.67) in those with NLR>4.46 mOS 15.05 (CI 95%, 7.56-22.53), p=0.090. 14 patients had good LIPI score, 46 intermediate and 40 poor LIPI. Median PFS in the good group was not reached, for the intermediate group it was 16.43 months (CI 95%, 6.95-25.9), and for the poor group 12.45 (CI 95%, 0.54-24.36), p=0.13. Median OS in the group with good LIPI was not reached, in the intermediate group was 18.17 (CI 95%, 12.58-23.25),in the poor group 11.04 months (CI 95%, 0-25.02), p=0.28. Also, 24 patients had GPS 0, 52 GPS 1 and 24 had GPS 2. Median PFS in patients with GPS 0 was 23.53 months (CI 95%, 7.17-39.86), with GPS 1 14.29 (CI 95%, 2.46-26.11) and with GPS 2 21.02 (CI 95%, 8.63-33.42), p=0.882. Median OS was 31.73 months (CI 95%, 5.29-58.17) for the group with GPS 0, 19.15 (CI 95% 10.44-27.86) for GPS 1 and 18.16 (CI 95%, 0.00-37.96), p=0.64.

Conclusions: There was an association between parameters of low systemic inflammation (NLR ≤4.46, good LIPI and GPR 0) and survival of this group of patients, but without statistical significance, which could be due to a low number of patients in certain subgroups. Investigations are ongoing on a larger group of our patients, with a hope of defining easy to measure, low cost parameters which could help in predicting response to ICIs.

Keywords: immune checkpoint inhibitors, inflammation parameters

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.10 Clinicopathologic Features, Genetic Characteristics and Prognostic Analysis of Advanced Non-Small Cell Lung Cancer, Not Otherwise Specified

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Introduction: Non-small cell lung cancer, not otherwise specified (NSCLC-NOS) is a type of undifferentiated/poorly differentiated NSCLC. To enhance the understanding of NSCLC-NOS, we systematically summarized and comprehensively analyzed its clinicopathological characteristics, genomic landscapes and prognostic factors.

Methods: From January 2021 to December 2023, we retrospectively screened 2324 undifferentiated/poorly differentiated NSCLC patients. Patients with NSCLC-NOS in stage III/IV diagnosed by morphology and immunohistochemistry (IHC) were included. The primary study endpoint was overall survival (OS). Clinicopathological and molecular features, as well as prognostic factors of survival for NSCLC-NOS were analyzed.

Results: 91 patients diagnosed as NSCLC-NOS were enrolled in this study. Most were male (92.3%), current/former smokers (78.0%), with a median age of 66 years. After a median follow-up of 21.6 months, the median overall survival (mOS) of NSCLC-NOS patients were 12.2 months (95%CI: 7.3-17.1). Among 91 patients, 37 undergoing gene test, the most common gene alterations were TP53 (45.9%) and KRAS (16.2%), and three patients were detected with driver gene mutations, including MET exon 14 skipping mutation (2/37) and KRAS G12C mutation (1/37). Univariate and multivariate regression analysis showed that ECOG PS score (HR: 2.36, 95%CI: 1.30-4.27, p = 0.01) and immunotherapy (HR: 0.16, 95%CI: 0.37-1.00, p = 0.05) were significantly associated with improved survival outcomes. Patients, whose ECOG PS score was 0-1, demonstrated superior mOS than ECOG PS score 2 patients (14.9 vs. 3.1 months, HR: 0.21, p < 0.01). Besides, ICIs (immune checkpoint inhibitors) treatment significantly improved mOS (15.8 vs. 7.3 months, HR: 0.48, p < 0.01) compared to non-ICIs treatment.

Conclusions: NSCLC-NOS is predominantly observed in elderly male smokers, with poor survival prognosis and rare driver gene mutations. The addition of ICIs significantly improved survival for advanced patients with NSCLC-NOS.

Keywords: NSCLC-NOS, Prognosis, Immunotherapy

EP.11.11 Real World Outcomes of First-Line Pembrolizumab With or Without Chemotherapy in Patients With Non-Small Cell Lung Cancer

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Introduction: Non-small cell lung cancer(NSCLC) remains the leading cause of cancer-related morbidity and mortality worldwide. Despite treatment advancements, prognosis for these patients remains poor. The use of immunotherapies such as pembrolizumab, an anti-PD-1 receptor antibody, in lung cancer treatment has dramatically improved outcomes for patients. Known associations with PDL-1 expression on tumour cells and efficacy of pembrolizumab treatment have been well described in other studies. This analysis aimed to evaluate survival outcomes and their predictors in patients with NSCLC who received either pembrolizumab monotherapy (mono-pembro) or combined pembrolizumab and chemotherapy (chemo-pembro).

Methods: This retrospective analysis included adult patients with NSCLC who received first-line pembrolizumab with or without chemotherapy between January 1, 2015 and March 31, 2024 at a major tertiary hospital network, identified through hospital prescribing records. Medical record data collection included biochemical and genetic testing results, severity of disease at diagnosis, and immunotherapy-related adverse events(irAE). Subgroup analyses were conducted for the mono-pembro and chemo-pembro cohorts. Kaplan-Meier methods were used to estimate survival as a function of time. Cox proportional hazards regression was used to analyse the primary outcomes of overall survival (OS) and progression-free survival (PFS). Variables of potential clinical significance and univariate analyses statistical significance were selected for inclusion in the multivariate analyses.

Results: The mono-pembro cohort included 73 patients with 2-year survival of 42% and the chemo-pembro cohort included 132 patients with 2-year survival of 33%. Univariate analysis revealed ECOG, LDH and albumin were markers of prognosis across both subgroups. The presence of irAE was also found to improve OS and PFS in both mono-pembro (HR 0.40, p=0.002; HR 0.27, p=<0.001 respectively) and chemo-pembro (HR 0.45, p=0.001; HR 0.49, p=0.002 respectively) cohorts. The presence of KRAS non-G12C mutation was associated with worse PFS outcomes in the mono-pembro group (HR 2.30, 95% CI 1.07 - 4.97, p=0.03), but not in the chemo-pembro group (HR 0.98, p=0.96).

Multivariate analysis demonstrated higher ECOG and Neutrophil-Lymphocyte ratio(NLR), and lower albumin were associated with worse OS and PFS in the mono-pembro group. Patients who smoked at higher volumes were associated with increased PFS (HR 0.54, p=0.008) whereas adenocarcinoma histopathology was related with poorer OS (HR 2.38, p=0.024). Statistically significant multivariate outcomes in the chemo-pembro group were ECOG and NLR, which both were associated with worse OS.

Conclusions: Patient characteristics which carried a favourable prognosis included the presence of irAE, favourable biochemical markers(LDH, Albumin, NLR) and functional baseline(ECOG) at the time of initial treatment. Improved PFS was demonstrated with KRAS G12C mutation in the chemo-pembro group but not in the mono-pembro group, which also demonstrated reduced PFS with KRAS non-G12C mutation. This may suggest that pembrolizumab efficacy in NSCLC patients with KRAS mutations is inferior to traditional platinum-based chemotherapy. A proposed mechanism for the association between irAE and improved primary outcomes may be that they are both indicative of a stronger systemic immunological upregulation response to immunotherapy. Alternatively, the increased lysis of malignant cells in treatment response may result in higher rates of systemic adverse events.

Keywords: Pembrolizumab, Non-small cell lung cancer, Survival

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.12 Real-World Impact of Immune Checkpoint Inhibitors in Elderly Patients With Advanced NSCLC: A Retrospective Cohort Study From South Korea

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Introduction: Immune checkpoint inhibitors (ICIs) are a preferred treatment option for advanced non-small cell lung cancer (NSCLC) without targetable oncogenic mutations. While evidence supporting their efficacy is increasing, data on their effectiveness in elderly patients remain inconclusive. In South Korea, PD-L1 inhibitors such as pembrolizumab and nivolumab were approved for second-line treatment of advanced NSCLC in August 2017. This study aimed to assess changes in treatment patterns following ICI approval and to evaluate the real-world effectiveness of ICIs in elderly patients with advanced NSCLC.

Methods: We retrospectively reviewed patients aged ≥75 years who were diagnosed with stage IV NSCLC between August 2015 and December 2021 at Seoul National University Hospital and Boramae Medical Center. We evaluated trends in systemic therapy use before and after ICI reimbursement and analyzed the proportion of patients who received ICI therapy. We compared 1-year survival rates and overall survival (OS) between ICI-treated and non-ICI-treated groups, with stratification by ECOG performance status and PD-L1 expression.

Results: A total of 395 patients were included (median age 79 [range 75-94]; 54% male). ECOG performance status was ≥2 in 184 patients (51.3%) and <2 in 174 (48.7%). Histologically, 29.8% had squamous and 70.4% had non-squamous NSCLC. Among 359 patients with treatment data, 49.3% received first-line chemotherapy and 21.4% received second-line therapy. ICI monotherapy was used in 9.7% of patients as second-line treatment; none received ICI as first-line therapy.Following ICI reimbursement approval, 41.5% (44/106) of patients who received first-line chemotherapy proceeded to second-line treatment, with 24 receiving ICIs. Before reimbursement, 46.5% (33/71) received second-line therapy, suggesting no substantial increase in treatment continuation post-reimbursement.Among patients with ECOG <2, those treated with ICIs had significantly higher 1-year survival (64.5% vs. 26.4%, P<0.001) and longer median OS (518 vs. 189.5 days, P=0.04) compared to those who did not receive ICIs. However, after adjusting for PD-L1 expression, this survival benefit remained statistically significant only in patients with high PD-L1 expression.

Conclusions: While ICI reimbursement approval did not significantly alter treatment patterns among elderly patients with advanced NSCLC, ICIs may confer meaningful survival benefits, particularly in those with preserved performance status. However, the benefit was not consistent across all subgroups and appeared limited to patients with high PD-L1 expression. Careful assessment of performance status and biomarker-driven patient selection is essential when considering immunotherapy in elderly patients with advanced lung cancer.

* This abstract is prepared with the assistance of ChatGPT(OpenAI).

Table 1.div>

Keywords: elderly, immune checkpoint inhibitor, NSCLC

EP.11.13 ICI Rechallenge in Non Small Cell Lung Cancer: A Retrospective Analysis of Efficacy and Prognostic Factors

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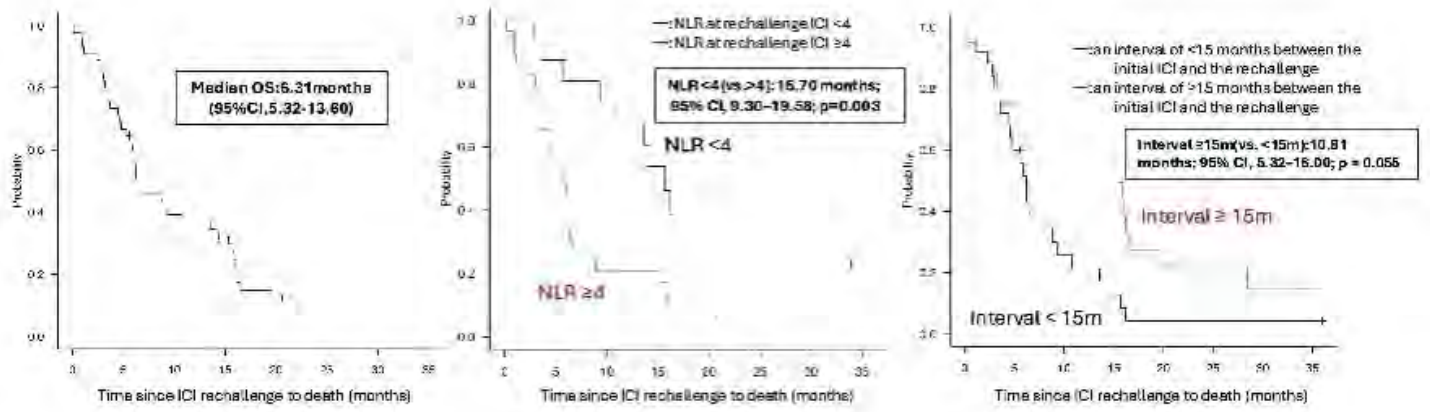
Introduction: Immune checkpoint inhibitor (ICI) rechallenge may benefit patients with non-small cell lung cancer (NSCLC) who previously discontinued therapy due to progression or toxicity. However, the therapeutic efficacy and safety of this approach remain uncertain. Predictive factors such as performance status (PS), PD-L1 expression, neutrophil-to-lymphocyte ratio (NLR), and lung immune prognostic index (LIPI) have been recognized for their influence on initial ICI effectiveness, but reliable predictive markers specific to rechallenge therapy are not yet defined. This retrospective study aims to evaluate the clinical efficacy of ICI rechallenge and identify relevant prognostic factors affecting treatment outcomes.

Methods: This single-center retrospective study involved NSCLC patients who underwent ICI rechallenge between August 2017 and November 2024. Clinical data were obtained from electronic medical records, assessing overall survival (OS), progression-free survival (PFS), and the incidence of immune-related adverse events (irAEs). Prognostic factors related to OS were also evaluated.

Results: 47 patients, with a median age of 67, participated. In PD-L1 tumor proportion scores (TPS), 14 patients (29.8%) had TPS <1%, 16 patients (34.0%) had TPS 1-49%, and 14 patients (29.8%) had TPS ≥50%. Initial ICI treatments included atezolizumab in 5 patients (10.6%),durvalumab in 7 patients (14.9%), pembrolizumab in 19 patients (40.4%), and nivolumab in 16 patients (34.0%). Performance status was PS 0 in 5 patients (10.6%), PS 1 and 2 in 42 patients (89.4%). Although the overall prognosis after ICI rechallenge was limited, with a median PFS of 2.17 months (95% CI, 1.87-3.94) and a median OS of 6.31 months (95% CI, 5.32-13.60), significantly prolonged OS was observed in specific subgroups: patients with an interval of ≥15 months between the initial ICI and the rechallenge (10.81 months; 95% CI, 5.32-16.00; p=0.055), those who experienced adverse events during initial ICI treatment (15.31 months; 95% CI, 3.68-16.55; p=0.048), and those with NLR <4 (15.70 months; 95% CI, 9.30-19.58; p=0.003). Multivariate Cox regression indicated that the presence of irAEs (HR: 0.29, 95% CI: 0.13-0.62, p=0.0016) and NLR <4 (HR: 0.34, 95% CI: 0.16-0.76, p=0.0080) were independently linked to enhanced OS. During the rechallenge ICIs, irAEs during ICI rechallenge were observed in 34.0% of patients, with 19.1% experiencing grade ≥3 events.

Conclusions: Patients with longer intervals since their initial ICI, prior irAEs, or a high NLR demonstrated improved survival outcomes with ICI rechallenge. This indicates that clinical and inflammatory markers might help identify suitable candidates for this treatment strategy.



Keywords: ICI rechallenge, NLR, irAE

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.14 Impact of Bone Metastases on the Efficacy of First-Line Immunotherapy in Advanced NSCLC: An Analysis From a Prospective Real-World Study

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Introduction: Preclinical studies suggest that bone metastases in non-small cell lung cancer (NSCLC) are associated with an immunologically "cold" tumor microenvironment, potentially impairing the efficacy of immune checkpoint inhibitors. However, clinical evidence remains limited to a few retrospective studies, most of which analyzed patients receiving different lines of therapy without stratification. Prospective clinical data with consistent treatment lines are needed to validate this observation.

Methods: This was a prospective real-world study enrolling patients with advanced NSCLC who had not received prior systemic therapy for advanced disease. Patients received PD-1 inhibitor-based treatment, including monotherapy, or in combination with chemotherapy or antiangiogenic agents. The PD-1 inhibitor was administered at a fixed dose every 21 days per treatment cycle.

Results: A total of 177 patients were analyzed, with a median age of 66 years. The overall median PFS and OS were 10.4 months (95% CI: 7.121-13.746) and 38.4 months (95% CI: 31.710-45.023), respectively. Among them, 63 patients had bone metastases and 114 did not. Patients with bone metastases had significantly shorter median PFS (9.8 vs. 13.7 months, P=0.048). OS was numerically shorter, but the difference was not statistically significant (26.6 vs. 39.5 months, P=0.065). ORR (19.05% vs. 27.19%, P=0.226) and DCR (96.83% vs. 95.61%, P>0.999) were comparable between groups. In patients with bone metastases, denosumab treatment was associated with prolonged PFS (P=0.031), whereas bisphosphonates showed no significant benefit (P=0.964). Patients receiving ≥5 doses of denosumab had significantly longer OS compared to those without bone-targeted therapy (P<0.001).

Conclusions: Bone metastases may negatively impact survival outcomes in advanced NSCLC patients receiving first-line immunotherapy. Denosumab combined with immunotherapy may improve clinical outcomes, and prolonged use may further enhance treatment efficacy.

Keywords: NSCLC, bone metastasis, Anti-PD-1 therapy

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.15 Bimodal Onset and Pan-Cancer Uniformity of Immune-Mediated Liver Injury: A Retrospective Cohort Study

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Introduction: Immune-mediated liver injury (IMLI) is a critical adverse event in patients treated with PD-1/PD-L1 inhibitors. The study aims to characterize the clinical heterogeneity, temporal dynamics, and immunological drivers of PD-1/PD-L1 inhibitor-associated IMLI and optimize surveillance and management strategies.

Methods: We retrospectively recruited 373 IMLI patients. We evaluated clinical data, including liver injury patterns, severity, temporal trends, and immune cell subsets. Statistical analyses identified risk factors for severe IMLI and temporal dynamics.

Results: Among 373 patients (median age: 65 years; male: 74.8%), IMLI severity was graded as G1 (53.9%), G2 (25.2%), G3 (17.9%), and G4 (2.7%), with hepatocellular (17.2%), mixed (42.6%), and cholestatic (40.2%) patterns observed. The median time to onset was 106-115 days across severity groups. In contrast, recovery time was significantly prolonged (G3/4: 23 days vs. G1/2:14 days, $P<0.05$), and recovery-phase $CD8^+$ T cells (524.9 vs. 270.68 cells/μL, P=0.026) were higher in severe cases. Bimodal onset peaks occurred at 1-2 months and 3-4 months, with 88% recovering within 100 days. No tumor-type differences existed in patterns (P=0.427) or severity (P=0.054). Elevated baseline NK cells (OR=1.004, P=0.036) predicted severe IMLI.

Conclusions: IMLI demonstrates bimodal onset and pan-cancer uniformity, driven by systemic immune dysregulation. Baseline NK cells are potential predictors of severity. Risk-adapted monitoring within 4 months post-ICI and standardized protocols are recommended.

Keywords: immune-mediated liver injury, PD-1/PD-L1 inhibitor, management

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.16 Immunotherapy Rechallenge of Advanced NSCLC Patients Who Progressed on 3rd-Generation of EGFR-TKI and Immunotherapy Sequentially

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Introduction: Whether patients with advanced NSCLC should choose immunotherapy rechallenge after the sequential treatment of EGFR-TKIs and immunotherapy is currently unclear.

Methods: We evaluated the following treatment (immunotherapy rechallenge or non-Immunotherapy) of 131 patients who progressed on 3nd generation of EGFR-TKIs and immuno-based therapy sequentially. We assessed progression-free survival (PFS) of these patients. We further explored the overall survival (OS) of patients choosing immunotherapy rechallenge and potential benefit group of immunotherapy rechallenge.

Results: The immunotherapy rechallenge group had higher PFS months of non-immunotherapy group with no statistical difference (3.33 (95%CI:2.83-3.90) vs 2.83 (95%CI: 2.47-4.13), P=0.609). The rechallenge of immunotherapy reached higher PFS for patients with a progression pattern of new organ metastases than non-immunotherapy(4.80 (95%CI: 3.31-6.30) vs 2.10 (95%CI:1.54-2.67) months, P=0.01). Those who responded positively to first-time immunotherapy reached better efficacy (PR of longer PFS). Patients achieved PR, SD and PD had median PFS of 5.38(95%CI:3.23-NA), 3.28(95%CI:2.67-3.90) and 2.23 months(95%CI:1.40-NA)(P=0.051)and median OS of 74.47(95%CI: 32.83-NA),59.03(95%CI: 37.87-68.23)and 23.67 months (95%CI:20.67-NA)(P=0.005). We chose the cut-off value of 7.7 months (10 cycles of immunotherapy) in first-time immunotherapy PFS. Patients who were sensitive to first-time immunotherapy (PFS>7.7 months) had longer PFS and OS than others (PFS:3.48 (95%CI:2.17-NA)vs 3.33 (95%CI:2.60-3.90)months(P=0.046), OS: 85.07 (95%CI:61.47 - NA) vs 41.50 (95%CI:31.77 - 52.33) months (P=0.006)).

Conclusions: Patients who progressed on EGFR-TKIs and immunotherapy sequentially with the progression pattern of new organ metastases and great response of first-time immunotherapy may be the optimal group of immunotherapy rechallenge.

Keywords: EGFR-TKI, Immunotherapy, Immunotherapy rechallenge

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.17 Promising Effect of Nivolumab With Carboplatin, Paclitaxel, and Bevacizumab in EGFR-Mutant NSCLC Following EGFR-TKI Therapy

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Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the standard first-line treatment for patients with EGFR-mutant non-small cell lung cancer (NSCLC). However, resistance to EGFR-TKIs inevitably develops, making platinum-based chemotherapy the primary subsequent treatment option. Although the ONO-4538-52/TASUKI-52 trial evaluated nivolumab in combination with chemotherapy and bevacizumab (NBCP) as a first-line treatment in patients with non-squamous NSCLC, its findings have raised interest in the potential utility of this combination beyond the first-line setting. This study evaluates the efficacy and safety of NBCP compared with ABCP (a combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel) in patients with EGFR-mutant advanced NSCLC who have progressed after EGFR-TKI therapy.

Methods: A single-center retrospective analysis was conducted on 31 patients with EGFR-mutant NSCLC treated with either ABCP or NBCP between 2019 and 2024. The primary endpoints were progression-free survival (PFS) and overall survival (OS), and the secondary endpoint was the incidence of adverse events (AEs). All patients had received prior EGFR-TKI therapy.

Results: NBCP demonstrated efficacy comparable to ABCP. The median PFS was 8.7 months versus 4.4 months, and the median OS was 23.4 months versus 9.9 months. The hazard ratio for PFS was 0.48 (95% confidence interval [CI]: 0.21-1.06), and for OS was 0.53 (95% CI: 0.20-1.37). The AE profiles were similar, though grade 3-4 neutropenia was more frequent in NBCP, while liver dysfunction was less common.

Conclusions: NBCP showed efficacy comparable to ABCP as a treatment for EGFR-mutant advanced NSCLC after EGFR-TKI therapy, with an acceptable safety profile. NBCP may be a viable alternative to ABCP for patients with EGFR-mutant advanced NSCLC who have experienced disease progression following EGFR-TKI treatment.

Keywords: EGFR-Mutant NSCLC Following EGFR-TKI Therapy

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.18 Non-Small Cell Lung Cancer Metastases to Adrenal Glands Are Not Differentially Sensitive to Immune Checkpoint Inhibitors

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Introduction: Adrenal gland metastases (AGM) are common in advanced-stage non-small cell lung cancer (NSCLC), occurring in up to 20% of patients. Immune checkpoint inhibitors (ICIs) have markedly improved the outcome of patients suffering from NSCLC. However, some case series/retrospective studies have suggested that responses to ICIs in AGM are lower than in other metastatic sites, particularly in melanoma, while a better overall survival (OS) with AGM than bone or cerebral metastases has been reported in NSCLC. The most-accepted hypothesis to explain a lower efficacy of ICIs in adrenal glands is the production of glucocorticoids in this organ, countering the action of ICIs. We aimed to investigate whether having AGM is associated with a poorer outcome and whether ICI responses are lower in adrenal glands as compared with other organs in patients with metastatic NSCLC.

Methods: We retrospectively compared tumor response rates, overall (ORR) and specifically in adrenal glands (AGMRR), central nervous system (CNSMRR), liver (LMRR), and bone (BoMRR), as well as OS in 42 patients with NSCLC and AGM and a control group of 86 patients with metastatic NSCLC but no AGM, who were treated with an ICI (PD-(L)1 inhibitor) in monotherapy in first or second-line at a single institution between January 2017 and January 2023. Tumor responses were evaluated using RECIST 1.1. OS was defined as the time between ICI initiation and death or last date known alive.

Results: In the AGM group vs the no-AGM group, patient main baseline characteristics were similar, with a median age of 65 years vs 67 years (P=0.4), 69% vs 69% males (P>0.9), and 71% vs 67% non-squamous NSCLC (P=0.6). ORR was 23.8% in patients with AGM vs 28% in those without AGM (P=0.8). AGMRR was 29% vs 23% CNSMRR (P=0.6), 44% LMRR (P=0.8), and 14% BMRR (P=0.5). Median OS was 8.9 months in the AGM group and 11.1 months in the no-AGM group (P=0.7).

Conclusions: In this monocentric cohort of patients with metastatic NSCLC treated with an ICI in monotherapy, we did not find any significant difference in ORR or OS between patients with AGM and those without AGM. Moreover, we did not find any significant difference between AGMRR and tumor response rates in the other frequent metastatic sites.

Keywords: Non Small Cell Lung Cancer, Immune Checkpoint Inhibitors, Adrenal Metastases

EP.11.19 Efficacy and Safety of Continuing Tislelizumab After Progression of First-Line Tislelizumab in Patients With Advanced NSCLC

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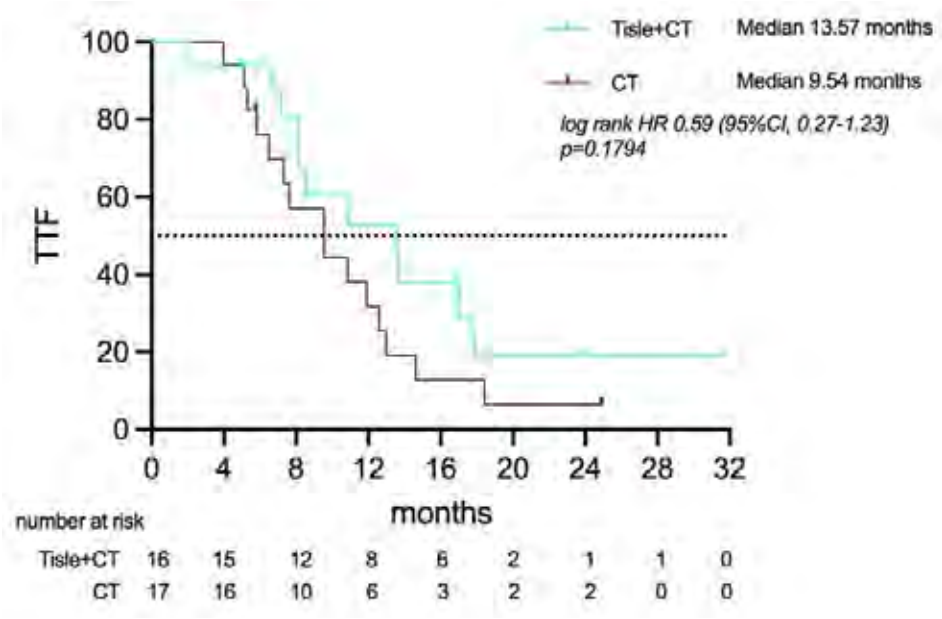
Introduction: Immune checkpoint inhibitors (ICIs) have changed the management of non-small cell lung cancer (NSCLC). However, resistance is inevitable and therapeutic options beyond resistance remain challenging. Treatment beyond progression of ICIs was evaluated in NSCLC patients from clinical trials as well as real-world clinical, but changing ICIs potentially introduced confounding factors.

Methods: A retrospective analysis was conducted on NSCLC patients who progressed after first-line treatment with tislelizumab (PD-1 inhibitor) at the Fifth Medical Center of the Chinese PLA General Hospital between January 2020 and December 2023. All enrolled patients had to have histologically or cytologically confirmed stage IIIB/IIIC or newly diagnosed stage IV NSCLC and have received at least two cycles of first-line treatment with tislelizumab. All patients had documented evidence of disease progression after the first line treatment. Eligible patients were divided into two groups: those who received second-line treatment with tislelizumab combined with chemotherapy and those who received chemotherapy alone. Patients received anti-angiogenic agents on the second line were permitted. The primary endpoint was time to treatment failure (TTF) for first-line plus second-line treatment.

Results: Thirty-three patients were included in the study, with 16 patients in the tislelizumab group and 17 in the chemotherapy group. The median age was 65 years, 63.64% of patients were stage IV, and the proportion of squamous versus adenocarcinoma patients was 66.67% and 21.21%, respectively. Baseline characteristics were balanced between the two groups. The median TTF for second-line treatment was longer in the tislelizumab group compared to the chemotherapy group (4.23 vs. 2.76 months, HR 0.55 [0.25-1.20]). The median TTF for first-line and second-line treatments combined was 13.57 months in the tislelizumab group and 9.54 months in the chemotherapy group (Fig. HR 0.59 [0.27-1.23]). No new safety signals were observed in continuing tislelizumab post-PD, only G1-2 irAEs were observed in 2 patients (2/16, 12.5%).

Conclusions: Continuing tislelizumab treatment post-PD is associated with a positive benefit risk in NSCLC patients. Further analysis with larger samples size is needed to identify the patients who gained more survival benefits and the optimal combination.



Keywords: Tislelizumab, second line, advanced NSCLC

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.20 Real World-Outcomes of Advanced Non-Squamous NSCLC Patients Treated With First-Line Chemo-Immunotherapy According to KRAS Status

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Introduction: Chemo-immunotherapy is the standard frontline treatment of advanced non-squamous non-small cell lung cancer (nsq-NSCLC). Among oncogenic drivers, KRAS mutation accounts for ~25% of lung adenocarcinomas, with KRAS p.G12C being the most common variant (~40%).This study aimed to explore the clinical characteristics and survival outcomes according to KRAS mutation in a real-life population of nsq-NSCLC patients treated with platinum-pemetrexed-pembrolizumab as first-line therapy.

Methods: This is a retrospective-prospective study including patients with nsq-NSCLC who received first-line platinum-pemetrexed-pembrolizumab from September 4th, 2018 in 33 Italian Centers.

Results: Of 874 patients assessable for KRAS status, 121 (13.8%) had KRAS p.G12C mutation, 201 (23.0%) KRAS non-p.G12C mutation and 443 (50.7%) KRASwt. KRAS-mutated (KRASm) patients were more often smokers compared to KRASwt (90.6% vs 84.1%, p=0.012). Bone metastases were more frequent in KRASm than KRASwt patients (44.1% vs 35.9%; p=0.022).Median real-world progression-free survival (PFS) was shorter in KRASm than KRASwt patients (median PFS 8.8 vs 10.8 months; adjusted Hazard Ratio [HR] 1.29, 95% Confidence Interval [CI] 1.04-1.59, p=0.018). Among KRASm patients, KRAS p.G12C exhibited the same PFS than KRAS non-p.G12C (8.8 months, HR 0.95, 95%CI: 0.70-1.30, p=0.756).No statistically significant difference in overall survival (OS) was found between KRASm and KRASwt patients (median OS 16.7 vs 18.2 months; adjusted HR 1.19, 95% CI 0.95-1.50, p=0.132). Among KRASm patients, no difference in OS was found between KRAS p.G12C and KRAS non-p.G12C (median OS 15.9 vs 17.0 months respectively, HR 0.93, 95%CI: 0.66-1.31, p=0.676). Real-world objective response rate (ORR) and duration of response (DoR) were similar between KRASm and KRASwt patients (ORR KRASm vs KRASwt 41.6% vs 47.6%, p=0.106; DoR KRASm vs KRASwt 13.8 vs 14.8 months, p=0.606).

Conclusions: KRAS mutation had a potential negative predictive role in advanced nsq-NSCLC patients treated with first-line chemo-immunotherapy in a real-life setting. The impact of co-mutations and post-progression outcomes warrant further investigation.

Keywords: NSCLC, chemo-immunotherapy, KRAS mutation

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.21 Efficacy of Immunotherapy in EGFR-Mutant NSCLC After Tyrosine Kinase Inhibitors: Real World Analysis at a Tertiary Oncology Center in Hong Kong

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Introduction: The efficacy of anti-PD1/PD-L1 immunotherapy (IO) added to platinum-based chemotherapy in EGFR-mutant NSCLC after tyrosine-kinase inhibitors (TKI) is unclear. Here we report real world outcomes in EGFR-mutant NSCLC patients who received anti-PD1/PD-L1 immunotherapy after progression on TKI.

Methods: We retrospectively identified patients with histological diagnosis of EGFR mutation positive advanced lung adenocarcinoma treated at Queen Mary Hospital between 1/1/2017 and 31/12/2022 from the electronic medical record of the Hospital Authority in Hong Kong. Patients with sensitizing mutations must have progressed on 1 or more TKI (gefitinib, erlotinib, afatinib, osimertinib) and subsequently received platinum-doublet chemotherapy with or without concurrent IO +/- bevacizumab. The date of commencement of chemotherapy was considered as index date. We explored the efficacy of any immunotherapy on overall survival (OS), and on real-world progression free survival (rwPFS)/OS with respect to PDL1 expression (<1%, 1-49%, >50% TPS). Survival was analyzed by the Kaplan-Meier method and between groups comparisons by the log-rank test or Fisher exact test.

Results: Of 104 patients with EGFR-mutant NSCLC, median age was 62.3 years (range 32.4-78.0), 65.4% were female and 79.8% non-smokers. All except 3 patients with exon-20 insertions had prior TKI, of which 38.6% received osimertinib (10.9% as 1st line TKI). At data cutoff on 31/12/2024, median OS was 20.0 months (95% CI 13.9 - 24.5). 36 patients who received any IO either in combination with anti-VEGF and chemotherapy (72.2%), with chemotherapy, or as late-line monotherapy, had an OS of 24.0 months (95% CI 16.8 - 33.1) vs 15.7 months (95% CI 10.0 - 24.5) for those without IO (log-rank P=0.83). PD-L1 expression by TPS was available in 75 patients (57.3%, 25.3%, and 17.3% in the <1%, 1-49%, and >50% category respectively), but was not predictive of rwPFS (P=0.37) or OS (P=0.76) in IO users. Patients who received IO in combination with platinum chemotherapy and bevacizumab showed a trend for improved OS (25.8 vs 16.3 months, P = 0.4) compared with those who did not receive the combination. This regimen showed meaningful improvement in rwPFS (9.7 vs 3.2 months, P=0.024) and objective response (34.5% vs 0%, P=0.15) among IO users.

Conclusions: Our real-world analysis highlights the limited therapeutic benefit of anti-PD1/PD-L1 immunotherapy in EGFR-mutant NSCLC after TKI progression. Our data suggests that the optimal efficacy of immunotherapy is in second line when prescribed with platinum chemotherapy and bevacizumab. PDL1 expression as a biomarker was not predictive of immunotherapy outcomes.

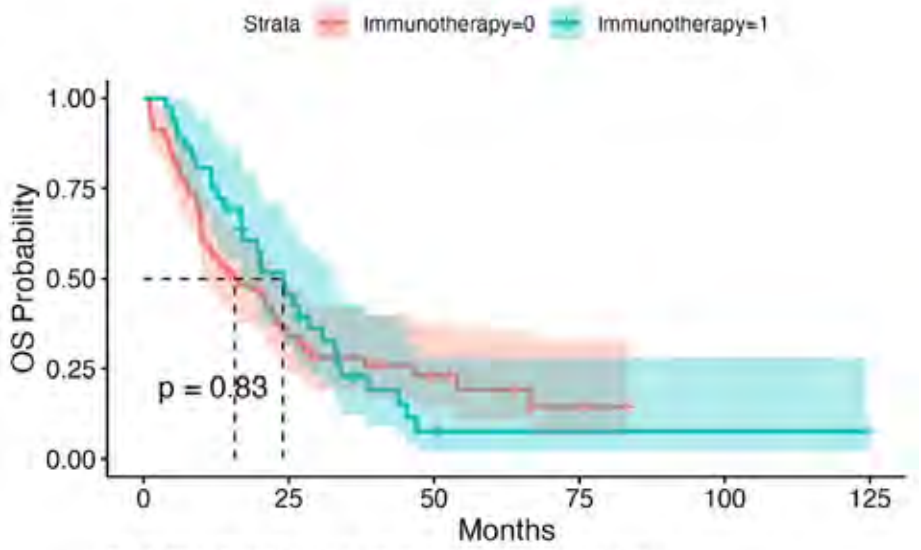

Fig 1: The effect of any use of immunotherapy on survival

Keywords: EGFR mutation, Immunotherapy, Chemotherapy

EP.11.22 Efficacy and Safety of Atezolizumab Plus Bevacizumab-Based Therapy in Non-Small Cell Lung Cancer: A Meta-Analysis of Clinical Trials

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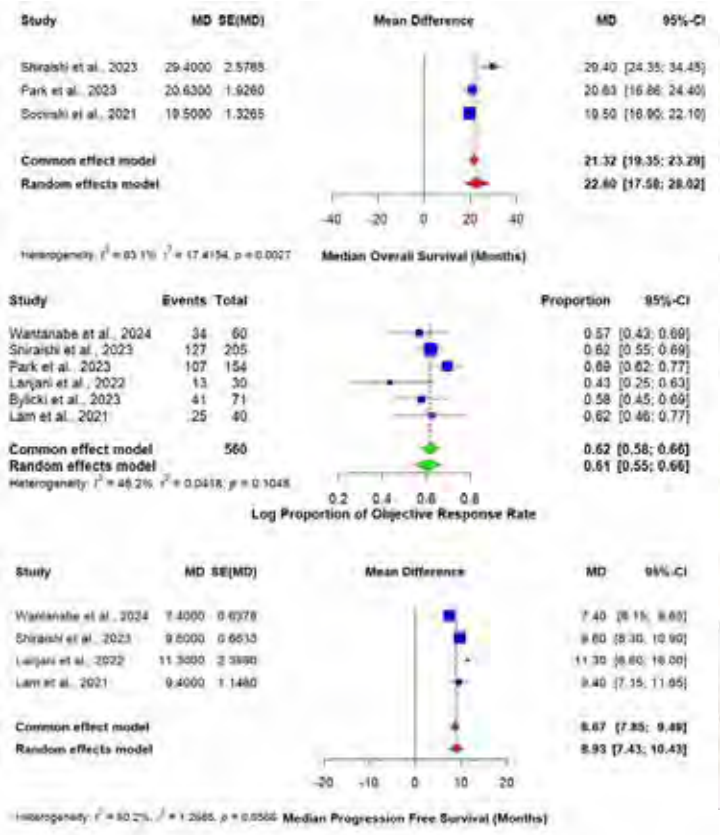
Introduction: Combination of immunotherapy, particularly anti-programmed cell death 1 protein and anti-programmed cell death 1 ligand 1 (PD-L1) with Antiangiogenic drug are a novel approach to treatment for lung cancer. However, its efficacy and safety remains limited in patients with Non-small Cell Lung Cancers (NSLC).

Methods: A systematic search was conducted on various databases, Pubmed, Embase and Scopus since inception until Jan 2025. Appropriate search strategy was done using MeSh terms for; Atezolizumab, Bevacizumab and Non-small cell lung cancer. Proportional analysis was done for the intervention group using the software R.

Results: A total of seven trials were included with 960 patients in the Atezolizumab and Bevacizumab group with mean age of 63.3 yrs and duration of follow up being 21.4 months. Efficacy outcomes meta-analysis: Median Objective Response; 61%, 95%CI: 55-66%, Median Progression Free Survival; 8.93 months, 95%CI: 743-10.43, Median Overall Survival, 22.8 months, 95%CI: 17.58-28.02 and Median Duration of Response; 7.44 months, 95%CI: 4.8-10.08. Safety outcomes meta-analysis: All Adverse Event; 99%, 95%CI: 97-99%, Any treatment emergent adverse event; 99%, 95%CI: 95-100%, Any Treatment Related Adverse Events (TRAE); 91%, 95%CI: 73-97%, Any Serious Adverse Event: 34%, 95%CI: 14-62%, TRAEs leading to dose interruption or modification; 25%, 95%CI: 2-82%, TRAEs leading to permanent discontinuation; 2%, 95%CI: 1-5%, and TRAEs leading to Death; 2%, 95%CI: 1-5%.

Conclusions: These findings suggest that Atezolizumab and Bevacizumab combination is a potential treatment for NSCLC. However, to validate this result more randomized trials are required.



EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.23 Sex-Based Differences in Immune Toxicity Without Survival Trade-Offinlate-Lineici Therapy for Lung Cancer

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Introduction: Sex-based immunological differences may shape both therapeutic efficacy and toxicity profiles of immune checkpoint inhibitors (ICIs). Although several first-line ICI trials have reported sex-specific variations in clinical outcomes, real-world evidence in the late-line setting remains limited. This study aimed to evaluate the impact of gender on treatment efficacy and immune-related toxicity in patients receiving late-line ICI therapy prior to the approval of ICIs in the first-line setting.

Methods: We conducted a retrospective analysis of administrative claims data from lung cancer patients diagnosed between 2015 and 2016 and insured under a major German statutory health fund. Patients who received at least two cycles of immune checkpoint inhibitor (ICI) therapy were included. Sex-based comparisons were performed for the incidence of immune-related adverse events (irAEs), other treatment-related toxicities, ICI treatment duration, and overall survival (OS), utilizing chi-square tests, Student's t-tests, and Kaplan-Meier survival analysis with log-rank testing.

Results: Among 342 patients (244 men, 98 women), female patients were significantly younger at treatment initiation (mean age 63.0 vs. 65.6 years; p=0.01). The median interval from diagnosis to initiation of ICI therapy did not differ significantly between sexes (506.5 days in women vs. 486 days in men; p=0.69). Although the overall incidence of immune-related adverse events (irAEs) was higher in women compared to men (43.9% vs. 34.4%), this difference did not reach statistical significance (p=0.13). However, specific toxicities were more frequent among female patients, including hyperthyroidism (13.3% vs. 6.1%; p=0.05) and nausea or vomiting (35.8% vs. 24.6%; p=0.01). No significant sex-based differences were observed in the number of ICI treatment cycles or overall survival (p=0.27).

Conclusions: This real-world analysis demonstrates that female patients undergoing late-line ICI therapy exhibit a distinct and more pronounced toxicity profile, despite no observable differences in treatment duration or overall survival. These findings challenge generalized assumptions regarding sex-based benefit in immunotherapy and underscore the importance of nuanced, sex-specific toxicity monitoring. As immuno-oncology advances toward increasingly personalized approaches, biological sex should be regarded as a critical variable in both therapeutic decision-making and toxicity management—rather than a simplistic surrogate for clinical benefit.

Keywords: non-small cell lung cancer, Sex Differences, Immune Checkpoint Inhibitors

EP.11 METASTATIC NON-SMALL CELL LUNG CANCER – IMMUNOTHERAPY

EP.11.24 A CT Based Tumor Microenvironment Specific Radiomics Signature for Predicting the Efficacy of Checkpoint Inhibitor Therapy in Advanced NSCLC

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Introduction: Develop a CT-based tumor microenvironment (TME)-specific radiomics signature model combined with clinical information to construct a nomogram for predicting the efficacy of immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancer (aNSCLC).

Methods: Data from TCGA, GEO, and TCIA were integrated. WGCNA was used to identify Immunotherapy Related Genes(IRGs) in GEO, which were used to build prognostic models in TCGA. The tumor immune microenvironment were analyzed. Radiomics features were extracted from TCIA's lung_3 cohort using PyRadiomics, with 94 features strongly associated (r > 0.4) with IRGs selected. A retrospective analysis of 210 NSCLC patients from Guangdong Provincial People's Hospital was conducted, with patients divided into training (n=147) and validation (n=63) groups. In the training group, use Least Absolute Shrinkage and Selection Operator (LASSO) to screen radiomic features, then build clinical-radiomic combined model and nomogram for predicting ICIs response via logistic regression. Evaluate model performance using Receiver Operating Characteristic (ROC) curve, calibration curve, and decision curve.

Results: IRGs related to the immune response activation pathway. The TME - based radiomics signature with clinical features effectively predicted ICI efficacy. The combined model outperformed individual models in both training (AUC = 0.725, 95% CI: 0.644 - 0.807) and validation cohorts (AUC = 0.706, 95% CI: 0.577 - 0.836). Calibration curve and decision curve analysis (DCA) of the nomogram confirmed its clinical utility.

Conclusions: The "genomic-radiomic-clinical" multidimensional predictive framework established in this study provides an interpretable biomarker combination and clinical decision-making tool for efficacy evaluation of immunotherapy in aNSCLC.

Fig.1 Kyoto Encyclopedia of Genes and Genomes (KEGG) (A) and Gene Ontology (GO) (B) pathway analysis of IRGs

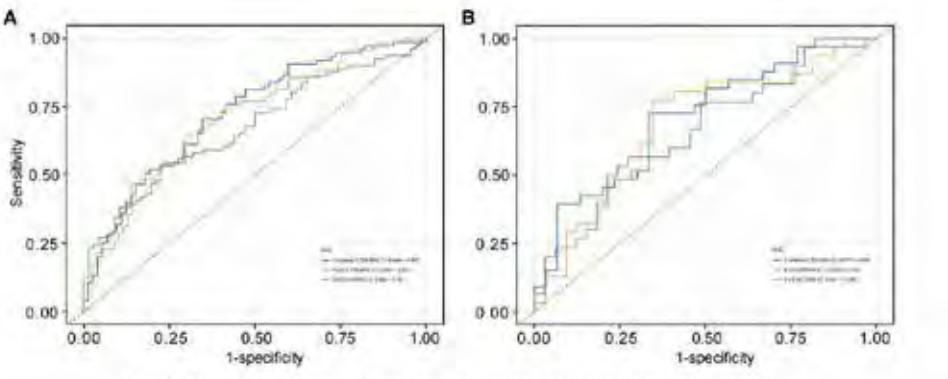

Fig.2 ROC curves of the multimodal model in training group (A) and validation group (B)

Keywords: Non small cell lung cancer, Immune checkpoint inhibitors, Machine learning

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.01 Real-World Data of ROS-1 Positive Nsclcs- Mutational Heterogeneity, Clinical Characteristics and Its Outcomes

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Introduction: ROS1 rearrangements occur in 1-2% of metastatic NSCLCs (mNSCLC), confer aggressive biology and Concurrent mutations may add to these challenges. We present here mutational profile and therapeutic outcomes of ROS1 fusions from a community oncology practice

Methods: A retrospective analysis was conducted for ROS-1-positive mNSCLCs treated between March 2018 and September 2024. Clinical and molecular data was extracted from electronic medical records, highlighting ROS-1 mutation types, treatment modalities, and clinical outcomes

Results: A total of 2281 patients were diagnosed with mNSCLC out of which 43 patients were ROS-1 positive (1.88%). The median age of the cohort was 60 years (32-83); with M:F ratio being 1.15:1 and 4 patients were diagnosed at less than 40 years of age. ROS1 alteration testing was done by FISH(3/43), IHC(10/33) and NGS(14/43) while no records of testing method were available for 16/43. On NGS testing, the most common rearrangement partners were SDC4 (n=3), SLC34A2 (n=2), CD74 (n=3), and EZR(n=2). ROS rearrangement was associated with co-mutations in 15/43 patients which constitute co-mutations with EGFR (n=9), TP53 (n=5), and EGFR+ALK (n=1). Brain metastasis at baseline were detected in 10/43 patients of which 4/10 underwent upfront Radiation treatment and 2/10 underwent surgical resection. Tyrosine Kinase Inhibitors (TKIs) were used alone in 28/43 (65.1%) and as a combination with chemotherapy in 2/43 (4.6%), only chemotherapy was used in 7/43 (16.2%) patients. Of the TKIs, Crizotinib was used in 20, Enterectinib was used in 6 and Lorlatinib was used in 3 patient. The median overall survival (mOS) of the cohort was 42.3 mo (with 95% CI 31.5-53.2) with a median follow-up of 32.8 mo (with 95% CI of 18.1-47.4) with no significant difference outcomes between males and females. The mOS was 39.1 mo (95% CI NA-NA) for ROS1-positive patients and 42.3mo (95% CI 16.9-67.8) for those with co-mutations (p = 0.33). The mOS was 42.3 mo for ROS1+EGFR co-mutations and 21.9 mo for ROS1+TP53 co-mutations

Conclusions: ROS-1 rearrangements are uncommon, availability of 1st generation TKIs has significantly improved survival however, access to newer-generation TKIs with intracranial penetration is important to further improve outcomes. Comutations have lower survival outcomes emphasizing the molecular profiling in these patients

Keywords: ROS 1 rearrangement, Tyrosine Kinase Inhibitors, Western India

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.02 Efficacy and Safety of Firmonertinib for EGFR Exon 21 L858R Mutation-Positive NSCLC Patients With Brain Metastases

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Introduction: The frequency of brain metastases is reported to be 48% to 50% in advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations. Patients with advanced EGFR exon 21 L858R mutation-positive NSCLC show poor outcomes compared with EGFR exon 19 deletion. Firmonertinib is a pan-EGFR tyrosine kinase inhibitor (TKI) known for its high brain penetration and broad therapeutic window. This study aims to prospectively evaluate the efficacy and safety of firmonertinib in EGFR mutation-positive NSCLC patients with brain metastases. Here we present preliminary data focusing on the EGFR exon 21 L858R mutation -positive NSCLC patients with Brain Metastases.

Methods: EGFR-mutant NSCLC patients with brain metastases who were prescribed Firmonertinib were enrolled. Eligible patients were aged at least 18 years old and had histological or cytological confirmed advanced NSCLC harboring an EGFR mutation. The primary endpoints in this prospective observational study included intracranial progression-free survival (iPFS), intracranial objective response rate (iORR) and intracranial disease control rate (iDCR). Secondary endpoints included PFS, ORR, DCR, and safety.

Results: Ten patients with EGFR exon 21 L858R mutation from Tang-Du Hospital were enrolled, including four (40%) with an ECOG score of ≥2. All patients received firmonertinib as first-line treatment. Six patients (60%) received 80 mg, while four patients (40%) were treated with 160 mg of firmonertinib. The median follow-up time was 16.8 months. The median iPFS was not reached (95%CI:NA-NA). Among 10 patients with measurable brain lesions, the iORR and iDCR were 80% and 100% respectively. Overall, the median PFS was not reached (95%CI:NA-NA), ORR and DCR were 90% and 100%. Specifically, in the 80 mg group, the ORR was 83.33% and DCR was 100%, while in the 160 mg group, both ORR and DCR were 100%. Notably, All four patients with an ECOG PS score ≥2 achieved PR (partial response) in both intracranial and overall assessments. Five patients experienced Grade 1 treatment-related adverse events (TRAEs), with no Grade 2 or higher TRAEs reported.

Conclusions: Firmonertinib showed encouraging anti-tumor efficacy and manageable safety in EGFR exon 21 L858R mutant NSCLC patients with brain metastases, despite a significant proportion of individuals having poor performance status.

Keywords: Firmonertinib, EGFR exon 21 L858R Mutation, Brain Metastases

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.03 Study on the Effects of Anlotinib Combined with PD-1 Antibody in Lung Cancer Rats and Its Impact on the PLGF/Flt-1 and TGF-ß1 Pathways

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Introduction: To investigate the effect of anlotinib combined with PD-1 monoclonal antibody on rats with lung cancer and its effect on placental growth factor (PLGF)/vascular endothelial growth factor receptor (Flt-1) and transforming growth factor-β1 (TGF-β1) pathways.

Methods: Fifty SD rats were selected as the subjects, 10 SD rats were randomly selected as the blank control group, and the remaining 40 SD rats were randomly divided into model control group, anlotinib group, PD-1 monoclonal antibody group, and combined treatment group, with 10 rats in each group. The model control group and the blank control group were intraperitoneally injected with the same amount of normal saline, the anlotinib group was treated with anlotinib by gavage, the PD-1 monoclonal antibody group was treated with PD-1 monoclonal antibody, and the combination group was treated with anlotinib combined with PD-1 monoclonal antibody. The immune cell infiltration, angiogenesis, PLGF/Flt-1 and TGF-β1 pathway levels in each group were compared.

Results: After 2 weeks of intervention, the combined treatment group had significantly higher counts of CD4+T cells, CD8+ red blood cells, and CD68+ macrophages than the model control, anlotinib, and PD-1 monoclonal antibody groups ($P<0.05$). The number of CD206+ macrophages was lower than that of the other three groups ($P<0.05$). The results of immunohistochemistry showed that the angiogenesis of the combined group was relatively less, and the number of yellow particles was less. There was no significant difference in angiogenesis between anlotinib group and PD-1 monoclonal antibody group. The results of real-time fluorescence quantitative PCR and Western Blot showed that the mRNA and protein levels of PLGF, Flt-1, and TGF-β1 in the combined group were lower than those in the model control group, anlotinib group, and PD-1 monoclonal antibody group ($P<0.05$).

Conclusions: Anlotinib combined with PD-1 monoclonal antibody can reduce immune cell infiltration and inhibit angiogenesis in rats with lung cancer, and the mechanism may be related to PLGF/Flt-1 and TGF-β1 pathways.

Keywords: Anlotinib, PD-1 monoclonal antibody, Lung cancer

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.04 Efficacy of EGFR TKIs of a Rare but Sensitive Subtype of EGFR L833V/H835L Mutation in Advanced NSCLC

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Introduction: Epidermal growth factor receptor (EGFR) gene mutations represent the most prevalent genomic aberrations in non-small-cell lung cancer (NSCLC). Among these, exon 19 deletions and exon 21 L858R mutations constitute approximately 90% of all EGFR mutations. Large-scale Phase III clinical trials have consistently demonstrated that NSCLC patients harboring these canonical mutations exhibit favorable responses to EGFR tyrosine kinase inhibitors (TKIs) with prolonged progression-free survival (PFS). However, 10%-15% of EGFR mutations are classified as uncommon variants, including compound mutations involving two rare variants or a combination of common and rare mutations. Due to their exclusion from most clinical trials, evidence regarding TKI efficacy in this subgroup remains limited to small retrospective cohorts. This study investigates the therapeutic activity of EGFR TKIs in advanced NSCLC patients with the rare L833V or H835L mutation.

Methods: We retrospectively analyzed 13 NSCLC patients diagnosed with L833V or H835L compound mutations at Guangdong Lung Cancer Institute between 2016 and 2022. Clinical data, treatment regimens, and survival outcomes were systematically collected. Additionally, a PubMed search identified 13 published cases of L833V/H835L mutations, yielding a pooled cohort of 26 patients for analysis.

Results: The median age of the 26 patients was 66 years (range: 36-89), with a predominance of adenocarcinoma histology (100%). Most patients were non-smokers (n=18) and male (n=11). TKI sensitivity was observed across generations of EGFR inhibitors. Notably, patients with L858R/L833V mutations achieved significantly longer PFS compared to historical data from trials involving common EGFR mutations. One elderly patient with an isolated H835L mutation exhibited sustained response to afatinib (PFS: 12.7 months). Furthermore, other L833V-containing compound mutations demonstrated superior survival benefits relative to classical EGFR variants.

Conclusions: The L833V/H835L compound mutation in advanced NSCLC demonstrates enhanced sensitivity to EGFR TKIs, with survival outcomes potentially surpassing those observed in common EGFR-mutated cohorts. These findings underscore the need for prospective studies to validate the therapeutic implications of rare EGFR variants.

Table 1. Clinical characteristics, treatment regimen and prognosis of NSCLC patients harboring the L833V or H835L mutation.

	Reported /Diagnosis Year	Sex	Age (year)	Pathological type	Smoking status	EGFR Mutations	Treatments	PFS (months)
Cases reported	2004	F	76	AD	NA	L833V/H835L	NA	NA
	2006	M	NA	AD	NA	L833V/H835L	NA	NA
	2011	M	89	AD	Y	L833V/H835L	Gefitinib (second-line)	>8+
	2012	M	48	AD	N	L833V/H835L	Pemetexed+Cisplatin	>4
	2016	M	70	AD	Y	E709K/L833V/H835L	Afatinib (first-line)	>2+
	2018	M	36	AD	N	R670W/H835L/L833V	Gefitinib (first-line), afatinib (third-line)	>7
	2018	F	77	AD	N	L833V/H835L	Gefitinib (first-line)	15
	2020	M	65	AD	N	L833V/H835L	Afatinib (first-line)	>10
	2021	M	75	AD	N	L833V/H835L	Afatinib (first-line), Osimertinib (second-line)	>13.5
	2022	M	65	AD	Y	L833V/H835L	Gefitinib	>18
	2023	F	53	AD	N	L833V/H835L	Osimertinib	>22
	2023	F	60	AD	Y	L833V/H835L	Osimertinib	19
	2023	F	44	AD	N	L833V/H835L	Ectinib+chemotherapy	5
Cases in our institute	2017	F	51	AD	N	L833V/H835L	Paclitaxol+CBP+bevacizumab	NA
	2019	F	67	AD	N	L833V/H835L	Afatinib (first-line), Osimertinib (second-line)- osimertinib+dabrafenib+trametinib(third-line)	>72
	2020	M	77	AD	N	L833V/H835L	Afatinib (first-line)	7.7
	2018	M	71	AD	N	H835L	Surgery	NA
	2019	M	77	AD	Y	H835L	Afatinib (first-line), Osimertinib (second-line)	12.7
	2021	F	70	AD	N	L833V/L838V	Osimertinib+bevacizumab(first-line), almonertinib+pemetexed+bevacizumab (second-line), sunvozertinib+Anlotinib(third-line)	>32
	2021	F	80	AD	N	L833V/G719S	Afatinib/Dacotinib	20
	2019	M	60	AD	N	L833V/G719C	Avitinib(first-line), pemetexed+CBP+bevacizumab (second-line), afatinib+bevacizumab(third-line), osimertinib(fourth-line)	35.3
	2018	M	57	AD	N	L858R/L833V	Osimertinib	>72
	2022	M	66	AD	N	L858R/L833V	Pemetexed+CBP+erlotinib (first-line), osimertinib (second-line), osimertinib+bevacizumab(third-line)	>111
	2020	F	56	AD	N	L858R/L833V	Osimertinib (first-line), osimertinib+Met-TKI (second-line), pemetexed+CBP+bevacizumab+sitāzumab (third-line), afatinib(fourth-line)	>56
	2021	F	69	AD	N	L858R/L833V	Dacotinib(first-line), dacotinib+anlotinib(second-line), pemetexed+CBP+bevacizumab(third-line), osimertinib(fourth-line)	28.7
	2016	M	66	AD	Y	L858R/L833V	Gefitinib(first-line), paclitaxol+CBP+bevacizumab (second-line)	97.3

AD: adenocarcinoma; NA: not available.

Keywords: L833V/H835L, uncommon mutation, EGFR

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.05 The Effect of a Dutch Breakfast on the Exposure of Alectinib Using a Microtracer Approach: A Proof-Of-Concept Study

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Introduction: Alectinib is advised to be taken with food to enhance bioavailability, based on a food-effect study with a high caloric and high fat breakfast. This breakfast does not reflect a standard breakfast in many countries, including the Netherlands (containing less energy and fat), making extrapolation of the food-effect to Dutch patients challenging. Thus the food-effect should be re-evaluated at a steady state, which requires extended periods of standardized meal intake and prolonged hospital stays, especially for drugs with long half-lives like alectinib. An alternative approach is using microdoses of stable isotopically labeled drugs (microtracers) to study the food-effect. The food-effect is determined on the pharmacokinetics (PK) of the microtracer without affecting therapeutic treatment of the oral anticancer drug. The aim of our study is to investigate the food-effect of a Dutch breakfast on alectinib PK using the microtracer 2H6-alectinib.

Methods: A prospective, single-centre, open-label, cross-over study assessed the food-effect on the microtracer 2H6-alectinib (100µg) in ALK-positive non-small cell lung cancer (NSCLC) patients on 600mg alectinib bidaily. Patients were hospitalised for twelve hours on two occasions, with at least a seven-day washout. On day one (fed state), patients received the microtracer with their regular dose and a standardized Dutch breakfast (320-392 kcal, 7.5-7.8g fat). On day two (fasted state), patients received the microtracer and alectinib without food. During the washout, they continued alectinib without dietary restrictions. PK samples were collected up to eight hours post-dose on both days.

A population PK model was developed to investigate the effect of food on relative bioavailability (F). Simulations (taking into account uncertainty in final model parameters) were performed to assess the area under the plasma concentration-time curve (AUC) and maximum concentration (Cmax) differences between fed and fasted states.

Results: Ten patients were included with a median age of 57 years (range: 40-72 years), and most of them were diagnosed with stage IV NSCLC. In total 140 PK samples of 2H6-alectinib were available for PK analysis, of which 15 samples were below the lower limit of quantification.

The results show that intake with a Dutch breakfast delays absorption with 28% and increases plasma concentration of the microtracer with 35% (F). The geometric mean of the simulation AUC in fed and fasted state was 980.8 pg*h/mL (coefficient of variation (CV): 31.0%) and 643.9 pg*h/mL (CV: 29.9%), respectively with a ratio (fed vs fasted) of 1.52 (90% Confidence Interval (CI): 1.25-1.89). The geometric mean Cmax in fed and fasted state was 78.2 pg/mL (CV: 28.5%) and 54.9 pg/mL (CV: 27.9%), respectively. The ratio (fed vs fasted) for Cmax was 1.42 (90% CI: 1.16-1.76).

Conclusions: These results show that the intake of a Dutch breakfast leads to a delay in absorption of alectinib, and to higher total exposure. Also, this study demonstrated the feasibility of a microtracer food-effect study using a study design with a relatively low patient burden with only two food-controlled drug administrations and a short period of sample collection.

Keywords: food effect, alectinib, microtracer

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.06 Brilliant First Analysis: A Real-World Study of Characteristics and Safety About Brigatinib as First-Line for Chinese Patients With ALK+ NSCLC

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Introduction: The Brilliant study is a non-interventional, ambispective (retrospective + prospective) study of Chinese patients (pts) treated with brigatinib as first-line therapy from 2022 to 2029 (NCT05721950). The aim is to better understand the real-world practice of brigatinib in China. Here, we report the baseline characteristics and safety based on the first analysis.

Methods: Pts with anaplastic lymphoma kinase positive (ALK+) locally advanced or metastatic non-small cell lung cancer (NSCLC) were eligible and will be followed for up to 3 years. The primary endpoint is real-world time-to-treatment discontinuation. Safety assessments included monitoring treatment-related adverse events (TRAEs), dose modification, and treatment interruption or discontinuation. Pts who received ≥1 dose of brigatinib constituted the safety analysis set.

Results: By June 30, 2024, 82 pts were enrolled with a median follow-up of 3.96 months. Baseline characteristics are shown in the table. The median age was 55.5 years (range 28-80). 7.3% (6 pts) were at stage III and 92.7% (76 pts) at stage IV. 92.7% (76 pts) were reported having ≥ 2 metastatic sites. Any grade and ≥ grade 3 TRAEs were reported in 42.7% (35 pts) and 7.3% (6 pts) of pts, respectively. Any grade TRAEs > 5% included increased aspartate aminotransferase (19.5%), increased blood creatine phosphokinase (17.1%), increased alanine aminotransferase (11%), and rash (6.1%). TRAEs leading to dose modification and interruption occurred in 4 (4.9%) and 3 (3.7%) pts, respectively. Grade 5 events occurred in 1 (1.2%) patient.

Conclusions: The real-world baseline characteristics and safety profile of pts with ALK+ locally advanced or metastatic NSCLC treated with brigatinib align with clinical experience. The study observed that pts with locally advanced stage IIIA and IIIC received brigatinib treatment in real-world clinical practice. Real-world effectiveness and post-treatment will continue to be evaluated.

Table. Baseline characteristics

Characteristic	Brigatinib N=82 n (%)
cTNM Stage (at trial entry)	
III	6 (7.3)
IIIA	3 (50.0)
IIIC	3 (50.0)
IV	76 (92.7)
IVA	16 (21.1)
IVB	30 (39.5)
Other	30 (39.5)
Metastatic site	
1	6 (7.3)
2	26 (31.7)
3	22 (26.8)
4	18 (22.0)
5	8 (9.8)
>5	2 (2.4)
ALK testing	
FISH	1 (1.2)
PCR	21 (25.6)
IHC	26 (31.7)
NGS	29 (35.4)
Other	5 (6.1)
EML4-ALK fusion	
V1	8 (9.8)
V2	2 (2.4)
V3	11 (13.4)
V5	2 (2.4)
Other	13 (15.9)
Unknown	46 (56.1)
TP53 status	
Mut	6 (7.3)
WT	2 (2.4)
Unknown	74 (90.2)
Brain metastases	
Yes	24 (29.3)
No	58 (70.7)
Previous treatment	
Chemotherapy	8 (9.8)
Chemotherapy + VEGFRi	5 (6.1)
No	70 (85.4)

ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; Mut, mutant; NGS, next-generation sequencing; N, number of patients (pts); n (%), number and percentage of pts in a specific category; PCR, polymerase chain reaction; TNM, tumor, node, metastasis; TP53, tumor protein 53; VEGFRi, vascular endothelial growth factor receptor inhibitor; WT, wild type.

Keywords: Brigatinib, ALK positive, First-line therapy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.07 Using Online Continuing Medical Education to Identify Ongoing Gaps in Global Clinicians' Understanding of HER2-Altered NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) treatment is evolving rapidly, with HER2 emerging as a critical biomarker for targeted therapy. Clinicians must accurately recognize HER2 alterations, apply appropriate testing methodologies, and interpret clinical trial data to optimize patient care across the globe. The objective was to assess the knowledge and skills of global oncologists and pathologists related to HER2-altered NSCLC and its ongoing management approaches, as well as highlight ongoing educational gaps to guide future educational efforts.

Methods: An online, text-based CME survey instrument comprising 20 multiple-choice knowledge, practice-based, and confidence questions assessed participants' clinical understanding of HER2-altered NSCLC. The activity launched on August 16, 2024, and data were collected through March 2025. Responses from global oncologists and pathologists were analyzed and compared by grouping questions into clinical themes and calculating the percentage of correct responses in each area.

Results: Analysis of participant data revealed several key trends in understanding of HER2-related concepts in NSCLC, with notable differences between US and outside the United States (OUS) clinicians. Generally, OUS oncologists and pathologists had lower remaining gaps compared to their US counterparts. The most persistent gaps across all clinicians were awareness of clinical trial data and ability to tailor care decisions.

Conclusions: This educational initiative yielded important insights into ongoing practice gaps related to the recognition, testing methodologies, clinical data, and management of HER2-altered NSCLC. The particular deficits related to awareness and applicability of data likely stems from the relative novelty of HER2 as a therapeutic target in NSCLC, highlighting the urgent need for targeted, practice-based education. Further studies are planned to assess the effect of ongoing medical education initiatives in closing these global clinical practice gaps.

Learning Theme	OUS Clinician Remaining Gaps		US Clinician Remaining Gaps	
	Oncologists (n=79)	Pathologists (n=16)	Oncologists (n=43)	Pathologists (n=32)
Recognizing characteristics of HER2 alterations	27%	35%	37%	41%
Understanding of testing methodologies	47%	53%	55%	62%
Awareness of clinical trial data	51%	67%	59%	63%
Ability to tailor care decisions	49%	68%	59%	64%

Table: Remaining gaps by clinician type and geographic practice setting

Keywords: HER2, NSCLC, CME

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.08 A Real-World Study of the Efficacy and Safety of Firmonertinib for Patients With Non-Small Cell Lung Cancer With EGFR Uncommon Mutati

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Introduction: Firmonertinib is a novel third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). The FAVOUR study (NCT04858958, a phase I b trial) demonstrated preliminary efficacy in patients with non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations (ex20ins). Additionally, the FURTHER study (NCT05364073, a phase Ib trial) showed promising activity in patients with EGFR P-loop and αC-helix compressing (PACC) mutations. Building on these findings, this study aims to evaluate the real-world efficacy and safety of firmonertinib in patients with locally advanced or metastatic NSCLC harboring uncommon EGFR mutations.

Methods: We retrospectively analyzed the clinical data of patients with locally advanced or metastatic EGFR uncommon mutations non-small cell lung cancer (NSCLC) who were treated with firmonertinib at Xiangya Hospital of Central South University and multiple medical centers in Hunan Province from October 28, 2022, to March 1, 2025. The evaluated endpoints included the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and Treatment-Emergent Adverse Event (TEAEs).

Results: As of the data cutoff date (March 31, 2025), 53 patients were enrolled. Mutations were classified based on structure-based classification, with ex20ins identified in 41.5% (22/53) and PACC in 47.2% (25/53). The median follow-up time was 289 days. The ORR and DCR were 77.4% (41/53) and 100.0% (53/53), respectively. The median PFS (mPFS) was 17.8 months (95% CI 10.7-24.8). Specifically, patients with brain metastasis (n=24) had a mPFS of 17.8 months (95% CI: 10.2-25.3), whereas those without (n=29) achieved 19.7 months (95% CI: 4.9-34.6). In terms of treatment line, first-line therapy (n=44) demonstrated a significantly longer mPFS of 17.8 months (95% CI: 7.9-27.6) compared to second-line therapy (n=9, mPFS 9.5 months; 95% CI: 4.1-14.9). In first-line patients, the 80 mg cohort (n=23) had a median PFS not reached (NR), while the 160 mg cohort (n=21) achieved 24.4 months (95% CI: 13.3-35.5). The PFS of patients in the PACC group was significant longer (24.4 months) compared to that of patients in the ex20ins group (14.0 months; P = 0.0345) and the Classical-like group (19.7 months; P = 0.0089). However, there was no statistically significant difference in PFS between the ex20ins and Classical-like groups (P = 0.1287). Overall survival (OS) data remain immature. TEAEs of any grade occurred in 30.2% (16/53) of patients, with Grade 3 TEAEs reported in 1.9% (1/53; oral ulceration). No Grade ≥4 TEAEs, treatment discontinuations, dose reductions, or treatment-related deaths were observed. The most common TEAEs included liver dysfunction (15.9%), oral ulceration (7.6%), rash (5.7%), and diarrhea (3.8%).

Conclusions: Firmonertinib has shown encouraging antitumor activity in patients with locally advanced or metastatic NSCLC harboring uncommon EGFR mutations and a manageable safety, supporting further clinical exploration. Corresponding author: Min Li, limin2050@csu.edu.cn; Lemeng Zhang, zhanglemeng@hnca.org.cn.

Keywords: EGFR uncommon mutations, Firmonertinib, Non-small cell lung cancer

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.09 Third-Generation EGFR-TKIs in T790M-Negative NSCLC After First/Second-Generation EGFR-TKI Failure: A Retrospective Study

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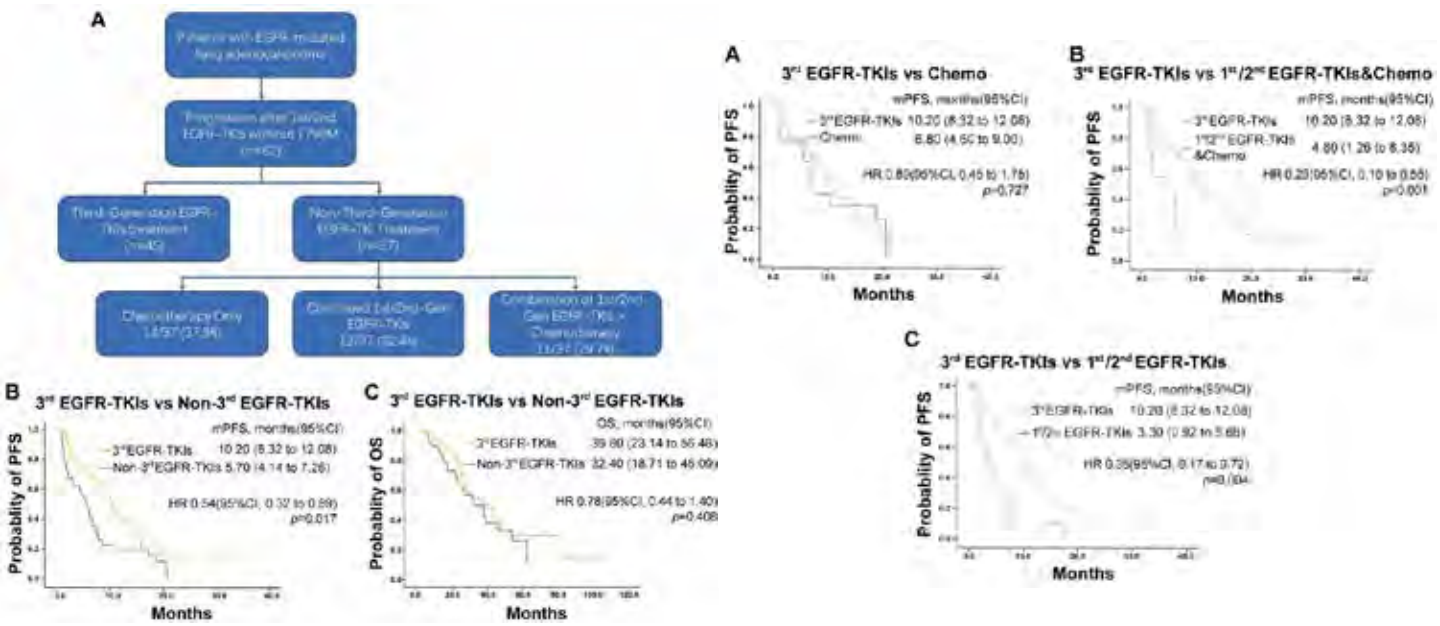
Introduction: In non-small cell lung cancer (NSCLC) patients resistant to first- or second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), only half develop T790M mutation and thus qualify for the treatment using third-generation EGFR-TKIs. For T790M-negative patients, chemotherapy is the recommended second-line treatment. We compared the efficacy between third-generation EGFR-TKIs and chemotherapy with or without first/second-generation EGFR-TKIs in T790M-negative patients.

Methods: This study included T790M-negative patients with EGFR-mutated advanced NSCLC and progressing after first-line treatment with first- or second-generation EGFR-TKIs. Data on clinical characteristics, disease features, and survival were collected, including general conditions, medical history, imaging, histology, and molecular profiling.

Results: Of 82 patients progressing after first- or second-generation EGFR-TKIs without acquiring T790M, 45 received third-generation EGFR-TKIs and 37 received chemotherapy and/or first/second-generation EGFR-TKIs. We found that third-generation EGFR-TKIs led to significantly longer median progression-free survival (mPFS) than other treatments [10.20 months vs. 5.70 months, P = 0.017]. Subgroup analyses indicated that third-generation EGFR-TKIs had similar mPFS to chemotherapy group but was significantly superior to first/second-generation EGFR-TKIs with or without chemotherapy (10.20 months vs. 4.80 months, P < 0.001; 10.20 months vs. 3.30 months, P = 0.004). The median overall survival (mOS) for patients treated with the third-generation EGFR-TKIs and with non-third-generation therapy was 39.80 months (95% CI 23.14 to 56.46) and 32.40 months (95% CI 18.71 to 46.09), P = 0.408, respectively.

Conclusions: Third-generation EGFR-TKIs significantly improved mPFS in T790M-negative patients with EGFR-mutated advanced NSCLC and resistant to first-line treatment with first- or second-generation EGFR-TKIs.



Keywords: tyrosine kinase inhibitor, resistance, T790M

EP.12.10 Clinical Investigators' (CIs) Preferences for First-Line Therapy of ALK-Positive Metastatic Non-Small Cell Lung Cancer

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Introduction: The management of patients with non-small cell lung cancer (NSCLC) harboring an ALK rearrangement (ALK+) is an important targeted therapy success story in cancer research. However, as is currently observed in a number of oncology scenarios, a lack of head-to-head comparisons between multiple agents in the same class mandates that clinicians consider other clinical, biologic and practical factors to guide decision-making. Little information is available with regards to how clinicians are selecting between the six approved ALK inhibitors.

Methods: In March 2025, 20 US-based and international CIs completed a survey evaluating their preferred first-line treatment for ALK+ metastatic NSCLC (mNSCLC). For each case-based question, one or more key variables (eg, age, sites and extent of metastases, comorbidities, prior therapy) were varied. A modest honorarium was provided.

Results: For a 60-year-old asymptomatic patient with ALK+ mNSCLC (PD-L1 tumor proportion score [TPS] 0) and no comorbidities, CIs preferred lorlatinib over alectinib as their first-line treatment of choice (80% vs 20%). For a patient with multiple bilateral brain metastases requiring whole-brain radiation therapy (WBRT), lorlatinib was also favored (90% vs 10%).

Among patients with various comorbidities (hypertension, diabetes, anxiety/depression, bradycardia, chronic kidney disease/dialysis), the choice of ALK inhibitor varied but lorlatinib was chosen by at least 50% of CIs (see Table 1). For an 80-year-old patient with no comorbidities, CIs were evenly divided between alectinib and lorlatinib (50% each).

From a global standpoint, most CIs (18 of 20) believed lorlatinib to have the greatest efficacy among the various ALK inhibitors as first-line treatment, and all felt it had the greatest CNS activity. Conversely, 16 of 20 CIs believed alectinib to be the most tolerable, with none selecting lorlatinib.

Furthermore, the CIs' median projected likelihood of dose interruption or reduction for patients receiving lorlatinib was 50% (range, 10%-100%) compared to 20% (range, 5%-50%) with alectinib. Similarly, the median estimated likelihood of permanent discontinuation with lorlatinib was 10% (range, 0%-20%) compared to 5% (range, 0%-15%) with alectinib.

Conclusions: The majority of CIs prefer lorlatinib as first-line treatment for ALK+ mNSCLC, perhaps due to the unprecedented outcomes reported from the 5-year follow-up of the Phase III CROWN trial. However, older age and specific preexisting conditions and comorbidities may lead to another treatment approach. Future work is needed to explore current decision-making in these situations for general medical oncologists practicing in a community setting.

Table 1: CI's Choice of First-Line Systemic Therapy in Various ALK-Positive mNSCLC Clinical Scenarios

Clinical scenario in ALK+ mNSCLC (PD-L1 TPS 0)	Choice of first-line systemic therapy
60-yo with no comorbidities	Lorlatinib (16/20) = 80% Alectinib (4/20) = 20%
60-yo with multiple bilateral brain metastases requiring WBRT	Lorlatinib (18/20) = 90% Alectinib (2/20) = 10%
60-yo with poorly controlled diabetes mellitus	Lorlatinib (10/20) = 50% Alectinib (10/20) = 50%
60-yo with a history of anxiety or depression	Lorlatinib (11/20) = 55% Alectinib (9/20) = 45%
60-yo with congenital long QT syndrome or preexisting bradycardia	Lorlatinib (13/20) = 65% Alectinib (5/20) = 25% Crizotinib (1/20) = 5% Ensartinib (1/20) = 5%
60-yo with preexisting hypertension	Lorlatinib (16/20) = 80% Alectinib (4/20) = 20%
60-yo with chronic kidney disease and on dialysis	Lorlatinib (13/20) = 65% Alectinib (7/20) = 35%
80-yo with no comorbidities	Lorlatinib (10/20) = 50% Alectinib (10/20) = 50%

Keywords: mNSCLC, ALK inhibitor, survey

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.11 Prognostic Impact of Metastatic Tumor Burden in Patients With Egfr-Mutated Lung Cancer: Real-World Data From a Single Center

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Introduction: Non-small cell lung cancer (NSCLC) with EGFR mutation constitutes a well-defined molecular subtype with specific clinical and therapeutic characteristics. In the metastatic setting, tumor burden—defined by the number of metastatic sites—may hold prognostic value. This study evaluates clinical outcomes in a real-world cohort of patients with EGFR-mutated metastatic NSCLC, stratified by baseline metastatic burden.

Methods: We conducted a retrospective observational study of patients with EGFR-mutated metastatic NSCLC treated at our institution between January 2020 and January 2024. Clinical, demographic, and tumor-related variables were collected. Patients were categorized according to tumor burden at diagnosis: low (≤2 metastatic sites) or high (>2 sites). Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier curves, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

Results: Thirty-eight patients were included. Median age was 62.5 years; 71.1% were female and 44.7% were never smokers. Median PFS and OS for the total cohort were 18.5 and 24.5 months, respectively. At data cutoff, 34.2% remained on first-line therapy.Patients with low tumor burden showed better outcomes: PFS was 23.4 vs. 13.6 months (HR 2.32; 95% CI 1.03-5.23) and OS was 34.6 vs. 20.3 months (HR 1.82; 95% CI 0.75-4.41). While OS differences did not reach statistical significance, a clinically relevant trend was observed.

Conclusions: Lower metastatic tumor burden was associated with significantly longer PFS and a possible OS benefit in patients with EGFR-mutated NSCLC. Its role as a prognostic marker warrants consideration in clinical practice.

Table 1. Baseline characteristics of EGFRm population

Variable	Distribution
Age	Median: 62,5 years (range 37–80)
Stage IV at diagnosis	100%
Histology	Adenocarcinoma (100%)
Sex	Male: 28,9% Female: 71%
ECOG at diagnosis	0–1: 89.5% ≥2: 10.5%
Smoking history	Yes: 15,8% No: 44,7% Ex: 39,47%
EGFR mutation type	Exon 19 Del: 63,1% Exon 21 L858R: 26,3% Others: 10,5%
PD-L1 expression	<1%: 36,4% 1–49%: 47,3% ≥50%: 15.8%
Visceral metastases	60,5%
Brain metastases	31,6%
Treated oligometastatic disease	21,5%
Response to targeted therapy	CR: 7.9% | PR: 71,05% | SD: 21% | PD: 0%
Patients on active treatment (cut-off 05/02/2025)	34.2%

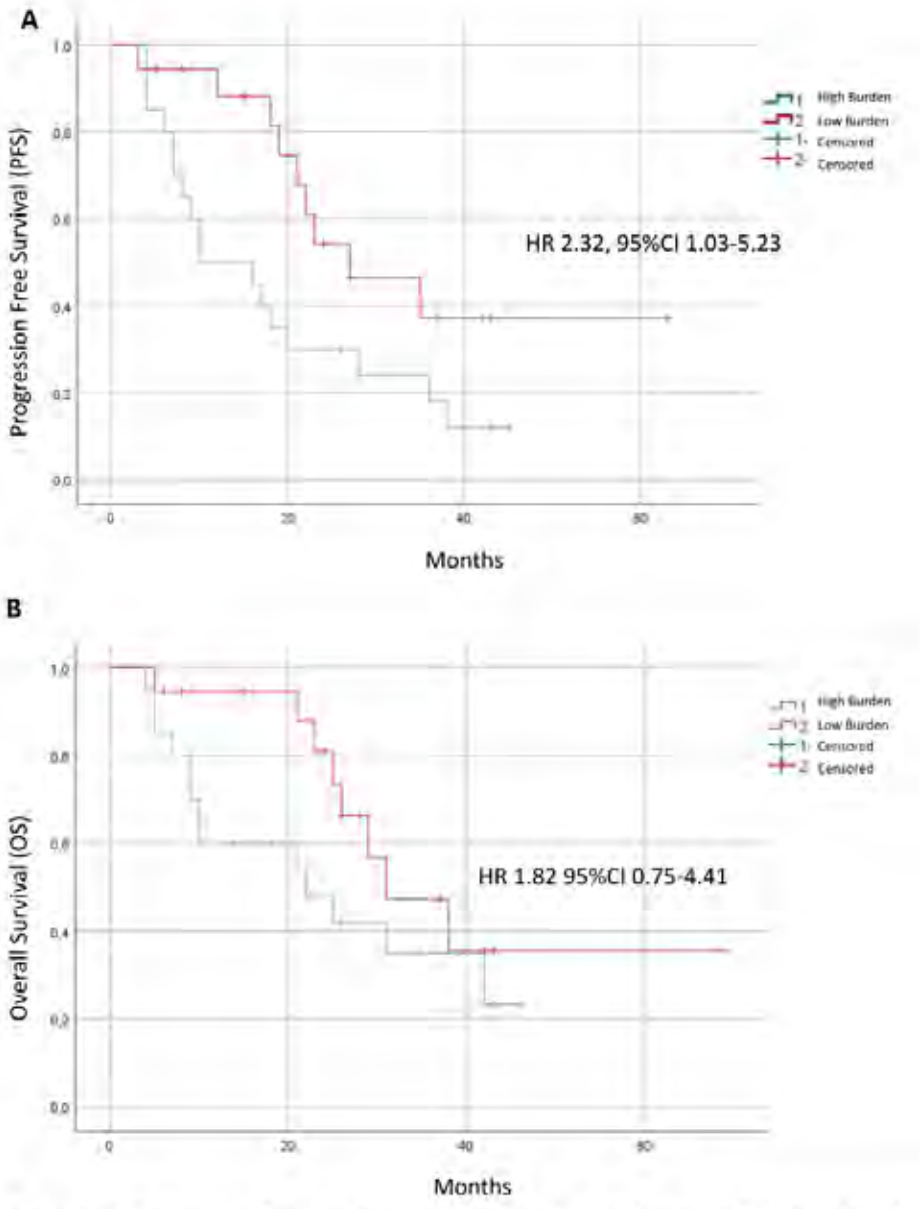

Figure 1. A. Progression free survival in the high burden of disease and low burden of disease groups. B. Overall survival in the high burden of disease and low burden of disease groups

Keywords: Real-world data, Tumor burden, EGFR-mutated NSCLC

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.12 Efficacy of Lazertinib in Treatment-Naive Patients for EGFR Mutated Non-Small Cell Lung Cancer With Brain Metastases

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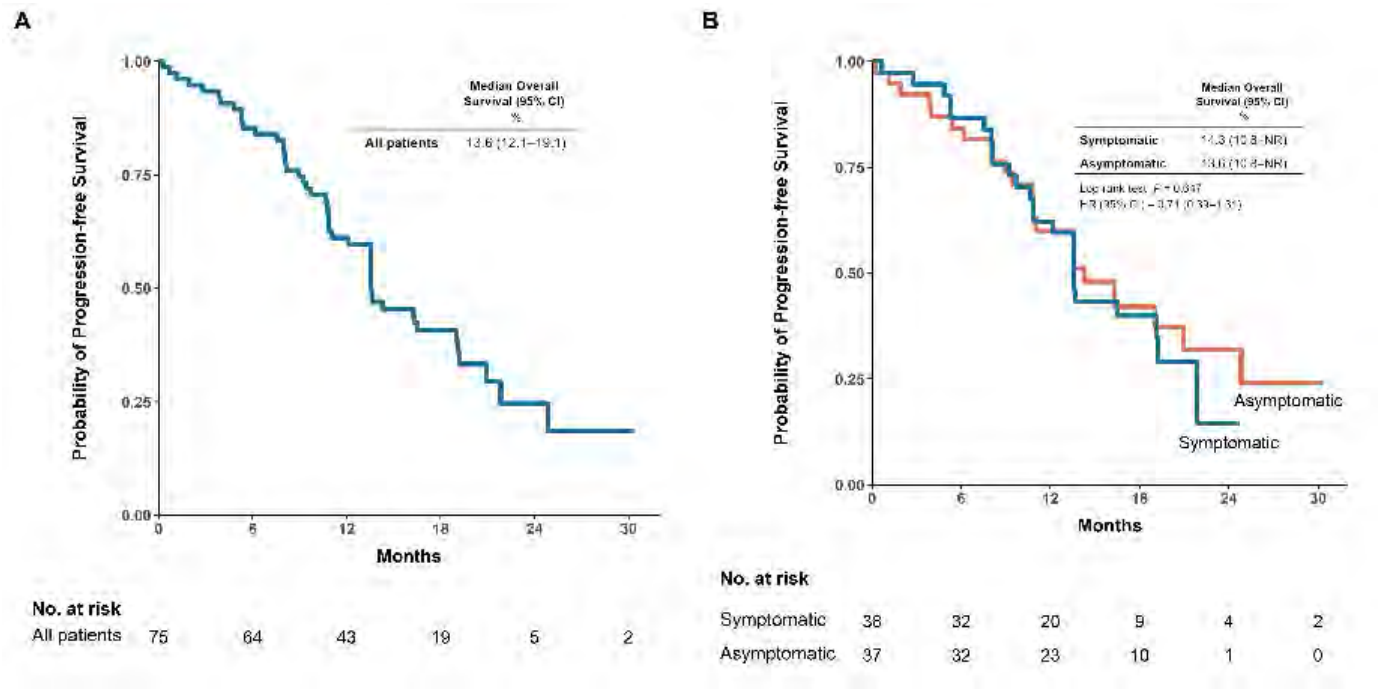
Introduction: Although non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) mutation is associated with brain metastasis, there is currently no guideline regarding local therapies combined with tyrosine kinase inhibitors (TKIs). We investigated the efficacy of the third-generation EGFR TKI, Lazertinib, in patients with EGFR-mutant NSCLC and brain metastases.

Methods: This study was a single-center, open-label, single-arm phase II trial. Patients with both symptomatic and asymptomatic brain metastases were included. All patients received oral Lazertinib 240 mg once daily, combined with local therapies based on multidisciplinary team discussions. The primary outcomes were progression-free survival (PFS), while key secondary outcomes included changes in symptoms based on the European Organization for Research and Treatment of Cancer (EORTC)-Quality of life Questionnaire 30 (QLQ-C30).

Results: A total of 75 patients were enrolled, with a median age of 65.0 years, 69.3% being female, and 25.3% having a history of smoking. Among EGFR mutation types, 53.3% had the E19del mutation, while 46.7% had the L858R mutation. Regarding brain metastasis symptoms, 37 patients were asymptomatic, 20 had mild symptoms, and 18 had moderate to severe symptoms. For the initial treatment modality, 56 patients received Lazertinib monotherapy, while 19 received Lazertinib with local therapy, including 2 with surgery, 8 with focal radiotherapy, and 9 with whole-brain radiotherapy. The median follow-up duration was 13.6 months, and the median PFS was 13.8 months (95% confidence interval [CI]: 12.1-19.1) among all study patients. There was no significant difference in median PFS between patients with initial neurologic symptoms and those without (14.3 vs. 13.6 months; log-rank test, P = 0.647). Among the 43 patients with disease progression, 16 (37.2%) experienced intracranial disease progression, while 27 (62.8%) had only extracranial disease progression. All QLQ-C30 symptom scores, except for diarrhea, improved after treatment initiation. There was no significant difference in symptom score changes between patients with initial neurologic symptoms and those without. The most common adverse event was paresthesia (71%), followed by skin rash (68%). Grade 3 or higher adverse events occurred in 17.3% of patients, and eight (10.7%) discontinued Lazertinib due to adverse events.

Conclusions: In the current trial including patients with symptomatic brain metastases, Lazertinib demonstrated a favorable PFS regardless of the presence of initial neurologic symptoms related to brain metastases. Further large-scale prospective studies involving patients with symptomatic brain metastases are warranted to establish guidelines for TKI treatment in combination with local therapies.



Keywords: Non-Small Cell Lung Cancer, EGFR Tyrosine Kinase Inhibitor, Brain Metastases

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.13 Gradually or Locally Progressed NSCLC Patients Benefit From Aumolertinib in Post-1L Dose-Escalation Treatment

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Introduction: Third-generation EGFR-TKIs demonstrate high selectivity for NSCLC with classical EGFR mutations and EGFR T790M mutations. Nevertheless, resistance is inevitable. Continuous EGFR-TKIs are recommended when patients experience localized progression. This study presents the efficacy and safety of using 165mg or 220mg of aumolertinib, a third-generation EGFR-TKI, in post-1L dose escalation treatment for gradual or localized progression NSCLC patients in the real world.

Methods: Patients with histologically confirmed metastatic NSCLC were enrolled and received first-line treatment with standard-dose aumolertinib (110 mg, once daily). When the patients showed gradual progression, a high-dose aumolertinib (165mg qd/220mg qd) was given subsequently until disease progression or intolerable toxicity. Gradual progression meant disease control ≥6 months, compared with the previous assessment, the tumor load was slightly increased by ≤2 points, symptom score ≤1 point or new brain metastasis. PFS1 was defined as the period from the initiation of first-line treatment to the second progression; PFS2 was defined as the period from the dose escalation treatment to the second progression. The primary endpoint was mPFS2. Secondary endpoints included mPFS1, ORR, DCR and safety.

Results: Forty-eight patients were enrolled. The median age was 63.02 years, and 41.7% were male. 21.7% were current/ever smokers. The dosage of aumolertinib was 165 mg in 11 cases and 220 mg in 37 cases depending on the presence or absence of brain metastasis. At the data cut-off (July 12, 2024), thirty patients (30/48) experienced disease progression after dose escalation, with CEA elevation in 12/30 cases and extracranial progression pattern in 24/30 cases. The median PFS2 of high-dose aumolertinib period was 13.2 months (95% CI 8.1-21.3). The ORR was 70.8% (55.9, 83.0), and the DCR was 100% (92.6, 100). Overall, the median PFS1 was 32.4 months (95% CI 26.4-36.5). The median OS was not reached. No new safety signals were identified. All common drug-related toxicities were mild rash and diarrhea. No grade≥3 AE was observed.

Conclusions: High-dose aumolertinib is an optional regimen for patients with advanced NSCLC who develop resistance following initial therapy. It demonstrates promising efficacy and an acceptable safety profile, thus warranting large-scale, multi-center clinical trials to optimize its dosing and patient selection criteria for enhanced clinical utility.

Keywords: Gradual or Localized Progression, Dose-Escalation, Aumolertinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.15 Predictive Value of Gastrin for the Absorption of pH-Dependent Small-Molecule Inhibitors in Patients With NSCLC

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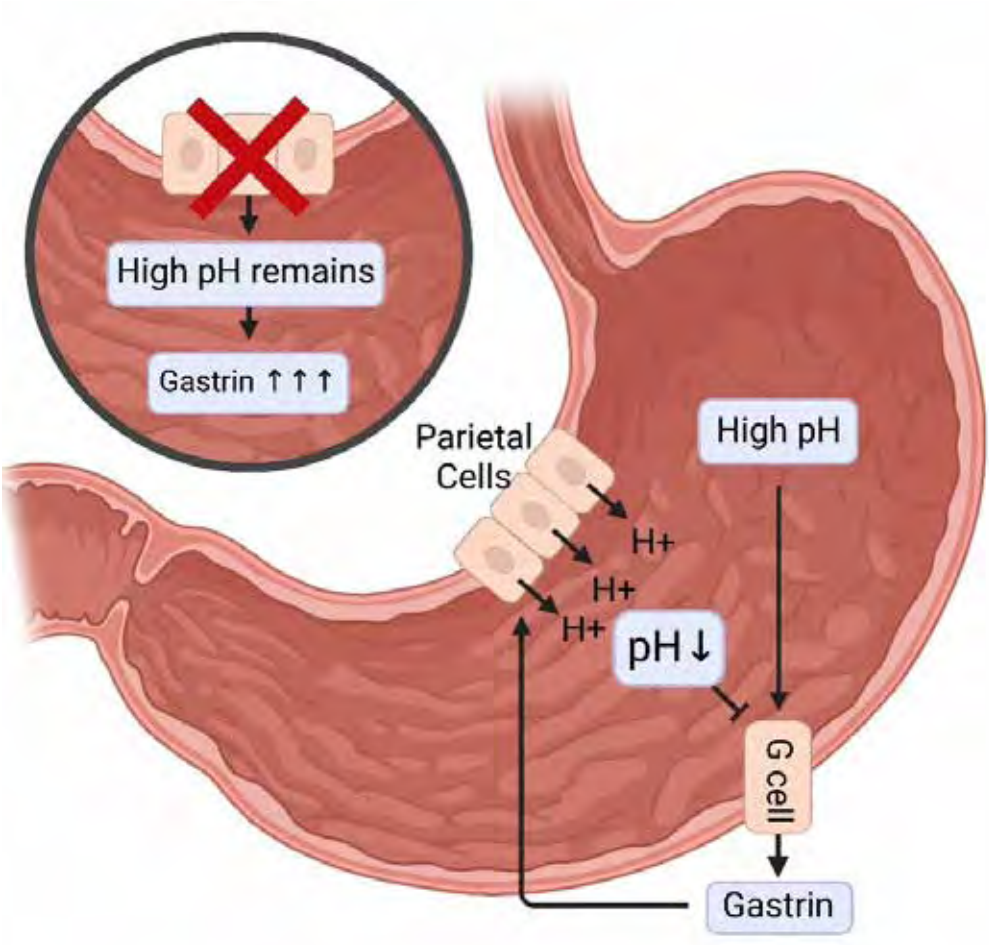
Introduction: Achlorhydria (AH) is the pathological condition characterized by chronically elevated gastric pH due to the destruction of acid-producing parietal cells. In response to the high gastric pH, gastrin levels are elevated (Figure 1). It is well established that proton pump inhibitors (PPIs), which elevate gastric pH iatrogenically, can significantly reduce the absorption of small-molecule inhibitors (SMIs) in metastatic lung cancer (LC) patients, potentially leading to treatment failure. Since the solubility and absorption of the SMIs erlotinib and sotorasib are pH-dependent, we hypothesize that gastrin, as marker of AH, could predict drug absorption and exposure in patients with LC.

Methods: We measured gastrin levels in prospectively collected samples from two cross-over drug-interaction studies with erlotinib in which dense blood sampling was performed during 24h. Also, consecutive single-day erlotinib and sotorasib samples from a prospective cohort study (NCT05221372) were used to quantify SMI and gastrin levels. For erlotinib, Area Under the Curve (AUC) and maximum (Cmax) and trough concentrations (Cmin 24h) were calculated. For sotorasib, only Cmin 24h was calculable. Spearman's correlation test used gastrin as a continuous variable, where the Mann-Whitney U test used gastrin ≥150 pg/ml to distinguish patients with AH for dichotomous comparison of the data.

Results: In total, SMI and gastrin levels were quantified from 52 patients who used erlotinib and 48 who used sotorasib. Gastrin as continuous variable showed a significant inverse correlation with erlotinib AUC0-12h (R = -0.277; p = 0.047) and Cmax (R = -0.423; p = 0.002). In 11 patients with AH, Cmax was 30% lower compared to 43 patients with physiological levels of gastrin (i.e. <150 pg/mL), c.q. 1169 vs 1672 pg/mL; p = 0.024. AUC0-12h was 26% lower in patients with AH, but this was not statistically significant (10052 vs 13529; p = 0.087) due to limited sample size. For sotorasib Cmin, no correlation was found with gastrin (R = 0.158; p = 0.255) in the total cohort.

Conclusions: Gastrin serves as an effective marker for the absorption and exposure of the pH-dependent SMI erlotinib. This was not the case for sotorasib Cmin. Patients with AH are at heightened risk for reduced erlotinib exposure and subsequent treatment failure. Future studies should focus on the pre-therapeutic assessment of gastrin levels to identify patients with AH, and explore interventions to mitigate treatment failure, such as adjusting the initial erlotinib dose or implementing therapeutic drug monitoring during treatment.



EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.16 Prolonged Survival in Oligometastatic ALK-Positive NSCLC: Impact of Local Ablative Therapy in a Multimodal Treatment Approach

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Introduction: Oligometastatic disease (OMD) in ALK-positive non-small cell lung cancer (NSCLC) presents a unique therapeutic challenge. Current guidelines advocate a multimodal approach, integrating tyrosine kinase inhibitors (TKIs) with local ablative therapy (LAT) to improve disease control and potentially prolong survival. However, long-term outcomes in this subset of patients remain poorly defined due to the rarity of the condition and the limited available data. This study aims to evaluate the prevalence, clinical impact, and survival outcomes of OMD in ALK-positive NSCLC.

Methods: This retrospective study included patients with oligometastatic ALK-positive NSCLC treated at Karolinska University Hospital from 2009 to 2021. Patient demographics, tumor characteristics, and treatment regimens were extracted from medical records. OMD was classified according to the Guckenberger framework as de novo (initial presentation with oligometastases), repeat (recurrence after prior oligometastatic disease), or induced (conversion from polymetastatic to oligometastatic disease following systemic therapy). Initial response to TKIs, median progression-free survival before first progression (PFS1), and sites of progression were recorded. A subset of patients with OMD underwent LAT, including radiotherapy or surgical resection of progressive lesions, while continuing the same TKI. Additionally, some patients were converted to an oligometastatic state but did not receive further LAT. Survival outcomes, including progression-free survival from first progression (PFS2) and overall survival (OS), were estimated using the Kaplan-Meier method.

Results: Among 160 patients with metastatic ALK-positive NSCLC, 64 (40.0%) developed OMD. The median follow-up was 74.0 months (95% confidence interval [CI]: 56.5-91.5), during which 16 patients died. The median OS was 160.0 months (95% CI: 101.4-218.6) for the whole cohort. Nine patients presented with de novo OMD, one experienced a recurrence (repeat OMD), and the majority (54 patients) developed induced OMD following systemic therapy. At the time of OMD diagnosis, 58 patients were receiving an ALK-TKI, four were on chemotherapy, and two had not started systemic therapy. LAT was administered to a total of 45 patients. Among these, 3 received consolidative external beam radiotherapy, 16 underwent stereotactic body radiotherapy (SBRT), 23 received stereotactic radiosurgery (SRS), and 2 underwent surgical procedures. The mPFS1 from the start of systemic therapy was 14.0 months (95% CI: 10.3-17.7), while the mPFS2 from the first progression was 14.0 months (95% CI: 5.6-22.4). Treatment-related toxicities were observed in a subset of patients, with pneumonitis reported in two cases, radiation-induced brain toxicity in seven cases, and radiation esophagitis in one case; all events were classified as CTCAE grade 1 to 3.

Conclusions: This study demonstrates that oligometastatic ALK-positive NSCLC is associated with a prolonged overall survival of over 10 years. LAT is linked to extended progression-free survival after first progression, supporting its inclusion in multimodal treatment strategies. While some patients experienced treatment-related toxicity, adverse events were generally mild to moderate and manageable. These findings underscore the potential role of LAT in carefully selected patients with OMD and highlight the need for prospective studies to refine treatment approaches and optimize patient outcomes.

Keywords: Oligometastatic disease, ALK-positive NSCLC, Local Ablative Therapy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.17 NNMT as a Therapeutic Target in EMT-Associated Osimertinib Acquired Resistance in EGFR-Mutant Lung Adenocarcinoma

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Introduction: EGFR-mutant lung adenocarcinoma demonstrates high initial sensitivity to osimertinib, a third-generation EGFR tyrosine kinase inhibitor. However, the emergence of acquired resistance remains a major clinical challenge, with limited therapeutic options available upon progression. Elucidating the molecular mechanisms driving resistance is essential for the development of more effective and durable treatment strategies.

Methods: Osimertinib-resistant cell lines (HCC827-OR) were established by exposing HCC827 parental cells to gradually increasing concentrations of osimertinib over six months. Cell viability was assessed using MTT assays. EMT marker expression was evaluated by western blotting, and functional changes were assessed using transwell migration and invasion assays, as well as 3D oncosphere formation assays. RNA sequencing (RNA-Seq) was performed to compare transcriptomic profiles between HCC827-OR and parental cells. Differentially expressed genes (DEGs) were identified and visualized through heatmaps and volcano plots. Expression changes were validated using qRT-PCR and western blotting. Functional enrichment analysis, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, was conducted based on DEG-associated protein-protein interaction networks.

Results: HCC827-OR cells exhibited mesenchymal-like morphology, accompanied by decreased E-cadherin and increased Vimentin and N-cadherin expression. Functionally, HCC827-OR cells showed significantly increased migration, invasion, and 3D sphere-forming capacity compared to parental cells. Transcriptomic profiling revealed 2,587 DEGs, including 1,621 upregulated and 966 downregulated genes. KEGG pathway enrichment of the upregulated genes highlighted activation of the PI3K-AKT signaling pathway, focal adhesion, and Rap1 signaling pathways. Among the top 10 upregulated genes, Nicotinamide N-methyltransferase (NNMT) was significantly overexpressed in resistant cells. Importantly, genetic knockdown of NNMT substantially restored osimertinib sensitivity in HCC827-OR cells, indicating its functional role in acquired resistance.

Conclusions: Our findings identify NNMT as a critical mediator of osimertinib resistance in EGFR-mutant lung adenocarcinoma. These findings support NNMT as a promising, actionable target to re-sensitize resistant tumors and improve outcomes in EGFR-mutant NSCLC. Further investigation is warranted to explore clinical translation of NNMT inhibition strategies.

Keywords: Osimertinib Resistance, Epithelial-to-Mesenchymal Transition (EMT), Nicotinamide N-methyltransferase (NNMT)

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.18 Osimertinib-Associated Asymptomatic Depigmented Skin Macules in a Mexican Cohort

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Introduction: First and second-generation EGFR-TKI's most commonly cause papulopustular acneiform rash, pruritus, and nail toxicities. Typically, cutaneous toxicities are low grade (Common Terminology Criteria for Adverse Events Grade 1-2) but reports of severe grades have been recorded and have led to dose modification or interruption of cancer treatment. Currently, less literature exists describing cutaneous toxicities from third-generation EGFR-TKI's, like Osimertinib. These skin reactions are well documented in patients with lighter skin, there is a paucity of literature and images to guide clinicians in their assessment in patients with darker skin tones. We present a series of cases of asymptomatic depigmented skin macules occurring during osimertinib treatment. To our knowledge, this is a pigmentary change secondary to a third-generation EGFR-TKI no reported previously.

Methods: A total of 42 patients with advanced NSCLC receiving Osimertinib in first line treatment were analyzed from January 2022 through May 2024. We summarize to better understand. We review patients with any dAE associated with osirmertinib use. For each case the following data were extracted, age, sex , Osimertinib dose, characterization of dAE, intervention and outcome. Skin toxicities were graded according to CTCAE version 4.03. All data presented are descriptive.

Results: The 42 patients included for this analysis. The average age of the patients was 64 years, and 64 % of patients were female. In the EGFR mutation-positive, (77.3%) were exon 19, 5 (22.7%) were exon 21. The median timing taking Osimertinb was 16.8 months. It develops after around 6 months of therapy and usually are more evident when treatment continues. Patients present progressive skin discoloration on upper arms, forearms, hands, thorax and facxe. This effect is characterized by well-defined depigmented skin macule on the measuring millimeters to centimeter (Figure 1). These were usually asymptomatic grade 2 or below, no dose reduction or discontinuation were necessary.

Conclusions: Pigmentary changes secondary to Osimertinib have been reported rarely and have been attributed to post-inflammatory changes. To our knowledge, this report represents a onset pigmentary changes due to Osimertinib in the published literature. This dAE has a female predominance, mostly in more pigmentated skin types primarily seen in our patient of Latin descent, in patient taking Osimertinib for at least 6 moths to over 2 years. The majority of patient has good and long responses, it will be important to weigh the benefit analysis. Treatment options have no yet been considered, but we hope our report encourages continued efforts in characterize this dAE.

Keywords: Pigmentary changes, Lung cancer, Osimertinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.19 Efficacy of Aumolertinib in Patients With Advanced NSCLC for Uncommon EGFR Exon 19 Deletion Mutations

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Introduction: The exon 19del L747_P753>S is associated with inferior progression free survival (PFS) compared with common E746_A750del mutation, with an incidence of only 2.8%. The purpose of this study is to investigate the clinical efficacy for patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring ex19del L747_P753>S who received the third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) aumolertinib at first-line therapy (1L) or subsequent-line therapy (≥2L), and to provide a valuable therapy regimen with a potential benefit for these pts.

Methods: We collected 10 pts confirmed NSCLC with uncommon ex19del L747_P753 > S mutation in our hospital over the last 5 years. All pts had 1-2 metastasis sites including lung, bone, brain, pleura and lymph nodes. Total 9 pts received 1L therapy, and 1 patient received fourth-line treatment (4L). The mutation was confirmed by NGS assay, of which 7 subjects were detected by tissue,, 2 pts were detected by blood and 1 pts were detected by pleural effusion. All pts were received aumolertinib (110 mg), and 5 of them were received aumolertinib plus platinum-pemetrexed.

Results: Among the 9 pts who received 1L treatment, 3 pts were treated with aumolertinib monotherapy, the PFS were 12 and 16 months respectively, and another patient is still received aumolertinib. For the combination therapy of 6 pts, 4 of them had PFS of 5,8,13,15 months respectively, 2 pts has not progression. In this study, there had 1 patient with 4L treatment and benefited from combination chemotherapy for 5 months so far.The pts were well tolerated during treatment, and there were no grade ≥3 adverse events (AEs) occurred after treatment with aumolertinib monotherapy, only 1 patient developed grade 2 abnormal liver function. The most common AEs of combination therapy were grade 2 gastrointestinal reactions(60%) and grade 3 leukopenia(60%).

Conclusions: This is the first report showed that aumolertinib monotherapy or combined with chemotherapy performed positive efficacy and safety in pts with ex19del L747_P753>S mutation. It is necessary to conduct further exploration for clinical efficacy of aumolertinib in uncommon ex19del mutations in a larger scale.

Keywords: uncommon EGFR mutations, NSCLC, Aumolertinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.20 A Realworld Study: Clinical Molecular Characteristics and Prognostic Factors of NSCLC With MET Alteration

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Introduction: The MET proto-oncogene, a member of the receptor tyrosine kinase (RTK) family, encodes the hepatocyte growth factor receptor (HGFR). In non-small cell lung cancer (NSCLC), MET dysregulation occurs through protein overexpression, gene amplification, or specific mutations such as MET exon 14 skipping (METex14). While MET tyrosine kinase inhibitors (TKIs) like capmatinib and savolitinib are FDA-approved for METex14-altered NSCLC, their efficacy in primary MET-amplified disease remains under investigation. Notably, combined MET- and EGFR-TKI therapy has shown promising activity in EGFR-TKI-resistant NSCLC with secondary MET amplification. However, real-world data on their clinical impact and optimal management remain limited. This real-world study aims to characterize the clinicopathological and molecular profiles of MET-altered NSCLC and to identify prognostic factors influencing progression-free survival (PFS) and overall survival (OS).

Methods: We retrospectively analyzed 170 NSCLC patients with MET alterations from a cohort of 2,180 cases at the First Affiliated Hospital of Xi'an Jiaotong University. Clinicopathological features, treatment responses, and survival outcomes were assessed. Prognostic factors were evaluated using Kaplan-Meier and Cox regression analyses. Statistical analyses were performed using GraphPad Prism 9.5, IBM SPSS Statistics R26.0.0.0, and R (v4.3.0).

Results: MET alterations were detected in 7.79% of NSCLC patients, predominantly in elderly (median age: 65 years), non-smoking (53%), and adenocarcinoma (83%) populations. Among primary MET alterations (n=112), including MET mutation (40 cases), of which METex14 skipping (36 cases) is the most common mutation, amplification (25 cases), and overexpression (58 cases). Acquired MET alterations were seen in 58 patients. Metastasis frequently involved bone (30%), lung (28%), and brain (22%). Savolitinib demonstrated superior efficacy over crizotinib. Crizotinib: For METex14 skipping vs. MET amplification, objective response rates (ORR) were 60% vs. 33.33%, and disease control rates (DCR) were 80% vs. 58.33%. Savolitinib: ORR was 53.33% vs. 68.75%, and DCR was 86.67% vs. 81.25% for METex14 skipping vs. MET amplification, respectively. First-line MET-TKI mPFS was 8.2 months (95% CI: 2.244-14.156) vs. 5.5 months (95% CI: 4.260-6.740) for later-line therapy. TP53 co-mutations (HR: 2.68, P=0.007) and second-/later-line MET-TKIs (HR: 2.9, P=0.002) independently predicted worse PFS. Median OS (mOS) was 24.8 months (95% CI: 22.08-27.52) overall and 14.5 months (95% CI: 1.71-27.29) for primary MET-altered cases. Independent OS predictors included smoking (HR: 2.21, P=0.043), stage IIIB-IV (HR: 3.58, P=0.036), and treatment with immunotherapy/chemotherapy (HR: 0.16, P=0.021) or targeted therapy (HR: 0.41, P=0.043). Common adverse events included edema (31.30%), liver dysfunction (13.91%), diarrhea (13.04%), fatigue (12.17%), and nausea/vomiting (8.69%).

Conclusions: MET-altered NSCLC exhibits distinct clinicopathological features. Next-generation MET-TKIs (e.g., savolitinib) show improved efficacy over crizotinib, particularly in METex14-mutated cases. TP53 co-mutations and treatment timing critically influence survival, highlighting the need for biomarker-guided therapeutic strategies. These findings underscore the need for optimized therapeutic strategies in MET-driven NSCLC.

Keywords: MET alteration, non-small cell lung cancer, Targeted therapy

EP.12.21 The Impact of Afatinib and Osimertinib Plasma Concentrations on Treatment Toxicities, Quality of Life, and Effectiveness in Patients With NSCLC

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Introduction: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are widely used as first-line treatments for advanced EGFR-mutated non-small cell lung cancer (NSCLC). However, inter-patient variability in drug exposure may influence treatment toxicities, quality of life (QoL), and therapeutic outcomes. This study evaluated the impact of afatinib and osimertinib plasma concentrations on toxicities, QoL, and treatment effectiveness.

Methods: This prospective study enrolled treatment-naïve NSCLC patients receiving afatinib or osimertinib. Plasma concentrations were measured at Week 2 using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Treatment-related toxicities and QoL were assessed at Weeks 2 and 4. Associations between plasma concentrations, toxicities, QoL, and progression-free survival (PFS) were analyzed.

Results: A total of 45 patients (25 afatinib, 20 osimertinib) were included. A trend of negative correlation between plasma concentration and body mass index (BMI) was observed, though not statistically significant (Fig.1). Higher afatinib plasma concentrations were significantly associated with increased dermatology life quality index (DLQI) scores (p=0.001) (Fig.1) and greater anti-diarrhea agent use (p=0.024) (Fig.2), indicating higher toxicity. Elevated osimertinib plasma concentrations were significantly correlated with impaired physical (p=0.017) and social functioning (p=0.003) (Fig.2). Additionally, patients with higher osimertinib plasma concentrations had longer PFS (p=0.022) (Fig.2).

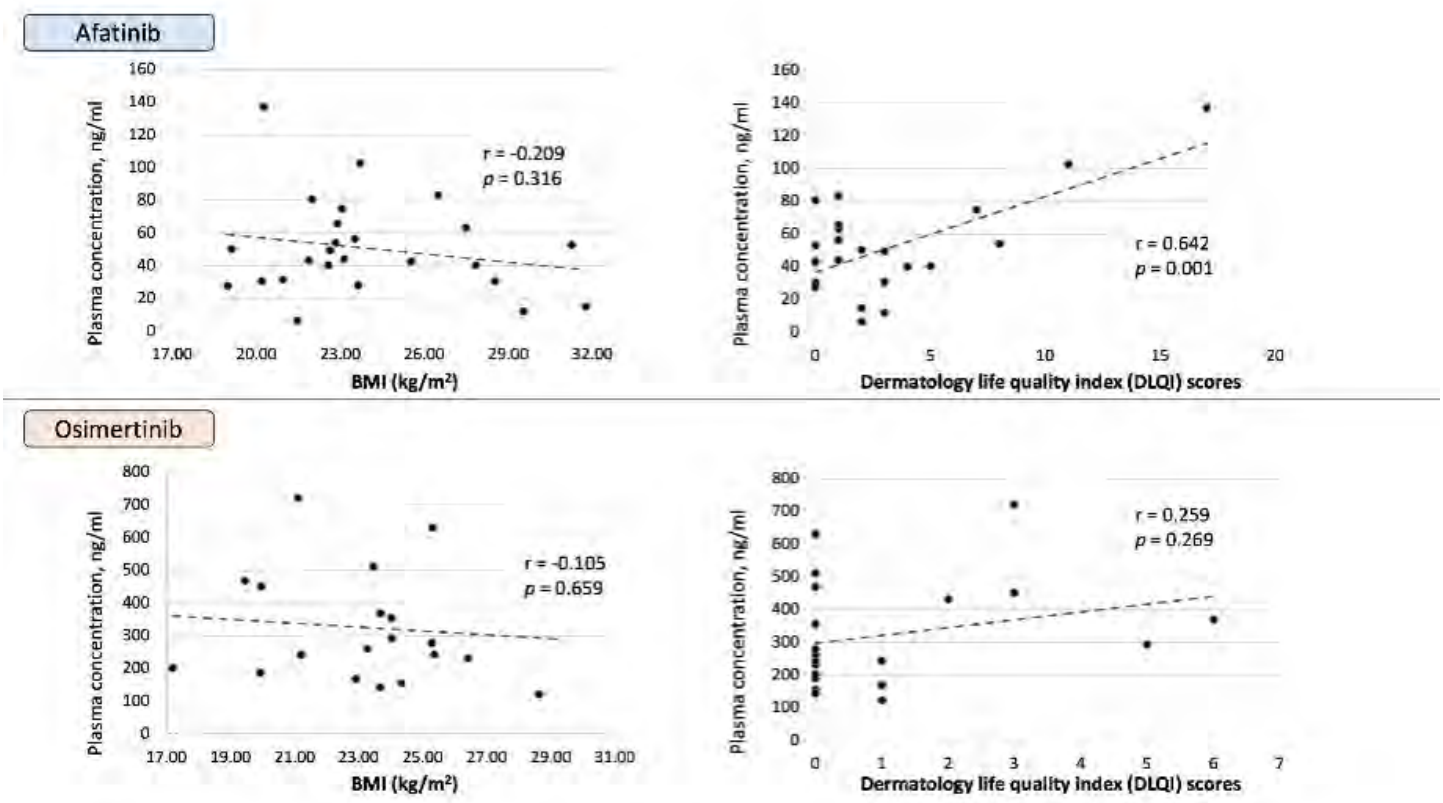

Fig. 1. Correlation analyses of plasma concentrations with BMI and treatment-related toxicities (DLQI) for afatinib and osimertinib.

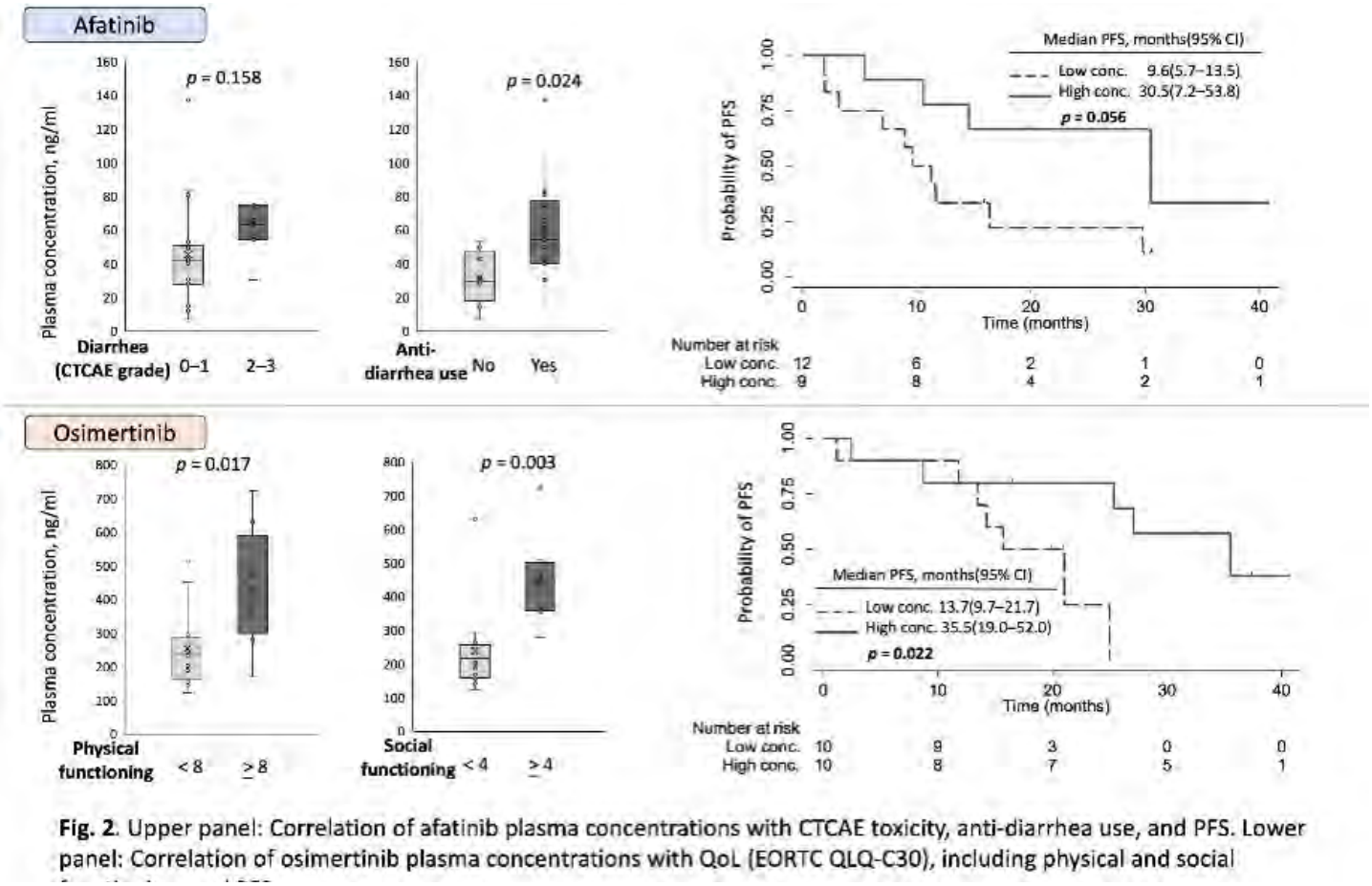

Fig. 2. Upper panel: Correlation of afatinib plasma concentrations with CTCAE toxicity, anti-diarrhea use, and PFS. Lower panel: Correlation of osimertinib plasma concentrations with QoL (EORTC QLQ-C30), including physical and social

Conclusions: Afatinib and osimertinib plasma concentrations are associated with treatment toxicities, QoL, and effectiveness. Therapeutic drug monitoring (TDM) may help optimize dosing strategies to minimize adverse events while maintaining efficacy in NSCLC patients.

Keywords: therapeutic drug monitoring, EGFR-TKI, precision medicine

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.22 Clinical Treatment Outcomes of Erlotinib in Metastatic Non-Small Cell Cancer Harboring Uncommon EGFR Mutations

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Introduction: Patients with non-small cell lung cancer (NSCLC) harboring uncommon epidermal growth factor receptor (EGFR) mutations often exhibit variable responses to EGFR tyrosine kinase inhibitors (TKIs). This study evaluates the clinical outcomes of first-line erlotinib in patients with advanced NSCLC harboring uncommon EGFR mutations, compared to those with common mutations.

Methods: We conducted a retrospective analysis of 193 patients with advanced NSCLC and documented EGFR mutations, treated with erlotinib at Chonburi Hospital, Thailand, from January 1, 2020, to December 31, 2023. We collected data on patient demographics, mutation types, treatment regimens, progression-free survival (PFS), overall survival (OS), and physician-assessed objective response rates.

Results: Patients with uncommon EGFR mutations (10.3%) had significantly shorter median OS (7.6 months, 95% CI: 3.2-12.0) and PFS (5.7 months, 95% CI: 0.0-11.4) compared to those with common EGFR mutations (median OS: 19.5 months, 95% CI: 15.8-23.2; median PFS: 11.0 months, 95% CI: 9.2-12.7). The objective response rate to erlotinib was lower in patients with uncommon mutations (33.3% had partial responses) compared to those with common mutations (78.1% for Exon 19 deletion and 82.4% for L858R). Multivariate analysis identified ECOG performance status as a significant prognostic factor for survival in patients with uncommon EGFR mutations.

Conclusions: Patients with advanced NSCLC harboring uncommon EGFR mutations exhibit poorer survival outcomes with first-line erlotinib treatment compared to those with common mutations. Alternative treatment strategies and personalized approaches are warranted for these patients.

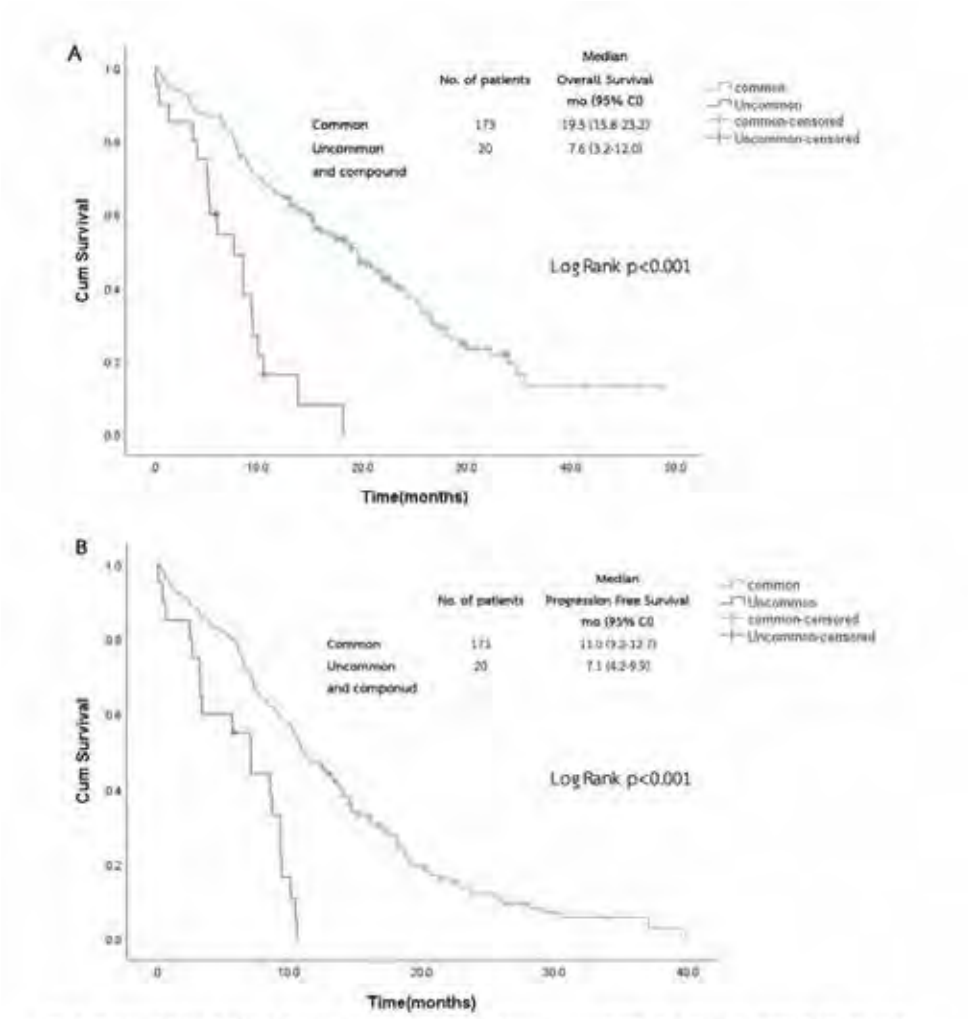

Fig 1. Kaplan-Meier Analysis Comparing Common and Uncommon EGFR Mutations in NSCLC (A) Overall survival (B) Progression free survival

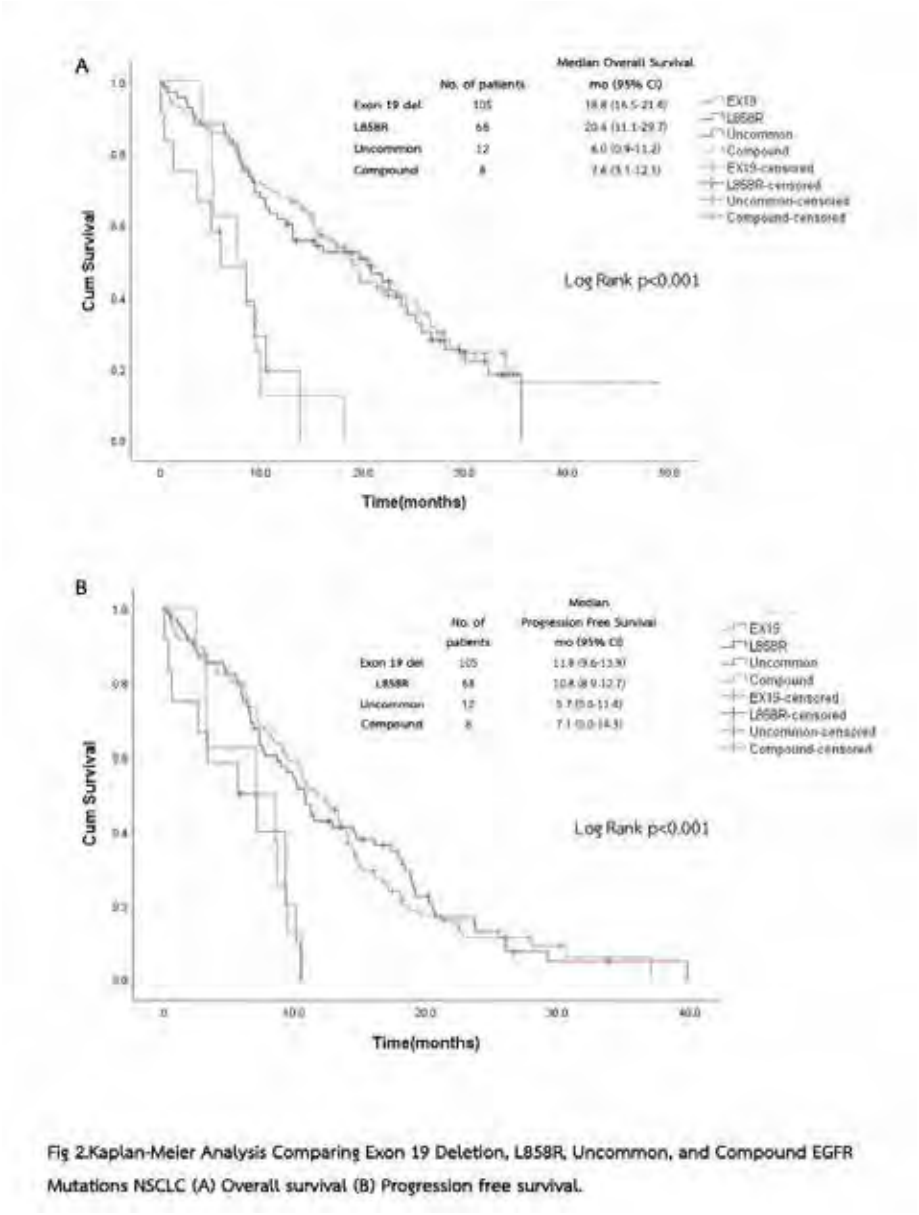

Fig 2.Kaplan-Meier Analysis Comparing Exon 19 Deletion, L858R, Uncommon, and Compound EGFR Mutations NSCLC (A) Overall survival (B) Progression free survival.

Keywords: Uncommon EGFR Mutations, Non-Small Cell Lung Cancer (NSCLC), Compound EGFR Mutations

EP.12.23 Disease Burden and rwPFS as a Surrogate Endpoint for rwOS in NTRK+ NSCLC and Other Advanced/Metastatic Solid Tumors

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Introduction: Neurotrophic tropomyosin receptor kinase rearrangements (NTRK+) are rare oncogenic fusions identified across solid tumors. However, incidence and prevalence remain poorly characterized. Real-world progression-free survival (rwPFS) provides key insights into treatment effectiveness and disease progression as a surrogate endpoint for real-world overall survival (rwOS) when follow-up time is limited. This study aimed to estimate disease burden (prevalence and incidence) and the relationship between rwPFS and rwOS in patients with NTRK+ advanced/metastatic solid tumors.

Methods: Patients were included from the US-based deidentified Flatiron Health (FH)-Foundation Medicine (FMI) solid tumor and pantumor Clinico-Genomic Databases with clinical data from the FH Research Database linked to genomic data derived from FMI comprehensive genomic profiling tests. Patients were diagnosed with advanced/metastatic solid tumors on/after 2011 and received ≥1 line of therapy in the advanced/metastatic setting (data cutoff: March 31, 2024). NTRK+ prevalence was assessed overall and by tumor type. Incidence was reported overall and between 2013-2024. We estimated rwPFS and rwOS from first-line treatment start (Kaplan-Meier); evaluated relationships between rwPFS and rwOS (Spearman's rank correlation coefficient [ρ]; Kendall's tau as a supportive measure); and evaluated rwOS between patients with/without progression at the 12-month landmark (Cox proportional hazard models, unadjusted and adjusted for prognostic factors).

Results: This study included 159 (0.20%) patients with NTRK+ advanced/metastatic solid tumors across 28 tumor types, most commonly non-small cell lung cancer (NSCLC, 23%), colorectal cancer (CRC, 22%), and breast cancer (BC, 16%). NTRK+ prevalence was highest in CRC (0.28%), BC (0.21%), and NSCLC (0.20%). Overall incidence was 201 per 100,000 cases (76-288/100,000 cases/year). Among 88 patients (55.3%) with progression, median rwOS was 21 months (95% CI, 18-47), and median rwPFS was 8.6 months (95% CI, 6.7-11). Correlation between rwPFS and rwOS was moderate (Spearman's ρ, 0.64 [0.44-0.77]; Kendall's tau, 0.46 [95% CI, 0.34-0.57]). Disease progression at 12 months was significantly associated with higher risk of death, in univariate and multivariate analyses (Table).

Conclusions: This is among the largest real-world studies to characterize disease burden of NTRK+ and first to assess rwPFS as a surrogate endpoint for rwOS. NTRK+ were rare and varied by tumor type. A statistically significant mortality risk between rwPFS and rwOS suggests rwPFS as a meaningful surrogate endpoint. Continued research is needed to optimize outcomes for these patients.

Table. Progression Landmark Analysis for Patients With Advanced/Metastatic *NTRK+* Solid Tumors

Landmark time	Landmark status	HR (95% CI) for rwOS	*P* value
Univariate analysis			
12-month	Progressed	2.87 (1.39-5.91)	<.01
12-month	Did not progress	Reference	
Multivariate analysis[a]			
12-month	Progressed	9.93 (2.87-34.33)	<.01
12-month	Did not progress	Reference	

[a] Multivariate analysis adjusted for prognostic factors, including age at advanced diagnosis, smoking status, stage at initial diagnosis, time from initial diagnosis to advanced diagnosis, and ECOG. Histology data are available only for breast cancer and NSCLC, thus not included in the model.

Keywords: NTRK+ solid tumor, Surrogacy endpoint, Disease burden

EP.12.24 Common vs Uncommon EGFR Mutations in NSCLC and the Potential Prognostic Role of Neutrophil-To-Lymphocyte Ratio

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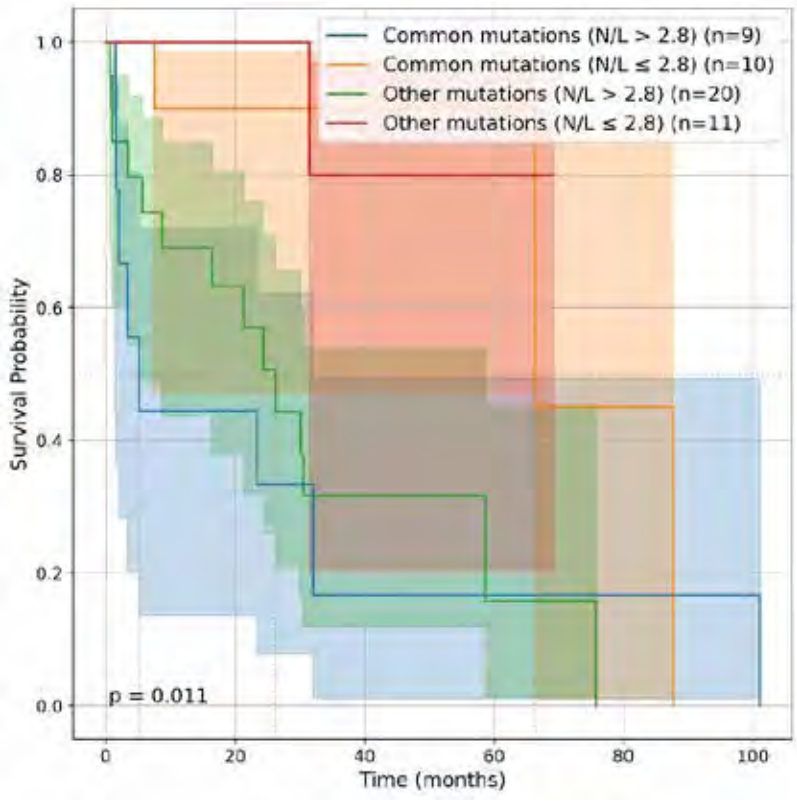
Introduction: Patients with advanced unresectable or metastatic Non-Small Cell Lung Cancer (NSCLC) harboring Epidermal Growth Factor Receptor (EGFR) mutations can achieve prolonged remission with targeted therapies. However, clinical outcomes vary considerably due to tumor heterogeneity and interindividual differences. EGFR mutations are traditionally classified as common (exon 19 p.Glu746_Ala750del and exon 21 p.Leu858Arg) or uncommon. The prognostic significance of these EGFR mutation subtypes remains uncertain. This study investigates survival differences based on EGFR mutation subtype in advanced NSCLC, incorporating the neutrophil-to-lymphocyte ratio (NLR) as an additional prognostic marker.

Methods: This single-center, retrospective study included 50 patients diagnosed and treated at the Medical Oncology Department of San Cecilio Hospital, Granada, Spain. All patients had confirmed EGFR-mutated NSCLC. Clinical and analytical data, treatments received, mutation types determined by Next Generation Sequencing (NGS), and survival outcomes were retrospectively reviewed. Survival analyses, including Progression-Free Survival (PFS) and Overall Survival (OS), were performed using Kaplan-Meier curves and log-rank tests. Patients were stratified by mutation subtype (common vs uncommon) and baseline NLR (≤2.8 vs >2.8).

Results: Of 50 patients analyzed, median age was 64 years (range 31-88), 86% presented stage III-IV disease, and 10% had brain metastasis at diagnosis. Common mutations included exon 21 p.Leu858Arg (30%) and exon 19 p.Glu746_Ala750del (20%). Uncommon mutations included exon 19 SNV p.Ala750Pro (8%), exon 19 DELINS p.Leu747_Ala750delinsPro (4%), exon 20 duplication p.Ser768_Asp770dup (4%), and exon 19 INDEL p.Glu746_Ala750del (4%). PD-L1 expression <1% was noted in 28%. Mean NLR at diagnosis was 5.8 ± 7.0, and 9.9 ± 21.0 at last follow-up.

No significant differences in survival were observed between mutation subtypes alone (median OS: common 32.0 months vs uncommon 31.5 months; p=0.895). However, integrating baseline NLR revealed significant prognostic stratification. Patients with common mutations and NLR >2.8 had significantly worse OS (5.2 months) compared to those with NLR ≤2.8 (66.3 months). In patients with uncommon mutations, OS was 26.2 months for NLR >2.8, while median OS was not reached for those with NLR ≤2.8 (p=0.011).

Conclusions: Incorporating neutrophil-to-lymphocyte ratio at diagnosis significantly enhances prognostic accuracy. Patients with high NLR (>2.8) have poorer survival outcomes, especially those harboring common EGFR mutations. NLR may thus represent a valuable biomarker complementing EGFR mutation analysis, potentially guiding therapeutic decisions.



Keywords: EGFR, Neutrophil-Lymphocyte Ratio, uncommon

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.25 Demographic Influences on Treatment Preferences in Advanced EGFR+ mNSCLC: A Qualitative Analysis of Patient Perspectives on Osimertinibb

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Introduction: As first-line treatment options for EGFR+ metastatic non-small cell lung cancer (mNSCLC) continue to expand, shared decision-making plays a crucial role in aligning treatment plans with patients' values. Targeted therapies such as Osimertinib offer benefits like convenience and independence. Recent studies, including FLAURA2 and MARIPOSA, investigate therapeutic combinations with intravenous drugs, demonstrating greater efficacy but increased side effects, highlighting the need for patient-centered, unbiased approaches. This study explores how demographic factors influence treatment preferences among patients with EGFR+ metastatic non-small cell lung cancer (mNSCLC) considering first-line therapies.

Methods: With ethics board approval, we carried out an interpretive descriptive qualitative study, guided by the Ottawa Decision Support Framework. Inclusion criteria were: adults aged 18 and older; diagnosis of mEGFR+ NSCLC; current or prior Osimertinib therapy; and proficiency in English. Interviews were held via Microsoft Teams using a standardized interview guide. We used purposeful sampling until we reached thematic saturation and recruited an additional 3 participants to ensure adequate saturation. Data were analyzed through inductive thematic analysis and identified themes were mapped onto the Ottawa Decision Support Framework.

Results: Sixteen participants were interviewed from Sep-Nov 2024: median age 62 years; 11 females; 13 currently taking Osimertinib; 10 diagnosed >1 year before participation. All participants recognized the advantage of Osimertinib in prolonging life and enabling them to continue daily activities. However, they also noted disadvantages, particularly specific side effects that caused physical discomfort. Considering these trade-offs, participants described that Osimertinib provided a sense of hope and stability. Men more commonly reported immediate physical relief, such as pain reduction, while women more frequently emphasized long-term quality of life and the ability to maintain daily activities. Younger participants (under 62) described advantages of survival and long-term treatment effectiveness. Younger participants also noted that taking Osimertinib made it easier to distance themselves from their cancer diagnosis, with some expressing that having just one pill a day felt less intrusive and served as a smaller reminder of their terminal illness. Older participants (over 62 [the median]) described advantages of pain management and sustaining normal routines. When it came to discussing hypothetical combination therapy of Osimertinib plus intravenous treatment, younger patients asked for more information on the evidence of effectiveness and described the importance of preserving access to future therapies, including second-line options. Both older and younger participants described the impact of IV treatment on their quality of life as a disadvantage. Patients who had previously undergone earlier treatments (e.g. afatinib, chemotherapy) had stronger opinions about whether they would be willing to try the combination therapy, influenced by their initial experience with the treatment.

Conclusions: Across different demographics, sex, age, and prior treatment experience, participants vary in how they perceive the drug's benefits and drawbacks. The findings emphasize the need to customize counseling based on personal characteristics and the importance of asking participants what advantages they want to gain and disadvantages they want to avoid to ensure their own preferences inform treatment decisions.

Keywords: Treatment preferences, Demographic influences, Shared decision-making

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.26 Multi-Omics Decipher the Molecular Landscape of EGFR+ Non-Small Cell Lung Cancer Patients Following Osimertinib Treatment

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Introduction: Targeted therapy with tyrosine kinase inhibitors (TKIs) against Epidermal Growth Factor Receptor (EGFR) is part of clinical routine for around 10-15% of advanced non-small cell lung cancer (NSCLC) patients with tumors harboring activating mutations in the kinase domain of EGFR. Osimertinib is a third-generation EGFR TKI displaying potency to both activating kinase domain EGFR mutations and the T790M gatekeeper mutation. Osimertinib is approved by the FDA and EMA for usage in the first-line setting to NSCLC patients with EGFR activating mutations regardless of presence of T790M. Despite improved clinical response following osimertinib treatment compared to treatment with first-generation EGFR TKIs, resistance is inevitable. Intriguingly, a significant fraction of resistant cases following osimertinib treatment cannot be linked to additional genetic aberrations. Here we analyzed if circulating RNAs as well as circulating proteins could provide clues of molecular factors associated with acquired resistance to osimertinib.

Methods: Plasma was collected at baseline and progression of disease using paired samples from 20 patients enrolled in the multicenter phase II study First-line treatment with osimertinib in EGFR-mutated non-small cell lung cancer (FIOL). Plasma was centrifuged at 16000g followed by exosomal RNA extraction using Qiagen exoRNeasy Midi kit according to manufacturers' instructions. Total RNA was subjected to paired-end 150 Illumina sequencing with ribodepletion (mRNA-seq, lncRNA-seq) or single-end 50 Illumina sequencing (microRNA-seq). For systematic protein analysis, plasma was subjected to the SomaLogic SomaScan 7K Assay Kit, measuring more than 7000 proteins.

Results: Systematic transcriptome profiling revealed hundreds of differentially expressed mRNA transcripts, adjusted p-value <0.05, while 13 microRNAs and 17 proteins displayed differential expression using an identical statistical cutoff. Interestingly, 16 out of 17 differentially expressed proteins were upregulated at disease progression, including proteins associated with VEGF and TGF-beta signaling, while 9 out of 13 differentially expressed microRNAs were downregulated at disease progression. Baseline samples clustered in a distinct manner compared to samples from disease progression when using either mRNAs and lncRNAs as input or proteins as input. We are currently investigating the therapeutic impact of modulating the expression of top-candidate RNAs and proteins in cell lines with acquired resistance to osimertinib. Additional data will be presented at the meeting.

Conclusions: Our study demonstrates the usage of circulating RNAs and proteins from plasma to unveil resistance signatures to the third-generation TKI osimertinib. Furthermore, it highlights the involvement of multiple RNAs and proteins of potential functional impact in osimertinib-refractory NSCLC patients.

Keywords: Non-small cell lung cancer, Osimertinib, Therapy resistance

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.27 Effect of PD-L1 Expression Level on Clinical Outcomes of Stage IV EGFR Mutant Lung Cancer Patients Treated With Osimertinib

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Introduction: Epidermal growth factor receptor (EGFR) and programmed death ligand 1 (PD-L1) are cell surface proteins that interact in the context of immune evasion to promote cancer growth. Mutations in EGFR signaling are linked to upregulation of PD-L1, though the associations between higher PD-L1 expression and clinical characteristics and disease features of EGFR mutant (EGFR-mut) non-small cell lung cancer (NSCLC), as well as response to Osimertinib (Osi), are unclear.

Methods: We retrospectively analyzed clinical outcomes in patients (pts) with EGFR-mut Stage IV NSCLC treated with first line (1L) Osi at three New York City (NYC) hospitals between 2018-2023. Response was defined as radiographic improvement in tumor burden. Progression-free survival (PFS) was defined as time from first Osi dose to radiographic evidence of progression of disease. Overall survival (OS) was defined as time from diagnosis to death. PFS and OS were calculated using log rank test and cox proportional hazard model.

Results: A total of 101 pts were included for final analysis. Median age was 68 and pts were predominately female (68%), Asian (58%), and never smokers (66%). PD-L1 score was divided into <1% (51%), 1-10% (25%), and >10% (24%). Sites of disease metastasis included bone (51%), pleural effusion (42%), adrenal gland (12%), liver (11%), and pericardium (5%). CNS disease was present in 56 pts (55%) and twenty pts (20%) had radiographic evidence of leptomeningeal disease. Forty-eight pts (48%) had only one site of metastatic disease. There were no significant differences in sites of metastatic disease between PD-L1 expression levels. There was a non-statistically significant higher rate of TP53 co-mutations in the PD-L1 > 10% cohort (Table 1). Overall response rate (ORR) to Osi varied based on PD-L1 expression, with higher expression levels associated with lower ORR. There was also a statistically significant decrease in OS and a trend towards worse PFS with higher PD-L1 expression.

Conclusions: PD-L1 expression level was generally low (≤10%) in our diverse population of EGFR-mut NSCLC pts treated across three NYC hospitals. PD-L1 level was not associated with sites of metastases. Higher rates of TP53 co-mutations were seen in the PD-L1 >10% cohort. Inferior ORR and OS were also seen in the PD-L1 >10% cohort, which was statistically significant.

	Total	PD-L1 <1	PD-L1 1-10	PD-L1 >10	p-value
N	101	52	25	24	
RR (%)	86 (85)	48 (92)	21 (84)	17 (71)	0.051[a]
PFS Median (95% CI)	19.0 (16.8, 25.0)	21.0 (18.5, 26.6)	18.1 (12.4, 41.5)	12.5 (7.2,34.7)	0.194[b]
OS Median (95%CI)	64.9 (33.9, not reached)	64.9 (38.8, not reached)	42.9 (28.6, not reached)	31.2 (15.1, not reached)	0.029[b]
TP53+ (%)	49 (49)	22 (42)	11 (44)	16 (67)	0.133[a]

[a] Fisher's exact test; [b] Log rank test

Table 1. Clinical endpoints and TP53 co-mutation rate by PD-L1 level. RR calculation and TP53 mutation rate included 101 pts. PFS and OS calculated in months and included 72 and 24 pts respectively.

Keywords: EGFR, Osimertinib, PD-L1

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.28 Real-World Clinical Outcomes in Chinese Patients With Advanced EGFR-Mutated NSCLC on First-Line Third-Generation EGFR-TKIs Treatment

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Introduction: Aumolertinib and osimertinib are both third-generation (3G), irreversible epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) that were approved for first-line treatment of advanced non-small cell lung cancer (aNSCLC) patients with EGFR mutation (EGFRm). The clinical outcome on first-line 3G EGFR-TKIs in clinical practice remains to be elucidated among Chinese patients. In this study, we present the real-world clinical outcomes of Chinese aNSCLC patients with EGFRm who were treated with first-line 3G EGFR-TKIs.

Methods: A retrospective analysis was conducted on the records of patients diagnosed with EGFRm aNSCLC who received 3G EGFR-TKIs between December 2019 and July 2024. At the data cut-off date of 9 November 2024, 169 eligible patients were included in the data analysis. The clinical outcomes (best response measured from the initiation of first-line treatment and PFS) were presented.

Results: A total of 169 pts were enrolled in this retrospective study, of whom 60 pts received aumolertinib and 109 pts received osimertinib. The median age of the 60 pts receiving aumolertinib was 69 years (range, 35 to 86), 38.3% was male, ECOG performance status (PS) was ≤1 in 32 pts, ≥2 in 28 pts, and 16 pts had brain metastasis or 3 pts had leptomeningeal metastasis. EGFR mutations included 19del (14 pts, 23.3%), L858R (42 pts, 70.0%) and others (4 pts, 6.7%). The median age of the 109 pts receiving osimertinib was 70 years (range, 33 to 87), 35.8% was male, ECOG PS was ≤1 in 44 pts, ≥2 in 65 pts, and 21 pts had brain metastasis or 3 pts had leptomeningeal metastasis. EGFR mutations included 19del (57 pts, 52.3%), L858R (45 pts, 41.3%) and others (7 pts, 6.4%). At data cut-off, the median follow-up for progression-free survival was 17.6 months (range, 5.6 to 31.9) for aumolertinib and 16.6 months (range, 1.3 to 51.3) for osimertinib. 11 and 47 pts progressed after first-line treatment with aumolertinib and osimertinib, respectively. The median progression-free survival was not reached (95% confidence interval [CI], not calculable) with aumolertinib and 26.5 months with osimertinib (95% CI, 22.9 to 30.1). The 18-month PFS rate was 80% with aumolertinib and 70% with osimertinib. The objective response rate was higher with aumolertinib than with osimertinib, 75.0% and 57.8%, respectively. The disease control rates were similar at 96.7% and 94.5%, respectively. Any grade AEs occurred in 31.7% of aumolertinib patients and up to 38.5% of osimertinib patients, with grade 3 or higher (G3+) AEs occurring in 6.7% and 13.8% of patients, respectively.

Conclusions: Unlike the phase 3 trials FLAURA (FLAURA-China) and AENEAS, the real-world baseline characteristics of Chinese patients diagnosed with EGFRm aNSCLC were more complex, yet 3G EGFR-TKIs demonstrated a more favourable clinical outcome. The results of this study have provided further insight into the clinical practice of using 3G EGFR TKIs in Chinese patients diagnosed with EGFRm aNSCLC in a real-world setting.

Keywords: NSCLC, EGFR-TKIs, Real-World clinical outcomes

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.29 Association Between Tepotinib-Induced Edema and Clinical Outcomes in Patients With MET Exon 14 Skipping NSCLC

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Introduction: The VISION study demonstrated that tepotinib, a highly selective MET inhibitor, was effective against MET exon 14 (METex14) skipping NSCLC. Edema is a common adverse event associated with this drug, but its relationship with patient characteristics and treatment outcomes remains unclear. The present study investigated the association between tepotinib-induced edema and clinical outcomes in patients with METex14 skipping NSCLC receiving first-line tepotinib therapy.

Methods: We retrospectively analyzed data on patients with METex14 skipping NSCLC, which was diagnosed in any of the six participating, Japanese hospitals between August 2020 and December 2024. Patient demographics, treatment details, and the efficacy and safety outcomes of first-line tepotinib were extracted from electronic medical records.

Results: Of 98 patients with METex14 skipping NSCLC, 62 (63.2%) who received tepotinib as first-line therapy, 38 (61.3%) were male and 24 (38.7%) were female, and 37 (59.7%) patients had a smoking history. Adenocarcinoma was the predominant histology (73.0%). The median patient age was 76 years (range: 56-90), and most patients had advanced-stage cancer (58.1%), with the second largest group comprising those with a recurrence (37.1%). There were 27 patients (43.5%) with PD-L1 ≥ 50%. The ECOG PS was 0 or 1 in 46 (74.2%) patients and 2 or higher in 16 (25.8%) patients. The median observation period was 29.1 months (range: 1.5-51.5). First-line tepotinib achieved an overall response rate (ORR) of 61.4% (95% confidence interval [CI]: 48.8-74.0), median progression-free survival (PFS) of 8.2 months (95% CI: 6.3-10.1), and median overall survival (OS) of 24.4 months (95% CI: 9.5-39.2). Edema occurred in 44 patients (71.0%), with Grade 3 or higher edema occurring in eight patients (12.9%). Diuretics were administered in 26 of 44 patients (59.1%). The ORR was higher in patients with edema (70.4% vs. 30.7%). Patients with edema had significantly longer PFS than those without edema (10.8 months [95% CI: 8.0-13.6] vs. 4.2 months [95% CI: 2.8-5.5]; hazard ratio: 0.31; 95% CI: 0.16-0.60; P < 0.001). While edema led to a dose reduction in 37.1% of patients and dose interruption in 25.8%, only 8.1% discontinued tepotinib therapy due to edema.

Conclusions: The present, real-world analysis found that tepotinib-induced edema was associated with better treatment efficacy in patients with METex14 skipping NSCLC receiving first-line tepotinib therapy. These findings provide valuable insights for optimizing tepotinib therapy management in clinical practice while highlighting the importance of appropriate supportive care for edema.

Keywords: Tepotinib, MET, Edema

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.30 Real-World Outcomes of Full and Reduced Dose Capmatinib and Tepotinib Treatment for MET Exon 14 Skipping Mutation NSCLC

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Introduction: Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers. Of these, approximately 3% have MET exon 14 skipping mutations (METex14) and MET amplifications. Capmatinib and tepotinib are FDA approved MET tyrosine kinase inhibitors (TKI) for METex14 advanced NSCLC. As part of our analysis of healthcare delivery at Northwestern Medicine, we investigated outcomes in METex14 NSCLC to evaluate response to MET TKI at full and reduced doses.

Methods: We queried the Northwestern Medicine OncoSET Molecular Database for patients with METex14 NSCLC between January 2013 and November 2024 at Northwestern Memorial Hospital and affiliates. Inclusion criteria included patients with METex14 or MET amplification advanced or metastatic NSCLC. Demographic information, stage, and prior treatment data were collected. Response rate, median Progression Free Survival (PFS) by Kaplan-Meier survival analysis, dose reduction data, and adverse events (AE) were analyzed from the medical record.

Results: 43 patients were treated with MET TKI. 36 (84%) had a METex14 and 7 had MET amplification. Median age was 71 years (range 46-93), 25 (58%) were female, 28 (65%) identified as White, 8 Asian, 4 Black, and 3 Hispanic. 21 (49%) had tobacco use history. ECOG Performance Status (PS) of 0-1: 27 (63%), ECOG PS of 2: 16 (37%). 42 (98%) had stage IV disease and 1 had unresectable advanced disease. 14 (33%) had CNS involvement. 23 (53%) were treatment naive prior to initiation of MET TKI. 41 (95%) patients had not previously received MET targeted therapy, 2 had received crizotinib.

28 (65%) patients were treated with capmatinib, of these, 23 (82%) had stable or partial disease as best response. 12 (52%) patients underwent dose reduction at median 63 days after treatment initiation (range 0-240). Median PFS for patients treated with full dose capmatinib was 11 months, median PFS was 13 months for dose reduced patients. This was not statistically significant by chi-square (p=0.19). 8 patients had dose reduction due to AE (5-edema and 3-liver function abnormalities), 4 were initiated on dose reduction due to advanced age and PS. The median duration of treatment after dose reduction was 11 months.

15 (35%) patients were treated with tepotinib, of these, 12 (80%) had stable or partial disease as best response. 5 (42%) patients underwent dose reduction at median 28 days after treatment initiation (range 0-173). Median PFS for full dose tepotinib treated patients was 9 months and 11 months for the reduced dose group, this was not statistically significant by chi-square (p=0.74). Of dose reduced patients, 3 had dose reduction due to AE (2-nausea and 1-edema), 2 were initiated on dose reduction due to advanced age and PS. The median duration of treatment after dose reduction was 9 months.

Conclusions: This single-institution analysis suggests patients on full and reduced dose capmatinib and tepotinib have similar median PFS despite dose reductions. Median PFS is similar to previous real-world analysis (Correia et al, JCO 2024). These data suggest that in older patients, often with comorbidities, or patients with AE necessitating dose reduction, patients have similar benefit to MET TKI.

Keywords: MET Exon 14 Skipping Mutation, Targeted Therapy, Real-world Outcomes

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.31 Dual Target Drug Discovery for EGFR and PIK3CA in Lung Adenocarcinoma Using Machine Learning and Molecular Simulation Techniques

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Introduction: With the advancement of personalized medicine, multi-target drug development has gained significant attention, particularly for complex diseases such as lung adenocarcinoma. This study identifies potential dual-target inhibitors for the epidermal growth factor receptor (EGFR) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), both of which are critically involved in lung adenocarcinoma progression. EGFR mutations are known to drive tumor growth and metastasis, while PIK3CA mutations contribute to resistance against EGFR-targeted therapies.

Methods: IC50 values of active compounds targeting EGFR and PIK3CA were obtained from the BindingDB database, standardized using RDKit software, and converted to PIC50 values. A total of 2048 extended connectivity fingerprints (ECFPs) were computed as molecular descriptors. Machine learning models, including support vector machine, decision tree, random forest, gradient boosting, k-nearest neighbors, and LightGBM, were utilized. Optimal parameters were determined through ten-fold cross-validation and grid search. Model performance was evaluated using mean absolute error, mean squared error, and R^2.

Results: The support vector machine model exhibited superior performance and was selected for predicting EGFR and PIK3CA activity in lung adenocarcinoma. A screening of 479 inhibitors from the Coconut natural product database was conducted, followed by molecular docking using AutoDock Vina. Ten natural product compounds were chosen for molecular dynamics simulations, revealing stable binding with EGFR and PIK3CA through hydrogen bonds and hydrophobic interactions.

Conclusions: Natural product compounds CNP0456830 and CNP0467494, which showed the lowest binding free energies with EGFR and PIK3CA, were identified as the most promising dual-target inhibitors for lung adenocarcinoma. These findings offer valuable insights into developing personalized therapeutic strategies that target both EGFR and PIK3CA to overcome resistance in lung adenocarcinoma treatment.

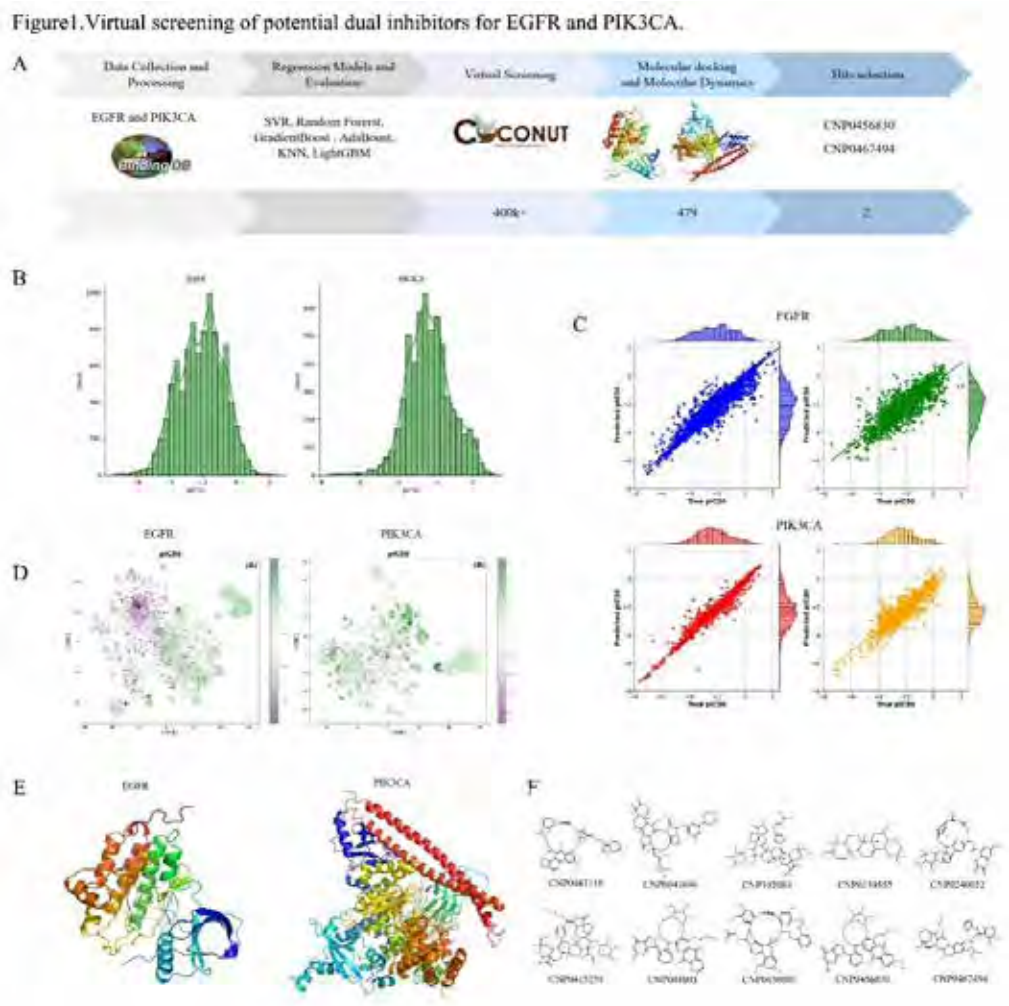
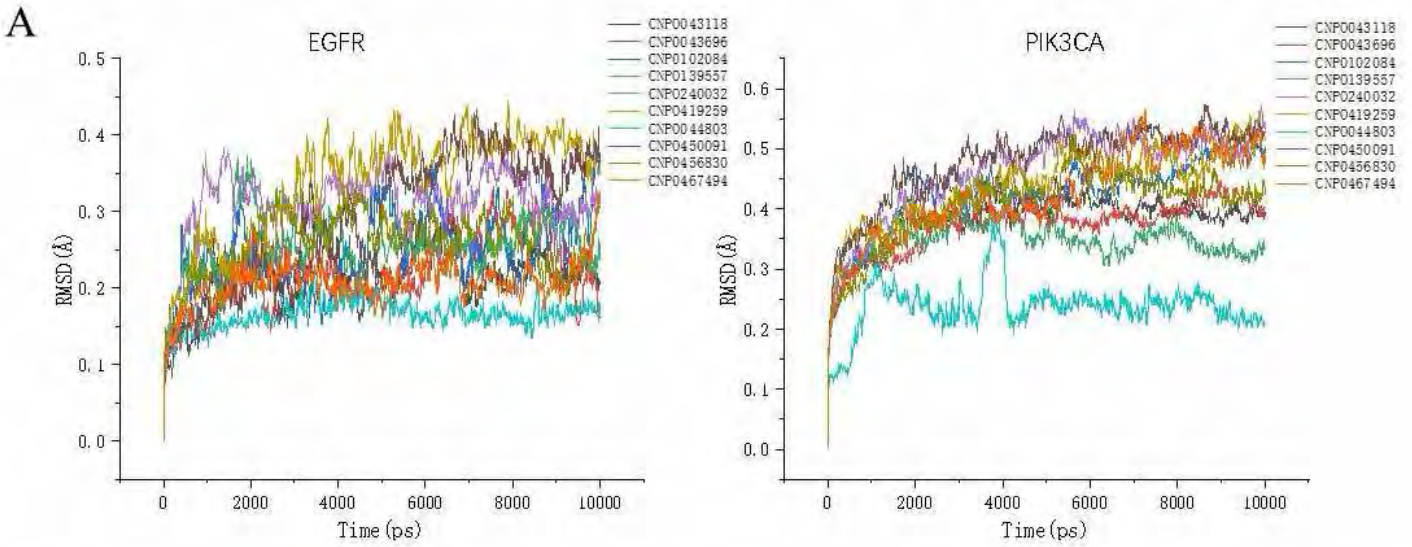
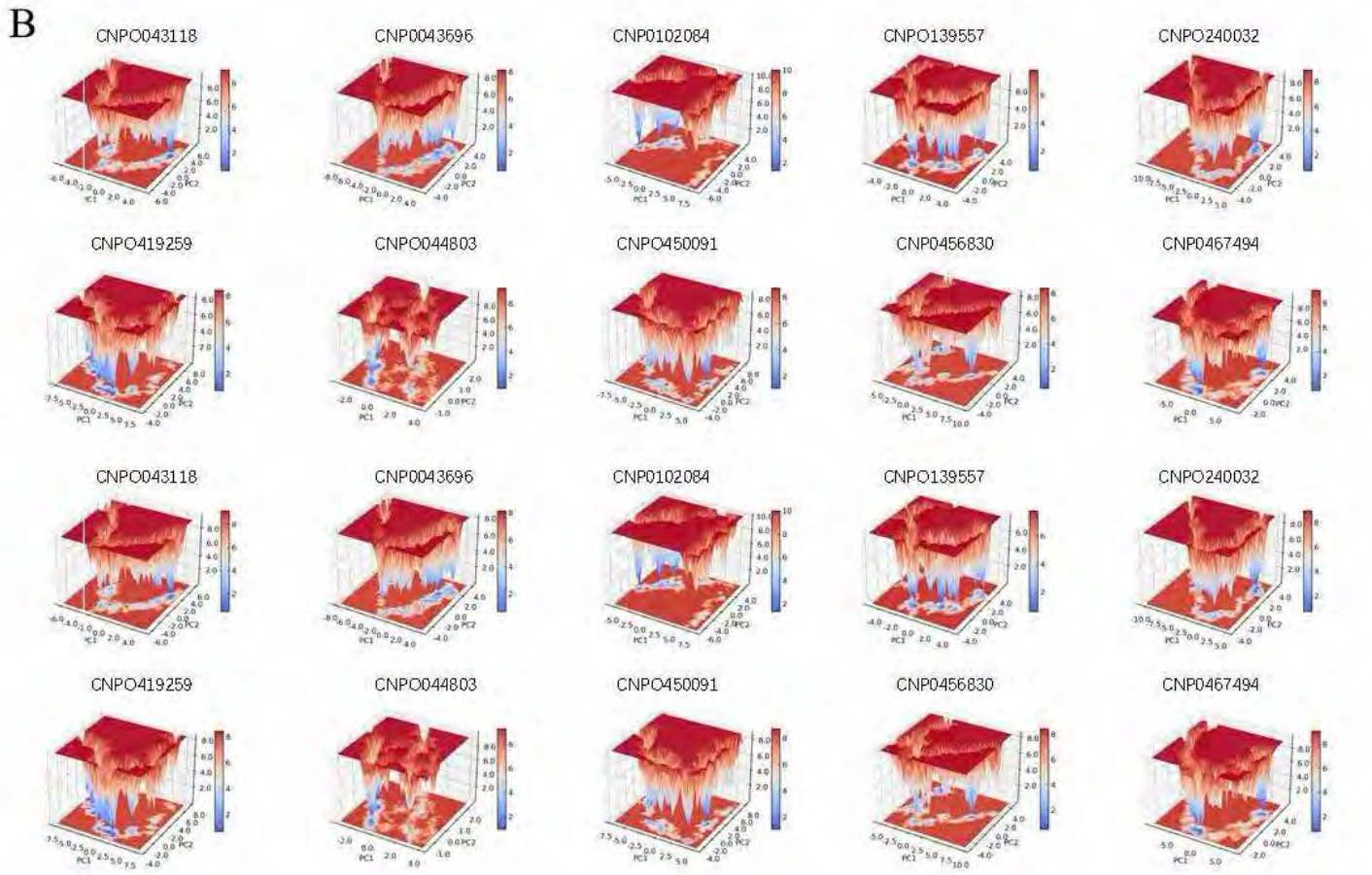


Figure2.The RMSD of EGFR and PIK3CA proteins with 10 candidate small molecule inhibitors.





Keywords: Multi target drugs, Machine learning, Molecular dynamics simulation

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.32 Targeted Therapy Utilization in Patients With Stage IV Non-Small Cell Lung Cancer Harboring Actionable Mutations

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Introduction: The NCCN guidelines recommend non-small cell lung cancer (NSCLC) patients (pts) who are stage IV that harbor actionable mutations such as EGFR Exon 19 Del or L858R, ALK, ROS1, BRAF V600E, MET Exon 14 Skipping, RET, NTRK1/2/3, KRAS G12C, ERBB2, and now recently NRG1, receive targeted therapy. We aim to show treatment practices among stage IV NSCLC pts who harbor such mutations receiving care at oncology practices in the U.S.

Methods: Among Integra Connect PrecisionQ's de-identified database the analysis included pts >= 18 years of age, who were confirmed via manual chart abstraction with newly diagnosed stage IV NSCLC and found positive for either of the following EGFR Exon 19 Del or L858R, ALK, ROS1, BRAF V600E, MET Exon 14 Skipping, RET, NTRK1/2/3, KRAS G12C, and ERBB2. Pts positive for EGFR Exon 19 Del or L858R, ALK, ROS1, BRAF V600E, MET Exon 14 Skipping, RET, and NTRK1/2/3 must have started first-line treatment on or after January 1, 2022. Pts positive for KRAS G12C must have started second-line treatment on or after January 1, 2022. Pts positive for ERBB2 must have started second-line treatment on or after September 1, 2022. Descriptive analyses were performed to analyze the data.

Results: The use of targeted therapy was as follows based on each of the first-line pts with actionable mutations so long as the pt did not harbor another first-line actionable mutation: 94% among EGFR Exon 19 Del or L858R pts (N = 144), 73% among ALK positive pts (N = 52), 60% among ROS1 positive pts (N = 45), 41% among BRAF V600E positive pts (N = 27), 52% among MET Exon 14 Skipping pts (N = 25), 61% among RET positive pts (N = 18), and 5% among NTRK1/2/3 positive pts (N = 19). The use of targeted therapy was as follows based on each of the second-line pts with actionable mutations so long as they did not harbor another second-line actionable mutation: 67% among KRAS G12C positive pts (N = 94) and 39% among ERBB2 positive pts (N = 31). Across all pts with actionable mutations in either first or second-line who did not harbor another actionable mutation for treatment in that respective line of therapy, the use of targeted therapy was 68% -- those with adenocarcinoma (N = 377) received targeted therapy at a rate of 71% compared to 36% for pts with squamous cell carcinoma (N = 28).

Conclusions: The real world shows that pts who harbor actionable mutations are not all equally treated with targeted therapy -- rates are highest in EGFR exon 19 and L858R at 94%, followed by ALK at 73%, ROS1 and RET at 60% with continued decline in use for other actionable mutations such as BRAF, MET and NTRK with rates of <60%. The pts with a histology of squamous cell carcinoma were less likely to receive targeted therapy.

Keywords: Targeted Therapy, Stage IV, Actionable Mutations

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.33 Retrospective Analysis of Adenocarcinoma of Lungs From Medical Oncology Clinic in Eastern India

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Introduction: Lung cancer (LC) is the most common cancer in the world and poses a significant health burden globally. The study aims to analyze the demographic, clinicopathological features and treatment outcomes of Adenocarcinoma of Lungs in patients presented to our medical oncology clinic at Aiims Bhubanesar.

Methods: The study is a retrospective descriptive study. A total of 145 patients with Adenocarcinoma of the lung were registered in the medical oncology clinic. Their demographic, clinical pathological, mutation profiles, and treatment outcomes were analyzed.

Results: Out of 145 Adenocarcinoma lung patients analyzed, 11 patients belonged to stage III (7.5%), and 134 (92%) were stage IV. The male-to-female ratio was 1.6:1, with males comprising 90 cases. The median age of patients was 58 years, with a range of (26 years to 84 years). ECOG performance status was > 2 in 38 (26%) patients. Among the data available, 24 patients had a prior history of smoking. Thoracic metastases alone were seen in 30(20%). Among the extra-thoracic metastases 102(70%) patients, bone metastases 80 (55%) were the commonest, followed by brain metastases 39(27%), and adrenal metastases 20(14%).

EGFR mutation was seen in 50/145(34%), ALK rearrangement was seen in 18/145(12%) and ROS in 2(1%). Among EGFR mutations, exon 19 was commonest (30/50) , followed by exon 21 (15/50), exon 20 insertion (4/50) and exon 18 deletion (1/50) mutation. Among patients who underwent NGS(85); EGFR was seen in 24 cases (28%), TP53 mutation was seen in 20, (24%), ALK in 8(5.5%), KRas in 4(5%) , ERBB2 in 4(5%), MET in 3(3%), BRAF in 3(3%), PTEN in 2(2%). PDL1-TPS score > 1% was present in 30 cases. Median PFS of the entire cohort for the first line of therapy received was 13 months (range 2 to 33), and the median OS for the entire cohort was 20 months (range 3 to 36). The median OS with ECOG-PS 0-1 was 21 months (range 9 to 6) and with PS ≥2 was 15 months (range 2 to 36 months) Among mutations (EGFR/ALK/ROS1), median PFS was 17 months in the positive subset versus 5 months in the negative subset. The median OS was 22 months in the positive versus 9 months in the negative subset. Among the EGFR positive subset, mPFS was 12 months in the TP53 positive subset versus 15 months in the TP53 negative. The median OS was 22 months in the TP53 positive subset versus 24 months in the negative patients.

Conclusions: Our study revealed that EGFR mutation was the most common in our patients, and ALK was seen in 12% of cases. NGS identifies 10-15% additional actionable mutations, and in patients with EGFR/ALK/ROS- WT, NGS can be considered. Patients with good ECOG-PS had a better mOS; EGFR, ALK, and ROS1 positive had better mPFS and mOS; patients with TP53 mutation positive had inferior outcomes

Keywords: Mutation analysis, Survival analysis, NGS requirement

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.34 Long-Term Control of Leptomeningeal Disease in NSCLC With EGFR Mutations: A Case Series

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Introduction: Leptomeningeal disease (LMD) is a rare and historically devastating complication of advanced non-small cell lung cancer (NSCLC). With an incidence of about 3-5%, LMD is associated with a poor prognosis, with median survival from 3-11 months.

Methods: A retrospective review was conducted on three patients diagnosed with metastatic EGFR+ NSCLC who developed LMD. Data on clinical presentation, diagnostic techniques, treatment strategies, and outcomes were collected from medical records. Patient follow-up was conducted to evaluate survival, neurological function, and disease progression.

Results: Case 1: A 48-year-old male with EGFR+ L858R NSCLC on frontline Osimertinib developed LMD after five months, presenting with cervical neck pain, dizziness, and hand paresthesia. Brain MRI revealed leptomeningeal enhancement, confirmed by CSF cytology. Double-dose Osimertinib led to temporary neurological improvement, but two months later, MRI showed progressive LMD. cfDNA testing identified EGFR V834L, associated with Osimertinib resistance. The patient received whole-brain radiotherapy and three cycles of carboplatin/ pemetrexed, followed by five cycles of intrathecal pemetrexed, achieving a significant reduction in CSF tumor cell capture by a thousandfold from baseline. Despite this, LMD progressed after six months, and weekly intrathecal pemetrexed (7 cycles) with double-dose osimertinib failed to control the disease. Overall survival 17 mos. Case 2: A 63-year-old female with EGFR+ L858R NSCLC and brain metastases presented with altered mental status. She underwent left parieto-occipital and suboccipital craniotomies, SBRT, and frontline osimertinib. She remained neurologically stable for six months until imaging showed progressive brain metastases, leading to salvage SRS. Two months later, lumbar spine MRI suggested early LMD, prompting osimertinib dose escalation, though limited by dermatologic toxicity. After six months of stable disease, new brain metastases were detected, but CSF cytology remained negative. She received multiple rounds of brain radiotherapy while continuing osimertinib for eight months until progression of LMD. She underwent craniospinal proton therapy and four cycles of carboplatin/ pemetrexed/ bevacizumab with osimertinib. Despite complications from a subdural hematoma post-fall, imaging five months later showed partial response. She resumed pemetrexed/ bevacizumab with osimertinib and remains stable. Alive 39 months from diagnosis. Case 3: A 63-year-old female with EGFR exon 19 deletion, TP53 P278R, and CHEK2 loss NSCLC presented with persistent cough, headaches, nausea, and vomiting. MRI showed marked cerebellar and occipital leptomeningeal enhancement. Frontline double-dose osimertinib led to a significant neurological and imaging response within six weeks. Stable disease lasted three months before new pleural/pericardial effusions revealed small-cell transformation (new RB1/MAP2K4 loss). She received four cycles of carboplatin/etoposide plus osimertinib, maintaining stable CNS disease. Three months later, worsening dysarthria prompted lumbar puncture, confirming persistent LMD. Craniospinal proton therapy was followed by progressive disease, with cfDNA revealing new EGFR C797S. She was referred for a clinical trial with T-cell engager targeting delta-like ligand 3 (DLL3). Overall survival 15 months.

Conclusions: These cases illustrate that NSCLC patients with LMD and actionable mutations can achieve prolonged responses to targeted therapies, challenging the historically grim prognosis of LMD. Early detection and initiation of targeted agents, in conjunction with close radiation oncology support, may be crucial in extending survival.

Keywords: Leptomeningeal disease, EGFR Lung Cancer, Targeted Therapy

EP.12.35 Insights on Treatment Experience From Patients With ALK+ NSCLC Treated With 1St-Line Brigatinib, Lorlatinib and Alectinib

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Introduction: Patients with non-small cell lung cancer (NSCLC) often present with respiratory and systemic symptoms. In anaplastic lymphoma kinase-positive (ALK+) NSCLC, next-generation ALK tyrosine kinase inhibitors (TKIs), brigatinib, alectinib, and lorlatinib, are typical first-line therapies. Each TKI has a unique efficacy/tolerability profile, yet little is known about how these treatments impact daily life from the patient perspective. This study explores patient-reported experiences regarding symptoms, functioning, and impacts on health-related quality of life (HRQoL) among ALK+ NSCLC patients treated with first-line ALK-TKIs.

Methods: A cross-sectional qualitative interview study was conducted in US adults with ALK+ NSCLC that received first-line TKIs for ≥4 weeks within the past 12 months. Participants were recruited via purposive sampling through the ALK-Positive patient advocacy group. One-time, virtual, semi-structured qualitative interviews (~60 minutes) captured patients' self-reported sociodemographic information, symptom and treatment burden, and impact on function and overall HRQoL. Interviews were transcribed and analyzed using ATLAS.ti; codebook was developed using deductive and inductive methods. After concept saturation was achieved, data were summarized descriptively and qualitatively.

Results: Forty-six patients (15, brigatinib; 15, alectinib; 16, lorlatinib) were interviewed (median age: 49 years; female: 67.4%; full/part-time employed: 60.9%); 13 reported brain metastases prior to their first use of a TKI. Some patients (n=21) spontaneously reported being misdiagnosed with conditions such as pneumonia, GERD, asthma, or allergies. The symptoms frequently expressed by participants as their most troublesome during first TKI treatment were weight gain among patients on lorlatinib (31.3%) and alectinib (20.0%), fatigue/tiredness in patients on alectinib (33.3%) and brigatinib (13.3%), GI symptoms in patients on brigatinib (20.0%), and neuropathy or cognitive issues in patients with lorlatinib (18.8%, each; Table). Patients provided ratings on a scale of 0 (least) to 10 (most troublesome/difficult) on their experience with daily pill intake (mean rating: 0.2, brigatinib; 1.3, lorlatinib; 2.1, alectinib) and taking medications as prescribed (mean rating: 0.1, brigatinib; 1.4, lorlatinib; 2.1, alectinib; Table). Treatment satisfaction ratings were reported on a scale of 0 (extremely dissatisfied) to 10 (extremely satisfied), with a mean rating of 9.3 in brigatinib patients, 7.9 in lorlatinib patients, and 7.7 in alectinib patients (Table).

Conclusions: Unique experiences were reported by patients with ALK+ NSCLC treated with different first-line ALK-TKIs. These data illustrate the multifaceted impact of ALK-TKI treatment on daily life, highlighting the importance of addressing both physical and psychosocial dimensions of patient care. These findings emphasize the importance of patient experience considerations in treatment decisions for ALK+ NSCLC.

Table. Patients' Self-Reported Perceptions of Treatment and Treatment Experiences by ALK-TKI

	Brigatinib (n=15)		Alectinib (n=15)		Lorlatinib (n=16)	
Patient rating: troublesome taking the tablet(s) daily,[1] mean (SD), [median, range]	0.2 (0.6) [0, 0-2]		2.1 (2.1) [1, 0-8]		1.3 (1.6) [1, 0-6]	
Patient rating: difficulty in taking medication as prescribed,[2] mean (SD), [median, range]	0.1 (0.3) [0, 0-1]		2.1 (1.9) [2, 0-8]		1.4 (1.0) [1, 0-3]	
Patient rating: treatment satisfaction,[3] mean (SD), [median, range]	9.3 (1.3) [10, 6-10]		7.7 (2.5) [8, 1-10]		7.9 (1.6) [8, 5-10]	
Most troublesome symptoms experienced by the patient **before** treatment[4]	**Symptom**	**n (%)**	**Symptom**	**n (%)**	**Symptom**	**n (%)**
	Shortness of breath	3 (20.0%)	Shortness of breath; Cough; Back pain	4 (26.7%), each symptom	Cough	6 (37.5%)
	Back pain	2 (13.3%)			Shortness of breath	4 (25.0%)
Most troublesome symptoms experienced by the patient **during** treatment[4]	**Symptom**	**n (%)**	**Symptom**	**n (%)**	**Symptom**	**n (%)**
	GI symptoms	3 (20.0%)	Fatigue/tiredness	5 (33.3%)	Weight gain	5 (31.3%)
	Fatigue/tiredness	2 (13.3%)	Weight gain	3 (20.0%)	Neuropathy; Cognitive issues	3 (18.8%), each symptom
Most troublesome impacts experienced by the patient **during** treatment[5]	**Impact**	**n (%)**	**Impact**	**n (%)**	**Impact**	**n (%)**
	Feeling loss of independence	3 (20.0%)	Emotional/ psychological distress	3 (20.0%)	Weight gain/poor body image; Emotional/ psychological distress; Cognitive issues; Relationship concerns; Limitations to work productivity	2 (12.5%), each impact
	Physical limitations; Relationship concerns; Limitations to work productivity	1 (6.7%), each impact	Weight gain/ poor body image	2 (13.3%)		

ALK: anaplastic lymphoma kinase; SD: standard deviation; TKI: tyrosine kinase inhibitors
[1]Defined as the extent to which participants perceived daily tablet intake as inconvenient or bothersome, rated on a scale from 0 (not at all troublesome) to 10 (extremely troublesome).
Question asked to the participant to elicit this rating was: "How troublesome did you find taking your tablet/s every day on a scale of 0-10, where 0 is not at all and 10 is extremely troublesome?"
[2]Defined as the degree of difficulty experienced by participants in adhering strictly to prescribed medication instructions, including missing or forgetting doses, rated on a scale from 0 (not at all difficult) to 10 (extremely difficult).
Question asked to the participant to elicit this rating was: "How difficult was it for you to take [first TKI therapy] as prescribed on a scale of 0-10, where 0 is not at all difficult and 10 is extremely difficult?"
[3]Defined as participants' subjective evaluation of their overall satisfaction with the medication, reflecting their perceived effectiveness and acceptability of the therapy, rated on a scale from 0 (extremely dissatisfied) to 10 (extremely satisfied).
Question asked to the participant to elicit this rating was: "On a scale of 0-10, where 0 is extremely dissatisfied and 10 is extremely satisfied, how satisfied are you with [first TKI therapy]?"
[4]Questions asked to the participant to elicit most troublesome symptoms before and during treatment were as follows:
Before: "Of all the symptoms you have mentioned, which of these symptoms was the most troublesome to you during the time BEFORE you started [first TKI therapy]? What made this symptom the most troublesome for you?"
During: "Of all the symptoms and/or side effect you have mentioned, which of these symptoms and/or side effects was the most troublesome to you when taking [first TKI therapy]? What made this symptom and/or side effect the most troublesome for you?"
[5]Questions asked to the participant to elicit most troublesome impacts during treatment were as follows:
During: "Of all the impacts you have mentioned, which of these impacts was the most troublesome to you when taking [first TKI therapy]? What made this impact the most troublesome for you?"

Keywords: ALK+ NSCLC, Tyrosine Kinase Inhibitor, HRQoL

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.36 Data Visualization of Treatment Patterns in Adults With BRAFV600EMutant mNSCLC in Real-World Setting

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Introduction: BRAF mutations are found in 1-8% of non-small cell lung cancer (NSCLC) patients (pts), primarily in lung adenocarcinomas. Of these, BRAFV600E is the most common variant. Due to its rarity, clinical characteristics and real-world treatment practices for patients with BRAFV600E mutant (BRAF MT) metastatic NSCLC (mNSCLC) are often not well described. Data visualization enables faster interpretation of data and identification of trends and relationships. The aim of this exploratory analysis is to visualize real-world data of treatment patterns in adult patients with BRAFV600E mNSCLC.

Methods: OCTOPUS (NCT05546905) is a multicenter, observational, descriptive, ambispective European study in adult patients who initiated a first systemic treatment for mNSCLC from 1st December 2017, and either before (retrospective cohort) or after (prospective cohort) study entry. Data on patient and clinical characteristics, BRAF mutation testing practices, treatment patterns, safety and effectiveness were collected. Results from the interim analysis of the retrospective cohort have been previously presented. Based on this interim analysis machine learning, time sequence analysis through K clustering (TAK), was used to identify and visualize patients with similar treatment sequences. Other advanced visualization techniques were used and will be displayed.

Results: A total of 152 pts were included, with a median follow-up (FU) time of 16.7 (0.2-71.6) months and median age at metastatic disease of 70.0 (44.0; 90.0) years. Visualization with Sankey diagram provided an overview of the diversity of treatment sequences observed from line 1 (L1) to line 3 and further. Among patients who received a 1st line of treatment (LoT), 45.3% (N=69) received a 2nd LoT, 37 pts (24,3%) were still under 1st LoT, and 15.1% (N=23) received a 3rd LoT during the FU period. At the end of the FU, 42,1% (N=64) of the pts were ongoing. Pts were gathered in groups depending on the type of 1st LoT received. “Targeted Therapy” (TT) group comprised 74 pts, “Chemotherapy + Immunotherapy” (Chemo-IO) 26 pts, “Chemotherapy” (Chemo) 24 pts, “Immunotherapy” (IO) 15 pts.15 pts were not classified in any of the previous groups and were grouped in “Other”. Pts who received TT in L1 had an average age (+/-sd) of 70.3 (+/- 10.3) years, while patients who received another type of L1 (N=78) had an average (+/-sd) of 66.9 (+/- 9.1) years. Chemo-IO group had the lowest rate of patients with comorbidities at 57.7% (N=15), while the TT group had the highest rate at 78.4% (N=58). Duration of 1st LoT was the longest in the TT group with 16.0 (+/- 14.8) months in average while IO, Chemo, Chemo-IO and “Other” (N=13) had shorter durations of 2.9 (+/- 3.6), 3.3 (+/- 3.0), 6.6 (+/- 6.4) and 10.5 (+/- 12.3) months, respectively.

Conclusions: Advanced visualization techniques reveal insights into clinical practices, pathways, and how patient differ by type of treatment. These findings highlight the varied treatment management patterns in real-world settings and the lack of clear treatment sequences despite the availability of recommendations in international guidelines. This is an exploratory analysis based on an interim analysis; data should be interpreted with caution.

Keywords: patterns, mBRAFV600E, mNSCLC

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.37 Targeted Treatment of NSCLC With? BRAF Fusions: A Systematic Review

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Introduction: BRAF fusions are rare oncogenic drivers (<1%) in non-small cell lung cancer (NSCLC). While the BRAF V600E mutation is an established therapeutic target, the role of BRAF fusions in guiding targeted treatment remains unclear due to limited clinical data. This systematic review was done to summarize the available literature on the targeted treatment of BRAF fusion-positive solid cancers. Here, we report on the available evidence on the efficacy of targeted therapies, including BRAF and MEK inhibitors, in patients with advanced BRAF fusion-positive NSCLC.

Methods: A systematic review was conducted to evaluate the reported efficacy, response rates and survival outcomes of targeted treatment in patients with BRAF fusion-positive solid tumors. PubMed, EMBASE, and Cochrane CENTRAL were searched for relevant studies between 2014 and 2024.

Results: A total of 8 studies, including 9 patients with BRAF fusion-positive advanced NSCLC treated with targeted therapy, were identified. Seven were case reports, and one was a phase I/II clinical trial that included two patients with BRAF fusion-positive NSCLC. Table 1 depicts BRAF fusion partner, targeted therapy, outcomes and toxicity. The targeted therapies used included MEK inhibitors (trametinib) or BRAF inhibitors (dabrafenib or vemurafenib) alone or in combination with other targeted agents. The BRAF fusion partners were heterogenous. The objective response rate (ORR) in NSCLC was 89%, the highest among all analyzed tumor types (including sarcoma, melanoma and CNS tumors with ORR of 57%, 52% and 41% respectively). However, survival and safety data remain limited due to the rarity of these fusions.

Conclusions: Targeted therapies, particularly BRAF and MEK inhibitors, show promising efficacy in BRAF fusion-positive NSCLC, with a high response rate in available reports. However, the current evidence is largely based on very limited case reports and clinical trial data. Given the rarity of these fusions, international collaboration and novel trial designs, such as basket and platform trials, are crucial to better define optimal therapeutic strategies and improve patient outcomes.

Table 1. Details on *BRAF* fusion partner, targeted therapy and outcomes

	Study (year)	Type of study	Number of patients	*BRAF* fusion partner	Treatment	Best radiological response	Toxicity
1	Chou et al 2022	Case Report	1	KIAA1549	Dabrafenib with trametinib, and capmatinib	SD	Grade 3 peripheral edema, Grade 2 fatigue, Grade 1 fever, rash and nausea
2	Kian et al 2023	Case Report	1	MKRN1	Osimertinib with trametinib and dabrafenib	PR	NA
3	Yu et al 2022	Case Report	1	SDN1	Trametinib	PR	Grade 1 acneiform rash
4	Wang et al 2021	Case Report	1	LIMD1	Trametinib	PR PFS: 7.4 months	Grade 1 acneiform rash
5	Yasui et al 2024	Case Report	1	SLC44A1	Trametinib	PR	NA
6	Zhu et al 2019	Case Report	1	TRIM24	Vemurafenib	PR PFS: 3.5 months	NA
7	Dagogo-Jack et al 2019	Case Report	1	AGK	Trametinib and osimertinib	PR	Grade 2 diarrhea and fatigue, grade 1 rash and gastrointestinal bleed.
8	Luo et al 2021	Phase 1/2	2	ZC3HAV1, ERC1	Trametinib and erlotinib	PR, Mixed response: PR at primary site	Grade 3 rash and diarrhea (13%), grade 1–2 fatigue, nausea and vomiting

SD, stable disease; PR, partial response; PFS, progression free survival; NA, not available

Keywords: BRAF fusion, NSCLC, targeted therapy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.38 Firmonertinib(160Mg) Combined With Chemotherapy as First-Line Treatment for Advanced NSCLC Patients With EGFR Mutations and Cns Metastas

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Introduction: This study aimed to evaluate the efficacy and safety of Firmonertinib (160 mg) combined with pemetrexed and platinum-based chemotherapy as a first-line treatment for non-small cell lung cancer (NSCLC) patients with EGFR mutations and central nervous system (CNS) metastases.

Methods: This prospective, single-arm, phase II clinical study enrolled 12 NSCLC patients with EGFR classic mutations and CNS metastases from multiple medical centers in Anhui Province between January 17, 2024, and March 16, 2025,moreover, the study is still ongoing with continuous enrollment. All patients received a combination therapy of Firmonertinib(160mg), pemetrexed plus platinum-based chemotherapy. Clinical baseline characteristics, efficacy outcomes, and safety data were systematically collected and analyzed.

Results: Among the 12 patients, 50% had EGFR exon 19 deletions, and 50% had L858R mutations, with 33% also presenting TP53 co-mutations. The objective response rate (ORR) and CNS ORR were 75% and 83.3%, while the disease control rate (DCR) and CNS DCR were 100% and 91.7%, respectively. With a median follow-up of 4.95 months, only 1 patient had experienced disease progression, with the remaining 11 patients continuing treatment. Progression-free survival (PFS) and CNS PFS data were not yet mature. The safety profile of the combination therapy was manageable, with 33.3% of patients requiring dose reductions due to treatment-related adverse events (TRAEs),the most common adverse events were anemia and leukopenia, which were more strongly associated with chemotherapy. However, no treatment interruptions, discontinuations, grade 4 adverse events, or treatment-related deaths were reported.

Conclusions: Firmonertinib (160mg)combined with pemetrexed and platinum-based chemotherapy demonstrated promising clinical efficacy and manageable toxicity in EGFR-mutated NSCLC patients with CNS metastases. These findings support its potential as a viable first-line treatment option for this patient population.

Keywords: Firmonertinib, EGFR Mutations NSCLC, CNS Metastases

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.39 Dynamic Evolution of Genomic and Microenvironment Landscape in ALK-Positive Non-Small Cell Lung Cancer

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Introduction: Resistance to tyrosine kinase inhibitor (TKI) has become a major therapeutic challenge in ALK-positive non-small cell lung cancer (NSCLC). The exact roles of genomic factors and tumor microenvironment characteristics in ALK-TKI resistance remain unclear and warrant thorough investigation, especially at the dynamic level.

Methods: To explore these mechanisms, we collected baseline and post-TKI treatment specimens from 16 patients with ALK-positive NSCLC, along with baseline samples from 28 ALK-negative NSCLC patients, for RNA and whole-exome sequencing. The comprehensive mutational landscape and mutation signatures analysis were conducted to explore genomic resistance mechanisms. Additionally, CIBERSORT, MCP-counter, xCELL, and quanTIseq were applied to evaluate immune infiltration.

Results: Notably, ALK-positive tumors displayed distinct TME features compared to ALK-negative NSCLC, characterized by enhanced antigen presentation and high expression of immunosuppressive components. Genomic analysis revealed novel mutation sites potentially linked to ALK-TKI resistance. From the microenvironment perspective, a “cold” tumor microenvironment with lower abundance of CD8+ T cells, memory B cells, and dendritic cells was observed in TKI-resistant samples, indicating that immunosuppressive transformation tumor microenvironment may promote ALK-TKI resistance. Furthermore, estrogen pathways were enriched in TKI-resistant samples, and a quantitative method of ER scores derived from estrogen pathways was associated with a poor prognosis under ALK-TKI therapy.

Conclusions: The study profiled the evolving mutational landscape and tumor microenvironment features of ALK-positive NSCLC across treatment stages, characterized the potential resistance mechanisms to ALK-TKI, and may provide insights for optimizing therapeutic strategies.

Keywords: ALK rearrangement, Tumor microenvironment, Tyrosine kinase inhibitors

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.40 Clinical Efficacy and Safety Analysis of Osimertinib Versus Aumolertinib in Real-World Treatment of EGFRm Advanced NSCLC

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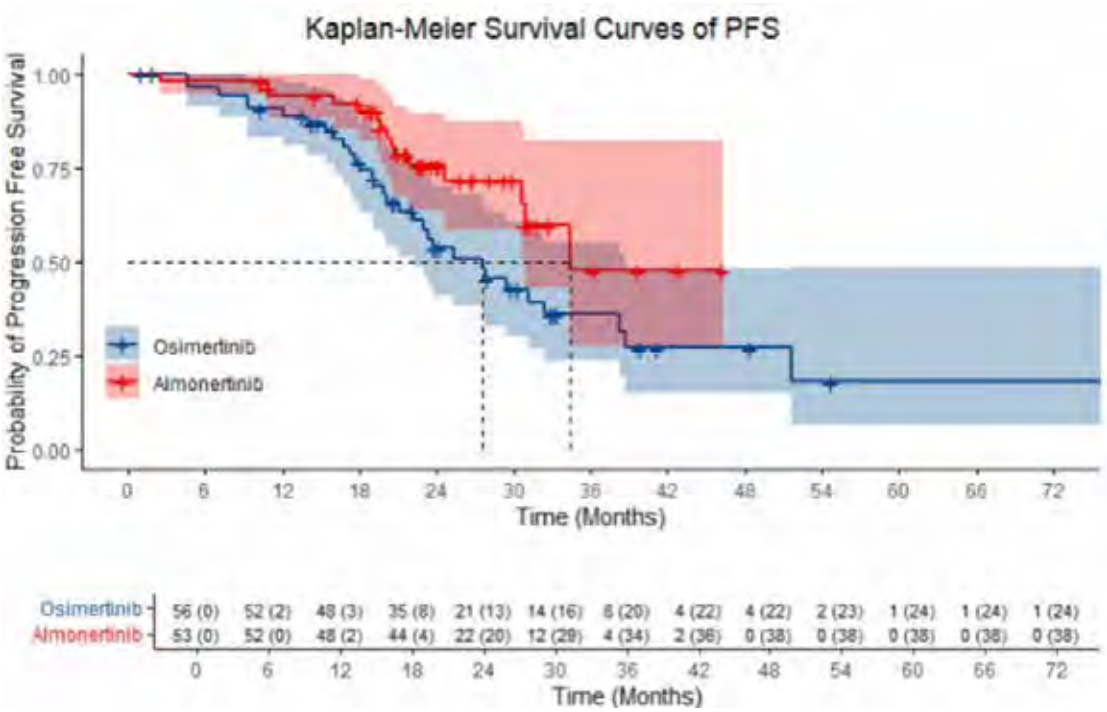
Introduction: China leads globally in the universality and availability of third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), with intense competition among these agents. Despite various treatment options, there remains lack of direct comparative studies to guide patients (pts) in making informed decisions regarding third-generation EGFR-TKIs. Aumolertinib, a highly potent and irreversible third-generation EGFR-TKI, has been developed independently in China.

Methods: This study retrospectively analyzed the clinical data of 168 EGFR-mutated non-small-cell lung cancer (NSCLC) pts who received osimertinib (85 pts) and aumolertinib (83 pts) at four medical centers from January 2015 to January 2024. Pts with stage IIIB-IV were divided into two cohorts and were given either 80mg osimertinib (56 pts) or 110mg aumolertinib (53 pts) as first-line treatment recommended by guidelines.

Results: At data cut-off (November 25, 2024), the median follow-up for the osimertinib and aumolertinib groups was 26.92 months and 24.44 months, respectively. The median PFS was significantly longer in aumolertinib group than osimertinib group at 34.4months (95% CI, 30.9-not reached) versus 26.9 months (95% CI, 22.2 to 40 ;HR, 0.52; 95% CI, 0.29 to 0.92; P = 0.031). Subgroup analyses(age, baseline brain metastasis, baseline liver metastasis, EGFR mutation types, and co-mutations)using a univariate Cox model indicated that the HR between two groups were all less than 1, suggesting that all subgroup pts benefit from aumolertinib. Adverse events of grade ≥ 3 severity (any cause) were observed in 3.57% and 3.77% of pts in two groups, respectively.

Conclusions: Presently, aumolertinib is undergoing global development studies to maximize benefits of pts worldwide. This study provides guidance for the future selection of third-generation EGFR-TKIs in countries beyond China.



Keywords: EGFR mutant NSCLC, Aumolertinib, targeted therapy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.41 FUTURE Trial:First-Stage Data of Initial Firmonertinib 160mg in EGFR+/PD-L1+ Locally Advanced or Metastatic NSCLC (Simon's Two-Stage Design)

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Introduction: Firmonertinib, a novel third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), demonstrates superior brain penetration, a broad therapeutic window, and a favorable toxicity profile. While third-generation EGFR-TKIs have become the established first-line standard for advanced EGFR-mutant non-small cell lung cancer (NSCLC), emerging evidence suggests that strong PD-L1 expression (TPS≥50%) may drive primary resistance to third-generation EGFR-TKIs, adversely impacting patient prognosis. Dose escalation of third-generation TKIs may represent a potential therapeutic strategy.

Methods: The FUTURE study is a prospective multicenter phase II trial evaluating firmonertinib (160 mg once daily) in patients with locally advanced or metastatic EGFR-sensitive mutations and PD-L1 positive status. Utilizing a Simon's two-stage design, the study plans to enroll 30 subjects in the first stage, requiring a 1-year progression-free survival (PFS) rate >60% to proceed to the second stage. An additional 32 subjects will be subsequently enrolled, totaling 62 patients. This trial will be deemed successful if the pooled 1-year PFS rate exceeds 70%. The primary endpoint is 1-year PFS rate, with secondary endpoints including objective response rate (ORR), PFS, and safety assessments. This report presents the data analysis of 30 subjects enrolled in Stage 1 of the study.

Results: As of March 1, 2025, the first stage of this study had successfully enrolled 30 subjects. The cohort comprised patients with a median age of 59 years (range: 45-76), predominantly never-smokers (80.0%) with stage IV lung adenocarcinoma (83.3%). Key characteristics included L858R mutation (56.7%) and brain metastases (26.7%), while 50.0% of patients exhibited high PD-L1 expression. Median follow-up was 27·1 months. Investigator-assessed outcomes demonstrated a confirmed objective response rate (cORR) of 86.7% (1 CR, 25 PR) and a disease control rate (DCR) of 96.7%, with a median tumor regression depth of 56.0%. The 1-year PFS rate reached 73.3%. Treatment-related adverse events (TRAEs) of grade ≥3 were observed in 6.7% of patients, primarily manifesting as elevated transaminases, rash, and diarrhea. The study has now progressed to Simon's second stage.

Conclusions: The FUTURE study has preliminarily demonstrated the excellent efficacy and manageable safety profile of firmonertinib as first-line treatment in patients with EGFR-sensitive mutations and PD-L1 positive status.

Keywords: Targeted therapy, EGFR TKI, PD-L1

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.42 Durable Response to ROS1-Tkis in Metastatic Squamous NSCLC With EZR-ROS1 Fusion

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Introduction: Molecular testing in patients with metastatic pulmonary squamous cell carcinoma is currently not standard of care (SOC) as the chances of finding a therapeutic target are generally very limited. However, it may be performed upon request from the oncologist for exploring further potential therapeutic options.

Methods: We present an 82-year-old man in PS 1, current light smoker, with hyperthyroidism as only comorbidity. The patient was diagnosed by EBUS-FNA from mediastinal lymph nodal station 4R, 7, 4L, and 11L in Maj 2020 with T4N3M0 pulmonary squamous cell carcinoma. The cell block from the EBUS-FNA contained keratinizing metastatic tumour cells, which immunohistochemically were positive for CK5 and p40, while reactions for CK7, TTF1, and synaptophysin were negative. The PD-L1 Tumour Proportion Score was > 50%. The patient initially received SOC curative-intended concomitant chemo-radiotherapy followed by Durvalumab. However, after five months, adjuvant treatment was stopped due to symptomatic failure with-in the radiotherapy field corresponding to the primary lung tumour in the left lower lobe with compression of the left bronchial tree. Relief from obstruction and hemoptysis due to intrabronchial tumour growth was obtained by argon beam therapy, but the patient had further progression of mediastinal lymph nodal metastases and malignant pleural effusion. Thus, extended molecular testing of the diagnostic EBUS-FNA was requested, while considering second-line Docetaxel

Results: DNA-NGS (Oncomine Comprehensive Assay v.3, ThermoFisher Scientific) showed a pathogenic mutation of the cell proliferation-inducing TERT promoter (c.-124C>T(C228T)), whereas RNA-NGS (Archer Fusionplex Lung panel, IDT V1) revealed the EZR (exon 9)-ROS1 (exon 34) fusion. In July 2021, the patient initiated second-line treatment with the ROS1-tyrosine kinase inhibitor (TKI), Crizotinib, with good clinical effect and radiographic partial response. Treatment continued until July 2022, at which time grade 3 peripheral edema occurred and was resolved during a 2-week treatment break. No radiographic progression was observed at this point, and in August 2022 the patient started treatment with the new-generation ROS1-TKI, Entrectinib, at a reduced dose. The patient is currently continuing Entrectinib treatment with maintained remission of the disease and good quality of life.

Conclusions: This case demonstrates the relevance of extended molecular testing by DNA- and RNA-NGS also in selected patients with pulmonary squamous cell carcinoma. Indeed, to our knowledge, this is the first case demonstrating objective and prolonged response to sequential ROS1-targeted treatment of metastatic pulmonary squamous cell carcinoma with EZR-ROS1 fusion. The patient's current progression-free survival on ROS1-TKIs is 45 months.

Keywords: ROS1 fusion, pulmonary squamous cell carcinoma, RNA-NGS

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.43 Long Progression-Free Survival With Sunvozertinib in EGFRm NSCLC Patients After Third-Generation EGFR TKI Failure: Case Series

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Introduction: Sunvozertinib is an oral, potent, irreversible EGFR TKI with strong efficacy against various EGFR mutations, including exon 20 insertions. In EGFRm patients, resistance to third-generation EGFR TKI often leads to poor outcomes with continued therapy. This real-world case series highlights sunvozertinib's potential in advanced NSCLC harboring with EGFR sensitizing mutations after third-generation EGFR TKI treatment failure.

Methods: We retrospectively collected data from EGFRm NSCLC patients who experienced treatment failure with third-generation EGFR TKI and subsequently received sunvozertinib. PFS was analyzed.

Results: At the data cutoff (Dec 11, 2024), three patients were reviewed: A 72-year-old male was diagnosed with stage IIIB lung adenocarcinoma (EGFR L858R) underwent lobectomy and adjuvant chemotherapy in Aug 2006. After relapsing in Jun 2010, he received various chemotherapy regimens until Aug 2012, followed by icotinib, then osimertinib (found T790M mutation) was administered as fifth-line therapy (Dec 2017-May 2023) combined with anlotinib from 2020, and nab-paclitaxel plus sugemalimab as sixth-line (May-Oct 2023). For seventh-line treatment, sunvozertinib 150 mg QD with vinorelbine maintained for over 12 months. The second patient, a 70-year-old male with stage IV lung adenocarcinoma (EGFR 19del, T790M) diagnosed in Nov 2018, received osimertinib until Jul 2023, along with radiotherapy. Second-line sunvozertinib 300 mg QD treatment for over 13 months. The third patient, a 61-year-old female with stage IIIB lung adenocarcinoma, underwent lobectomy and adjuvant chemotherapy in Jun 2011. After relapsing in 2016, she received gefitinib. In Sep 2018, genetic testing revealed EGFR R776H, T790M, and L858R mutations, leading to osimertinib until Oct 2020. After third-line anlotinib and fourth-line anlotinib combined with S1, she began sunvozertinib 225 mg QD as fifth-line therapy, resulting in reduced lung nodules and continuing treatment for 12 months.

Conclusions: This case series demonstrates that sunvozertinib offers promising clinical benefits for EGFRm NSCLC patients after third-generation EGFR TKI treatment failure, highlighting its potential as an optional subsequent treatment strategy.

Table 1. Case summary (Data cutoff: Dec 11, 2024)

Cases	Sex	Age	EGFR mutation subtype	Treatment line of sunvozertinib	Previous third-generation TKI treatment	Previous chemotherapy treatment	Adverse events	Progressive disease	PFS (months)
1	Male	72	EGFR L858R, T790M	7	Yes	Yes	Diarrhea	None	12
2	Male	70	EGFR 19del, T790M	2	Yes	No	Paronychia	None	13
3	Female	61	EGFR R776H, T790M and L858R mutations	5	Yes	Yes	Fatigue, poor appetite	None	12

Keywords: Sunvozertinib, NSCLC, EGFR TKI

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.44 The Efficacy of Capmatinib in Treating NSCLC Patients With MET Amplification in a Multi-Center Real-World Setting

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Introduction: In non-small cell lung cancer (NSCLC), MET amplification is recognized as an independent oncogenic driver. Capmatinib is an oral, ATP-competitive, highly potent, and selective type Ib inhibitor of the MET receptor tyrosine kinase. It was approved for use in NSCLC patients with MET exon 14 skipping mutations. However, no agents have been approved for patients with MET amplification. This study aims to investigate the efficacy of capmatinib in patients with either de novo or acquired MET amplification through a multi-center retrospective analysis.

Methods: This study was a multi-center retrospective investigation. Patients with de novo and acquired MET amplification treated with capmatinib between January 2020 and June 2024 were recruited. Patient-related disease information and treatment regimens were gathered from the hospital medical records system. Kaplan-Meier analysis was utilized to evaluate the real-world progression-free survival (rwPFS) of patients who received at least one dose of capmatinib. The objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety profile were also analyzed.

Results: A total of 14 patients from 5 centers in China were enrolled in the study. The median number of treatment lines using capmatinib was 3 (ranging from 1 to 6). Regarding the MET status, there were 2 patients with de novo MET amplification, 8 patients with acquired MET amplification. 4 patients were detected to have a MET gene copy number (GCN) ≤5, and 6 patients had a MET GCN >5. The median observation period was 38.6 months (95% CI: 30.47-NA]). The median rwPFS for patients with both de novo and acquired MET amplification was 8.08 (95%CI: 4.3-NA), and the median rwOS was14.6 (95% CI: 1.13-NA). When stratified by GCN, no significant difference was observed in the median rwPFS (8.08 months vs 8.68 months for GCN>5 and GCN≤ 5 respectively, p = 0.84). Although the median rwOS for patients with GCN>5 was numerically longer than that for patients with GCN≤ 5 (40 months vs 14.60, p = 0.78), due to the limited sample size, no statistically significant difference was found.The ORR for patients with de novo and acquired MET amplification was 40% (4/10) (95%CI: 12.16-73.76). The DCR was 90%(95%CI: 55.5-99.75). When stratified by MET copy number, the ORR for patients with a gene copy number (GCN)>5 was 66.7% (4/6), while the ORR for patients with GCN ≤ 5 was 0%. The most commonly reported adverse event was peripheral edema, which was consistent with previous reports.

Conclusions: In a real-world context, capmatinib emerges as a promising treatment alternative for patients with either de novo or acquired MET amplification. The MET GCN holds potential as a biomarker for predicting the efficacy of capmatinib in treating patients with MET amplification. Moreover, the fact that adverse events are manageable further validates its application in clinical practice.

Keywords: Capmatinib, MET amplification, NSCLC

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.45 Concurrent ROS1-Rearrangements of Brain Metastasis in EGFR-Mutation Lung Adenocarcinoma

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Introduction: A 51-year-old female, who smoked over 20 pack-year suffered from productive cough and left chest pain for 2 weeks. Chest computer tomography (CT) showed perivascular consolidation at RUL (3.2x 0.9x 1.5cm), an ill-defined nodule (2.1x 1.9x 1.4cm) at RML with enlarged nodes including subcarinal region. Brain MRI found at least 7 intracranial small nodular metastases. Pathologic report from RLL tumor showed adenocarcinoma. The AJCC 8th TNM staging is cT4N2M1c, stage IVB. Gene mutation showed 1. EGFR Del19 under Real-time PCR/ cobas EGFR mutation 2. PD-L1 TC<1% under SP263 3. ROS-1 IHC 2+ under SP384, ROS-1 FISH negative under Abbott Vysis ROS1 Break Apart FISH Probe Kit 4. ALK equivocal under D5F3 with Ventana. She received afatinib.

Methods: However, RUL tumor progression and severe headache occurred after 2 months of afatinib use. She received palliative whole brain radiotherapy, but in vain. Due to lung tumor progression, she received CT guide biopsy from RML consolidation. Neurosurgery suggested and she also received separated supratentorial and infratentorial craniotomy for tumor removal.

Results: Molecular mutation examination from RML lung tissue showed adenocarcinoma without EGFR mutation. Pathologic result from brain tumor showed metastatic adenocarcinoma, and NGS report by Roche foundation medicine found ROS1 EZR-ROS1 fusion. Therefore entrectinib 200mg 3 tabs per day was given. She tolerated it well and it showed partial response in the primary lung tumor in RML and no occurrence in brain metastasis.

Conclusions: We suggest the patient may have concurrent EGFR mutation and ROS-1 rearrangement in different part of lung tumor

Keywords: cocurrent ROS-1 rearragement and EGFR mutation, target therapyt

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.46 Efficacy of Sunvozertinib in Advanced NSCLC With HER2 Exon 20 Insertion After Prior Treatment Failure: A Real-World Case Serie

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Introduction: Non-small cell lung cancer (NSCLC) with HER2 exon 20 insertion mutations represents an aggressive disease subset with limited treatment options and poor prognosis. Sunvozertinib, a novel tyrosine kinase inhibitor (TKI) designed for EGFR exon 20 insertions, has shown potential activity against HER2 exon 20 insertions. This case series assesses the efficacy and safety of sunvozertinib as ≥second-line therapy in patients with HER2 exon 20 insertion mutations after prior treatment failure.

Methods: We retrospectively reviewed data from patients with advanced NSCLC harboring confirmed HER2 exon 20 insertion mutations who received sunvozertinib following progression on prior therapies. Data encompassed patient demographics, disease stage, previous treatments, sunvozertinib dosage, treatment response (per RECIST 1.1 where applicable), adverse events (AEs), and clinical outcomes.

Results: At data cutoff (Nov 20, 2024), three patients were retrospectively reviewed: 1): A 59-year-old female who was diagnosed with stage IIIA lung adenocarcinoma (HER2 p.G776delinsLC) in 2022, received sunvozertinib 300 mg once daily (QD) as third-line therapy in December 2023. Prior treatments included first-line chemotherapy plus immunotherapy (PFS 3 months) and second-line dacomitinib (PFS 4 months). She achieved a partial response (PR) with 40% tumor shrinkage with sunvozertinib monotherapy, which sustained for 9 months until September 2024. Subsequent sunvozertinib plus vinorelbine yielded stable disease (SD) for 1 month, followed by progression after 2 months. AEs (rash, diarrhea, mucositis, and appetite loss) were managed without discontinuation. 2): A 58-year-old female with stage IIIB lung adenocarcinoma (HER2 p.Y772-A775dup), who was diagnosed in 2023, started sunvozertinib 300 mg QD as second-line therapy in May 2024 after progression on first-line immunotherapy plus chemotherapy (PFS 8 months). She achieved PR with 40% tumor shrinkage, with AEs including diarrhea, rash, oral mucositis, and decreased appetite, which were all tolerable. 3): A 48-year-old female with advanced NSCLC (HER2 p.Y772-A775dup), who was diagnosed in 2022, received sunvozertinib 300 mg QD as sixth-line therapy starting from April 2024. She was heavily pretreated with chemotherapy, immunotherapy, radiotherapy, and targeted agents across five prior lines. Sunvozertinib resulted in stable disease (SD) with 10% tumor shrinkage observed after one month, which sustained for 6 months until progression. AEs comprised diarrhea, rash, oral mucositis, decreased appetite, and leg cramps, which were managed conservatively.

Conclusions: Sunvozertinib exhibited clinical efficacy in advanced NSCLC with HER2 exon 20 insertions across second to sixth-line settings with tumor obvious shrinkage post-prior treatment failures. The AE profile (rash, diarrhea, mucositis) was tolerable and manageable. These real-world data suggest sunvozertinib as a promising option for this population, meriting further prospective research.

Keywords: NSCLC, HER2 Exon 20 Insertion, Sunvozertinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.47 Persistent Response of Sunvozertinib in Lung Adenocarcinoma Patient With EGFR Exon 20 Insertion Mutation

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Introduction: Sunvozertinib is an oral, potent, highly selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) approved in China for the treatment of advanced non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion (exon20ins) mutation. The clinical trial of sunvozertinib in first-line setting is under exploration. Here, we firstly report the encouraging efficacy and safety of sunvozertinib as first-line maintenance therapy in a lung adenocarcinoma patient with EGFR exon20ins mutation after receiving immunotherapy and chemotherapy.

Methods: Medical records were reviewed retrospectively. The data analyzed by investigators included response assessment by RECIST1.1 and safety outcomes.

Results: A 67-year-old male patient underwent CT scan in February 2022 which showed left lung malignancy with bilateral hilar and mediastinal lymph node metastasis, bilateral rib and thoracic vertebrae metastasis. The longest diameter of the tumor was 7.4 cm. A lymph node biopsy of left neck was performed, and immunohistochemistry confirmed lung adenocarcinoma with PD-L1 expression of 80%. Next-generation sequencing (NGS) showed EGFR exon20ins mutation (p.P772delinsPH). The TNM stage was cT4N3M1c, IVB (AJCC 8th edition). From March 2022, the treatment of tislelizumab, pemetrexed and carboplatin was given every 3 weeks for 6 cycles. The tumor size shrank from 7.4 cm to 4.9 cm. Maintenance treatment with tislelizumab and pemetrexed and then pemetrexed alone was started from July 2022, and the tumor lesion remained stable. However, the patient refused to continue using tislelizumab or pemetrexed due to tolerance issues. The patient started sunvozertinib 300mg QD monotherapy from Dec 2023 based on the accessibility and efficacy. After the drug change, the tumor continuously shrank under the treatment of sunvozertinib with good safety and tolerability. Only grade 1 diarrhea and paronychia occurred, which were improved by symptomatic treatment. The most recent follow-up CT scan showed the tumor size shrank to 3.8 cm. By March 2025, the patient's progression-free survival reached 36 months.

Conclusions: For lung adenocarcinoma patient with EGFR exon20ins mutation, sunvozertinib showed sustained efficacy and safety benefits as first-line maintenance treatment after the patient developing intolerance to immunotherapy and chemotherapy.

Keywords: EGFR exon20ins, Sunvozertinib, First-line treatment

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.48 Identifying Optimal First-Line Treatment Strategy for Advanced-Stage EGFR Mutant NSCLC: A Network Meta-Analysis

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Introduction: Epidermal growth factor receptor (EGFR) mutations drive 50-60% of unresectable non-small cell lung cancer (NSCLC) in Asian populations, positioning EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy. Although numerous head-to-head randomized controlled trials (RCTs) have emerged comparing novel agents and combination therapeutic strategies, the comparative efficacy among these regimens remains to be systematically evaluated. The meta-analysis was conducted to assess the individual and comparative clinical outcomes of various first-line EGFR-TKI-based treatment strategies.

Methods: This PROSPERO-registered (CRD42024572724) network meta-analysis followed PRISMA guidelines, systematically searching PubMed, Embase, Cochrane Library, Web of Science, and major conferences as of January 2025 for II/III RCTs comparing EGFR-TKI regimens. Outcomes included survival metrics (PFS/OS), response rates (ORR/DCR), and adverse events (AEs).

Results: A total of 54 RCTs, involving 12,344 patients and 35 first-line EGFR-TKI-based treatment strategies were included. Osimertinib combined with chemotherapy demonstrated superior PFS (SUCRA=0.8235) and OS (SUCRA=0.8932). Osimertinib and savolitinib achieved the highest ORR (SUCRA=0.9238), while first-generation TKI plus chemotherapy ranked first for disease control rate (SUCRA=0.8226). The safety analysis revealed that second-generation TKI-antibody combination therapy (afatinib plus cetuximab) was associated with the highest incidence of adverse events, evidenced by the maximum SUCRA values for both any-grade AEs (SUCRA=0.8207) and grade 3 or higher AEs (SUCRA=0.8252), while osimertinib plus chemotherapy also showed high incidence of grade 3 or higher AEs (SUCRA=0.7472).

Conclusions: For patients with advanced EGFR-mutated NSCLC, osimertinib plus chemotherapy is considered the optimal choice due to its superior efficacy in improving PFS and OS compared with other EGFR-TKI-based treatment strategies. However, the toxicity of third-generation EGFR-TKI plus chemotherapy requires careful attention.

Keywords: Epidermal growth factor receptor mutation, Tyrosine kinase inhibitor, Treatment strategy

EP.12.49 Osimertinib Distribution in Brain Metastases From Patients Withmetastatic Non-Small Cell Lung Cancer

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Introduction: Osimertinib is a small-molecule kinase inhibitor used for EGFR+ non-small cell lung cancer (NSCLC) with relative good penetration into the cerebrospinal fluid (CSF) compared to other EGFR-inhibitors. CSF concentrations from lumbar punctures range from 0.77 to 18.1 ng/ml, which represents 0.2% to 5% of the systemic osimertinib exposure1-4. It is however unknown how much osimertinib actually reaches brain tissue and central nervous system (CNS) metastases.

Methods: Patients with EGFR+ metastatic NSCLC were included in a prospective biomarker cohort study (NCT05221372). For this sub-study, patients who used osimertinib and underwent metastatectomy of a CNS metastasis were selected for collection of blood, CSF, and CNS tumour tissue. Also, other (peritumoral brain) tissue which became available during the procedure was collected, e.g. the entry cortex. Samples were quantified using validated LC-MS/MS assays.5,6

Results: Three patients underwent CNS metastatectomy because of progression of a single CNS metastasis during osimertinib treatment of 80mg QD. Patient 1 received osimertinib after 10 months of erlotinib treatment, because she developed new CNS metastases. Regardless of the highest concentration in the tumour, osimertinib did not result in CNS response. Molecular diagnostics showed new MET and EGFR amplifications as resistance mechanisms. Patients 2 and 3 received osimertinib as first-line treatment. Patient 2 was pre-treated with cranial stereotactic radiotherapy, including the later progressive metastasis. She had CNS response to osimertinib for 12 months, despite low concentrations in plasma, tumour, and peritumoral brain tissue. Ultimately, no resistance mutations were found. Patient 3 did only have extracranial response on osimertinib, with progressive CNS disease. He also had low osimertinib plasma and CSF concentrations, but higher tumour-to-brain tissue ratio than patient 2. Less vascularised areas, such as necrotic tumour centres and CSF, had lower osimertinib concentrations relative to other tissue. All osimertinib concentrations are shown in table 1.

Conclusions: This is the first analysis describing the distribution of osimertinib in various CNS compartments in patients with CNS progression. The results could further help guiding studies that focus on optimising osimertinib penetration in this difficult-to-understand body compartment. Osimertinib accumulates into the tumour tissue, which could explain its clinically relevant effectivity against CNS metastases. However, no comparison could be made with osimertinib concentrations in patients with stable CNS disease. The large interpatient variability could indicate a subset of patients with progression due to low osimertinib CNS penetration. This data underlines the importance for future studies to focus on the individual differences in osimertinib's CNS distribution.

Table 1. Osimertinib concentrations in blood, CSF, peritumoral brain tissue and CNS metastases

Patients	***Patient 1***	***Patient 2***	***Patient 3***
Osimertinib concentrations			
Plasma (ng/mL)	*234*	*84.6*	*92.1*
Tumour (ng/mg)	*13104*	*1000*	*3622*
Peritumoral brain tissue (ng/mg)	-	*1165*	*2290*
Necrotic tumour centre			
Solid component (ng/mg)	*890*	*86.0*	-
Liquid component (ng/mL)	*106*	*49.6*	*23.0*
Cerebrospinal fluid (ng/mL)	*19.9*	*13.7*	*5.33*
Tumour:blood ratio	*56.0*	*11.8*	*39.3*
Tumour:peritumour brain tissue ratio	-	*0.86*	*1.58*
Molecular profile			
Co-mutations primary tumour	*TP53 exon 8*	*EGFR/HER2 amplification*	*PIK3CA*
New molecular resistance mechanism	*MET/EGFR amplification*	*No*	*Unknown*
Clinical information			
Previous treatment	*Erlotinib for 10 months*	*Metastatectomy and SRT*	*No*
Osimertinib CNS-response	*None*	*Partial response for 12 months*	*None*

Abbreviations: SRT: stereotactic radiotherapy. CNS: central nervous system.

Keywords: Osimertinib, Central nervous system metastasis, Pharmacology

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.50 Tepotinib Plus an EGFR Tyrosine Kinase Inhibitor as an Effective Subsequent Line: A Case Series From Kuwait

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Introduction: Epidermal Growth factor receptor Tyrosine Kinase inhibitors (EGFR-TKIs) are the primary therapy for EGFR mutant NSCLC. Inevitable resistance develops with acquired resistance often driven by MET alterations and MET amplification being the most common of about 5-50% post osimertinib. Selective MET-TKIs (like tepotinib) plus third generation EGFR-TKIs show promise with trials like INSIGHT reporting improve survival outcomes in MET amplification patients

Methods: We conducted a retrospective case series of 4 patients with EGFR mutant NSCLC and MET mediated resistance treated in Kuwait Cancer Control Center (KCCC). Patients received tepotinib plus osimertinib after progressing on first line EGFR TKI. Data on treatment response, PFS and OS were collected from our medical records and analyzed.

Results: This case series of 4 patients with EGFR mutant NSCLC and MET amplification resistance to osimertinib, treated in Kuwait highlights tepotinib efficacy. Tepotinib effectively controlled extracranial disease but CNS penetration remains limited, underscoring the need for further research to optimize combination therapy in this population with poor prognosis

Conclusions: Our case series highlights the critical unmet need for patients with advanced EGFR mutant, MET-altered NSCLC in clinical practice demonstrating the clinical utility of tepotinib plus EGFR TKI in overcoming resistance, aligning with prior trials data. Compassionate use programs may play a critical role in facilitating access to novel therapies and generating real world evidence of treatment efficacy.

Keywords: EGFR-TKI resistance, MET amplification, Tepotinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.51 Clinical Landscape and Future Perspectives of Targeted Protein Degradation Therapies in Lung Cance

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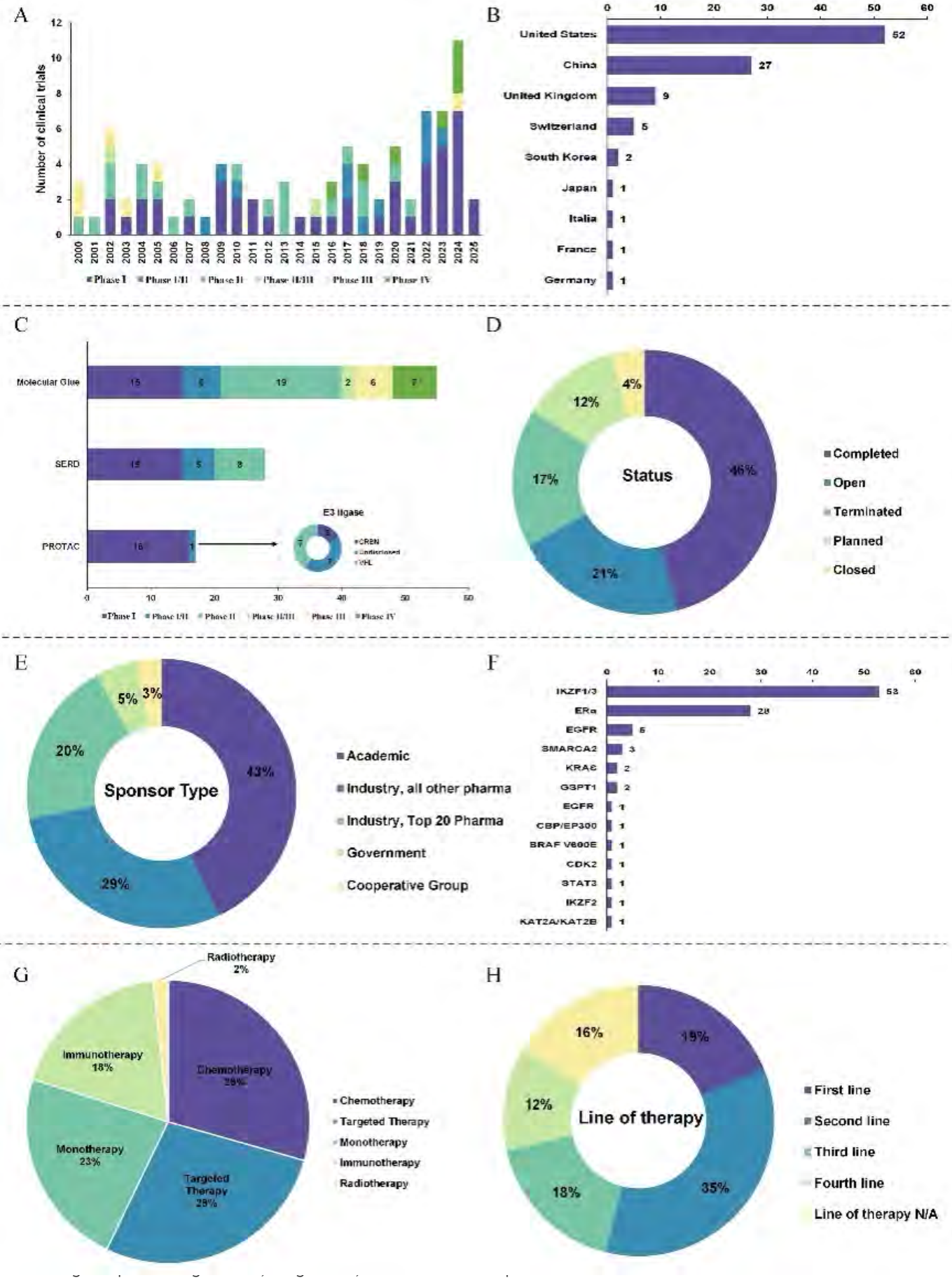
Introduction: As the leading cause of cancer-related mortality worldwide, lung cancer presents three major challenges: acquired resistance, treatment-related toxicity, and limited efficacy. Some patients respond poorly to standard therapies, prompting the exploration of novel approaches. Due to the lack of druggable binding sites in certain intracellular proteins, conventional drugs often fail, rendering these targets "undruggable". Targeted protein degradation (TPD), an emerging strategy, recruits pathogenic proteins to E3 ligases, inducing their degradation via proteasomal, lysosomal, or autophagic pathways, thereby overcoming the limitations of conventional therapies.

Methods: This study analyzed the global profile of clinical trials of TPD drugs in lung cancer using the Trialtrove database system. Search criteria included "mechanism of action as a protein degrader" and lung cancer subtype (non-small cell lung cancer and small cell lung cancer), and a total of 108 trials were identified, of which 100 were confirmed after manual screening. Data were extracted and statistically analyzed for trial phase, treatment combination, funding source, and target protein.

Results: From 2000 to 2025, the number of clinical trials involving TPD drugs increased significantly, peaking in 2024. Geographically, trials cover nine regions, with the United States and China leading. Molecular glues dominate the clinical pipeline (55%), followed by SERDs (28%) and PROTACs (17%). Most trials are in early stages (Phase I and II: 85%), with few advancing to Phase III (8%) or IV (7%). Trial statuses include completed (46%), planned (12%), ongoing (21%), terminated (17%), and concluded (4%), reflecting the ongoing evaluation of TPD safety and efficacy. Funding mainly comes from academic institutions (43%) and biotech companies (29%). Notably, TPD drugs are primarily used as first-line (19%) and second-line (35%) therapies. Target protein analysis shows a shift from conventional targets (ERα, IKZF1/3) to emerging "undruggable" proteins like KRAS and SMARCA2. Increasingly, combination therapies are explored, especially with chemotherapy (29%) and targeted therapy (28%), aiming to improve efficacy.

Conclusions: TPD drugs, by targeting "undruggable" proteins, are advancing precision therapy for lung cancer to a new stage. As clinical trials progress, the integration of TPD therapies with existing treatment modalities holds the potential to effectively overcome resistance and improve patient outcomes.


A
Number of clinical trials
Phase I
Phase I/II
Phase II
Phase II/III
Phase III
Phase IV
B
United States 52
China 27
United Kingdom 9
Switzerland 5
South Korea 2
Japan 1
Italia 1
France 1
Germany 1
C
Molecular Glue
SERD
PROTAC
E3 ligase
D
Status
Completed
Open
Terminated
Planned
Closed
46%
21%
17%
12%
4%
E
Sponsor Type
Academic
Industry, all other pharma
Industry, Top 20 Pharma
Government
Cooperative Group
43%
29%
20%
5%
3%
F
IKZF1/3 53
ERα 28
EGFR 5
SMARCA2 3
KRAS 2
GSPT1 2
EGFR 1
CBP/EP300 1
BRAF V600E 1
CDK2 1
STAT3 1
IKZF2 1
KAT2A/KAT2B 1
G
Radiotherapy 2%
Immunotherapy 18%
Chemotherapy 29%
Monotherapy 23%
Targeted Therapy 28%
Chemotherapy
Targeted Therapy
Monotherapy
Immunotherapy
Radiotherapy
H
Line of therapy
First line
Second line
Third line
Fourth line
Line of therapy N/A
19%
35%
18%
12%
16%

EP.12.52 A High-Fat Meal Optimizes the Pharmacokinetic Profile of DO-2, a Novel MET-Kinase Inhibitor for NSCLC

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Introduction: DO-2 is a selective MET-kinase inhibitor with potential in non-small cell lung cancer (NSCLC) for MET-exon 14 skipping and MET-amplification. DO-2 is a deuterated version of JNJ-38877605, redesigned to reduce toxic metabolite (M5) formation via AOX-1. Currently, in a phase 1 study in patients with solid tumours, DO-2 is being evaluated for safety and pharmacokinetics. Preclinical data suggest that a Time over Threshold (ToT) of 8-10 hours for DO-2 is necessary and sufficient for anti-tumor efficacy but avoids continuous wild-type MET-inhibition causing edema. In the current study, the effects of food and green tea extract (EGCG; an AOX-1-inhibitor) were studied in healthy volunteers.

Methods: This randomized crossover study compared a single 40mg DO-2 dose in fasted state versus after a high-fat meal in humans. Participants were randomized 1:1 to start with either condition, followed by the alternate condition. Each period included 24-hour pharmacokinetic sampling of DO-2 and metabolites. Additionally, half of the patients received EGCG, while the other half did not, to explore its potential AOX-1 inhibition and the formation of M3 and M5.

Results: The ToT of DO-2 was prolonged from 7.6 hours in the fasted state compared to 11.6 hours with food (p=0.003), while the Tmax was extended from 1.52 hours (IQR: 1.44-1.97) in the fasted state compared to 4.49 hours (IQR: 3.95-4.97) in the fed state (p=0.002). The Cmax of DO-2 was reduced by 16.2% (90%CI: -3.1% to -31.0%, p=0.047) while the total exposure (AUC0-24h) of DO-2 was comparable to fasted state (+3.9%; 90%CI: -2.8% to +10.1%, p=0.308). EGCG showed a trend for lower formation of M3, with a difference in AUC0-24h of -23.3% (p=0.128) and Cmax of -13.7% (p=0.291) with EGCG compared to no EGCG, see table 1. The ratio of DO-2:M3 in AUC0-24h was higher (+13.2%; p=0.590) as well for Cmax (+12.4%; p=0.977) with EGCG.

Conclusions: This study shows that food significantly prolongs ToT and reduces Cmax for DO-2 in a clinically relevant way, likely due to an increase in pH following food intake, as DO-2 solubility and hence absorption is known to be pH-dependent. Total exposures (AUC0-24h) to DO-2, DO-5 and M3 are similar with and without food. Since an 8-10 hour ToT is ideal for efficacy and toxicity, food optimizes the pharmacokinetic profile of DO-2, which is further evaluated in the extension phase of the phase 1 study in patients (NCT05752552). Possibly, EGCG could reduce M3 formation and should be studied further.

Table 1 – Pharmacokinetics of DO-2, DO-5 and M3 in Fed and Fasted States with/without EGCG

	Fasted	*Food*	*Relative difference food vs. fasted (90% CI)*	*p-value*
DO-2				
AUC_{0-24} - ng*h/mL *(CV)*	3,604 (31%)	3,785 (35%)	+3.9% [-2.8% to +10.1%]	0.308
C_{max} - ng/mL *(CV)*	615 (28%)	485 (15%)	-16.2% (-3.1% to -31.0%)	**0.047**
ToT – hours *[IQR]*	7.60 [6.88 - 14.85]	11.6 [5.48 - 7.50]	+3.95; +52.6%	**0.003**
T_{max} – hours *[IQR]*	1.52 [1.44 – 1.97]	4.49 [3.95 – 4.97]	+2.97; +195%	**0.002**
DO-5				
AUC_{0-24} - ng*h/mL *(CV)*	457 (50%)	453 (60%)	+1.39% [-13.1% to +12.1%]	0.857
C_{max} - ng/mL *(CV)*	71.5 (52%)	61.2 (37%)	-1.26% (-18.3% to +13.4%)	0.887
T_{max} – hours *[IQR]*	2.96 [1.95 – 3.02]	4.96 [4.24 – 5.05]	+2.00; 67.6%	**0.002**
*M3**				
AUC_{0-24} - ng*h/mL *(CV)*	792 (38%)	800 (41%)	+0.12% (-8.6% to +9.1%)	0.980
C_{max} - ng/mL *(CV)*	90.3 (31%)	78.6 (32%)	-9.3% (-23.9% to +3.6%)	0.228
T_{max} – hours *[IQR]*	2.48 [1.65 – 2.98]	4.96 [4.96 – 5.04]	+2.48; 100%	**0.002**
	No EGCG	*EGCG*	*Difference EGCG vs. no EGCG*	*p-value*
*M3**				
AUC_{0-24} - ng*h/mL *(CV)*	884 (32%)	717 (50%)	-167; -23.3%	0.128
C_{max} - ng/mL *(CV)*	89.8 (24%)	79.0 (41%)	-10.8; -13.7%	0.291
*DO-2:M3 ratio**				
AUC_{0-24} *[IQR]*	4.7 [3.5 – 6.0]	5.3 [3.9 – 6.6]	+13.2%	0.590
C_{max} *[IQR]*	6.5 [5.4 – 7.9]	7.3 [4.9 – 9.8]	+12.4%	0.977

Abbreviations: AUC: Area Under the Curve, expressed as geometric mean, C_{max}: maximum concentration; expressed as geometric mean, ToT: Time over Threshold; expressed as median, T_{max}: Time to reach maximum exposure; expressed as median.

**M3 is a non-toxic soluble surrogate marker for M5 since M3 is the precursor to M5.*

Keywords: NSCLC, Food Interaction, MET-inhibition

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.53 Case Report Response to Treatment With Erdafitinib in a Patient With FGFR2 Mutation in Adenocarcinoma Lung Cancer

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Introduction: Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor approved in the US for the treatment of locally advanced or metastatic urothelial carcinoma in adults with susceptible FGFR3 alterations; however, mutations in FGFR are found in various solid tumors, including lung cancer. Multiple studies are demonstrating the efficacy of anti-FGFR therapies in patients with solid tumors with FGFR alterations. The etiology of non-small-cell lung cancer (NSCLC) and the distribution of associated molecular aberrations vary according to the patient's profile and origin, with the most frequent mutations being KRAS, EGFR, ALK, ROS1, and TP53. However, FGFR aberrations, including mutations, fusions, and gene amplifications, were detected in 1.9% of the population. FGFR abnormalities were more frequently observed in lung squamous cell carcinomas (6.8%) than in lung adenocarcinomas (1.3%). Due to the low prevalence of this mutation, the response to novel therapies in patients with lung adenocarcinoma is limited.

Methods: Collect the information through the patient's medical history

Results: We present a 65-year-old female patient from Lima, Peru, with an ECOG score of 1, diagnosed with INVASIVE MUCINOUS LUNG ADENOCARCINOMA Stage IV, multi-treated and with poor response to chemotherapy and radiotherapy. After failing a third line with Docetaxel, next-generation sequencing (NGS) studies were conducted, revealing: FGFR2 rearrangement intron 17, FGFR2-MYH16 rearrangement. Based on these findings, targeted treatment with Erdafitinib was initiated, resulting in Grade 2 dermatological toxicity and a progression-free survival (PFS) of seven months, with PET-CT imaging showing a partial response in the lungs but disease progression in the liver.

Conclusions: This report presents the case of a patient with advanced lung adenocarcinoma who underwent multiple lines of treatment and responded to anti-FGFR targeted therapy (Erdafitinib), achieving a progression-free survival of seven months without altering quality of life. The adverse effects related to the therapy were not the reason for discontinuation; however, treatment had to be stopped due to disease progression. This report aims to provide greater insight into the response to novel treatments in patients with FGFR mutations in non-small cell lung cancer.

Keywords: Lung cancer, FGFR, Erdafitinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.54 Real-World Use of Targeted Therapy Combinations to Manage Secondary Oncogenic Addiction in Non-Small Cell Cancer

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CHU Larrey Toulouse, TOULOUSE/FR

Introduction: The identification of oncogenic addictions has significantly improved the prognosis of Non-Small-Cell Lung Cancer (NSCLC), paving the way for targeted therapy development including tyrosine kinase inhibitors (TKIs) or antibody drug-conjugate (ADC) . However, the duration of therapeutic response is often limited by the emergence of acquired resistance. In case of disease progression during targeted therapy, rebiopsy (or liquid biopsy if tissular biopsy is not possible) is recommended to identify the underlying resistance mechanisms. Activations of bypass pathways can potentially be addressed through combination therapies, a strategy currently under investigation in clinical trials. In clinical practice, molecular tumor boards are increasingly proposing off-label combinations for selected patients, based on their individual resistance profiles, to optimize therapeutic outcomes.

Methods: This French monocenter ambispective cohort study collected real-world outcomes of targeted therapy combinations in patients with advanced Oncogene-Addicted Non-Small-Cell Lung Cancer who harbored other oncogenic driver(s) as resistance mechanisms. Patients from the University Hospital of Toulouse who received a combination of targeted therapy since 2015, were included in the analysis. Key endpoints analyzed include clinical characteristics, progression-free survival (PFS), overall survival (OS), and treatment-related adverse events.

Results: Eighteen patients were included (66,7% women, median age : 59 years, history of smoking : 27,8%). At diagnosis, sixteen patients (88.9%) exhibited EGFR oncogenic alteration, while two patients (11.1%) had an ALK fusion. Fifty-five percent of the patients (n=10) received a combination of targeted therapies as a second-line treatment. Six out of the eighteen patients (33.3%) had previously been treated with chemotherapy before initiating combination of targeted therapy.We identified MET amplification as the major resistance mechanism which required targeted therapy combinations, detected in 14 out of 16 EGFR-positive patients and in 50% of ALK-positive patients. Crizotinib was the most frequently used agent in combination therapy. Overall, median real-world PFS was 5,8 months and the Duration of Treatment (DoT) was 9,9 months. While efficacy and safety data are still immature, preliminary findings show that 31.6% of patients experienced toxicities of grade 3 or higher according to the CTCAE. Dose reductions were required for 38.9% of patients, and 22.2% discontinued treatment due to toxicity. Furthermore, one patient death has been attributed to toxicity associated with the targeted therapy combination.

Conclusions: Combination targeted therapy were predominantly utilized for addressing MET amplification in our cohort. Combination strategies could provide clinical benefit with real-world progression-free survival (rwPFS) data aligning with efficacy findings from clinical trials. Such combinations represent an alternative to chemotherapy, which is still the standard of care, potentially delaying its use. However, the risk of overlapping toxicities and resulting dose adjustments may impair effectiveness of these combinations, necessitating careful patient monitoring. Further investigations are needed and the ongoing KOMBILUNG study, an international multicenter ambispective cohort study, aims to provide comprehensive data on the outcomes of patients receiving combination targeted therapies.

Keywords: targeted therapy, resistance mechanisms, Combinations

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.55 Aumolertinib Combined With Metronomic Oral Vinorelbine in Advanced EGFR-Mutant NSCLC

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Introduction: The monotherapy of 3rd generation EGFR-TKIs has been the standard first-line treatment for advanced NSCLC patients harboring EGFR mutation. However, the PFS monotherapy is around 20months, which seems to be insufficient and how to further prolong patients' survival time remains a clinical issue that is required to attach great importance. FLAURA2 study showed the combination of EGFR-TKI and chemotherapy significantly improved PFS, whereas intravenous chemotherapy has its distinct drawbacks, including inconveniency of administration, relatively severe adverse reactions and repeated hospitalizations. EGFR-TKI plus metronomic oral chemotherapy is a promising approach to address above clinical concerns, particularly, both aumolertinib and oral vinorelbine have been identified efficacious in treating advanced NSCLC patients. Hence, a single-arm, prospective study was conducted.

Methods: An estimated 165 untreated EGFR-mutant advanced NSCLC patients will be enrolled in the study and all participants will be given aumolertinib (110mg once daily) and metronomic oral vinorelbine (40mg once, three times a week for continuous 3 weeks of a four-week cycle). The primary endpoint is PFS and secondary endpoints conclude ORR, DCR, DoR and safety.

Results: 11 patients were recruited and analyzed with a median age of 61 years old. All patients were pathologically diagnosed with adenocarcinoma harboring EGFR mutations. Among all the subjects, 72.7% were evaluated as ECOG 1 or greater. At data-cutoff (March 2025), 10 patients were evaluated as PR and 1 patient maintained SD. The ORR of the combination therapy is 90.9% and the DCR is 100%. During the treatment process, no grade≥3 AE was observed.

Conclusions: Aumolertinib plus metronomic oral vinorelbine has preliminarily shown superior efficacy and the combination therapy is well-tolerated. Enrollment will continue for further analyses.

Keywords: EGFR-mutant NSCLC, targeted therapy, oral regime

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.56 Ipd Meta-Analysis of Intracranial Efficacy: Can CNS Data Refine First-Line Choices in EGFR-Mutant NSCLC?

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Introduction: Central nervous system (CNS) progression remains a major unmet need in EGFR-mutant non-small cell lung cancer (NSCLC). Although osimertinib has demonstrated intracranial activity, the CNS efficacy of emerging EGFR-targeted combinations may offer enhanced CNS control.

Methods: To clarify the relative intracranial efficacy of EGFR-targeted regimens, an individual patient data (IPD) meta-analysis of the MARIPOSA (amivantamab plus lazertinib [AMI+LAZ]) and FLAURA2 (osimertinib plus chemotherapy [OSI+CT]) trials was conducted. Intracranial endpoints included intracranial progression-free survival (iPFS), intracranial objective response rate (iORR), CNS complete response (CR) rate, and time to CNS progression. A one-stage mixed-effects IPD model was used. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression; odds ratios (ORs) were derived from logistic models adjusted for trial and baseline CNS involvement. Cumulative incidence of new CNS metastases was evaluated using competing risks methodology.

Results: A total of 705 patients (n=429 AMI+LAZ, n=276 OSI+CT) were included, of whom 188 (26.7%) had brain metastases at baseline. In this subgroup, median iPFS was 17.6 months for AMI+LAZ and 18.2 months for OSI+CT, with 12-month iPFS rates of 71.3% and 74.0%, respectively (HR 0.92; 95% CI 0.66-1.28; p=0.61). iORR was similar (60.2% vs 58.7%), while CNS CR occurred in 31.0% (AMI+LAZ) vs 43.1% (OSI+CT) of patients (OR 0.60; 95% CI 0.32-1.12; p=0.11).

Among patients without baseline CNS involvement (n=517), the 18-month cumulative incidence of new brain metastases was numerically lower with AMI+LAZ (10.2%) compared to OSI+CT (14.6%), although the difference was not statistically significant.

Conclusions: AMI+LAZ demonstrated comparable intracranial efficacy to OSI+CT in patients with baseline brain metastases and showed a trend toward lower CNS progression in those without. These findings support AMI+LAZ as a CNS-active first-line option in EGFR-mutant NSCLC and highlight the need for dedicated CNS-specific endpoints in future EGFR-targeted trials.

Keywords: EGFR-Mutant NSCLC, CNS efficacy, IPD Meta-Analysis

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.57 Ensartinib Exhibits Potential Synergistic Effects With Radiotherapy in ALK-Positive Non-Small Cell Lung Cancer

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Introduction: Ensartinib, an ALK inhibitor, has been shown to significantly improve outcomes in ALK-positive non-small cell lung cancer (NSCLC) patients. Radiotherapy serves as a critical local therapeutic modality for lung cancer. In multiple treatment strategies, systemic therapy often requires combination with local therapies. However, the efficacy of combining ensartinib with radiotherapy remains unknown.

Methods: A re-analysis of clinical trial data for ensartinib was conducted. A total of 97 NSCLC patients with baseline brain metastases who were ALK-positive and crizotinib-resistant received ensartinib treatment. Among them, 37 (38%) had previously received brain radiotherapy. Efficacy analyses compared outcomes between patients with and without prior brain radiotherapy to explore the potential synergistic interaction between ensartinib and radiotherapy. The H3122 human cell line (EML4(13)-ALK(20) variant 1 fusion) was used as the model. Ensartinib monotherapy, radiotherapy alone (doses of 0, 2, 4, 6, and 8 Gy) and combination were administered to evaluate the antitumor activity in vitro.

Results: Clinical data analysis revealed that among patients with baseline measurable intracranial lesions, those who had received prior brain radiotherapy achieved an intracranial objective response rate (ORR) of 88% (95% CI: 47-100) and disease control rate (DCR) of 100% (95% CI: 63-100). In contrast, patients without prior brain radiotherapy showed an intracranial ORR of 66% (95% CI: 47-81) and DCR of 97% (95% CI: 84-100). The median progression-free survival (PFS) was 13.9 (95% CI: 11.8, NE) months and 7.7 (95% CI: 5.4-11.8) months, respectively. The incidence of neurological treatment-emergent adverse events (TEAEs) was 29.7% (11/37) and 28.3% (17/60), respectively. There was no difference in the incidence of neurological adverse events between the two cohorts, patients with prior brain radiotherapy did not exhibit an increased risk of neurological adverse events, suggesting that the combination of radiotherapy and ensartinib exhibits a synergistic interaction in enhancing antitumor efficacy with good toleration and safety. Furthermore, in-vitro experiments demonstrated that ensartinib combined with radiotherapy at various doses exhibited significantly enhanced inhibition of cell proliferation ($P < 0.0001$).

Conclusions: Both in-vitro experiment and clinical study data demonstrate that the combination of ensartinib and radiotherapy exhibits a potential synergistic effect.

Keywords: NSCLC, ALK, Ensartinib

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.58 Feasibility of Aumolertinib Followed by SRT in EGFR+ NSCLC Patients With Intracranial Oligo-Progression: A Phase II, Prospective Study

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Introduction: Third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs), such as aumolertinib, have demonstrated significant efficacy in EGFR-mutant non-small cell lung cancer (NSCLC)with brain metastases. The timing of SRT and optimal treatment strategy for patients with intracranial oligo-progression during EGFR-TKI therapy remains unclear. This phase II, prospective study evaluates the efficacy and toxicity of aumolertinib followed by stereotactic radiotherapy (SRT) for intracranial oligo-progression in EGFR-mutant NSCLC patients.

Methods: This prospective, single-arm phase II trial enrolled EGFR-mutant NSCLC patients with brain metastases (≤10 brain lesions). All patients were initially treated with aumolertinib (110 mg orally once daily), upon intracranial oligo-progression, patients received stereotactic radiotherapy (SRT) to the progressive brain lesions while continuing aumolertinib thereafter if extracranial disease is stable. The primary endpoint was intracranial progression-free survival (iPFS). Secondary endpoints included overall survival (OS), progression-free survival (PFS), intracranial objective response rate (iORR), and safety. Intracranial responses were evaluated using RECIST v1.1 criteria, and adverse events were graded according to CTCAE v5.0.

Results: From August 2021 to July 2024,a total of 41 patients were enrolled, with a median age of 65 years (50% female). The majority of patients had EGFR exon 19 deletions (56%). The median follow-up duration was 23.2m(17.8-28.6). The median intracranial progression-free survival (m-iPFS) has not yet been reached, 1-year iPFS rate: 80.5%(95% CI:68.4%-94.6%) ,2-year iPFS rate: 65.6 %(95% CI:50.6%-85.0%).2-year OS: 94.7%(95% CI: 88.1%-100%),3-year OS: 82.9%(95% CI: 68.3%-100%). Intracranial objective response rate (iORR): 78%, including 14.6% (N=6)complete responses (CR) and 63.4% (N=26) partial responses (PR).A total of 11 patients experienced intracranial progression, 3 patients developed leptomeningeal progression, and 11 patients had extracranial progression, including 6 cases of pulmonary progression (2 of which also had simultaneous intracranial progression), 3 cases of bone lesion progression, 1 case of mediastinal lymph node progression, and 1 case of liver lesion progression. 18 patients remained free of disease progression. Among the 11 patients with intracranial progression, 7 underwent the planned intracranial stereotactic radiotherapy (SRT), 3 received whole-brain radiotherapy (WBRT) due to extensive intracranial lesions, and 1 patient refused radiotherapy. Grade 1-2 adverse events, such as headache (20%) and fatigue (45%), were common. Grade 3 adverse events occurred in 12% of patients, with no Grade 4 or 5 events reported.

Conclusions: The combination of SRT and Aumolertinib therapy is an effective and well-tolerated treatment strategy for EGFR-mutant NSCLC patients with intracranial oligo-progression. We are currently conducting a phase III randomized trial (ALMORA STUDY,NCT05800223) based on this phase II clinical study to investigate the optimal timing of intracranial stereotactic radiotherapy (SRT) in the treatment of brain metastases in patients with EGFR-mutant NSCLC during third-generation EGFR-TKI therapy.

Keywords: EGFR-mutant NSCLC, aumolertinib, SRT

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.59 Calcium Channel Blockers and Irreversible EGFR TKIS. Opportunities Missed?

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Introduction: EGFR TKIs are standard of care (SOC) for EGFR+NSCLC. Recent real-life data shows a median overall survival (OS) of 17 months in patients with Stage IV - L858R EGFR+ NSCLC treated with first-line Osimertinib in the Netherlands. Patients with EGFR+ Del19 NSCLC have longer but limited OS due to resistance to EGFR TKIs. A recent study suggests that these patients (especially those with L858R) could benefit from upfront chemotherapy. The potential improvement in OS is modest, still this could improve the SOC for L858R patients. Could SOC be improved by addition of calcium channel blockers (CCB)? Two recent retrospective studies support this.

Methods: Literature review.

Results: Two seminal studies were published in 2021 and in 2023, spanning several years. Total patients included: 63 + 345 (n 408). Both studies reported longer OS (6 months longer OS), largest study reported a 2-year PFS rate of 44.4% for the patients that used CCB and EGFR TKI vs. only 8.4% for EGFR TKI alone. This should spur further investigations and clinical trials. Most likely these patients were treated with first generation EGFR TKIs and the combination of CCB and second generation or third generation (both irreversible) EGFR TKIs might be even better. This should be tested in a clinical trial. Study in cell lines concluded that β-Catenin could become a novel therapeutic target in combination with irreversible EGFR-TKIs, such as Afatinib, but not with reversible EGFR TKIs such as Erlotinib. It has been reported that Wnt/β-catenin, EGFR, clathrin pathway and endocytosis are connected. There are several possible mechanisms that could explain how CCB could promote an OS advantage in EGFR+ NSCLC: Inhibition of β-Catenin and the Wnt/Ca2+ PLC/NFAT signaling pathway. Verapamil could do this through the FRZB (Frizzled/LRP5/6) complex. An ongoing (2024) study of Osimertinib and Tegavivint, a novel ß-catenin / Wnt inhibitor indicate that β-catenin could be a relevant target with Osimertinib, an irreversible EGFR TKI. Another study showed that irreversible EGFR TKI Afatinib and Ethacrynic Acid, a diuretic agent, have strong antitumor effects in vitro and in mice models of EGFR/T790M NSCLC by inhibiting WNT/ß-catenin pathway. Intriguingly one study did report that EGFRs internalized via Clathrin-mediated endocytosis (CME) will be recycled to the cell surface. Clathrin-independent internalization will degrade the EGF receptors. Verapamil might attenuate the clathrin-independent pathway and stimulate clathrin-mediated endocytosis. Amlodepine or Verapamil are candidates for clinical trials with Afatinib or Osimertinib. Verapamil inhibits pancreatic cancer tumor growth in vivo potentially by targeting stem-like cells. Verapamil inhibits P-GP/MDR1/ABCB1 transport and was successful in clinical trials with chemotherapy. Deletions of the P-GP/MDR1/ABCB1 genes in mice result in higher levels of Erlotinib.

Conclusions: EGFR is part of the Wnt9a-Fzd9b complex. Targeting ß-catenin / Wnt with inhibitors and the therapeutic potential of understanding and optimizing EGFR endocytosis are rapidly developing. Repurposing of existing medications can save patients' time and provide safe, affordable and effective treatments that improve SOC. Industry sponsorship of repurposed drugs and clinical trials are not readily achievable and other mechanisms for financial incentives and sponsorship should be considered.

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.60 Multiple Primary Lung Cancer With Driver Gene Mutations: Is Targeted Therapy Always the Optimal Choice?

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Introduction: With the widespread adoption of CT screening, the detection rate of multiple primary lung cancer (MPLC) has significantly increased. While targeted therapy remains the standard treatment for driver-positive lung cancer, most MPLC patients exhibit inter-lesional molecular heterogeneity, leading to suboptimal outcomes with single-agent targeted therapy. This study reports a classic case of synchronous MPLC to explore clinical treatment challenges and strategies.

Methods: .Tissue specimens were obtained via CT-guided percutaneous biopsy, bronchoscopic biopsy, and surgical resection. Collaborative diagnosis was performed using immunohistochemistry (IHC) and next-generation sequencing (NGS). EGFR+ osimertinib targeted therapy was administered, and a multidisciplinary team (MDT) formulated a combination regimen of nab-paclitaxel, carboplatin, and nivolumab.

Results: Initial CT revealed 34 pulmonary nodules highly suspicious for MPLC. Pathological confirmation of the larger right upper lobe lesion identified lung adenocarcinoma, with NGS detecting an EGFR L858R mutation. After 12 weeks of osimertinib treatment, a "mixed response" was observed: the larger right upper lobe lesion shrank, but smaller right upper lobe and left upper lobe lesions enlarged, with mediastinal lymph node progression, precluding surgical eligibility. Following MDT discussion, chemotherapy-immunotherapy combination therapy was initiated for 2 cycles, resulting in significant shrinkage of all visible lesions and enabling successful right upper lobectomy. The smaller lesion in the right lung was adenocarcinoma without detectable driver mutations, confirming the diagnosis of MPLC.Seven months postoperatively, a recurrence developed in the surgical bed; lymph node biopsy revealed poorly differentiated NSCLC-NOS (non-small cell lung cancer-not otherwise specified), with NGS showing no driver mutations, indicating aggressive tumor progression.

Conclusions: This case highlights marked therapeutic heterogeneity in MPLC, where single-agent targeted therapy may not be optimal. Regardless of whether MPLC lesions present as multi-driver-positive or driver-positive plus driver-negative, chemotherapy-based combination regimens are recommended. Early multi-site biopsies are advised to clarify molecular profiling of individual lesions.

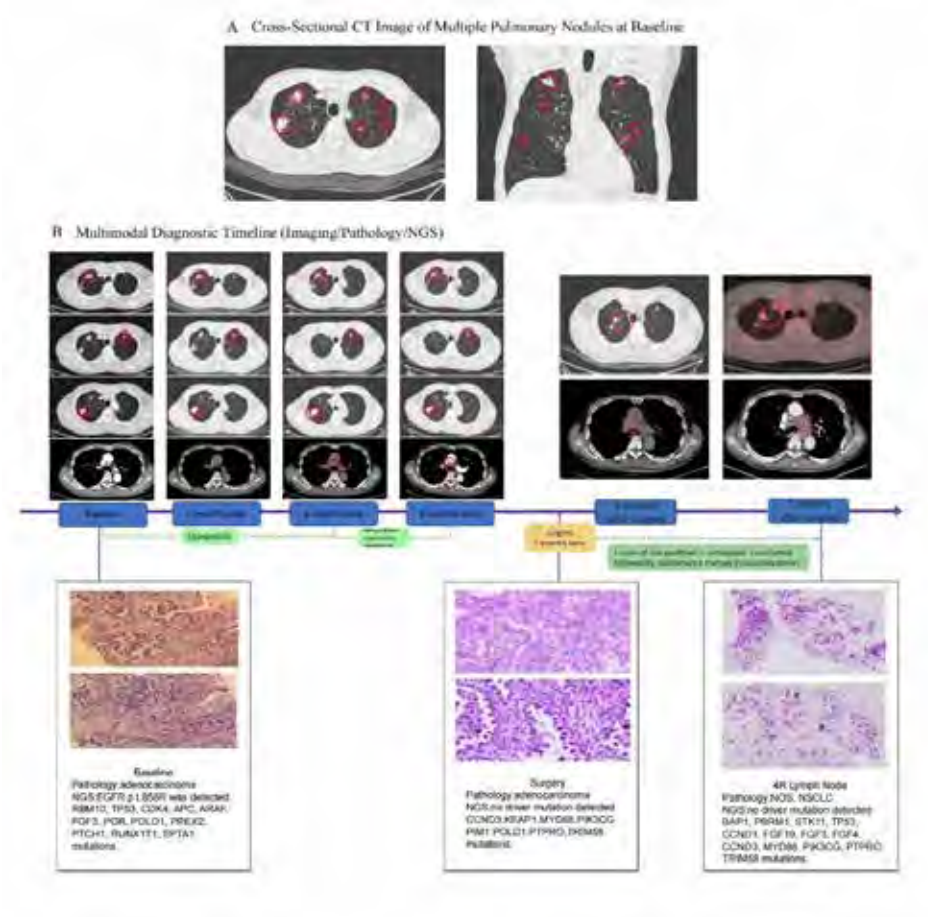

Table 1 Summary of Multiple Pulmonary Nodules at Baseline

	location	characterization	size
nodule 1	RUL apical segment	Mass	30*21mm
nodule 2	RUL apical segment	Solid nodule	25*19mm
nodule 3	RUL anterior segment	Solid nodule	20*18mm
nodule 4	LUL apicoposterior segment	GGN	13*11mm
nodule 5	RLL posterior segment	GGN	16*11mm
nodule 6	RUL anterior segment	GGN	15*13mm
nodule 7	LUL apicoposterior segment	Part-solid nodule	21*12mm
nodule 8	RLL posterior segment	Ground-glass nodule	26*20mm
nodule 9	LUL superior lingular segment	Ground-glass nodule	20*12mm
nodule 10	RUL apical segment	GGN	12*9mm
nodule 11	LUL apicoposterior segment	Solid nodule	2*2mm
nodule 12	RUL posterior segment	Solid nodule	3*2mm
nodule 13	LUL apicoposterior segment	Solid nodule	12*8mm
nodule 14	LUL anterior segment	Solid nodule	2*2mm
nodule 15	RUL anterior segment	GGN	5*3mm
nodule 16	RLL superior segment	Solid nodule	12*7mm
nodule 17	LUL apicoposterior segment	Solid nodule	10*8mm
nodule 18	LUL superior lingular segment	GGN	7*5mm
nodule 19	LLL superior segment	GGN	10*8mm
nodule 20	RLL posterior basal segment	GGN	13*8mm
nodule 21	RML lateral segment	GGN	9*8mm
nodule 22	RLL anterior basal segment	GGN	9*8mm
nodule 23	LLL anteromedial basal segment	Solid nodule	6*6mm
nodule 24	RLL lateral basal segment	GGN	13*9mm
nodule 25	RLL medial basal segment	GGN	14*12mm
nodule 26	RLL anterior basal segment	GGN	4*2mm
nodule 27	RML medial segment	Solid nodule	7*4mm
nodule 28	RLL anterior basal segment	Solid nodule	4*4mm
nodule 29	RLL posterior basal segment	GGN	5*4mm
nodule 30	RUL apical segment	GGN	5*4mm
nodule 31	RUL apical segment	GGN	5*3mm
nodule 32	RUL anterior segment	Solid nodule	7*5mm
nodule 33	LUL apicoposterior segment	GGN	5*4mm
nodule 34	RLL posterior segment	Solid nodule	3*3mm

Abbreviation: RUL-Right upper lung, LUL-Left upper lung, RLL-Right upper lung, LLL-Left lower lung, RML-Right lower lung, mm-millimeter.

Keywords: multiple primary lung cancer (MPLC), driver gene mutation, targeted therapy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.61 Prognostic-Predictive Modeling in Advanced Non-Small Cell Lung Cancer: A Review of Biomarkers Using AI, ML and DL

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Introduction: Lung cancer remains the most prevalent cancer globally and the leading cause of cancer-related mortality. With the majority of cases diagnosed at a later stage, prognosis remains poor. Advanced non-small cell lung cancer (NSCLC) presents a particularly formidable challenge, with the absence of a practical prognostic-predictive model to guide treatment decisions. However, the advent of artificial intelligence (AI) has emerged as a promising avenue for advancing such models in lung cancer. Machine learning (ML) plays a pivotal role, enabling systems to enhance their performance over time through experience and data-driven adaptation. The components of AI, particularly ML and Deep Learning (DL), have witnessed extensive research applications in lung cancer, ranging from staging and diagnosis to treatment and surveillance. This review explores AI-driven analytics in shaping clinical, inflammatory, genomic, and radiomic data to develop a superior prognostic-predictive model for advanced NSCLC, promoting global, equitable cancer care.

Methods: A systematic exploration of peer-reviewed literature was conducted, focusing on studies employing AI, ML, and DL to enhance prognostic modeling in advanced NSCLC. A diverse array of biomarkers were examined, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), advanced lung cancer inflammation index (ALI), eastern cooperative oncology group (ECOG) performance status, lactate dehydrogenase (LDH), albumin, PD-L1 Combined Positive Score (CPS), tumor mutational burden (TMB), circulating tumor DNA (ctDNA), long non-coding RNAs (lncRNAs), histone modifications, chromatin remodeling, and radiomic signatures. The assessment focused on AI-driven methodologies for integrating biomarkers into a reliable prognostic-predictive mode. Inclusion criteria focused on AI techniques, particularly ML and DL, in developing prognostic models for advanced NSCLC, with study limitations critically addressed for a comprehensive perspective.

Results: AI-driven analytics significantly outperformed conventional prognostic models, enhancing risk stratification and outcome prediction with unparalleled precision. ML algorithms effectively identified high-risk patient subgroups and those poised to benefit from targeted therapies, offering a refined approach to treatment personalization. Notably, radiomics and ctDNA-based biomarkers emerged as key players in prognostic modeling, bridging the gap between imaging, liquid biopsy, and molecular profiling.

Conclusions: The integration of parameters and AI algorithms presents a transformative approach in the management of advanced NSCLC patients. By utilizing AI driven prognostic markers, clinicians can tailor treatment strategies, enhance decision-making, and improve patient outcomes. However, challenges persist, including dataset variability, algorithmic transparency, and clinical interpretability, underscoring the need for further standardization and validation.

Major parameter	Primary task	AI tool
PDL1, ECOG, LDH, NLR, ANC, TNM staging	IO efficacy	CB, LR, NN, RF, SVM
Cytokines	ICI response;	ML-CIRI
Tumor microenvironment, RNA expression levels, PD1/PDL-1	Expression profiles; ICI response	ML
Genomics (PDL-1, TMB) Transcriptomics, Proteomics, Microbiomics, and Radiomics	IO efficacy	AI
PDL-1, TIL	Expression levels	DL, WSI-DP
LDH, Neutrophil count, CRP, ALT	Fast Progression (FP) predictors	ML
Radiomics, PDL-1	Radiomic feature extraction	ML
Radiomics (GLCM), serum albumin, ECOG, PDL-1, NLR	ICI response	AI, CART
Radiomics (274 LoG features, 728 wavelet features, 14 shape features, 18 histogram features, and 68 texture features)	ICI efficacy and treatment response	ML classifiers: SVM, LR, GNB
Radiomics (mRMR, LASSO), PDL-1	Treatment response	LR
Radiomics (LASSO), ECOG	ICI response	Training nomogram models
Multi-OMICs	ICI efficacy	AI/ML
Ct-DNA/ Liquid biopsy, radiomics	Cancer biology and treatment response	AI
Multi-OMICs	Prognosis	XGBoost, SVM, LR
ECOG	Prognosis	LR, KNN, RF, Decision Tree, and XGBoost, LIME
ECOG, Tumor associated Inflammation markers	Prognosis	LR, XGB, RF, SVM, K-NN
ECOG, Patient- reported Outcomes (PRO)	180-day mortality prediction	LR, GLM, SVM, XGBoost

Figure 1: Key Prognostic-Predictive Biomarkers and AI Models in NSCLC

TNM: Tumor, node, metastasis; **CB**: CatBoost; **LR**: Logistic Regression; **NN**: Neural Network; **RF**: Random Forest; **SVM**: Support Vector Machine; **DCR**: Disease control rate; **TTF**: Treatment failure; **CIRI**: Cytokine-based ICI Response Index, **TIL**: Tumor-infiltrating lymphocytes, **WSI**: Whole-slide images; **DP**: Digital pathology; **ALT**: Alanine transaminases; **CRP**: C-reactive protein; **GLCM**: gray-level co-occurrence matrix; **CART**: Classification and regression tree; **LoG**: Laplacian of Gaussian; **GNB**: Gaussian Naïve Bayes; **mRMR**: Minimum Redundancy Maximum Relevance; **LASSO**: Least Absolute Shrinkage and Selection Operator; **XGBoost**: extreme gradient boosting; **LIME**: Local Interpretable Model-Agnostic Explanations; **ADB-C model**: AdaBoost classification model; **TN-C model**: TabNet Classification model; **XGB**: Extreme Gradient Boosting; **RF**: Random Forest; **K-NN**: K-Nearest Neighbors; **GLM**: generalized regression with elastic net regularization.

Keywords: Lung cancer, Prognostic model, Artificial intelligence

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.62 Identification of Optimal Candidates for the FLAURA2 Regimen in EGFR-Mutated NSCLC Based on PFS2 Analysis

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Introduction: The FLAURA2 trial demonstrated the efficacy of osimertinib in combination with platinum-pemetrexed chemotherapy for previously untreated EGFR-mutated non-small cell lung cancer (NSCLC). However, optimal patient selection for this regimen remains unclear. The aim of this study is to investigate clinical characteristics associated with shortened second progression-free survival (PFS2) to identify appropriate candidates for the FLAURA2 regimen.

Methods: We retrospectively analyzed 87 patients diagnosed with EGFR-mutated NSCLC at Kanazawa University Hospital between 2008 and 2022. PFS1, PFS2, and overall survival (OS) were evaluated. PFS2 was defined as the time from the start of first-line treatment to second disease progression or death. Univariate and multivariate analyses were performed to identify factors associated with shorter PFS2.

Results: Patient characteristics: median age was 69 (range: 34-91) years. male/female: 31/56. Peformance status 0/1/2: 53/29/5. EGFR mutations del19/L858R/others: 41/39/7. First-line EGFR-TKI usage included first/second/third-generation: 23/17/47 cases.Median PFS1, PFS2, and OS were 13.9, 24.3, and 34.3 months, respectively. Multivariate analysis revealed that the presence of central nervous system (CNS) metastases at diagnosis (HR 2.90, p = 0.00049) and EGFR mutation subtype (19del vs L858R, HR 1.88, p = 0.020) were significant predictors of shorter PFS2. Subgroup analysis revealed that patients with CNS metastases had significantly worse outcomes, even when treated with second-line chemotherapy after EGFR-TKI failure.

Conclusions: Patients with L858R mutations and CNS metastases at diagnosis have a significantly shorter PFS2 with standard sequential therapy and may derive greater benefit from the FLAURA2 regimen. These results suggest that such patients are an appropriate subset for upfront combination therapy with osimertinib and chemotherapy.

Keywords: EGFR mutations, FLAURA2, PFS2

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP.12.63 Combining Chemotherapy With Osimertinib Beyond Progression in EGFR-Mutant NSCLC: A Case-Based Experiencecombining Chemotherapy and Osimertinib Beyond Progression in EGFR-Mutant NSCLC: A Case-Based Experience

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Introduction: Osimertinib is the standard first-line therapy for advanced non-small cell lung cancer (NSCLC) harboring EGFR-sensitizing mutations. However, most patients eventually develop resistance, and platinum-based chemotherapy remains the recommended second-line option when no targetable alterations are identified and local ablative strategies are not feasible. While the addition of immunotherapy to chemotherapy has failed to show clear benefit in this setting, the strategy of continuing osimertinib beyond progression in combination with chemotherapy has gained interest, particularly in light of the FLAURA2 trial, which demonstrated a significant progression-free survival (PFS) benefit for the combination in the first-line setting. Retrospective studies also suggest that maintaining osimertinib with platinum-pemetrexed in second line may prolong disease control and delay central nervous system (CNS) progression.

Methods: We reviewed the clinical history of three patients with EGFR-mutated NSCLC treated at our institution who received platinum-based chemotherapy combined with osimertinib beyond radiological progression. Clinical characteristics, timing of progression, treatment response, and tolerability were analyzed. All patients were treated in accordance with standard clinical practice, and the decision to continue osimertinib beyond progression was based on multidisciplinary evaluation.

Results: Case 1: A 51-year-old male with stage IV EGFR L858R-mutated NSCLC received first-line osimertinib in July 2023 with an initial systemic and CNS complete response. In April 2024, he started platinum-pemetrexed chemotherapy combined with ongoing osimertinib due to new pulmonary lesions not suitable for radical treatment. A partial response was documented in May 2024, with disease control ongoing as of March 2025, over 11 months after starting combination therapy.

Case 2: A 72-year-old female with EGFR exon 19-mutated NSCLC progressed in August 2023 under first-line osimertinib, with pleural carcinomatosis and bone involvement. She began second-line treatment with carboplatin, pemetrexed, and osimertinib in March 2024. Initial disease stabilization was achieved and maintained until January 2025, when bone progression led to functional decline due to severe pain, unresponsive to palliative radiotherapy. Due to poor performance status, she was not considered a candidate for further systemic therapy and was referred to supportive care.

Case 3: A 79-year-old never-smoker female initially enrolled in the ADAURA trial received adjuvant osimertinib for 3 years. In late 2022, systemic relapse was treated with osimertinib reintroduction and focal radiotherapy. Due to oligoprogression with pleural and vertebral involvement in March 2024, combination therapy with platinum-pemetrexed and osimertinib was started. The patient achieved disease stabilization and continued on maintenance pemetrexed plus osimertinib from June 2024 onward, with good tolerance.

Conclusions: In selected patients with EGFR-mutant NSCLC and non-curable progression to first-line osimertinib, continuation of osimertinib combined with platinum-pemetrexed chemotherapy may represent a valid therapeutic strategy, particularly when access to novel agents such as amivantamab is limited or contraindicated. This approach appears to be safe and may contribute to extended disease control, especially in preventing early CNS relapse. While prospective validation is awaited from ongoing trials like COMPEL, our case series supports this combination as a feasible and clinically relevant option in real-world practice, offering a potential bridge in the evolving treatment landscape of EGFR-mutated lung cancer.

Keywords: EGFR-mutant NSCLC, Osimertinib beyond progression, Chemotherapy combination strategy

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP12.64 Real-World Effectiveness of First-Line Osimertinib in EGFR-Mutated NSCLC: Interim Results From the French POSITHES Study

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Introduction: Osimertinib is a tyrosine kinase inhibitor (TKI) indicated in first-line (1L) treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating common mutations (Ex19del and L858R) of the epidermal growth factor receptor (EGFR). POSITHES study aimed to complement the evidence of osimertinib monotherapy efficacy observed in clinical trial by describing its effectiveness in real-world (RW).

Methods: POSITHES (NCT05103605) is a French observational multicenter ambispective study combining a descriptive cross-sectional survey and a prospective cohort. NSCLC patients with an activating common EGFR mutation newly treated with 1L osimertinib were recruited in 47 sites in France. Patients were enrolled from May 2021 to November 2022 and interim data are now available with a 24-month overall follow-up.

Results: A total of 233 patients were included. The majority of patients were women (n=154, 66.1%), never-smokers (n=138, 59.5%) and had an ECOG status ≤1 (n=189, 82.2%). One third (31.7%) of patients presented brain metastases (BM) at initial diagnosis (ID). The median age [IC95%] was 73 years [64;83] with a proportion of 59.6% aged ≥70y. Regarding the best overall response, 19 (9.1%) patients presented a complete response, 130 (62.5%) a partial response, 47 (22.6%) a stable disease, 5 (2.4%) a progressive disease. The median [IC95%] progression-free survival (mPFS) after osimertinib initiation was 16.6 months [14.3;18.8] in the overall population, while patients with BM at ID had a lower mPFS (12,9m) compared to those without BM (18,8m). No difference was observed in patients ≥70y vs <70y (mPFS 16,8m [13.0;23.8] vs 16,6m [13.2;19.2] respectively). More than half of patients (52.8%) were still treated by osimertinib at data cut-off. The safety profile was consistent with the expected safety profile of osimertinib.

Conclusions: POSITHES is the first ambispective study in France to investigate the effectiveness of osimertinib in a RW setting. POSITHES shows very similar efficacy outcomes to those observed for osimertinib monotherapy in the FLAURA and FLAURA2 trials, despite the broader eligibility criteria, confirming its clinical utility as a 1L treatment for EGFRm NSCLC.

Keywords: NSCLC, osimertinib, Real-World

EP.12 METASTATIC NON-SMALL CELL LUNG CANCER – TARGETED THERAPY

EP12.65 Factors Impacting Targeted Therapy Use in Stage Iv Non-Small Cell Lung Cancer Patients With Infrequent Actionable Mutations

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Introduction: The NCCN guidelines recommend non-small cell lung cancer (NSCLC) patients (pts) who are stage IV that harbor actionable mutations receive targeted therapy for first-line treatment. We aim to show among pts with infrequent actionable mutations, defined by less than 10% positivity, who receive care at oncology practices in the U.S. what clinical or demographic factors impact whether such pts receive targeted therapy or not.

Methods: Among Integra Connect PrecisionQ's de-identified database the analysis included pts >=18 years of age, who were confirmed via manual chart abstraction as newly diagnosed stage IV NSCLC and found positive for either of the following ALK, ROS1, BRAF V600E, MET Exon 14 Skipping, RET, or NTRK1/2/3 and started first-line treatment between 1/1/2022 to 12/31/2024. Pts were assessed as to whether age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, histology, stage, site of metastatic (mets) disease, and test turnaround time (TAT) impacted receiving targeted therapy. Descriptive analyses were performed, and chi-squared analysis were used for comparisons.

Results: Targeted therapy utilization (TTU) occurred in 101/185 pts (55%) with less common actionable mutations. The mean age of pts receiving targeted therapy was 65.2 compared to 70.2 for those who did not receive targeted therapy. Comparing pts by gender, TTU was 55/95 (58%) among females and 45/89 (51%) among males. Comparing pts by race, TTU was 71/137 (52%) among White pts, 11/21 (52%) among Black/African American pts, 6/7 (86%) among Asian pts, and 13/20 (65%) among other pts. Comparing pts by ECOG, TTU was 47/94 (50%) among 0-1 pts, 9/22 (41%) among 2+ pts, and 45/69 (65%) among pts with an unknown ECOG. The TTU by histology was 75/129 (58%) among pts with adenocarcinoma, 3/18 (17%) among pts with squamous cell carcinoma, and 23/37 (62%) among pts all others subtypes or unknown histology ($p < 0.01$). TTU among stage IVA was 35/72 (49%) compared to stage IVB at 34/60 (57%), and unspecified stage IV at 32/53 (60%). Comparing pts by site of metastatic disease, TTU was 37/56 (66%) among pts with bone mets, 21/37 (57%) among pts with brain/central nervous system mets, and 12/31 (39%) among pts with liver mets ($p < 0.05$). Based on test TAT, the TTU was 23/42 (55%) for TAT of <7 days, 43/88 (49%) for TAT of 7-to-14 days, and 9/21 (43%) for TAT of >14 days.

Conclusions: The real-world data shows stage IV NSCLC pts who harbor less common actionable mutations tend to receive targeted therapy if they had a histology of adenocarcinoma compared to squamous cell carcinoma or had bone mets compared to liver or brain/CNS mets. Factors such as age, sub-stage, ECOG, gender, race, and test TAT showed a difference in use of targeted therapy not to be statistically significant.

Keywords: Targeted Therapy, Stage IV, Actionable Mutations

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.01 Survival Analysis of Malignant Pleural Effusion in Small Cell Lung Cancer: A Single-Center Retrospective Analysis

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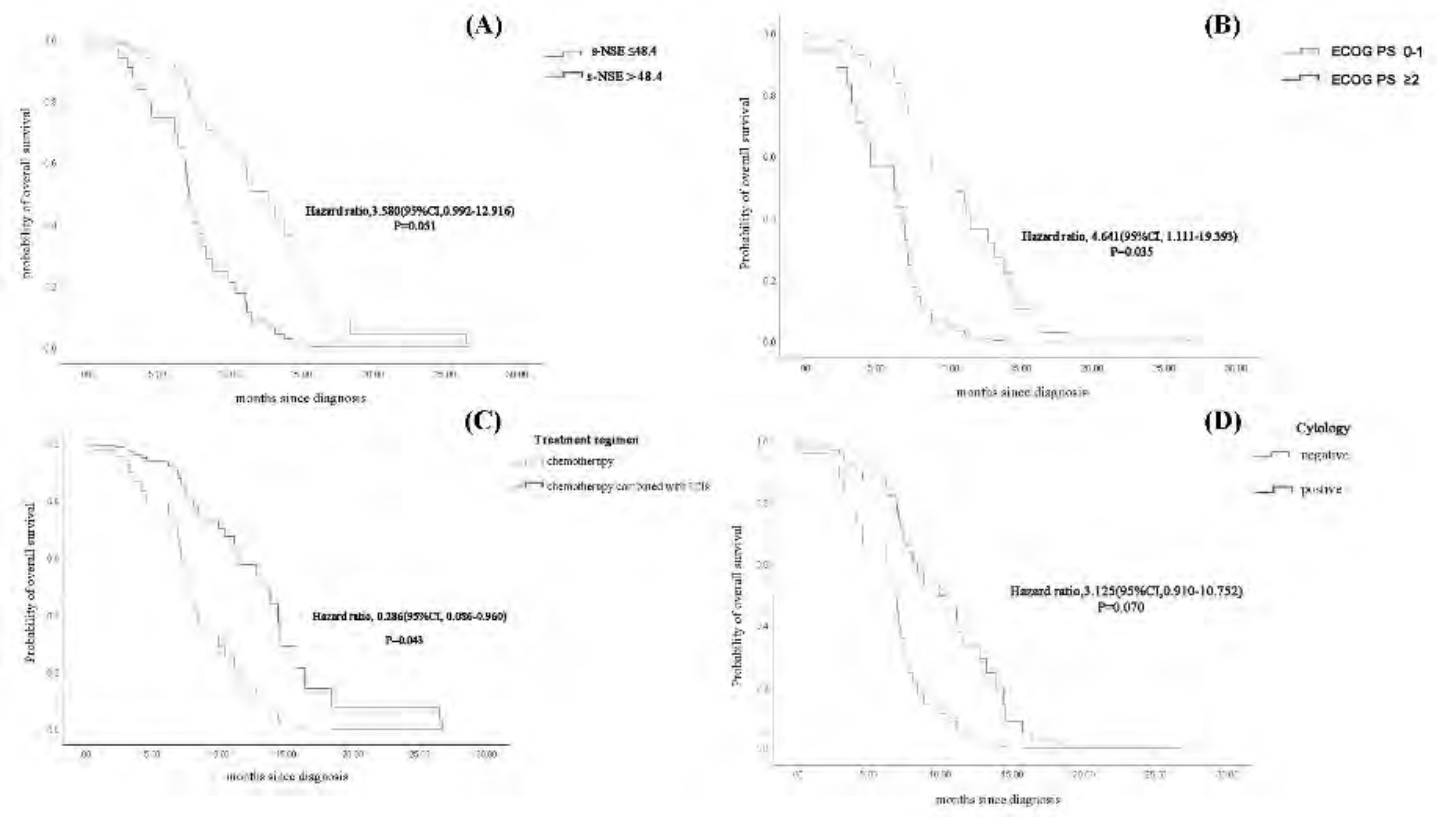
Introduction: Malignant pleural effusion (MPE) is a negative prognostic factor for non-small cell lung cancer (NSCLC). However, the occurrence rate of MPE varies in small cell lung cancer (SCLC), and the prognostic implications and associated factors in SCLC patients with MPE have been underreported

Methods: Patients diagnosed with SCLC at Jinling Hospital were enrolled from 2008 to 2024. Cox regression analyses were used to identify risk factors affecting the survival of patients with indwelling pleural catheters (IPCs). Logistic regression analyses were employed to explore independent risk factors for MPE occurrence. The primary survival outcome measured was overall survival (OS)

Results: Among the 1026 patients, 363 (36.4%) presented with pleural effusion (PE). 284 (27.6%) patients had at the diagnosis, with 129 undergoing pleural fluid analysis via IPCs, of which 80 showed positive cytology. An ECOG performance status (PS) ≥2 (P=0.035), elevated serum neuron-specific enolase (s-NSE) levels (P=0.05), and positive cytology (P=0.07) were perceived as risk factors for poorer survival in patients with IPCs. Patients with maximal PE had the shortest median OS of 5.2 months, while those with minimal effusion had a median OS of 13.8 months (P<0.001), comparable to patients without effusion, whose median OS was 14.8 months. Longer OS was observed in MPE patients who received immunotherapy, had low sNSE levels, and had negative cytology

Conclusions: Approximately one-third of SCLC patients present with PE, with an MPE incidence of 12.6%. SCLC patients with MPE exhibit the poorest survival outcomes. However, the difference in OS between patients with minimal PE and those without PE is unobvious



Keywords: small cell lung cancer, malignant pleural effusion, prognostic

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.02 Incidence and Characteristics of Small Cell Lung Cancer at the National Respiratory Center of Persahabatan Hospital, Indonesia in 2023-2024

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Introduction: Globally, lung cancer is the leading cause of death from all types of cancer. In Indonesia, lung cancer accounted for 8.6% of all cancer incidence and 12.6% of all cancer deaths, making it the leading cause of cancer-related death. Small cell lung cancer (SCLC) comprises only 15-25% of lung cancer cases, but it is known as one of the most aggressive malignancies, characterized by rapid growth and high metastatic ability. Therapy modalities for Non-Small Cell Lung Cancer (NSCLC) have evolved, the use of chemotherapy, targeted therapy and checkpoint inhibitors has been standardized. Meanwhile, management for SCLC has not changed much, perhaps because the number of cases is small, especially in Indonesia. The aim of this study to evaluate characteristic, risk factor and outcome treatment of patient with SCLC in Indonesia.

Methods: A retrospectives observational study conducted at Persahabatan Hospital for 2 years in 2023 and 2024. This study includes patients with confirmed results of small cell lung carcinoma pathology. Demographic, risk factor, and treatment of patient were analyzed. The Indonesian Association for the Study of Thoracic Oncology (IASTO)-Indonesian Society of Respirology (ISR) 2023 Risk Factor score was used to examine the risk factor level.

Results: In this study, based on anatomical pathology data, 1,677 cases of lung cancer were obtained in the period 2023-2024. There were 1,583 (94.39%), NSCLC (diagnoses adenocarcinoma, squamous cell carcinoma, large cell carcinoma and rarer cases such as neuroendocrine/carcinoid tumors) and only 94 (5.61%) SCLC. The characteristics of the SCLC patients based on age: there was median 61 (30 -80) years old. Gender: male was 82 (87.23%) and female were 16 (19.51%). Using a scoring system to determine the level of risk factors obtained low risk was 1 (3.13%), medium risk was 43 (44,79%) and high risk was 50 (52.08%). We used the chemotherapy carboplatin/cisplatin and etoposide regimen but for various reasons only 31 people received chemotherapy at Persahabatan Hospital.

Conclusions: Until today, the reason why the SCLC incident is low in Indonesia has not been found when compared to the percentage of global data which reaches 15-25%. On the other hand, based on the results of multi-center observations in Indonesia, Persahabatan Hospital has a higher incidence than other centers in Indonesia. Perhaps because most of them are referral cases, especially for difficult cases. After a definite diagnosis is obtained, a back referral is made for therapy.

Keywords: Small Cell Lung Cancer, Incidents, Treatment

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.03 A Single-Center Experience With Tarlatamab in Relapsed/Refractory Advanced Small Cell Lung Cancer and Neuroendocrine Carcinomas

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Introduction: High-grade neuroendocrine carcinomas, including extensive-stage small cell lung cancer (ES-SCLC), are aggressive malignancies with poor prognoses, with most patients developing resistance to first-line chemoimmunotherapy within 6 months. Tarlatamab, a DLL3-CD3 Bispecific T-Cell Engager, is now commercially available as a promising second line or later option for patients with ES-SCLC. The safety and efficacy of tarlatamab in a real-world setting in patients with ES-SCLC and other neuroendocrine tumors remains to be fully characterized.

Methods: We conducted a single-center retrospective analysis of clinicopathologic data, safety, and outcomes in patients receiving tarlatamab from September 2023 to March 2025, with a focus on cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Data cut off was April 2, 2025.

Results: 22 patients with advanced neuroendocrine carcinoma (77.3% ES-SCLC) received at least 1 dose of tarlatamab (Table 1). 4 patients had baseline interstitial lung disease and 1 patient had CHF. All patients had prior exposure to an immune checkpoint inhibitor (ICI) with a median 3.5 months (range 1.1 - 65.3) between last dose of ICI and tarlatamab. 10 patients had brain metastases, with 8 patients fully treated, 1 partially treated (16/25 lesions), and 1 untreated pre-tarlatamab. 14 (63.6%) patients developed any grade CRS (two Gr. 3, one Gr. 4) and 9 (40.9%) developed any grade ICANS (three Gr. 3), with all Gr. 3 toxicities occurring at the C1D1 1mg dose and one Gr. 4 CRS at the C1D8 10mg dose. At data cutoff, 16 patients are alive and 11 remain on treatment. Of 14 evaluable patients, initial responses were 6 partial responses (PR) including in a patient with prostate small cell carcinoma, 1 stable disease, 5 mixed responses, and 2 progressive disease. Objective response rate and disease control rate were 42.9% and 50% respectively. 9 patients progressed, with a median PFS of 2.9 months (0.5-5.5), of which 4 had CNS-only progression.

Conclusions: Tarlatamab was well tolerated in a real-world setting, including in patients with ILD and CHF. The rates of Grade 3 or higher CRS or ICANS were comparable to that reported in the clinical trial. Importantly, patients with primary extra-pulmonary small cell carcinoma and large cell neuroendocrine histologies did respond to tarlatamab. CNS progression remained common, including CNS-only events. Further studies such as DLL3 expression characterization and molecular analyses of patient samples will be essential to determine predictors of response and risk factors for severe adverse events to tarlatamab.

Table 1. Baseline Characteristics	
	n=22
Age at Diagnosis (years)	
Median (Range)	64.5 (52 - 84)
Age at First Dose Tarlatamab (years)	
Median (Range)	66 (53 - 85)
Sex, n (%)	
Female	13 (59.1)
Race, n (%)	
White	20 (91.0)
Black	1 (4.5)
American Indian/Alaska Natives	1 (4.5)
Ethnicity, n (%)	
Non-Hispanic	20 (91.0)
Smoking History, n (%)	
Never Smoker	0 (0.0)
Former Smoker, <20 py	1 (4.5)
Former Smoker, ≥20 py	16 (72.8)
Current Smoker	5 (22.7)
Baseline Comorbidities	
ILD	4 (18.2)
Autoimmune	1 (4.5)*
Heart Failure	1 (4.5)**
Pulmonary Hypertension	1 (4.5)
CVA	3 (13.6)
Prior Unrelated Malignancy	7 (31.8)
ECOG PS at 1st Dose Tarlatamab, n (%)	
0	5 (22.7)
1	16 (72.8)
2	1 (4.5)
Histology, n (%)	
SCLC	17 (77.3)
LCNEC	1 (4.5)
Combined SCLC/LCNEC	1 (4.5)
Extrapulmonary Small Cell Carcinoma	2 (9.1)
High Grade Neuroendocrine of the Lung, NOS	1 (4.5)
Ki-67 %	
Median (Range)	70 (5-99)
Prior Lines of Systemic Treatment, n (%)	
1	9 (40.9)
2	11 (50)
3	2 (9.1)
Prior CNS Radiation, n (%)	
Yes	12 (54.5)
WBRT	7 (31.8)
GKSRS	7 (31.8)
Prior ICI, n (%)	
Yes	22 (100)
Time from Last Dose ICI, months	
Median (Range)	3.5 (1.1 - 65.3)
Treatment Context , n (%)	
Standard of Care	17
Expanded Access Protocol	5‡
Clinical Trial	2‡
Prophylactic Tocilizumab Prior to C1D8, n (%)	
Yes	1 (4.5)
Charles Comorbidity Index	
Median (Range)	4 (1 - 12)
Referral from Satellite Cancer Center Site, n (%)	
Yes	10 (45.5)
Distance of Patient Home from Yale New Haven Health (km)	
Median (Range)	28.4 (2.1 - 302.1)

WBRT = Whole Brain Radiation Therapy, CNS = central nervous system; ICI = immune checkpoint inhibitor; ILD = interstitial lung disease; CHF = congestive heart failure; LN = lymph node; SCLC = small cell lung cancer; LCNEC = large cell neuroendocrine (lung) cancer

*psoriasis

**HFimpEF

‡ 2 patients were transitioned to standard of care after initial treatment on trial or expanded access protocol

Keywords: Small cell lung cancer, tarlatamab, real-world

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.04 Patients With Limited Stage Small Cell Lung Cancer Detected Through Lung Cancer Screening May Have Improved Survival

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy with poor prognosis. Our study aims to evaluate patients diagnosed with limited stage (LS) SCLC through the lung cancer screening (LCS) program at UI Health to determine if there is a survival difference when compared to patients diagnosed outside of the screening program.

Methods: A retrospective chart review was conducted on a database of 1743 patients diagnosed with lung cancer between 2015 and 2024 in a single center analysis at UI Health. Of these, a total of 164 patients were diagnosed with SCLC and 45 of these patients were determined to be LS (stage I, II, or III). Of the 45 patients diagnosed with LS SCLC, 6 were identified through the LCS program. We collected data on baseline demographics, date of initial diagnosis, disease characteristics, and outcomes. Survival was analyzed using the Kaplan-Meier method and two-sided Fisher's exact testing.

Results: Of the 39 patients diagnosed with LS SCLC outside of the LCS program, 46% were Black and 51% were White. Five (5%) percent identified as "other" race. Of the 6 patients diagnosed through the screening program 50% were Black, 33% were White, and 17% were identified as "other" (p-value 0.66). Patients who smoke made up 70% of the non-screened group and 50% of the screening group, whereas patients with a smoking history made up 30% of the non-screened group and 50% of the screening group (p-value 0.37). When comparing overall survival (OS), the patients diagnosed outside of the screening group have an OS of 1.6 years versus 4.2 years for patients in the screening program (p-value 0.13).

Conclusions: While this study was limited by the sample size, the large numerical increase in OS observed in the individuals diagnosed with LS SCLC through the LCS program warrants further investigation. Traditionally, SCLC is thought to evolve rapidly and progress quickly to extensive stage disease. Our data suggests that when caught early through the lung cancer screening program, SCLC outcomes are potentially greatly improved.

Keywords: Small cell, Screening program, Limited stage

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.05 Twice Daily Hyperfractionated vs Once Daily Normofractionated Chemo-Radiotherapy in LS-SCLC: A Monocentric Experience

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Introduction: The appropriate thoracic radiotherapy (TRT) schedule in limited-stage Small-Cell Lung Cancer (LS-SCLC) is still a matter of debate. Three randomized phase III trials compared twice daily (BID) schedule and once daily (OD), so that BID 45 Gy/30 fractions with concurrent cisplatin-etoposide (CDDP/VP16) chemotherapy represents the standard of care. These results were then confirmed by two clinical trials, where higher doses in the OD group were used. Nevertheless, in clinical practice not all patients (pts) are suitable for concurrent chemo-radiotherapy (cCRT), nor fit for CDDP. The aim of this study is to compare clinical outcomes in pts treated with BID or OD TRT given concurrently or sequentially (sCRT) to platinum-based chemotherapy in a real-world cohort.

Methods: A retrospective analysis was conducted on 68 pts affected by LS-SCLC treated with OD (60 Gy/30 fr) or BID CRT (45 Gy/30 fr) at Modena University Hospital from 2013 to 2024. Kaplan-Meier methods estimated Overall Survival (OS), progression-free survival (PFS) and metastasis-free survival (MFS). Treatment-related toxicities and patterns of failure were additionally analyzed.

Results: Pts features are summarized in Table 1. Mean follow-up was 15.8 months (3-148). 27 pts (39.7%) were treated with BID schedule while 41 (60.3%) underwent OD schedule. 54.4% of pts received cCRT, 45.6% received sCRT. 35 pts (51.5%) underwent prophylactic cranial irradiation (PCI). The most frequent sites of first metastatic progression were brain (51.3%) and liver (33.4%). 51.5% pts had a loco-regional recurrence. Acute grade≥3 toxicities were reported in 38 pts (55.9%), mostly hematological (35 pts, 92.1%) followed by esophagitis (3 pts, 4.3%), pneumonitis (2 pts, 2.9%) and cardiac events (1 pt, grade 3 heart failure). Of note, 2 grade 5 neutropenia were described. Five pts experienced grade≥3 late toxicities, 4 pulmonary-related and 1 renal failure. No grade 5 late toxicity were reported. Toxicity was comparable between the BID and OD schedules. 3- and 5-year OS, MFS and PFS were 38.8%(SE±6.5%) and 25.5%(SE±6.6%), 41.1%(SE±6.6%) and 41.1%(SE±6.6), 30.5%(SE±5.8%) and 26.1%(SE±6.4%), respectively. In terms of OS and MFS, there was a trend favoring pts who underwent PCI ($p<0.07$ for both), while the difference was statistically significant for PFS ($p < 0.02$). No significant differences in clinical outcomes were observed according to BID or OD schedule.

Conclusions: Both BID and OD schedules showed to be safe and effective when modern RT-techniques are used in LS-SCLC. Furthermore, PCI PCI appears to influence key clinical outcomes and should be considered for the majority of patients.

Median Age	67.5 years	
Gender	Female	27 (39.7%)
	Male	41 (60.3%)
Smoking Habits	Never	0 (0%)
	Former	29 (42.6 %)
	Active	35 (57.4 %)
Staging	T	
	1	7 (10.3%)
	2	14 (20,6%)
	3	26 (38.2%)
	4	16 (23.5%)
	N	
	0	7 (10.3 %)
	1	19 (27,9%)
	2	31 (45,6%)
	3	11 (16,2 %)
	I-II	7 (10.3%)
	III	61 (89.7 %)

Keywords: small cell lung cancer, hyperfractioneted radiotherapy, PCI

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.06 Immunotherapy for ES-SCLC Comorbid With COPD: A Real-World Retrospective Study

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Introduction: The prognosis and reliable survival predictors for small cell lung cancer (SCLC) patients with comorbid chronic obstructive pulmonary disease (COPD) remain unclear. We aimed to discuss the effect of COPD on SCLC in the settings of immunotherapy and explore the candidate pulmonary function or serum parameters, which might help the selection of the COPD population benefiting from immunotherapy.

Methods: We retrospectively recruited histologically confirmed ES-SCLC patients receiving first-line chemoimmunotherapy and pulmonary function tests in Nanjing Jinling Hospital. Baseline information was extracted, including pulmonary function parameters such as vital capacity (VC) (% of predicted), forced expiratory volume in one second (FEV1) (% of predicted), forced expiratory volume in one second/ forced vital capacity (FEV1/FVC) and peak expiratory flow (PEF) (% of predicted), serum parameters such as lactate dehydrogenase, albumin, counts for neutrophil, lymphocyte, monocyte and eosinophil, and clinical parameters such as age, gender and treatment regimens. The primary outcome was overall survival (OS). Step-wise multivariate Cox regression was used to identify candidate variables. Cox regression analysis, Log-rank tests, and landmark analysis were applied to determine candidate survival predictors.

Results: During the median follow-up period of 19 (13.9-27.7) months, a total of 100 ES-SCLC patients undergoing first-line chemoimmunotherapy with additional pulmonary function tests were retrospectively enrolled, among whom 59 patients were diagnosed with COPD. According to the global initiative for chronic obstructive lung disease (GOLD) criteria, most patients were categorized into stages I-II [46 (78.0%)], while 13 (22%) patients were grouped into Level 3-4. Within 9 months' follow-up, patients with COPD exhibited superior OS compared to those without COPD (P=0.041), while thereafter, COPD patients were prone to unfavorable survival (P=0.011). However, there existed no distinct disparities for PFS between the two subgroups (P=0.76). Multivariate Cox regression analysis suggested that three variables were suggestive of the prognosis, including maximum VC%>68.8 [hazard ratio (HR)= 0.23, 95% confidence interval (CI): 0.08-0.72, P=0.01], PEF%>65 (HR=0.37, 95% CI: 0.10-1.34, P=0.13) and neutrophil>3.80 (HR=0.20, 95% CI: 0.07-0.59, P=0.004).

Conclusions: For ES-SCLC patients, comorbid COPD is a protective factor for immunotherapy in the short term but a risk factor in the long term. Elevated levels of neutrophils and VCMAX% are indicative of favorable prognosis in ES-SCLC patients with comorbid COPD. Our findings convince the positive effect of COPD on the survival of SCLC patients in the settings of immunotherapy and might guide the selection of appropriate COPD patients benefiting from immunotherapy.

Keywords: immunotherapy, chronic obstructive pulmonary disease

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.07 Association of Gut Microbiota and Metabolites With Thalidomide-Induced Antiemetic Efficacy in Small Cell Lung Cancer Patients

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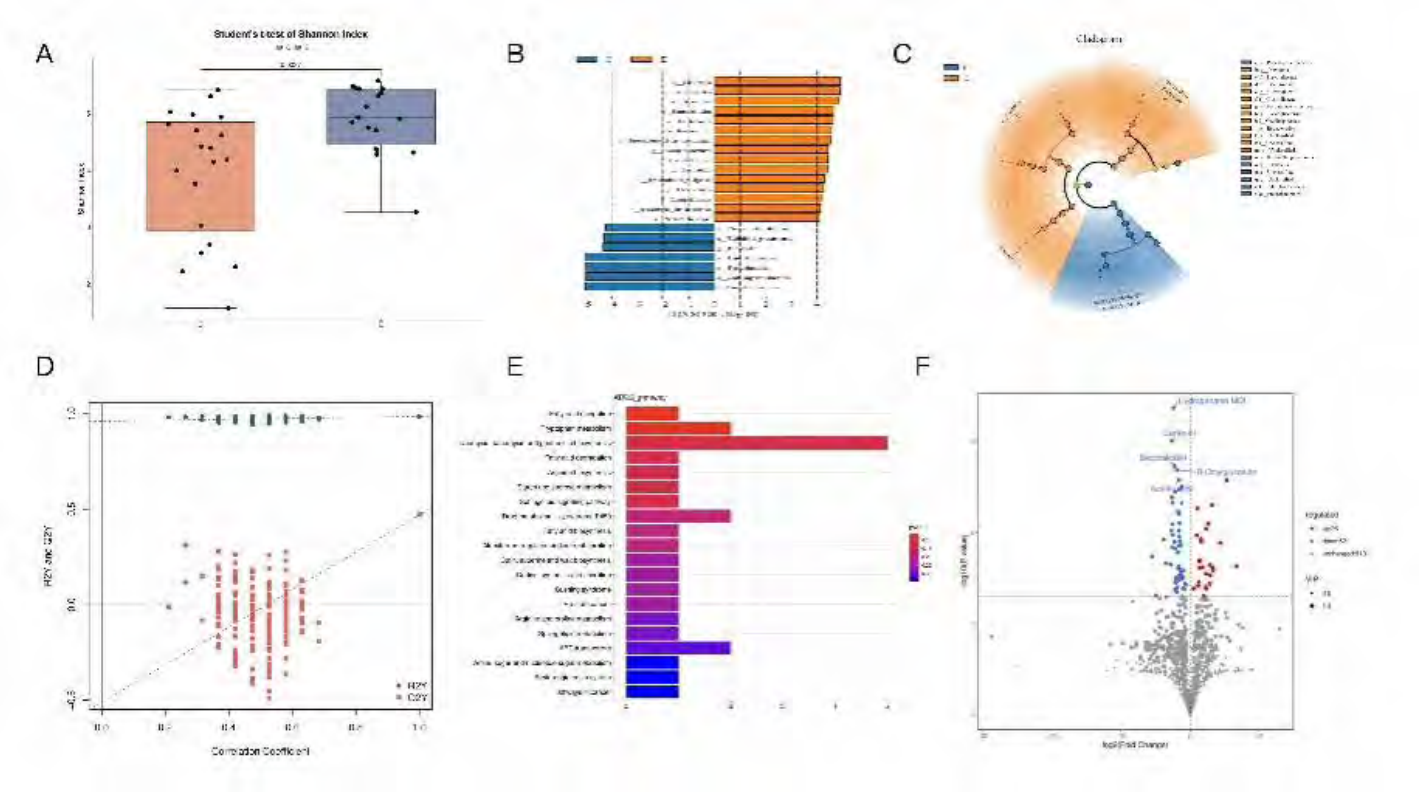
Introduction: Small cell lung cancer (SCLC) is highly aggressive and has a poor prognosis. Platinum-based chemotherapy often reduces the tolerance of treatment due to chemotherapy-induced nausea and vomiting (CINV). A previous study (CLOG1302 study, NCT02203253) confirmed that thalidomide (THD) combined with palonosetron and dexamethasone could significantly improve the complete response rate of delayed CINV after hyperemetogenic chemotherapy with good safety. Recent studies have found that intestinal flora and its metabolites are involved in the occurrence and development of CINV through multi-dimensional mechanisms. The aim of this study is to explore whether gut microbiota and metabolites synergistically enhance the antiemetic efficacy of THD in SCLC patients.

Methods: Baseline fecal samples were collected from 38 SCLC patients, stratified into two groups: the THD (E) group (n=18), comprising patients receiving THD for antiemetic intervention, and the control (C) group (n=20), comprising those without THD intervention. Metagenomic and metabolomic sequencing were performed to compare differences in gut microbiota composition and metabolite profiles between two groups.

Results: Significant disparities in gut microbiota and metabolites were observed between two groups. Metagenomic analysis revealed higher α diversity in the E group, as evidenced by an elevated Shannon index (P=0.037), suggesting THD enhanced gut microbial diversity. Gut microbiota with increased relative abundance in the E group included c_Clostridia (P<0.05), o_Eubacteriales (P<0.05), p_ Firmicutes (P<0.05), o_Bacteroidales (P<0.05), and c_Bacteroidia (P<0.05). Metabolomic profiling identified higher levels of Hydrogenated MDI (P<0.05), Carteolol (P<0.05), Becocalcidiol (P<0.05), B-Octylglucoside (P<0.05), and Azelaic acid (P<0.05) in the C group. KEGG pathway analysis highlighted significant differences in Neomycin, kanamycin, and gentamicin biosynthesis and Tryptophan metabolism.

Conclusions: These findings suggest that THD may alleviate CINV in SCLC patients by modulating gut microbiota and associated metabolites. Gut microbiota composition and metabolite profiles may correlate with THD antiemetic efficacy, positioning them as potential predictive biomarkers and therapeutic targets for optimizing CINV management in SCLC patients treated with THD.



Keywords: Small cell lung cancer, Gut microbiota, chemotherapy-induced nausea and vomiting

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.08 Early Hospitalization During Chemoradiation for Limited-Stage Small Cell Lung Cancer Is Associated With Inferior Survival

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Introduction: Consolidative durvalumab significantly improves survival outcomes and is a new standard of care in limited-stage small cell lung cancer (LS-SCLC); however, not all eligible patients will receive this therapy. Approximately 30% of patients with locally advanced non-small cell lung cancer treated with chemoradiation (CRT) do not receive consolidative durvalumab as intended, primarily due to ongoing toxicity from CRT. We, therefore, aimed to analyze early hospitalization rates and the association of hospitalizations with toxicity and outcomes in a cohort of LS-SCLC patients treated with definitive intent in order to establish a benchmark prior to the consolidative immunotherapy era.

Methods: We conducted a retrospective, single-institution review of consecutive patients with LS-SCLC who were treated with definitive concurrent chemoradiation (cCRT) between 2017 and 2024. cCRT was defined as initiation of radiation within the first two cycles of first line chemotherapy. Baseline characteristics, toxicity, and outcome data were collected. Early hospitalization was defined as occurring during or within 30 days of cCRT end. Overall survival and progression free survival were analyzed using the log-rank test (significance: $p<0.05$). Toxicity outcomes were analyzed using Fischer's exact test (significance: $P<0.05$)

Results: A total of 211 patients who met inclusion criteria were identified. Of these, 70 (33.0%) were hospitalized during or within 30 days of radiation therapy. The most common reasons for hospitalization were due to infectious (51.4%), hematologic (37.1%), pulmonary (20%), esophagitis (18.6%), and failure to thrive (17.1%). The baseline characteristics of hospitalized vs non hospitalized patients were well balanced with respect to smoking history, history of cardiac disease, and history of pulmonary disease. Baseline performance status was worse in patients who were hospitalized (median ECOG 1 vs 0, $p = 0.04$). Patients had early hospitalization had shorter median overall survival (30.3 months vs 52.21 months, $p = 0.02$), although progression free survival was not significantly different between cohorts (median 12.2 months vs 15.9 months, $p = 0.57$). Hospitalized and non-hospitalized patients received similar treatment courses including median number of chemotherapy cycles (3 vs 3), receipt of twice daily radiation (62.9% vs 63.8%,and receipt of prophylactic cranial radiation (31.4% vs 40.4. Despite this, hospitalized patients were more likely to discontinue radiation therapy early (14.3% vs 1.4%, $p = 0.003$), experience grade 2+ esophagitis midway through radiation treatment (17.1% vs 6.4%, $p = 0.03$), and develop grade 2+ radiation pneumonitis (28.6% vs 15.6%, $p=0.03$).

Conclusions: Early hospitalization is associated with inferior survival and early chemoradiation toxicities in this pre-immunotherapy cohort. Patients who are hospitalized earlier may be less likely to receive consolidative durvalumab as intended, and this survival disparity may be amplified further. Predictive models are needed to personalize treatment strategies to mitigate toxicity risk and increase the number of patients eligible to receive durvalumab consolidation.

Keywords: small cell lung cancer, hospitalization, toxicity

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.09 Neoadjuvant Chemoimmunotherapy Versus Chemotherapy for LS-SCLC

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Introduction: This study aimed to analyze the safety and effectiveness of neoadjuvant immunotherapy combined with chemotherapy for people with limited-stage small cell lung cancer (LS-SCLC) and to explore new treatment ideas.

Methods: This study was a retrospective analysis of clinical data from participants with LS-SCLC who underwent neoadjuvant therapy followed by surgical resection at the Fourth Hospital of Hebei Medical University between April 2018 and February 2024. The participants were divided into the neoadjuvant immunotherapy combined with chemotherapy group (NICT, 13 cases) and the neoadjuvant chemotherapy group (NCT, 25 cases) to compare the pathological complete response (pCR) rate, major pathological response (MPR) rate, overall survival (OS), and disease-free survival (DFS).

Results: The NICT group demonstrated significantly higher rates of pCR (46.2% vs. 12.0%) and MPR (53.8% vs. 16.0%) compared to the NCT group ($P < 0.05$). Additionally, the lymph node pCR rate was markedly elevated in the NICT group (76.9% vs. 40.0%, $P < 0.05$). However, no statistically significant differences were observed between the two groups in OS, DFS, R0 resection rate, intraoperative parameters, or postoperative complication rates.

Conclusions: Neoadjuvant immunotherapy combined with chemotherapy improved pathological responses and lymph node downstaging in people with LS-SCLC. Long-term survival outcomes require further follow-up. The regimen demonstrated comparable safety to chemotherapy alone. Prophylactic cranial irradiation is recommended for people with clinical TNM stage III LS-SCLC after neoadjuvant therapy.

Keywords: Neoadjuvant therapy, Limited-stage small cell lung cancer, Immunotherapy

EP.13.10 Superior Vena Cava Syndrome in Extensive Stage (ES)-SCLC: A Marker of Aggressive Disease but Also a Window for Achieving Prolonged Survival?

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Introduction: Superior Vena Cava Syndrome (SVCS), arising from obstruction of the superior vena cava, often due to external tumor compression or thrombosis, It is most commonly associated with malignancies—particularly small cell lung cancer (SCLC)—given the disease's aggressive biology and frequent central tumor location, may lead to an oncologic emergency and compromise prognosis. This study explores the relationship between SVCS and survival outcomes in patients with ES-SCLC, focusing on clinical and prognostic implications.

Methods: We analyzed data from the Mayo Clinic's Epidemiology and Genetics of Lung Cancer (EGLC) database, a prospective lung cancer cohort, to identify patients with ES-SCLC. Clinical variables included demographics, comorbidities, tumor characteristics, treatments, and outcomes. "Excellent survival" was defined as the top 10th percentile of ES-SCLC patients, while "Ordinary survival" was defined as the median ± 2 standard errors. A 1:4 matching was performed based on age at diagnosis, sex, smoking history, ECOG performance status, and year of diagnosis. Statistical analyses included t-tests, chi-square tests, and logistic regression.

Results: Of 20170 lung cancer cases diagnosed between 1997 and 2016 and followed through 2024, 2309 (11.4%) were SCLC, of which 1340 (58%) had ES-SCLC. Among the 1259/1340 (94%) ES-SCLC patients with known smoking history, 96.6% were current or former smokers. Disease progression was noted in 80.3% of patients, with local recurrence in 84.3%. Treatment modalities included chemotherapy (74.1%) and chemoradiotherapy (25.9%). The median overall survival was 0.80 years (95% CI: 0.73-0.86), and median progression-free survival was 0.52 years (95% CI: 0.49-0.58). ECOG performance status was 1 in the majority of cases (77.2%). After matching, 509 patients (118 Excellent survival and 391 Ordinary survival) were analyzed. Excellent survivors showed higher rates of several comorbidities diagnosed before ES-SCLC treatment, including mental illness (p=0.04), depression (p=0.02), peripheral vascular disease (p=0.0005), GERD (p<0.0001), paraneoplastic syndromes (p=0.0038), and coronary artery disease/myocardial infarction (p=0.0137). The presence of liver metastases was significantly associated with worse survival (p<0.0001), while bone (p=0.0059) and brain metastases (p=0.0170) were more frequent in Ordinary survivors. Interestingly, SVCS was notably more common among Excellent survivors (12.7%) than among Ordinary survivors (3.6%, p=0.0002).

Conclusions: Contrary to its traditional association with poor prognosis, SVCS may be linked to prolonged survival in certain patients with ES-SCLC. These findings suggest that SVCS could represent a distinct clinical subset with potential prognostic value. Further investigation is warranted to validate these observations and better understand the underlying mechanisms.

Keywords: Small Cell Lung Cancer, Superior Vena Cava Syndrome, Prognostic Factors

EP.13.11 Real-World Survival Data Over 25 Years in Extensive-Stage Small-Cell Lung Cancer: The Impact of Immune Checkpoint Inhibitors

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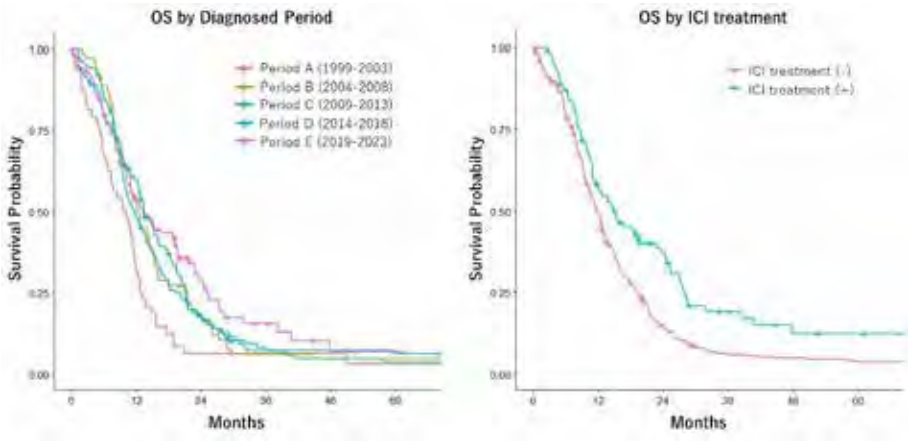
Introduction: Unlike in non-small-cell lung cancer (NSCLC), therapeutic advancements for extensive-stage small-cell lung cancer (ES-SCLC) have been relatively scarce. Although immune checkpoint inhibitors (ICIs) have been approved for the treatment of ES-SCLC since 2019, their impact on patient survival in real-world settings remains uncertain. This study aimed to evaluate the survival trends in patients with ES-SCLC over the past 25 years.

Methods: This single-center retrospective study analyzed survival data from 452 patients diagnosed with ES-SCLC between 1999 and 2023. The patients were divided into five groups according to their diagnosis year: Period A (1999-2003), Period B (2004-2008), Period C (2009-2013), Period D (2014-2018), and Period E (2019-2023). Overall survival (OS) was estimated using the Kaplan-Meier method, and survival differences were assessed with the log-rank test. Additionally, a multivariate Cox proportional hazards model was applied to identify the independent prognostic factors affecting OS.

Results: The patient characteristics are summarized in Table. The median follow-up period was 11.6 months, during which 394 out of 452 patients experienced an OS event. The median OS (mOS) was 9.8, 12.5, 13.4, 11.8, and 13.6 months for Periods A through E, respectively. The corresponding 2-year OS rate was 6.2%, 18.2%, 18.6%, 17.3%, and 29.3% (Figure). The proportion of patients who received ICIs was 14.1% in Period D and 73.1% in Period E. Patients treated with ICIs had a significantly longer mOS compared with those who were not (15.2 vs. 11.8 months, $p < 0.005$) (Figure). Multivariate analysis identified performance status, history of chemotherapy, and history of ICI treatment as independent prognostic factors influencing OS.

Conclusions: Survival outcomes for patients with ES-SCLC improved over time. Our results indicate that ICIs are associated with improved OS in real-world clinical settings.

Characteristics	Period A (1999-2003)	Period B (2004-2008)	Period C (2009-2013)	Period D (2014-2018)	Period E (2019-2023)
N	48	71	101	128	104
Age					
<75	38 (79.2)	56 (78.9)	76 (75.2)	100 (78.1)	72 (69.2)
≥75	10 (20.8)	15 (21.1)	25 (24.8)	28 (21.9)	32 (30.8)
Sex					
Female	5 (10.4)	12 (16.9)	14 (13.9)	33 (25.8)	29 (27.9)
Male	43 (89.6)	59 (83.1)	87 (86.1)	95 (74.2)	75 (72.1)
Smoking history					
Yes or unknown	46 (95.8)	67 (94.4)	97 (96.0)	125 (97.7)	97 (93.3)
No	2 (4.2)	4 (5.6)	4 (4.0)	3 (2.3)	7 (6.7)
Performance Status					
0-1	31 (64.6)	59 (83.1)	81 (80.2)	89 (69.5)	81 (77.9)
2-4 or unknown	17 (35.4)	12 (16.9)	20 (19.8)	39 (30.5)	23 (22.1)
History of Chemotherapy					
Yes	47 (97.9)	71 (100.0)	100 (99.0)	125 (97.7)	93 (89.4)
No	1 (2.1)	0 (0.0)	1 (1.0)	3 (2.3)	11 (10.6)
History of 2nd line Chemotherapy					
Yes	18 (37.5)	56 (78.9)	77 (76.2)	83 (64.8)	64 (61.5)
No	30 (62.5)	15 (21.1)	24 (23.8)	45 (35.2)	40 (38.5)
History of ICI administration					
Yes	0 (0.0)	0 (0.0)	0 (0.0)	18 (14.1)	76 (73.1)
No	48 (100.0)	71 (100.0)	101 (100.0)	110 (85.9)	28 (26.9)



Keywords: Extensive-Stage Small-Cell Lung Cancer, Real-World Survival Data, Immune Checkpoint Inhibitors

EP.13.12 A Retrospective Study of the Efficacy of Chemoimmunotherapy for Extended-Stage Small Cell Lung Cancer in Elderly Patients

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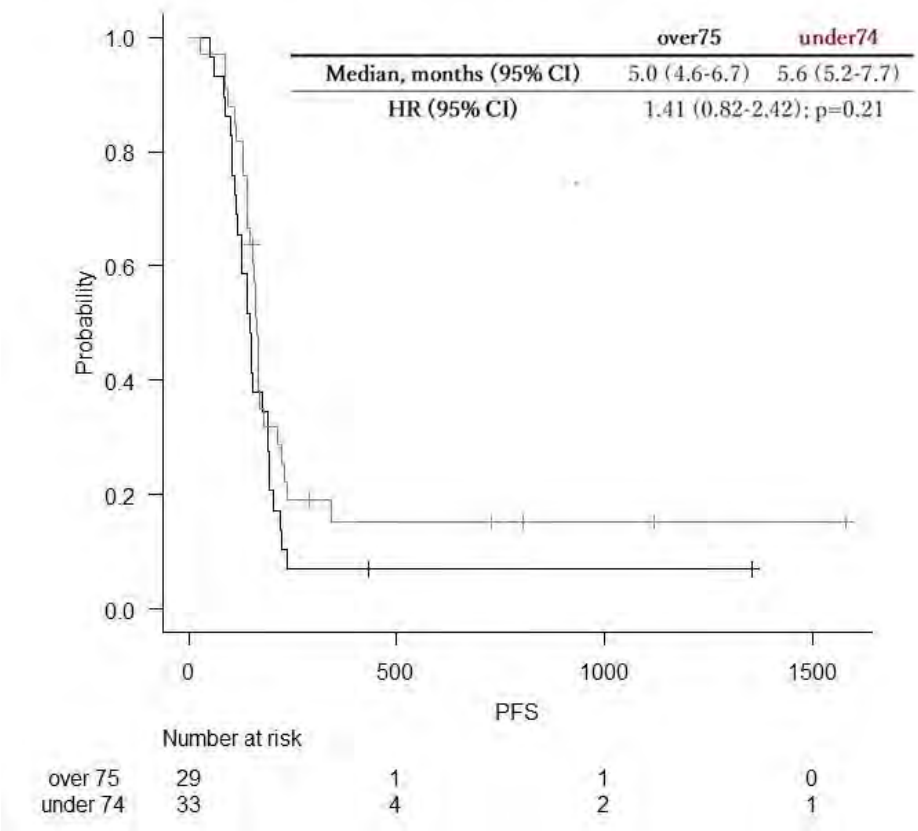
Introduction: In recent years, combination therapy with immune checkpoint inhibitors has been approved for extensive-stage small cell lung cancer (ES-SCLC) and becoming the standard treatment. However, there are little is known about regarding the safety and effectiveness of this treatment in the elderly. Therefore, we tried to compare and examine the effects of treatment using the age of 75 years old, which is generally considered an elderly person in a medical sense in Japan.

Methods: We retrospectively collected pure ES-SCLC patients who received primary treatment with Carboplatin + Etoposide + Atezolizumab or Durvalumab at four institutions from August 22, 2019 to December 31, 2023. Safety and efficacy were then analyzed separately for the elderly group (over 75 years old) and the non-elderly group (under 74 years old).

Results: The number of cases was 77, of which 40 were in the elderly group (median age 78 years [range: 75-86 years]) and 37 were in the non-elderly group (median age 68.5 years [range: 51-74 years]). There were 33 (82.5%) and 29 (78.4%) males in each group. The response rate was 70.0%/78.4%, disease control rate was 92.5%/83.8%, PFS was 148/161 days and OS was 305/294 days in each group. The hazard ratio for PFS in the elderly group versus the non-elderly group was 1.4119 (95% CI, 0.8233 to 2.421; p=0.210), and OS was 1.3788 (95% CI, 0.8051 to 2.361: p=0.242). Only one patient in the non-elderly group had over Grade 3 immune-related adverse events (irAE).

Conclusions: The effectiveness of the treatment was also demonstrated in the elderly group, and there was no obvious increase in the frequency of serious irAE compared to the non-elderly group. Combination therapy with immune checkpoint inhibitors is considered to be an effective option for patients with ES-SCLC in elderly patients.

Figure 1. Progression-free Survival



Keywords: ES-SCLC, Elderly

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.13 Treatment Outcome in Limited Stage Small Cell Lung Cancer: National Retrospective Study

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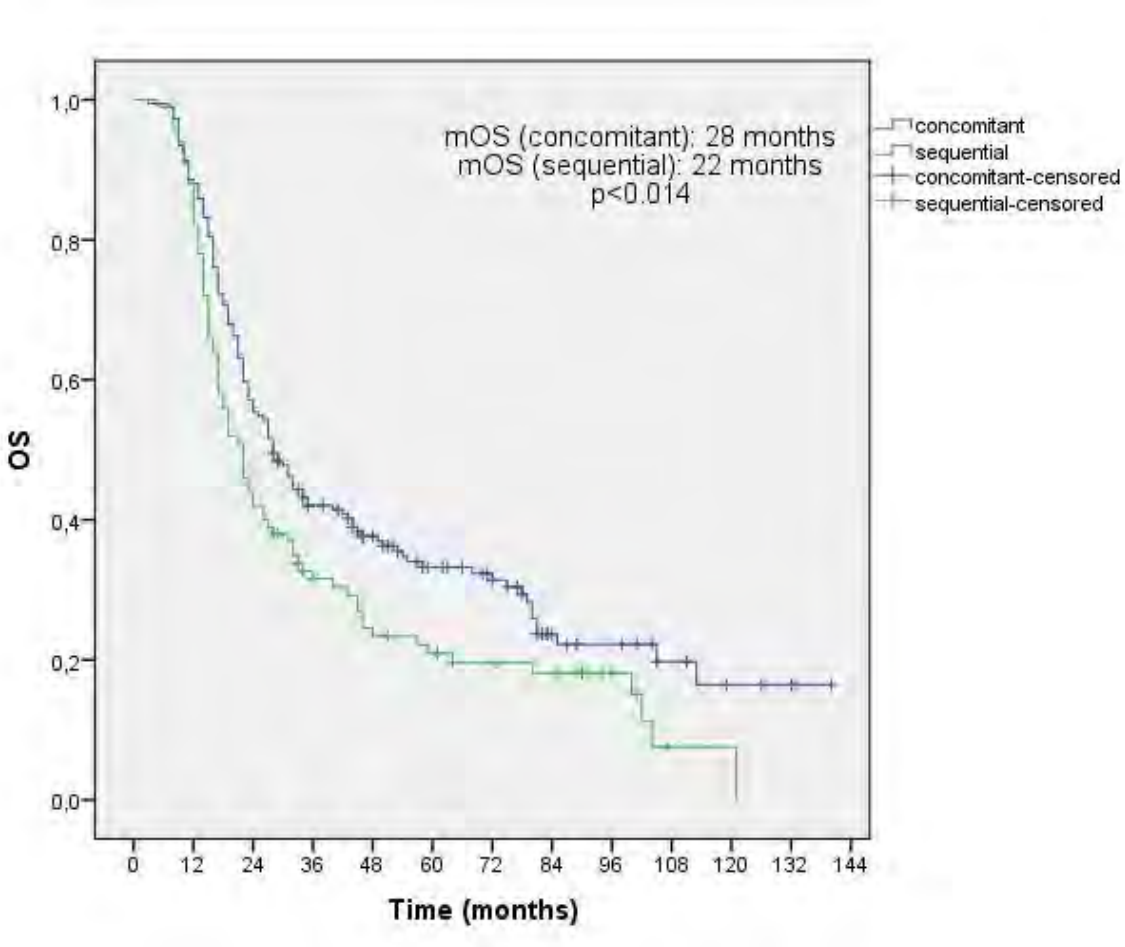
Introduction: Small cell lung cancer (SCLC) accounts for approximately 15% of lung tumours and only 30% of these have limited disease that can be cured with combined chemotherapy (CT) and radiotherapy (RT) followed by prophylactic cranial irradiation (PCI). After several decades without significant therapeutic progress, adjuvant treatment with durvalumab after CT-RT in a group of these patients showed significantly longer overall survival (OS) and progression-free survival than placebo.

Methods: We performed a retrospective analysis of patients with limited SCLC treated at the Institute of Oncology Ljubljana from January 2013 to December 2022. We evaluated the outcome of patients according to demographic factors and treatment characteristics. The survival outcomes were calculated using Kaplan - Meier actuarial survival methods.

Results: We included 284 patients with limited SCLC (152 men and 132 women) with a median follow-up of 83 months and a median age of 64 years. The majority of patients (97.5%) completed 1-6 cycles of platinum-based CT combined with etoposide, of whom 69.3% completed 5-6 cycles. Majority of patients (64.8%) were treated with at least one concurrent CT during RT, the others were treated with sequential CT. Median OS was 26 months, 2-year survival was 50.7% and 5-year survival was 28.3%. There were no differences in survival according to sex, age, performance status, TNM stage, number of CT cycles (3 or less, 4 or more), radiotherapy technique (3D or IMRT). In patients who had diagnostic PET CT compared to those without it, we observed a significantly longer mOS, 31 months (CI 23.4-38.5) vs 22 months (CI 18.4-25.6), p<0.048. Patients with concomitant CT had a significantly longer mOS compared to patients with sequential CT, 28 months (CI 22.8-33.2) vs 22 months (CI 17.9-26.1), p<0.014, and 5-year survival (32.3% vs 19.6%). The RT doses were heterogeneous, but patients with BED10 greater than 70 Gy had significantly longer mOS, 28 months (CI 22.7-33.3) vs 21 months (CI 17.3-24.7), p<0.016, and 5-year survival (33.4% vs 16.6%) compared to BED 69 Gy or less. In our group, only 28.9% of the patients completed PCI without any impact on survival. Disease progression was observed in 65.1% of patients, 58.4% of them had metastases in the brain only or in combination with metastases in other organs.

Conclusions: Our findings on treatment outcomes in patients with limited SCLC are consistent with other published real-world data before adjuvant durvalumab era.



Keywords: Small Cell Lung Cancer, chemoradiotherapy, durvalumab

EP.13.14 Real-World Data Analysis of Treatment Pattern and Prognosis of Patients With Limited-Stage Small Cell Lung Cancer in Japan

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Introduction: Over the decades, first-line (1L) treatment for inoperable limited-stage small cell lung cancer (LS-SCLC) has not changed from concurrent chemoradiotherapy (cCRT). Sequential chemoradiotherapy (sCRT) and chemotherapy (CT) alone are also 1L treatment options, when cCRT is unfeasible. Treatment selection and prognosis for LS-SCLC patients (pts) in real-world practice is unknown, and there are no data on large-scale treatment patterns and their rationale. Here, we investigated treatment patterns, effectiveness and safety of 1L options in Japanese clinical practice.

Methods: This multicenter, retrospective, observational cohort study collected clinical data of LS-SCLC pts diagnosed between Jan 2014-Dec 2020 (data cut-off Mar 31, 2024) and who underwent cCRT, sCRT, or CT alone as 1L treatment. The primary outcome was median overall survival (OS) in each cohort (cCRT, sCRT, CT alone). Secondary outcomes were median real-world progression-free survival (rwPFS) in each cohort, median OS/rwPFS by platinum choice (cisplatin [CDDP] or carboplatin [CBDCA]) in cCRT, reasons for choosing 1L treatment other than cCRT, and adverse events (AEs) associated with cCRT.

Results: In total, 504 pts (median [range] age: 70.0 [40-88] years [yrs]) were analyzed. Type of 1L treatment was cCRT in 301 pts (59.7%), sCRT in 106 pts (21.0%), CT alone in 97 pts (19.2%). Table 1 shows the reasons for choosing 1L treatment other than cCRT. The most common reason for selection was older age (61.3%) for sCRT and interstitial lung disease (54.6%) for CT alone. Median OS/rwPFS was 4.3 yrs/1.2 yrs, 2.3 yrs/1.0 yr and 1.5 yrs/0.5 yrs for cCRT, sCRT, and CT alone, respectively. Median OS/rwPFS by chemotherapy regimen in cCRT was 4.6 yrs/1.2 yrs and 4.1 yrs/1.1 yrs for CDDP + etoposide (ETP) and CBDCA + ETP, respectively. AE incidences associated with cCRT were radiation esophagitis (any grade) in 176 pts (58.5%), radiation pneumonitis (any grade) in 213 pts (70.8%). Other AEs leading to cCRT discontinuation were observed in 7 pts (2.3%).

Conclusions: Concurrent thoracic radiotherapy was used in approximately 60% of LS-SCLC pts who received chemotherapy. Our study demonstrated that appropriate treatment choices were made according to characteristics of pts (e.g., age, comorbidities) in clinical practice. As the treatment options for LS-SCLC increase in the near future, it is desirable that treatment decisions will be made more appropriately based on the differences in survival outcomes and potential adverse events associated with the specific treatment choices presented in this study.

Table 1. Reasons* for choosing 1L treatment other than cCRT

	sCRT	CT alone
Patients who received 1L treatment, n	106	97
Reason for choosing 1L treatment other than cCRT*, n (%)		
Older age	65 (61.3)	33 (34.0)
Poor PS	4 (3.8)	3 (3.1)
COPD	11 (10.4)	9 (9.3)
Interstitial lung disease	9 (8.5)	53 (54.6)
Extra-pulmonary comorbidities	13 (12.3)	6 (6.2)
Home oxygen therapy	1 (0.9)	0 (0.0)
Renal dysfunction	10 (9.4)	3 (3.1)
Large irradiation field	8 (7.5)	5 (5.2)
Pleural effusion	2 (1.9)	1 (1.0)
Obstructive pneumonitis, atelectasis	1 (0.9)	2 (2.1)
Patient's choice	1 (0.9)	2 (2.1)
Others	12 (11.3)	7 (7.2)

*Multiple choices are allowed.
Abbreviations: 1L, first-line; cCRT, concurrent chemoradiotherapy; CT, chemotherapy; COPD, chronic obstructive pulmonary disease; PS, performance status; sCRT: subsequential chemoradiotherapy.

Keywords: Limited Stage Small Cell Lung Cancer, Multicenter retrospective study, Chemoradiotherapy

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.15 Outcome and Safety of Lurbinectedin as Compassionate Use in SCLC: A Retrospective Multicentric International Study

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Introduction: Lurbinectedin has recently emerged in the treatment landscape of small cell lung cancer (SCLC). We report the real-world outcomes and safety of lurbinectedin within a named patient program.

Methods: Clinical data of patients with SCLC treated with lurbinectedin at the Erasmus Medical Center (EMC, Rotterdam-The Netherlands) and the Veneto Institute of Oncology (IOV, Padua-Italy) were retrospectively collected in this multicentric, international study. The primary endpoints were the effectiveness and safety of lurbinectedin; the effectiveness according to the chemotherapy-free interval (CFI) was secondarily assessed.

Results: At data cutoff (30th September 2024), 238 patients (204 from EMC and 34 from IOV) receiving lurbinectedin as second- (37%), third- (45%) or further-line (18%) were included. Median age was 65 (39-87) years, 51% were females. At lurbinectedin start, patients had metastasis in brain, bone and liver in 22%, 32% and 46% of cases, respectively; the performance status ECOG was ≥ 2 in 24% of cases, the CFI < 90 days in 201 (84%) patients. Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was administered in 33 (14%) patients, exclusively from the Italian cohort. A central venous catheter (CVC) was applied in 29 (85%) Italian and in 22 (11%) Dutch patients. The objective response rate was 24% (26% at EMC and 15% at IOV). The disease control rate was 47%, 50% in the Dutch, and 29% in the Italian patients. The median duration of response (mDOR) was 2.8 months (95%CI 2.0-3.5), the median progression free survival (mPFS) 2.2 months (95%CI 1.6-2.8) and the median overall survival (mOS) 5.4 months (95%CI 4.5-6.3). The 6-months PFS and OS rates were respectively 12.2% (95%CI 8.3-17.0) and 42.4% (95%CI 36.1-49.0). Considering the Dutch cohort, the mDOR, mPFS and mOS were respectively 2.8 (95%CI 2.1-3.4), 1.8 (95%CI 1.0-2.7) and 5.6 (95%CI 4.7-6.4) months, with a 6-months PFS rate of 11.2% (95%CI 7.3-16.4) and 6-months OS rate of 43.6% (95%CI 36.7-50.7). Among the Italian cohort, the mDOR was 4.6 months (95%CI 3.7-5.5), the mPFS 2.3 months (95%CI 2.0-2.7) and mOS 3.6 months (95%CI 1.8-5.3). The 6-months PFS and OS rates were 17.6% (95%CI 6.7-34.5) and 35.3% (95%CI 19.8-53.5), respectively. Patients with a CFI ≥ 90 days showed a longer mPFS (3.1 vs 1.8 months, HR 0.46, 0.30-0.71, p<0.001) and mOS (6.8 vs 4.5 months, HR 0.56, 0.37-0.85, p=0.006). Adverse events were recorded in 218 (92%) patients, with grade 3-4 in 70 (29%) cases and dose reduction in 47 (20%) patients. A higher rate of venous thrombosis and phlebitis was observed in patients without a CVC. The rate of neutropenia was higher in the Dutch than in the Italian cohort (39% vs 12%), however the febrile neutropenia rate was 2%.

Conclusions: Considering its manageable safety profile and modest but consistent effectiveness, lurbinectedin represents a therapeutic option as compassionate use in patients with SCLC. Heterogeneous outcomes of the two cohorts may be explained by differences in the diagnostic-therapeutic management. The role of G-CSF should be carefully evaluated and the use of central venous catheters may be beneficial in preventing thromboembolic events and phlebitis.

Keywords: SCLC, Lurbinectedin, Real-world

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.16 Safety and Efficacy of Chemoimmunotherapy in Stage IV Small Cell Lung Cancer: A Single-Center Retrospective Analysis

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Introduction: Since IMPOWER-133 and CASPIAN chemoimmunotherapy has become a first-line systemic treatment option for extensive disease SCLC. We conducted a retrospective study on safety and efficacy of a single-center patient cohort.

Methods: A retrospective cohort study was performed on stage IV SCLC patients started on carboplatin-etoposide-atezolizumab between January 2018 till December 2022 at the University Hospitals Leuven. Follow-up data were collected till February 2025. The Kaplan Meier method was used for estimating survival outcomes, and Cox regression models were used to assess the association between baseline clinical characteristics (age, ECOG PS, metastatic sites, s-albumin, s-LDH, s-CRP, s-NSE, Neutrophil-Lymphocyte Ratio (NLR), modified Glasgow Prognostic Score (mGPS) and LIPI score) and survival outcomes.

Results: A total of 74 patients were included, of whom 47% current and 51% former smokers. Median number of induction and maintenance cycles was 4 (range 1-4) and 3 (range 0-84), respectively. The objective response rate was 80%. The median progression-free survival (PFS) was 4.8 months (95%CI 4.5-5.0) and median overall survival (OS) was 11.5 months (95%CI 8.9-14.6). The 1-year, 2-year and 3-year PFS and OS rates (Figure 1) were 16.2% (95%CI 8.9-25.5), 9.5% (95%CI 4.2-17.4), and 8.1% (95%CI 3.3-15.7), and 47.3% (95%CI 35.6-58.1), 18.9% (95%CI 11.0-28.5) and 11.9% (95%CI 5.7-20,5), respectively. In multivariable analysis, bone metastasis (HR 2.21; 95%CI 1.26-3.87), age (+1yr, HR 1.03; 95%CI 1.00-1.07), s-NSE >250 µg/L (HR 4.55; 95%CI 2.13-9.72), and s-albumin ≥35g/dl (HR 0.49; 95%CI 0.25-0.99) were significantly associated with OS. Treatment related adverse events (TRAEs) occurred in 95% of patients: during induction (n=74) 89% experienced TRAEs, of whom 55 patients (74%) TRAEs G≥3; and during maintenance immunotherapy (n=58) 36% experienced immune-related adverse events (irAEs). During induction phase, chemotherapy dose reduction and discontinuation occurred in 31% and 8%, respectively. Overall, irAEs occurred in 21 patients (28%) leading to discontinuation of atezolizumab in 7 patients (9.5%).

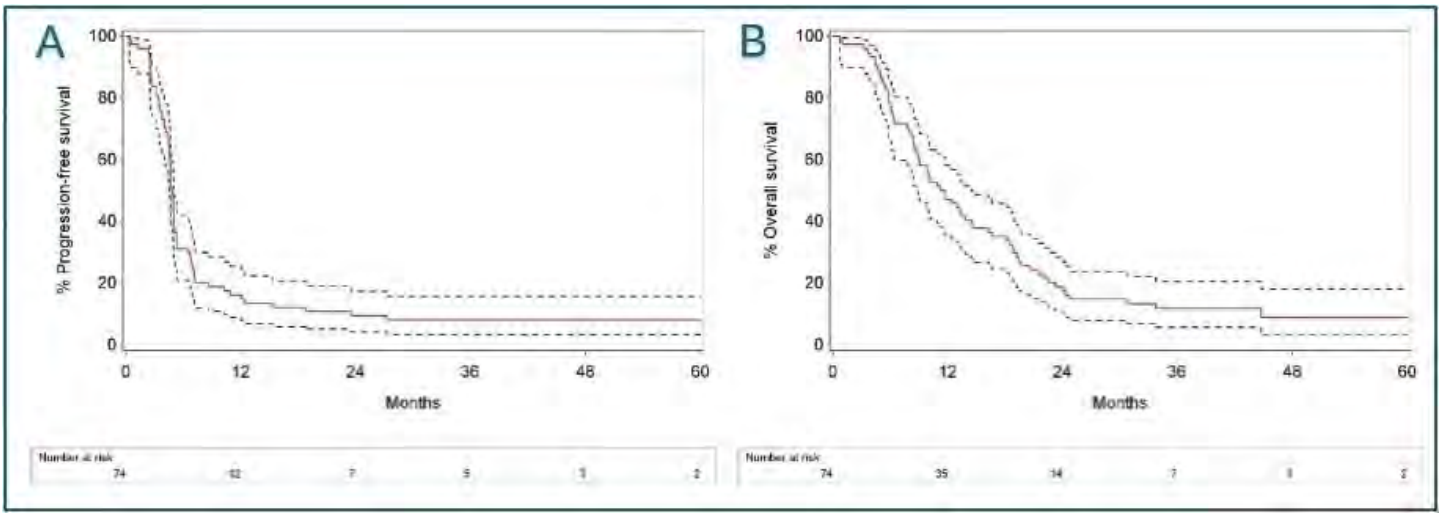

Figure 1: Kaplan-Meier curve of (A) progression free survival and (B) overall survival. The dashed lines indicate the 95% confidence intervals.

Conclusions: Our study provides long-term safety and efficacy outcomes of first-line chemoimmunotherapy in a real world cohort of stage IV SCLC, similar to the IMPOWER-133 registrational study. In multivariable analysis, we found that baseline conventional biomarkers (age, bone metastasis, s-albumin, and s-NSE) did significantly predict overall survival, while systemic inflammation scores (NLR, mGPS and LIPI) did not.

Keywords: Small Cell Lung Cancer, Extended disease, Chemoimmunotherapy

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.17 Efficacy of First-Line Chemoimmunotherapy With Durvalumab or Atezolizumab in SCLC - Experiences From Practice of Two Polish Oncology Centers

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Introduction: Small-cell lung cancer (SCLC) is characterised by an aggressive course with the early development of distant metastases. First-line chemotherapy was recommended treatment for extensive stage of SCLC (ES-SCLC), however the addition of immune checkpoint inhibitors significantly improved the systemic therapy in clinical trials. The aim of the study is to compare the effectiveness of two immunochemotherapy regimens in patients with ES-SCLC with different clinical characteristic in daily practice.

Methods: Here we presented retrospective analysis of patients qualified to immunochemotherapy in two independent oncology centers in 2021-2023. All patients were smokers with good or very good performance status. Clinical data were extracted from electronic database. Overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were compared according to treatment methods and clinical data. Statistical calculations were performed in MedCalc software version 18.11.6 using the chi-square test and the Kaplan-Meier survival analysis.

Results: 152 patients were diagnosed with ES-SCLC treated in first-line with chemotherapy in combination with atezolizumab (98 patients) or durvalumab (54 patients). 48 women and 104 men with an average age of 61.5 years were enrolled. Disease control rate was similar in the patients treated with atezolizumab and durwalumab (84.7% vs. 85.2%). Partial response (PR), stable disease (SD) and progressive disease (PD) occurred with similar prevalence in the patients treated with durvalumab and atezolizumab. Median of PFS in whole group of patients was 6 months (95% CI: 5.7-6.5), and median OS was 11.5 months (95% CI: 9.7-16). Method of treatment, as well as, the presence of metastases to the bones had no effect on the risk of progression and death. The risk of progression (HR=1.5406, 95% CI: 1.0024-2.3677, p=0.0487) and risk of death (HR=1.7808, 95% CI: 1.1096-2.8581, p=0.0168) were significantly higher in the patients with central nervous system (CNS) metastases. The presence of liver metastases significantly increased the risk of death (HR=1.9727, 95% CI: 1.707-3.3241, p=0.0107), while the risk of progression was insignificantly higher (HR=1.4976, 95% CI: 0.9552-2.3481, p=0.0784) in this group of patients.

Conclusions: Immunochemotherapy can be effective treatment in patients diagnosed with advanced small-cell lung cancer in daily practice. The presence of CNS and liver metastases are the main clinical factors shortening OS and PFS in ES-SCLC patients treated with chemioimmunotherapy. It seems, that the type of chemoimmunotherapy does not influence on treatment efficacy.

Keywords: chemoimmunotherapy, SCLC, CNS metastases

EP.13.18 Retrospective Evaluation of the Prognostic Impact of Anti-PD-L1 Antibodies in ECOG-PS 2-3 Patients With Extensive-Stage SCLC

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Introduction: The IMpower133 and CASPIAN clinical trials demonstrated the efficacy of adding immune-checkpoint inhibitors to platinum-doublet standard chemotherapy. This evidence led to the approval of atezolizumab and durvalumab for the treatment of patients with extensive-stage small cell lung cancer (SCLC) in Japan. In both studies, enrollment was restricted to patients with Eastern Cooperative Oncology Group-performance status (ECOG-PS) 0-1. Therefore, the clinical significance of combining these anti-programmed death-ligand 1 (anti-PD-L1) antibodies with chemotherapy in patients with ECOG-PS 2-3 remains unvalidated. The objective of this study was to evaluate the efficacy and tolerability of the concomitant use of anti-PD-L1 antibodies in ECOG-PS 2-3 patients with extensive-stage SCLC. This study refined the results presented at the 64th Annual Meeting of the Japan Lung Cancer Society.

Methods: Patients who visited Saitama Medical Center, Saitama Medical University (Kawagoe, Japan) (September 1, 2019-December 31, 2022) and received treatment for pathologically confirmed extensive-stage SCLC were enrolled in this study. Patients with other types of cancer were excluded. Enrolled patients were followed up until February 29, 2024. The objective response rate (ORR) to the first-line chemotherapy and overall survival (OS) were evaluated. These outcomes were stratified based on ECOG-PS and compared between patients treated with chemotherapy plus anti-PD-L1 antibodies and those treated with chemotherapy alone. This study was approved by the ethics board of Saitama Medical Center, Saitama Medical University (approval number: 2023-056).

Results: A total of 74 patients were included in this study (median age: 72 years [range: 43-84 years]). Of those, 32 patients (median age: 70 years [range: 49-82 years]) received anti-PD-L1 antibodies (atezolizumab: n=22; durvalumab: n=10) as first-line chemotherapy, while 42 patients (median age: 75 years [range: 43-84 years]) were treated with chemotherapy alone. Patients in the chemotherapy+PD-L1-antibody group were significantly younger (p=0.0065) than those in the chemotherapy alone group. In all patients (ECOG-PS: 0, n=3; 1, n=37; 2, n=15; 3, n=16; and 4, n=3), the ORR and median OS was 67.6% and 327 days, respectively. Among patients with ECOG-PS 0-1 (n=40), the ORR in the chemotherapy+PD-L1-antibody group (n=17) and the chemotherapy alone group (n=23) was 76.5% and 56.5%, respectively, with no significant difference. The median OS was also not significantly different between these groups (406 vs. 379 days, respectively). Among patients with ECOG-PS 2-3 (n=31), the ORR in the chemotherapy+PD-L1-antibody group (n=15) and the chemotherapy alone group (n=16) was 93.3% and 56.3%, respectively (p=0.0226). The median OS was significantly longer in the chemotherapy+PD-L1-antibody group compared to the chemotherapy alone group (448 vs. 169 days, respectively; p=0.00661). Only one patient underwent chemotherapy at a reduced dose due to poor PS. In five patients with ECOG-PS 2-3, the administration of anti-PD-L1 antibodies was discontinued due to immune-related adverse events.

Conclusions: In patients with extensive-stage SCLC and ECOG-PS 2-3, the addition of anti-PD-L1 antibodies was feasible and improved the ORR, leading to better prognosis.

Keywords: extensive-stage small cell lung cancer, anti-PD-L1 antibodies, performance status

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.19 30-Year Review of Real-World Outcomes in Small Cell Lung Cancer at Hospital Clinic of Barcelona

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Introduction: Limited-Small cell lung cancer (LS-SCLC) is a highly aggressive malignancy with high metastatic potential. Landmark phase III trials have established concurrent Chemotherapy and Radiotherapy (cCh+RT) as the standard of care for SCLC. This study reviews survival and toxicity from our clinical practice at Hospital Clinic of Barcelona over the past 30 years, comparing it with results of pivotal clinical trials.

Methods: This retrospective and unicentric study, analyzed intention to treat outcomes from 218 patients diagnosed with LS-SCLC between 1994-2020, compared to phase III trial data. Radiological responses were evaluated using RECIST criteria. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier and Cox regression models. Toxicity was also documented using CTCAE v5.0.

Results: Among 218 patients, 79% (170) received chemotherapy and radiotherapy (Ch+RT) (69.3% (151) of them cCh+RT and 9,6% (21) sequential RT), 8,3% (18) surgery + Ch, 10,1% (22) received Ch, 1 (0.5%) received only RT and 4 (1,8%) best supportive care. The median radiation dose was 45Gy (12-70Gy) administered over 21 days (7-43 days). Esophagitis (Grade 2-3) was the most frequent radiotherapy toxicity 40.4% (88 patients) and grade 3-4 neutropenia was the most common chemotherapy-related toxicity 75.3% (164). While median OS of all patients was 19.56 months, patients treated with Ch+RT had a median OS of 22.29months (95% CI 1.379-2.33) (cCh+RT 26 months (95% CI 1.602-2.732), compared to 14.6 months (95% CI 1.10-1.338) with sequential RT (p= 0.006)), surgery and chemotherapy 106.18months (95% CI 6.527-11.17) and Ch alone 4.3months (95% CI 0.38-0.68). We selectively analyzed patients who received protocol treatment (n:199) showing median OS of 28 months, OS at one year was 77.4%, 47.2% at 2 years, at 3 years 37.2% and 28.6% at 5y. Compared to landmark trials, including all 218 patients, our median OS is lower. However, analyzing selected patients that received protocol treatment, the 5 years survival in our cohort is comparable to the studies by Jeremic and Takada, superior to Turrisi and only slightly inferior to the results of the Favre-Finn study, despite our higher proportion of negative prognostic factors (Men, PS 3-4) (Table 1).

	Jeremic (1977) (n= 52)	Turrisi (1999) (n= 206)	Takada (2002) (n= 231)	Favre Finn (2017) (n= 274)	Casas (2025) (n= 218)
Age	59 (40-67)	61 (63-80) <65/>65% 60%/40%	65 (39-74)	62 (29-84)	64 (38-89) <65/>65 50.9%/49.1%
Sex					
Male /Female	60%/40%	59% / 41,8%	82% / 18%	54 / 46%	78.9%/21.1%
PS					
ECOG 0		88 (43%)	51 (22%)	123 (46%)	20 (9.7%)
ECOG 1		105 (51%)	168 (73%)	137 (50%)	126 (58%)
ECOG 2		10 (5%)	12 (5%)	8 (3%)	47 (21.7%)
ECOG 3					21 (9.7%)
ECOG 4					2 (0.9%)
KPS	52% (90-100) 48% (50-80)				61.5% (80-100) 29.8% (50-70) 8.7% (40)
Stage					
I - II		48%	6%	1%	16%
III A		59%	57%	12%	40%
III B		3%	37%	80%	44%
Not known				7%	
Treatment					
Ch+RT	100%	100%	231 (100%)	98%	170 (79%)
-Concurrent	100%	206 (100%)	115 (49.5%)	249 (91%)	151 (69.4%)
-Sequential			116 (50.2%)	5 (2%)	21 (9.6%)
Surgery + Ch					18 (8.4%)
Chemotherapy					22 (10.2%)
RT					1 (0.5%)
BSC					4 (1.9%)
Median OS	36 months	23 months	31.3 months	29 months	19.56 months (n: 199) 28mo*
Survival					
1 year					77.4%
3 years		30%	24%		37.2%
5 years	30%			34%	28.6%

Table 1. PS: Performance status; KPS: Karnofsky performance status; Ch: Chemotherapy; RT: Radiotherapy; BSC: Best supportive care; OS: Overall survival.
**Median overall survival of our patients that received treatment protocol.*

Conclusions: Our real-world data shows a lower survival rate compared to pivotal clinical trials. However, when selecting patients who received protocol treatment, survival rates are comparable. These findings suggest that adhering to protocol treatments significantly improves survival with acceptable toxicities.

Keywords: SCLC, Radiotherapy, Real world data

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.20 Stereotactic Body Radiotherapy for Limited-Stage Small Cell Lung Cancer: Outcomes From a Single-Institution Retrospective Study

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy that represents approximately 13-15% of all lung cancers and is typically associated with poor prognosis and early metastatic spread. Traditionally, early-stage SCLC is treated with surgery followed by chemotherapy or chemoradiation, but many patients are not surgical candidates due to comorbidities or poor performance status. In such cases, stereotactic body radiotherapy (SBRT) offers a high-precision, high-dose alternative. Trials in early-stage NSCLC have demonstrated excellent local control and safety, prompting interest in its use for SCLC. Although evidence remains limited, retrospective studies suggest SBRT may yield outcomes comparable to surgery, including a multi-institutional series reporting favourable survival in Stage I SCLC. This study aims to evaluate outcomes of limited-stage SCLC patients treated with SBRT at a single institution.

Methods: We conducted a retrospective review including patients with histologically confirmed SCLC treated with curative-intent SBRT at a single cancer center between 2018 and 2023. Tumours were considered inoperable due to comorbidities or patient refusal. SBRT was delivered using the TrueBeam® system with the following regimens: 30 Gy in 1 fraction, 54 Gy in 3 fractions, 50 Gy in 4 fractions, and 45 Gy in 5 fractions. Endpoints were Time to Local Recurrence (TTLR), Time to Progression (TTP), and Overall Survival (OS). Toxicity was assessed using CTCAE v5.0. Statistical analysis was primarily descriptive. Time-to-event outcomes were estimated using the Kaplan-Meier method.

Results: Twelve patients with 12 lesions were included. Median age was 78 years (range 59-87), 75% were male, and 83.4% had a history of smoking. Most tumours (75%) were peripheral and staged as T1a-T2a. Chemotherapy (carboplatin-etoposide) was given to 58.3%, and one patient received prophylactic cranial irradiation. The most used SBRT regimen was 30 Gy in a single fraction (n=6), followed by 54 Gy in 3 fractions (n=3), 50 Gy in 4 fractions (n=2), and 45 Gy in 5 fractions (n=1). Median SUVmax was 14.2, and mean volume of the planning target volume was 34.7 cm^3. At a mean follow-up of 31.5 months, 8 patients (66.7%) had died, 7 (58.3%) experienced any type of disease progression. Local recurrence occurred in 25%, and distant metastases in 58.3%. Kaplan-Meier analysis estimated median OS at 48.2 months (95% CI: 6.0-90.5; IQR: 40.5), TTP at 24.2 months (95% CI: 1.5-46.8) and TTLR at 52.7 months (95% CI: 36.0-69.4; standard error: 8.5); the median TTLR time was not reached. No grade ≥2 toxicities were observed; pneumonitis grade 1 occurred in 18.2%, with no esophagitis or hemoptysis.

Conclusions: SBRT appears to be a feasible and well-tolerated treatment option for selected patients with SCLC who are unfit for or refuse surgery. In this single-institution retrospective analysis, SBRT provided encouraging outcomes in terms of TTLR, TTP, and OS, with minimal toxicity. Despite the exploratory nature of this study, the results support the role of SBRT as a potentially effective alternative for patients with limited-stage SCLC ineligible for standard treatment. Larger prospective studies are warranted to validate these findings and define optimal patient selection criteria.

Keywords: SCLC, SBRT

EP.13.21 Extended Follow-Up of First-Line Atezolizumab in Extensive-Stage Small Cell Lung Cancer: Real-World Multicenter Study

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Introduction: We previously reported the short-term real-world effectiveness and safety of first-line atezolizumab combined with chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC). This study provides an updated analysis on the long-term effectiveness, prognostic factors, and subsequent treatment patterns of first-line immuno-chemotherapy.

Methods: This prospective multicenter observational study enrolled patients with ES-SCLC diagnosed at seven university hospitals throughout Korea between June 2021 and August 2022. Primary outcomes were 1-year overall survival (OS) and progression-free survival (PFS), whereas secondary outcomes included OS, objective response rate, disease control rate, second progression-free survival, and safety, evaluated based on established clinical guidelines.

Results: A total of 100 ES-SCLC patients (median age, 69 years) were enrolled, with a median follow-up duration of 26.0 months. (Table) The median PFS and OS was 6.2 and 17.1 months, respectively, with a 1-year OS rate of 62.5%. (Figure) Favorable prognostic factors for OS included partial response (PR) and stable disease (SD) as the best responses (SD, hazard ratio [HR] 0.79, p=0.003; PR, HR 0.38, p=0.053) and a longer platinum-free interval (HR 0.84, p<0.001). Brain radiotherapy significantly improved OS in patients with brain metastases (p=0.001), whereas thoracic radiotherapy during first-line treatment tended to prolong survival in patients who responded to systemic treatment (p=0.050). Patients receiving second-line treatment after progression had significantly longer OS than did those receiving only best supportive care (p=0.017)

Conclusions: This study outlined the long-term real-world effectiveness and safety of first-line atezolizumab immuno-chemotherapy for ES-SCLC, with our findings showing that implementation of local treatments and subsequent therapies after progression improved survival.

Variable	Total patients (n = 100)	IMpower-133 (n = 201)
Median follow-up duration (months)	26.0 (23.7–31.4)	13.9 (N/E–N/E)
Best response		
Complete response	1 (1.0)	5 (2.5)
Partial response	74 (74.0)	116 (57.7)
Stable disease	16 (16.0)	42 (20.9)
Progressive disease	8 (8.0)	22 (10.9)
Not evaluated	1 (1.0)	16 (8.0)
Objective response rate (%)	75	60.2
Disease control rate (%)	91	78.6
Median PFS (months)	6.2 (4.3–12.7)	5.2 (95% CI 4.4–5.6)
Median OS (months)	17.1 (7.9–35.7)	12.3 (95% CI 10.8–15.9)
OS rate at 1 year (%)	62.5	51.7

Table. Effectiveness of atezolizumab plus chemotherapy treatment
Values are presented as median (IQR) or number (%) unless otherwise specified.
N/E, not evaluated; PFS, progression-free survival; OS, overall survival; IQR, interquartile range; 95% CI, 95% confidence interval.

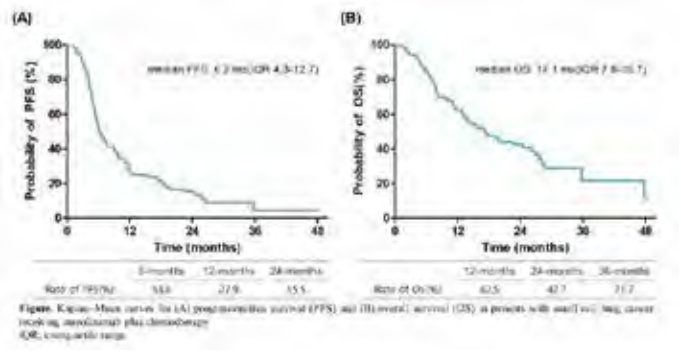

Figure. Kaplan–Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) in patients with small cell lung cancer receiving atezolizumab plus chemotherapy
IQR, interquartile range

Keywords: Small cell lung carcinoma, Atezolizumab, Real-world

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.22 Survival and Treatment Patterns in Limited Disease-SCLC: Real World Data From the Swedish National Lung Cancer Registry

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy with overall poor prognosis. Treatment options in limited and extensive disease have remained largely unchanged for decades until the addition of immunotherapy to standard chemotherapy in first line (1L) extensive disease SCLC. Recently, results from the ADRIATIC trial (NCT03703297) showed significant survival improvements when adjuvant immunotherapy (IO) was added following chemoradiotherapy (CRT) with curative intent in patients primarily diagnosed with limited disease. The aim of this study was to provide real world survival data in the limited disease (LD) setting as well as to describe treatment strategies and outcomes in patients experiencing relapse prior to the approval of IO.

Methods: Data of patients diagnosed with SCLC between 2014-2023 was extracted from the Swedish National Lung Cancer Registry. LD was defined as TNM stage I-III. CRT was defined as a minimum of 45 Gy thoracic radiotherapy administered in conjunction with chemotherapy (CT). If radiotherapy started within 42 days of the start of chemotherapy, it was classified as concomitant CRT (cCRT); if it commenced after 42 days, it was considered sequential CRT (sCRT).

Results: The LD SCLC cohort included 1046 patients, primarily with stage III (n=836, 80%). Median age at diagnosis was 71 years, 60.9% were female and 98.2% had current or previous smoking history. ECOG PS distribution was PS 0 22.3%, PS 1 43.5%, PS 2 22.2%, PS 3 8.9% and PS 4 1.8%. CRT (n=380) and systemic therapies (n=365), [including CT (n=344) and CT+IO (n=21)] were the most common treatments in 1L. cCRT (n=310) was used more frequently than sCRT (n=70). In the CRT group, the median overall survival (mOS) was 27.9 months with 2-year survival 55.2% and 5-year survival 29.1%. In patients receiving systemic therapies, mOS was 10.5 months with 2- and 5-year survival at 20% and 8.3%, respectively. In the CRT group, the median progression-free survival (mPFS) was 16.5 months versus 7.4 months for the systemic therapies group, with CRT patients being younger (70 vs 73 years), having better PS (80% vs 51.5% for PS 0-1) and a lower proportion of stage IIIB-C patients (52.1% vs 61.6%). In patients receiving prophylactic cranial irradiation (PCI) after CRT (n=158), mPFS was 16.5 months and mOS 33.3 months compared to mPFS 7.1 months and mOS 18.9 months for those without PCI. The PCI group had better PS (85.4% vs 76.6% for PS 0-1) and a higher proportion of stage III patients (86.7% vs 77%). Relapse was reported in 238 CRT patients receiving CT as a subsequent treatment (n=203, 85%) resulting in a mPFS of 6.5 months in second line.

Conclusions: Patients who received CRT had more favorable outcomes and better prognostic baseline characteristics than those who received systemic therapy (i.e., CT or CT+IO). Overall results in this nationwide real-world, unselected cohort were similar to recent phase 3 trial of CRT data in terms of mOS and mPFS for the CRT group. The addition of PCI to CRT improved survival results reinforcing the role for this treatment modality in this setting.

Keywords: SCLC, Limited disease, Chemoradiotherapy

EP.13.23 Tislelizumab Plus Sitravatinib or Anlotinib as Maintenance Therapy in Extensive-Stage Small-Cell Lung Cancer (ES-SCLC)

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Introduction: First-line induction chemo-immunotherapy, followed by maintenance immune-monotherapy, significantly improved survival for ES-SCLC. However, rapid disease progression frequently occurs (mPFS: 4.5-5.8 months from induction therapy). We assessed an enhanced treatment strategy by adding an anti-angiogenic agent to immune-monotherapy during maintenance to delay recurrence. This report presents the efficacy and safety of two phase II trials evaluating maintenance tislelizumab (TIS, a PD-1 inhibitor) plus sitravatinib (Sitra, Trial 1) or anlotinib (Anlo, Trial 2) in ES-SCLC patients following induction TIS + chemo.

Methods: Untreated ES-SCLC patients received TIS + platinum-based chemo Q3W for 4 cycles (induction), followed by maintenance TIS (200 mg) and Sitra (70 mg QD; Trial 1) or Anlo (12 mg QD on D1-14; Trial 2) in a 21-day cycle for up to 2 years (including both the induction and maintenance phases). The primary endpoint was 1-year PFS rate in maintenance analysis set (MAS). MAS included patients receiving ≥1 dose maintenance therapy. Efficacy and safety in MAS were calculated from the start of maintenance therapy.

Results: 21 patients were enrolled separately in trial 1 and trial 2, with most patients had an ECOG PS of 1 (95.2% in each trial), and had more than 3 metastatic sites (90.5% in Trial 1 and 85.7% in Trial 2). 18 patients entered maintenance phase in each trial. From the start of maintenance therapy, median follow-up was 17.0 mo and 9.5 mo, respectively. Median PFS was 6.4 mo and 7.8 mo; median OS was 18.3 mo and not reached, with corresponding 1-year OS rates of 61.1% and 87.8%. In MAS, 4 patients in Trial 1 and 3 in Trial 2 achieved further partial responses, resulting in a confirmed ORR of 22.2% and 16.7%, respectively (Table). In MAS, the most common grade ≥3 TRAEs included hypertension (22.2%) in Trial 1 and fatigue (5.6%) in Trial 2. No patients died from TRAEs.

Conclusions: TIS plus Sitra or Anlo yielded promising efficacy with manageable toxicities as maintenance therapy in ES-SCLC patients after induction TIS + chemo. This enhanced maintenance strategy warrants further exploration in larger-scale trials.

Table

	Trial 1		Trial 2	
	MAS, N=18	IAS*, N=21	MAS, N=18	IAS*, N=21
Confirmed ORR, % (95% CI)	22.2 (6.4, 47.6)	76.2 (52.8, 91.8)	16.7 (3.6, 41.4)	85.7 (63.6, 97.0
DCR, % (95% CI)	88.9 (65.3, 98.6)	95.2 (76.2, 99.9)	77.8 (52.4, 93.6)	90.5 (69.6, 98.8
Median PFS, mo (95% CI)	6.4 (4.5, 9.0)	9.1 (7.3, 11.8)	7.8 (3.0, NR)	10.8 (5.8, NR)
1-year PFS rate, % (95% CI)	22.2 (6.9, 42.9)	26.3 (9.6, 46.8)	NR (NR, NR)	33.1 (10.0, 58.7
Median OS, mo (95% CI)	18.3 (7.8, NR)	17.6 (10.2, NR)	NR (NR, NR)	NR (NR, NR)
1-year OS rate, % (95% CI)	61.1 (35.3, 79.2)	66.7 (42.5, 82.5)	87.8 (59.5, 96.8)	78.7 (52.4, 91.5

*IAS=induction analysis set. IAS included patients who received ≥1 dose of induction therapy. Efficacy and safety in IAS were calculated from the start of induction therapy.
*MAS=maintenance analysis set. MAS included patients who received ≥1 dose of maintenance therapy. Efficacy and safety in MAS were calculated from the start of maintenance therapy. NR=not reached.

Keywords: Extensive-stage SCLC, immunotherapy, anti-angiogenic therapy

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.24 ES-SCLC Outcomes Following SBRT And/Or Thoracic Consolidation After Induction Systemic Therapy

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Introduction: Small cell lung cancer (SCLC) is an aggressive malignancy strongly linked to tobacco use and comprises 10-15% of all lung cancers. At diagnosis, approximately 70% of patients present with extensive-stage disease (ES-SCLC). While platinum-doublet chemotherapy (CTX) has long been the standard of care, the addition of immunotherapy (IO) has modestly improved outcomes. The role of radiation therapy (RT), including stereotactic body radiation therapy (SBRT) to oligometastatic sites or thoracic consolidation (TC), particularly following chemo-immunotherapy, remains poorly defined. We conducted a retrospective analysis to evaluate outcomes in ES-SCLC patients who received RT after induction systemic therapy.

Methods: We reviewed single-institution registry data from January 2013 to December 2023, identifying 29 ES-SCLC patients who received RT following CTX or CTX/IO induction. Patient demographics, clinical characteristics, treatment details, and outcomes were extracted through detailed chart review. RT included SBRT to extracranial metastases (SBRT-ECM), SBRT to cranial metastases (SBRT-CM), and TC.

Results: Of 29 patients receiving RT, 18 underwent CTX alone and 11 received CTX/IO. SBRT-ECM doses ranged from 800-3000 cGy (median 2000), SBRT-CM from 1800-3300 cGy (median 2000), and TC from 2000-12000 cGy (median 4500). Compared to 114 ES-SCLC patients treated with CTX or CTX/IO without RT (median OS 8.9 months), SBRT-ECM (n=12) conferred no OS benefit (median OS 6.5 months, p=0.5222) (Fig. 1). However, SBRT-CM (n=6) and TC (n=18) were associated with improved OS (median OS 24.4 months, p=0.0594 and 18.9 months, p=0.0189, respectively) (Fig. 1). Among patients treated with CTX/IO alone (n=70; median OS 9.5 months), neither SBRT-ECM (n=6) nor SBRT-CM (n=2) significantly improved OS (median OS 8.3 months, p=0.7102 and 18.2 months, p=0.7145). TC following CTX/IO (n=6) showed a trend toward improved OS (median OS 20.7 months, p=0.1388), though limited by sample size.

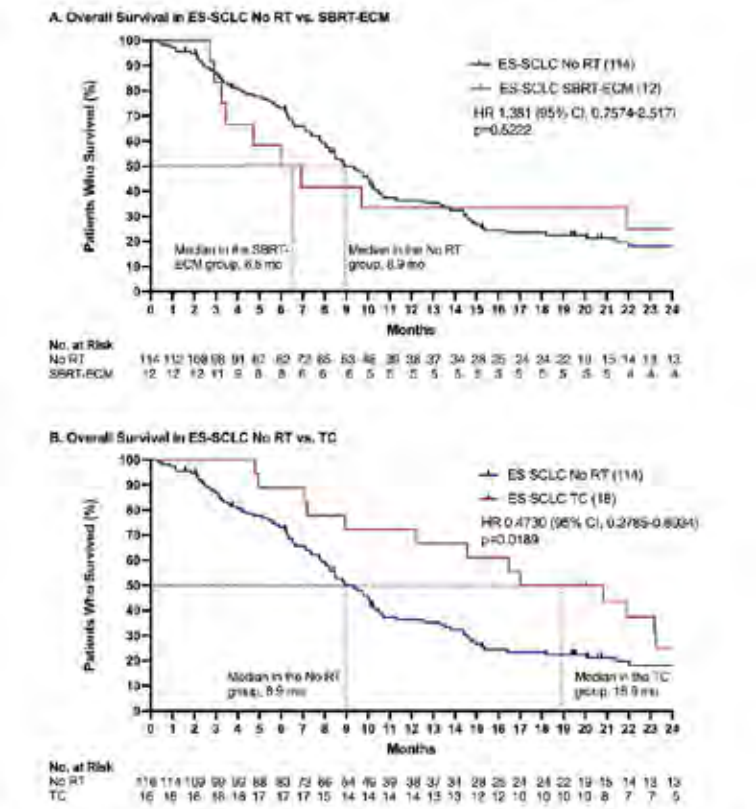

Figure 1. Overall survival of extensive stage small cell lung cancer (ES-SCLC) treated with no radiation therapy (RT) versus (A) stereotactic body radiation therapy to extracranial metastases (SBRT-ECM) (p=0.5222) or (B) thoracic consolidation (TC) (p=0.0189).

Conclusions: Our retrospective study suggests that thoracic consolidation and SBRT to cranial metastases may be associated with improved overall survival in patients with ES-SCLC following induction therapy with this trend maintained after addition of IO. In contrast, SBRT to extracranial metastases did not yield a survival benefit. While limited by small sample size and potential selection bias, these findings support further prospective investigation into the role of RT, particularly TC, in the management of ES-SCLC in the era of chemo-immunotherapy.

Keywords: SCLC, Immunotherapy, SBRT

EP.13.25 Real-World Treatment Patterns in ES-SCLC Highlight Continued Unmet Medical Need in the Era of New Therapies: ESSENCE Study

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Introduction: Most patients with small cell lung cancer (SCLC) have extensive-stage (ES) disease at diagnosis and, despite advances in therapy, usually relapse within 6 months of initial treatment. Real-world (RW) evidence detailing contemporary treatment of relapsed SCLC is limited. This longitudinal, retrospective study assessed treatment utilisation and sequencing in a RW cohort of patients with ES-SCLC.

Methods: Dataextracted from the US-based, de-identified, longitudinal Flatiron HealthResearch Database included all adults diagnosed with ES-SCLC from 1 January2019 to 3 months prior to data cutoff (31 December 2024). Treatments forES-SCLC were described by line of therapy. Treatment utilisation in second-line(2L) and third-line (3L) was described in a subpopulation of patients with denovo ES-SCLC, stratified by platinum sensitivity status.

Results: Overall,13,105 patients with ES-SCLC were included; median age was 68 years (interquartilerange [IQR] 62, 75); 48.1% were male; 98.1% had a history of smoking; 81.0% werediagnosed with de novo ES-SCLC; 28.6% had brain metastases at diagnosis. Medianfollow-up was 6.5 months (IQR 2.5, 11.9). There were 10,548 patients with a known disease stage at initial SCLCdiagnosis who received at least first-line (1L) therapy for ES-SCLC. Nearly half (48.8%) of patients in theoverall cohort received only 1L therapy, and 20.2% only 1L and 2L therapyfollowing ES-SCLC diagnosis. Most patients received 1L platinum-basedchemo-immunotherapy with a variety of regimens in subsequent lines (Table 1). 2Land 3L treatment in the de novo cohort varied by platinum sensitivity (Table2).

Conclusions: ThisRW study underscores the heterogeneity of treatment of ES-SCLC in the 2L+ setting,highlighting a high unmet need for effective treatments. Novel therapies,including B7-H3-targeted antibody-drug conjugates and DLL3 bispecifics, maychange treatment options. RW clinical outcome results are forthcoming.

Table 1. Treatment utilisation by line of therapy among patients with ES-SCLC in the US

	Overall ES-SCLC cohort N=13,105			de novo ES-SCLC cohort N=10,633		
Line of therapy[a]	1L N=10,548	2L N=4159	3L N=1517	1L N=9167	2L N=3622	3L N=1322
Treatment regimen						
Platinum-based chemotherapy + immune checkpoint inhibitor[b]	8011 (75.9%)	471 (11.3%)	70 (4.6%)	7496 (81.8%)	425 (11.7%)	60 (4.5%)
Platinum-based chemotherapy	1281 (12.1%)	469 (11.3%)	151 (10.0%)	1163 (12.7%)	431 (11.9%)	131 (9.9%)
Topotecan	105 (1.0%)	459 (11.0%)	290 (19.1%)	26 (0.3%)	381 (10.5%)	245 (18.5%)
Lurbinectedin	308 (2.9%)	1684 (40.5%)	439 (28.9%)	54 (0.6%)	1496 (41.3%)	397 (30.0%)
Tarlatamab	13 (0.1%)	40 (1.0%)	56 (3.7%)	8 (<0.1%)	28 (0.8%)	47 (3.6%)
Clinical trial	134 (1.3%)	163 (3.9%)	35 (2.3%)	104 (1.1%)	147 (4.1%)	29 (2.2%)
Other[c]	696 (6.6%)	873 (21.0%)	476 (31.4%)	316 (3.4%)	714 (19.7%)	413 (31.2%)

[a]Treated sub-cohorts are not mutually exclusive. N reflects patients across treated sub-cohorts with known disease stage at initial SCLC diagnosis. [b]Includes platinum-based therapy in combination with PD-1/PD-L1 inhibitors. [c]Other therapies include PD-1/PD-L1 +/- CTLA-4 inhibitor immunotherapy, other chemotherapy and other regimens.

Table 2. Treatment utilization in the cohort with de novo ES-SCLC at diagnosis by platinum sensitivity status in 2L and 3L

	Platinum-sensitive[a] (N=2262)		Platinum-resistant/ refractory[b] (N=2651)		Unknown[c] (N=3761)	
Line of therapy[d]	2L N=1473	3L N=588	2L N=1439	3L N=436	2L N=535	3L N=232
Treatment regimen						
Platinum-based chemotherapy + immune checkpoint inhibitor[e]	164 (11.1%)	21 (3.6%)	77 (5.4%)	14 (3.2%)	142 (26.5%)	20 (8.6%)
Platinum-based chemotherapy	261 (17.7%)	53 (9.0%)	105 (7.3%)	37 (8.5%)	46 (8.6%)	34 (14.7%)
Topotecan	162 (11.0%)	111 (18.9%)	190 (13.2%)	103 (23.6%)	18 (3.4%)	24 (10.3%)
Lurbinectedin	663 (45.0%)	203 (34.5%)	742 (51.6%)	103 (23.6%)	42 (7.9%)	77 (33.2%)
Tarlatamab	13 (0.9%)	23 (3.9%)	12 (0.8%)	20 (4.6%)	3 (0.6%)	3 (1.3%)
Clinical trial	57 (3.9%)	16 (2.7%)	52 (3.6%)	9 (2.1%)	37 (6.9%)	2 (0.9%)
Other[f]	153 (10.4%)	161 (27.4%)	261 (18.1%)	150 (34.4%)	247 (46.2%)	72 (31.0%)

Note: Platinum sensitivity status is defined by chemotherapy-free interval (CTFI), which represents time from the last dose of 1L platinum chemotherapy to date of first progression event or until start of 2L, whichever occurs first. [a]Platinum-sensitive patients are those with CTFI ≥90 days. [b]Platinum-resistant/refractory patients are those with CTFI <90 days. [c]Unknown platinum-sensitive patients are those who did not have a progression event within 1L platinum chemotherapy. [d]Treated sub-cohorts are not mutually exclusive. [e]Includes platinum-based therapy in combination with PD-1/PD-L1 inhibitors. [f]Other therapies include PD-1/PD-L1 +/- CTLA-4 inhibitor immunotherapy, other chemotherapy and other regimens.

Keywords: SCLC, ES-SCLC, Real-world treatment

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.26 Gut Microbiota and Metabolites as Potential Biomarkers for Immunotherapy Efficacy in Patients With Extensive-Stage Small Cell Lung Cancer

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Introduction: Extensive-stage small cell lung cancer (ES-SCLC), an aggressive form of lung cancer with poor prognosis, continues to yield less clinical benefit compared to non-small cell lung cancer (NSCLC). While immune checkpoint inhibitors (ICIs) have shown some efficacy in treating ES-SCLC, their response rates and duration of remission remain suboptimal. It is necessary to identify effective biomarkers for predicting the response to immunotherapy in patients with ES-SCLC.

Methods: Patients diagnosed with primary ES-SCLC who were treated with at least one of the ICIs were enrolled from Dalian Medical University Affiliated Second Hospital between May 1, 2021, and September 30, 2023. Baseline fecal samples were collected from the patients before receiving the first treatment, and were tested through metagenomics and untargeted metabolomics. Treatment efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Results: A total of 41 patients with ES-SCLC were included in the study. The median progression-free survival (PFS) time was 3.57 ± 5.73 months (ranging from 0.23 to 26.13 months). Patients were categorized into non-responsive (N group) and responsive (R group) based on the median PFS time. No significant differences were observed between the two groups in terms of demographic characteristics, including age, gender, smoking, and alcohol history. The baseline gut microbiota composition and species diversity were similar between the two groups. However, the most enriched microbiota in the R group were Phascolarctobacterium, Acidaminococcales, and Clostridium, while the N group was enriched with Subdoligranulum, Lactobacillales, and Bacilli. Significant differences were observed in the baseline gut microbiota metabolites and their enriched metabolic pathways between the two groups. A total of 34 metabolites were significantly different, with 13 upregulated and 21 downregulated in the R group. L-Norvaline and 20-Hydroxyecdysone were enriched in the R group, while Chenodeoxycholic acid sulfate and N-Acetylneuraminate were enriched in the N group, potentially serving as predictive biomarkers for immunotherapy efficacy in ES-SCLC. Upregulated metabolites in the R group were enriched in sphingolipid metabolism, while downregulated metabolites were enriched in amino sugar and nucleotide sugar metabolism pathways and diterpenoid biosynthesis pathways (Figure 1).

Conclusions: Baseline gut microbiota composition, metabolites, and metabolic pathways differ significantly between ES-SCLC patients responsive and non-responsive to immunotherapy. These findings suggest that gut microbiota and its metabolites may serve as potential biomarkers for predicting the efficacy of immunotherapy in patients with ES-SCLC.

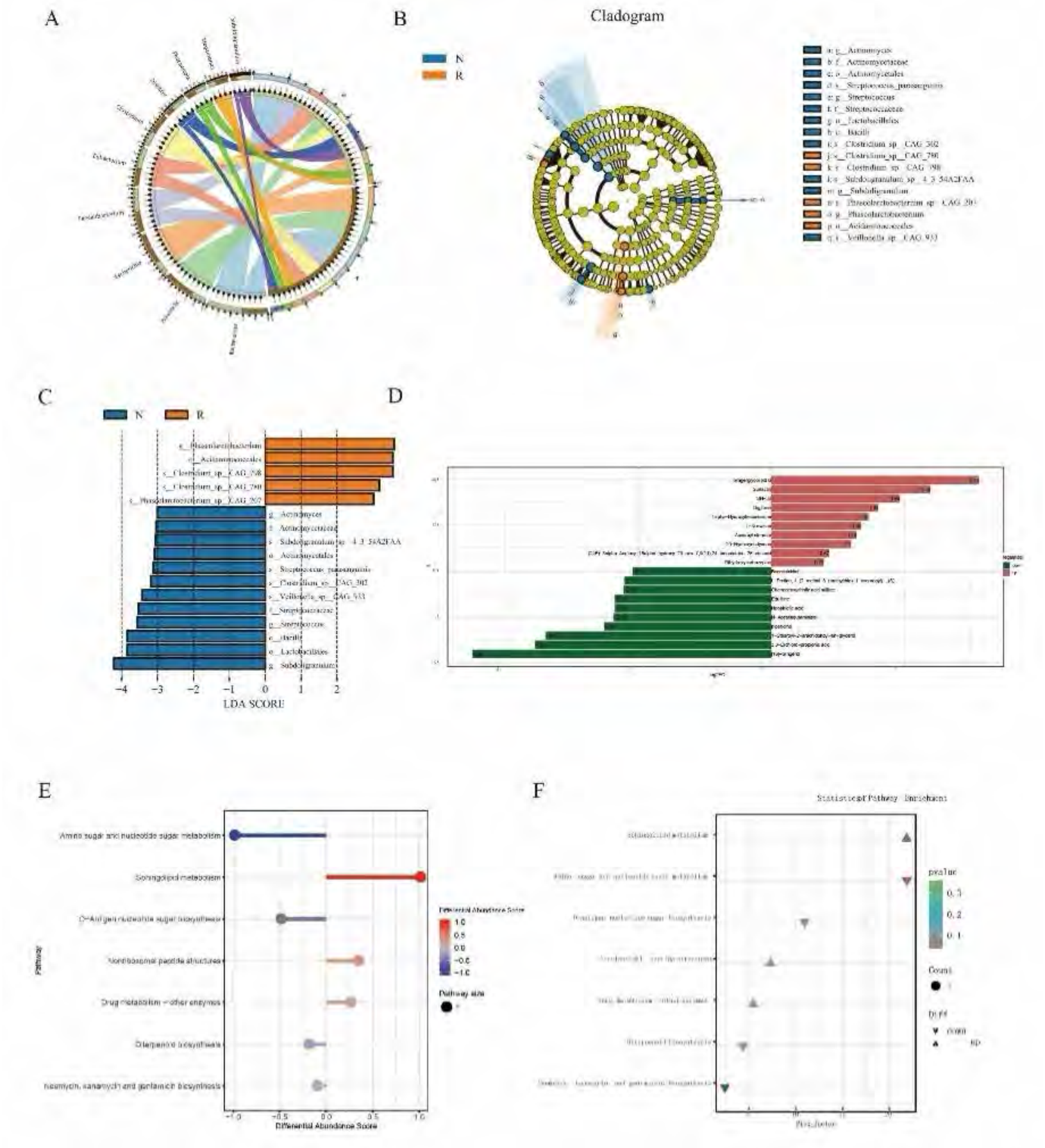

Figure 1. A. Circos plot showing gut microbiota composition in the N and R groups. B. LEfSe classification diagram for the N and R groups. C. LDA score plot highlighting differentially abundant taxa in the N and R groups. D. Fold change of the top 10 upregulated and downregulated metabolites in the R group relative to the N group. E, F. KEGG-based enrichment analysis of differentially abundant metabolites, including score plots and pathway enrichment dot plots.

Keywords: Extensive-stage small cell lung cancer, Gut microbiota, Biomarker

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.27 Co-Targeting SFKs and DNA Damaging Chemotherapy Drugs as a Novel Therapeutic Strategy in SCLC

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Introduction: Small cell lung cancer (SCLC) is an aggressive and often fatal tumor for which effective therapeutic options remain limited. For decades, the standard first-line treatment has been etoposide-based chemotherapy combined with a platinum derivative (E/P), but this regimen has not led to significant improvements in survival outcomes. Despite initial responses to treatment, nearly all patients experience disease progression and require second-line therapies. However, second-line treatments are typically palliative, with patients surviving less than a year. Available second-line options include topotecan, lurbinectedin, and maintenance chemoimmunotherapy. We have previously demonstrated the role of Src family kinases (SFKs) in SCLC. These kinases can be targeted with Dasatinib, an FDA approved drug for hematological malignancies. Our goal was to identify new drug vulnerability by co-targeting SFKs with drugs that cause DNA damage.

Methods: Human SCLC H209 and DMS53 and murine SCLC RP cell lines were used for the study of these novel vulnerabilities in SCLC. We selected drugs either currently used in SCLC patients (in first- or second-line treatments) or that might target the DNA damage repair (DDR) in combination with Dasatinib: lurbinectedin, topotecan, etoposide, cisplatin and VE-821. Single drug toxicity and combinatory drugs were assessed by MTS or Cell Titer Glo 2.0. Synergy combination was calculated with CompuSyn software. DNA damage markers were studied by Western Blotting and immunofluorescence staining. Effect of combinatory drugs was studied by apoptosis assay. Two therapeutic combinatory strategies were tested in vivo in athymic nude mice. The effect of these therapies is being tested in immunocompetent mice.

Results: Chemotherapeutics drugs (cisplatin, etoposide and topotecan) inhibited cell proliferation with low IC50 doses of approximately less than 1 µM in a variety of human and murine SCLC cell lines, except for RP that exhibited an IC50 for cisplatin of 2 µM. Moreover, lurbinectedin had a higher cytotoxic effect, with IC50 dose less than 0,1 ng/mL in vitro. Additional combination of Dasatinib exerted a synergistic anti-proliferative and pro-apoptotic effect than that of chemotherapeutics alone. Increasing concentrations of chemotherapeutics alone showed higher amount of pH2Ax, which was increased when combining with different doses of Dasatinib in both H209 and DMS53 cell lines. Other DNA damage markers such as pCHK1 and cleaved PARP were also increased when combined with Dasatinib. These results were in concordance with the increasing intensity of pH2Ax found by immunofluorescence. The combinatorial strategies of Lurbinectedin or Topotecan with Dasatinib exerted a strong anti-tumor activity in DMS53- and H209-bearing nude mice treated with the corresponding combination. Besides, no signs of toxicity, weight loss or changes in hemogram were detected.

Conclusions: Combination of Dasatinib with the DNA damaging chemotherapeutic drugs Lurbinectedin and Topotecan showed synergistic pro-apoptotic and anti-proliferative effect in vitro. Tumor volumes were significantly reduced compared to single drugs when mice were treated in vivo. Thus, combining Dasatinib with Lurbinectedin or Topotecan represent two novel therapeutic strategies for SCLC treatment.

Keywords: small cell lung cancer (SCLC), DNA damage, synergistic combination

EP.13.28 Assessment of Clinical Characteristics and Outcomes of Brazilian ES-SCLC Patients on First Line Durvalumab + Chemotherapy

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Introduction: Extensive-stage small cell lung cancer (ES-SCLC) presents significant treatment challenges with limited survival outcomes. Immunotherapy, including durvalumab, has become front-line standard-of-care in these patients. This study aimed to evaluate the demographic characteristics, efficacy, and safety profile of durvalumab-based regimens in a real-world Brazilian cohort of ES-SCLC patients.

Methods: EDUR-BRA (LACOG 0322) is a real-world, single-arm, multi-center observational analysis across seven private healthcare facilities in Brazil. Eligible participants were adult patients with histologically or cytologically confirmed ES-SCLC receiving durvalumab-based regimens in first-line. Data were collected retrospectively and prospectively from patients' medical records with a maximum follow-up of 24 months post-treatment initiation. The primary outcome was the assessment of demographic and clinical characteristics, while secondary outcomes included real-world progression-free survival (rwPFS) and overall survival (OS). Safety was assessed by the incidence of adverse events. NCT06008353

Results: A total of 59 patients were enrolled from January to November 2024, with a median age of 69 years; 66% of patients were 65 years or older. Patients were predominantly males (51%). At durvalumab initiation, 44 (75%) patients had a WHO status of 0-1 and 6 (10%) had WHO ≥2. Regarding smoking history, 7 (12%) patients were never smokers, 35 (59%) were former smokers, and 14 (24%) were current smokers. Baseline assessments revealed that a total of 8 (14%) patients had locally advanced disease not amenable to locoregional treatment and most patients (N=51, 86%) had metastatic disease: 10 (20%) patients had brain metastases and 11 (22%) had liver metastases. Most patients (N=56, 95%) received carboplatin-etoposide with a median number of 4 cycles. As per inclusion criteria, all patients were treated with durvalumab. The duration of durvalumab treatment was 23 (0-93) weeks and the median number of durvalumab cycles received was 8 (IQR 5-11). The main reason for treatment discontinuation was disease progression (N=20, 59%); only 2 patients discontinued durvalumab due to adverse event. At the median follow-up of 24.8 months (95% CI: 13.9 - 26.7), the median OS was 13.4 (9.9-15.4) months and the median rwPFS of 6.9 (95% CI: 5.1-7.9 months). Adverse events of any grade and grade ≥3 were observed in 33 (56%) and 16 (25%) patients, respectively. The most frequently observed adverse events included fatigue and nausea. Serious adverse events occurred in 14 (23%) patients.

Conclusions: The present study assessed the clinical characteristics, efficacy and safety of durvalumab-based regimens in a real-world ES-SCLC cohort in Brazil. Overall, the patients from this cohort were older, had a worst performance status and had more brain metastasis compared to the CASPIAN study. Nevertheless, efficacy and safety results were consistent with those observed in the phase III clinical trial.

Keywords: Extensive Stage Small Cell Lung Cancer, Durvalumab, Brazil

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.29 Safety and Efficacy of DLL3 CAR-T Cells Armored With dnTGFBR2 in a Patient With Recurrent Small-Cell Lung Cancer

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Introduction: LB2102 comprises autologous DLL3-targeted CAR-T cells armored with dominant-negative TGBFR2 to overcome tumor-mediated immunosuppression. One-time infusion is being tested in a phase 1 trial of patients with recurrent high-grade neuroendocrine carcinoma or SCLC. We report the case of a patient with recurrent SCLC who received 1 infusion of LB2102 under a single-patient investigational new drug (IND) application after becoming ineligible from the trial.

Methods: The patient (51 years old, female) had SCLC progression, symptomatic brain metastases, and a lung lesion approximately 8 months after starting platinum-based combination chemotherapy and 3 months after starting atezolizumab maintenance therapy. After whole-brain radiation (WBRT) in February 2024, she was enrolled the study (phase 1, 3+3 design) and planned to receive 2.0×106 CAR+ T cells/kg (LB2102 dose level 3). She received 2 cycles of irinotecan, given weekly as bridging therapy. The patient had recurrent altered mental status (AMS) (delirium). After 1 day of lymphodepletion (fludarabine 30 mg/m2 and cyclophosphamide 300 mg/m2), she was excluded from the trial due to safety concerns from AMS (prior to LB2102 infusion). AMS was ultimately found to result from overuse of opioids for pain control. The investigator obtained single-patient IND permission for administration of LB2102 at 2.3x106/kg after another 3 days of lymphodepletion.

Results: At baseline, the patient had 98% DLL3 expression in tumor specimens, based on immunohistochemical analysis, with 88% ≥2+ in staining density. She tolerated the infusion well, without dose-limiting toxicity, cytokine-release syndrome, or neurotoxicity. Four weeks after LB2102 infusion, Grade 2 (G2) anemia and G4 neutropenia improved to G1 and G2, respectively; her G1 thrombocytopenia resolved by Day 11. After 21 days, contrast computed tomography of the chest showed marked central necrosis within the 7.6 cm target lesion. By 12 weeks, the lesion had decreased by 45%, meeting partial response (PR) criteria for RECIST1.1 and with no new metastases. At 6 months, the central lesion was reduced 76% from baseline (to 1.8 cm); pharmacokinetic data indicated persistence of CAR-T cells (at 2710/mL) and 0.86% CD3+ CAR+ cells (of total CD3+ T cells). Peripheral blood samples contained 0 circulating tumor cells (CTC) (from 27/mL at baseline), 0 DLL3+ CTC (from 6/mL at baseline), and 160 CD4+ T cells/mL. Markers that peaked at Day 11 after CAR-T-cell infusion (C-reactive protein [160 mg/L], ferritin [829 ng/mL], and lactate dehydrogenase [307 U/L], had returned to normal by 6 months; levels of GGT were reduced from peak of 141 to 40 U/L. One year after the first WBRT, MRI showed stabilization of the brain metastases with no new lesions. The patient is pain- and treatment-free with ECOG-1, without additional anti-cancer therapy.

Conclusions: In a case study of a patient with relapsed and refractory SCLC, a single infusion of LB2102 led to a sustained PR (> 6 months) and improvement of disease-related symptoms. No serious LB2102-related adverse events were observed other than those expected with lymphodepletion. The CAR-T cells expanded and persisted for more than 6 months. These findings warrant further research of DLL3-targeted autologous cell therapies for cancer.

Keywords: Recurrent small cell lung cancer, DLL3, CAR-T therapy

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.30 Real-World Analysis of Treatment Patterns in Limited-Stage Small Cell Lung Cancer: Implications for Clinical Practice

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Introduction: Unresolved issues complicate treating limited-stage small-cell lung cancer (LS-SCLC). We conducted a real-world study analyzing LS-SCLC treatment patterns to address clinical needs.

Methods: We retrospectively enrolled patients with LS-SCLC treated at Peking Union Medical College Hospital between May 2008 and December 2023. Information was collected on clinicopathological features, cancer-related treatments, laboratory test results, and clinical and prognostic data. Kaplan-Meier survival analysis was performed to evaluate progression-free (PFS) and overall survival (OS). Cox regression models were used to assess the factors influencing survival.

Results: Among the 203 patients with LS-SCLC, the median OS (mOS) was 28.8 months. A log-rank test indicated significant differences in mOS across radiotherapy-timing groups (P = 0.031): 30.1 months for concurrent chemoradiotherapy (cCRT), 27.5 months for sequential therapy, and 21.7 months for no radiotherapy. Notably, early cCRT was associated with a longer mOS trend (38.3 months) compared to late cCRT (29.5 months), though the difference was not statistically significant (P = 0.058). mOS was comparable in the prophylactic cranial irradiation (PCI) group or in the non-PCI group (PCI 36.9 vs. non-PCI 29.6 months; P=0.27). Peripheral blood biomarkers were unreliable as prognostic indicators. In multivariate analysis, poor survival was predicted by Eastern Cooperative Oncology Group performance status >1 (hazard ratio [HR] 3.652, 95% confidence interval [CI] 1.579-8.448; P=0.002), and N2 (HR 2.872; 95%CI 1.312-6.286; P=0.008) and N3 (HR 2.645; 95%CI 1.195-5.856; P=0.016) lymph node metastasis. Compared with the early cCRT group, the sequential radiotherapy group had an increased risk of death (HR 1.701, 95% CI 1.125-2.573; P=0.012).

Conclusions: Performance status and lymph node metastasis are prognostic factors for patients with LS-SCLC. cCRT improve the prognosis of LS-SCLC, with early cCRT providing a significant survival benefit and late cCRT being an acceptable option.

Keywords: Limited-stage small-cell lung cancer, Concurrent chemoradiotherapy, Prophylactic cranial irradiation

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.32 Multi-Institutional Real-World Experience of Early Tarlatamab-Related Toxicities for Extensive Stage Small Cell Lung Cancer

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Introduction: Tarlatamab, a novel bispecific T-cell engager (BiTE) targeting delta-like ligand 3 (DLL3) and CD3, has shown promising efficacy in treating small cell lung cancer (SCLC) and other neuroendocrine malignancies beyond 1st line treatment. However, real-world data on its safety profile remains limited. Clinical trials have reported notable toxicities, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hospitalization rates, however, the applicability of these observations to broader, uncontrolled clinical contexts remains uncertain. This study presents a multi-institutional real-world experience analyzing toxicity patterns in 25 patients treated with tarlatamab, with a focus on CRS, ICANS, and readmission rates.

Methods: A retrospective cohort study was conducted across two academic cancer centers, evaluating 25 patients who received tarlatamab for relapsed/refractory SCLC between October 2024 through March 2025. Data were extracted from electronic medical records, including patient demographics, prior therapies, treatment duration, and adverse events. Toxicity profiles were assessed and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The severity CRS was further classified using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria. Primary endpoints included the incidence and severity of CRS, the incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), early mortality rates, and hospitalization events directly attributable to treatment-related toxicities.

Results: Among the 25 patients, the median age was 68.2 years (range: 50-84), with 48% (12/25) male and 52% (13/25) female. There were 44% (11/25) patients identifying as Hispanic/Latinx. The majority (72%, 18/25) received tarlatamab as a second line therapy. 7/25 had received at least 2 lines of therapy. CRS occurred in 48% (12/25) of patients, with 100% (n=12) experiencing Grade 1-2. There were no Grade ≥3 CRS reported. CRS onset typically occurred within 12 hours post-infusion and was resolved with antipyretics for fever and intravenous fluids for hydration. Corticosteroids were required in 75% of cases (9/12). No tocilizumab was required. ICANS occurred in 16% (4/25) of patients, 1 case required ICU admission (grade 3 event). Regarding readmissions, 20% (5/25) of patients required readmissions due to treatment-related toxicities, with a median length of stay of 2.2 days. The most common reason for hospitalization was CRS (60%, 3/5). Treatment discontinuation was required in 32% (8/25) of patients due to toxicity (8%, 2/25), progression (12%, 3/25), and death (12%, 3/25). Among the deaths, 3 patients expired due to disease progression within 2 cycles of treatment.

Conclusions: This multi-institutional analysis highlights the toxicity profile associated with real-world use of tarlatamab, particularly CRS and ICANS. In general, CRS and ICANS were low grade and mostly manageable with standard interventions. Readmissions due to treatment related toxicities were uncommon. However, there were 3 early deaths due to disease progression within 2 cycles of treatment. These findings underscore the need for patient selection, vigilant monitoring, early intervention, and potential optimization of preemptive management strategies. This is the largest case series of Hispanic patients treated with tarlatamab. Future studies should refine toxicity mitigation protocols to enhance the safety and tolerability of tarlatamab in broader patient populations.

Keywords: small cell lung cancer, tarlatamab, real world experience

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.33 Treatment Timeliness and Impact on Survival in Extensive Stage Small Cell Lung Cancer

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Introduction: Rapid diagnosis and treatment initiation are widely viewed as key principles in the management of extensive-stage small cell lung cancer (ES-SCLC). The Australian Optimal Care Pathway (OCP) for lung cancer recommends confirmation of diagnosis within 2 weeks of initial specialist review and initiation of treatment within 6 weeks of specialist referral. The impact of adhering to these timeliness recommendations in the real-world setting is unknown.

Methods: The Victorian Lung Cancer Registry, a multicentre lung cancer clinical quality registry, was analysed to identify patients with newly-diagnosed ES-SCLC. The referral-to-diagnosis interval (RDI), referral-to-treatment interval (RTI) and diagnosis-to-treatment interval (DTI) were calculated and, in line with OCP guidelines, defined as timely if they were less than 28 days, 42 days and 14 days, respectively. The impact of timeliness on overall survival was determined using univariate and multivariable Cox proportional hazards regression and propensity score matching.

Results: From January 2012 to April 2023, there were 995 evaluable patients with ES-SCLC who were treated with chemotherapy, with a median age was 68 years (interquartile range (IQR) 61-74 years). 59.8% were male. The median RDI, RTI and DTI were 8 days (IQR 4-17 days), 18 days (IQR 10-31 days) and 7 days (IQR 4-13 days), respectively. Overall survival was worse when the DTI was <14 days compared to ≥14 days, with hazard ratios (HR) of 1.31 (95% confidence interval (CI) 1.12-1.54, p=0.001) in the univariate analysis, a 1.32 (95% CI 1.13-1.56, p=0.001) in the multivariable analysis and 1.30 (95% CI 1.07-1.58, p=0.008) in the propensity score-adjusted analysis. Shorter RDI and RTI were also associated with poorer survival. Using multivariable regression, the HR for RDI <28 days relative to RDI ≥28 days was 1.37 (95% CI 1.10-1.71, p=0.005), while the HR for RTI <42 days relative to RTI ≥42 days was 1.58 (95% CI 1.28-1.95, p<0.0001).

Conclusions: The majority of patients received care that met defined timeliness targets, but earlier diagnosis and treatment were associated with poorer survival. This may be explained by unmeasured confounders. Delivery of timely care may also have benefits on symptom burden and quality of life, but these factors were not prospectively captured in our registry data.

Keywords: SCLC, Timeliness, Clinical quality registry

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.34 Meta-Analysis of First-Line Immunochemotherapy in ES-SCLC: Does ECOG PS =2 Affect Survival Outcomes

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Introduction: Multiple randomized controlled trials (RCTs) have demonstrated that adding immunotherapy significantly improves the prognosis of patients with extensive-stage small cell lung cancer (ES-SCLC), establishing it as a global standard of care. However, stringent eligibility criteria in RCTs limit the generalizability of these findings to real-world clinical settings. Most trials predominantly included patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, leaving the efficacy of immunochemotherapy in ECOG PS ≥2 patients uncertain. This meta-analysis evaluates the survival benefits of first-line immunochemotherapy in ES-SCLC patients with ECOG PS ≥2.

Methods: A systematic review was conducted across PubMed, Embase, Cochrane Library, Web of Science, and Scopus using keywords related to "ES-SCLC," "first-line," "immunochemotherapy," and "clinical trials." Inclusion criteria were: (1) adult patients (≥18 years) diagnosed with ES-SCLC; (2) explicit reporting of ECOG PS, including a subgroup of ECOG PS ≥2; (3) treatment with immunochemotherapy; (4) reported progression-free survival (PFS) and/or overall survival (OS); and (5) stratified data comparing ECOG PS ≥2 vs. PS <2 or data allowing derivation of hazard ratios (HRs) with 95% confidence intervals (CIs). Exclusion criteria were: (1) non-first-line studies; (2) lack of ECOG PS data or HRs; (3) studies focusing on pediatric, adolescent, or atypical SCLC populations; (4) chemotherapy-only or immune checkpoint inhibitors (ICIs) monotherapy studies; and (5) incomplete or unavailable studies. The pooled HRs for OS and PFS were calculated based on treatment type (chemotherapy vs. immunochemotherapy) and ECOG PS subgroups (PS <2 vs. PS ≥2).

Results: Of 1,529 screened studies, 17 met inclusion criteria, comprising 3,022 ES-SCLC patients. The pooled analysis estimated that 20.02% (95% CI 14.39-26.29) of newly diagnosed ES-SCLC patients had ECOG PS ≥2. Meta-analysis results demonstrated that ECOG PS did not significantly impact survival outcomes following first-line treatment. Compared to patients with ECOG PS <2, those with ECOG PS ≥2 exhibited no significant difference in OS (HR = 1.14, 95% CI: 0.80-1.63) or PFS (HR = 1.19, 95% CI: 0.88-1.62). Subgroup analysis further revealed that among patients receiving first-line immunochemotherapy, OS (HR = 1.25, 95% CI: 0.77-2.03) and PFS (HR = 1.10, 95% CI: 0.78-1.54) did not differ significantly between ECOG PS ≥2 and PS <2 subgroups. Notably, in the ECOG PS ≥2 subgroup, immunochemotherapy conferred a significant survival advantage compared to chemotherapy alone, with an OS HR of 0.64 (95% CI: 0.47-0.87) and a PFS HR of 0.44 (95% CI: 0.28-0.68), indicating both short- and long-term survival benefits.

Conclusions: Our findings suggest that baseline ECOG PS at diagnosis does not significantly impact long-term prognosis in ES-SCLC patients, and those with ECOG PS ≥2 can also derive substantial survival benefits from first-line immunochemotherapy. However, most of the included studies were retrospective real-world studies, necessitating cautious interpretation of the results. Further large-scale prospective trials incorporating patients with poor ECOG PS are warranted to comprehensively assess the efficacy and safety of first-line immunochemotherapy in this population.

Keywords: Immunochemotherapy, ES-SCLC, Meta-Analysis

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.35 Sequential Atezolizumab Regimens (Chemo Followed by Anlotinib) for ES-SCLC: Real-World Data

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Introduction: Immunotherapy combined with chemotherapy followed by immunotherapy maintenance has demonstrated clinical activity in extensive-stage small cell lung cancer (ES-SCLC). The addition of anti-vascular therapy to immunochemotherapy may further improve survival but could also increase the incidence of adverse events. It remains unclear whether incorporating anti-vascular therapy during the maintenance phase rather than the induction phase could provide additional benefits for treatment-naive ES-SCLC patients.

Methods: This multicenter, prospective, single-arm, open-label, real-world trial evaluated the efficacy and safety of atezolizumab plus chemotherapy (induction phase) followed by atezolizumab plus anlotinib (maintenance phase) as first-line therapy in patients with ES-SCLC. Patients received four to six cycles of atezolizumab plus etoposide and carboplatin (EC), followed by atezolizumab plus anlotinib for up to 2 years. The primary endpoint was progression-free survival (PFS). Safety was assessed in all patients who completed at least four cycles of treatment.

Results: Between July 1, 2020, and December 30, 2024, 69 patients were enrolled. At the data cutoff date (April 1, 2025), the last enrolled patient had been followed up for approximately four months. Among 69 evaluable patients, one (1.4%) achieved a complete response (CR), 49 (71.0%) achieved a partial response (PR), and 16 (23.2%) achieved stable disease (SD), resulting in an objective response rate (ORR) of 72.4% and a disease control rate (DCR) of 95.6%. The median PFS was 9 months (95% CI, 7-12 months). Grade 3 or higher treatment-related adverse events occurred in 17.4% of patients, including neutropenia, anemia, nausea, pneumonia, myocarditis, and liver/kidney damage. Treatment-related deaths occurred in four patients (5.8%), due to pneumonia (n=2), kidney damage (n=1), and myocarditis (n=1).

Conclusions: Atezolizumab plus chemotherapy followed by atezolizumab plus anlotinib as first-line therapy provided a clinically meaningful PFS benefit in patients with ES-SCLC. With the prophylactic use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in real-world practice, the grade 3 or higher safety profile was favorable compared to previously reported regimens.

Keywords: SCLC, Atezolizumab, Anlotinib

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.36 Induction Immunochemotherapy Followed by Concurrent Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer

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Introduction: Immunotherapy, chemotherapy, and radiotherapy all play significant roles in the management of small cell lung cancer (SCLC). Combining radiotherapy with chemotherapy followed by immunotherapy shows promise for limited-stage SCLC (LS-SCLC), offering good tolerability and survival benefits. However, there is limited data on whether immunotherapy combined with chemotherapy for LS-SCLC can be performed before chemoradiotherapy. Therefore, we investigated the safety and effectiveness of induction immunochemotherapy followed by concurrent chemoradiotherapy (CCRT) in patients with LS-SCLC, aiming to contribute new insights to the treatment of SCLC.

Methods: A retrospective analysis was conducted on 138 patients with LS-SCLC who received chemoradiotherapy between January 2019 and January 2025. This study included 34 patients receiving induction immunochemotherapy and 104 patients receiving induction chemotherapy. All patients underwent 2-4 cycles of induction therapy before CCRT. Clinical outcomes, including survival and toxicity, were compared between the two groups. Imaging assessments were performed before and 1 month after radiotherapy. The evaluations included the tumor response to induction therapy, treatment-related adverse events, complications during and after CCRT, tumor response after CCRT, progression-free survival (PFS), and overall survival (OS). Follow-up data were collected through regular check-ups or inpatient records. If unavailable, patients were contacted by phone.

Results: Compared to the induction chemotherapy group, the objective response rate (ORR) of tumors after induction treatment in the induction immunochemotherapy group was 67.6% (23/34) versus 45.2% (47/104) (P = 0.023). After CCRT, the ORR in two groups was 79.4% (27/34) versus 60.6% (63/104) (P = 0.045). The median follow-up time was 27.9 months for the induction immunochemotherapy group and 30.3 months for the induction chemotherapy group. The median progression-free survival (PFS) for two groups was 21.3 months versus 13.1 months (P = 0.007), and the median overall survival (OS) was not reached versus 41.7 months (P = 0.031). Treatment-related toxicities of grade 1-2 were 64.7% versus 54.8% (P = 0.311), and grade 3-4 toxicities were 41.2% versus 41.3% (P = 0.986). No grade 5 treatment-related toxicities were observed in either group.

Conclusions: Induction immunochemotherapy followed by CCRT for patients with LS-SCLC is effective and safe with a high ORR, PFS and OS rate, as well as a tolerable toxicity profile. Larger, randomized controlled trials are required to confirm our findings.

Characteristics	Induction immunochemotherapy (n=34)	Induction chemotherapy (n=104)
Best response to induction therapy–n(%)		
CR/PR	23 (67.6)	47 (45.2)
SD	10 (29.4)	53 (51.0)
PD	1 (2.9)	4 (3.8)
Best response to CCRT–n(%)		
CR/PR	27 (79.4)	63 (60.6)
SD	6 (17.6)	34 (32.7)
PD	1 (2.9)	7 (6.7)
The median progression–free survival–months	21.3	13.1
The median overall survival–months	NR	41.7

Keywords: Immunotherapy, Induction treatment, Limited-Stage small cell lung cancer

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.37 Immunotherapy Plus Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Randomized Trials

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Introduction: For patients with limited-stage small cell lung cancer (LS-SCLC) planned for definitive chemoradiotherapy (CRT), the optimal approach of integrating immune checkpoint inhibitors (ICIs) remains uncertain. This study aimed to clarify the overall effect of adding ICIs to CRT in patients with LS-SCLC and evaluate whether this effect varied according to prespecified treatment characteristics.

Methods: Various medical databases were searched to identify randomized controlled trials (RCTs) evaluating the addition of ICIs to CRT in patients with LS-SCLC. Primary outcome was overall survival (OS). The overall pooled effect was estimated using a two-stage, fixed-effect meta-analysis approach. Differences in overall effect based on treatment characteristics were analysed using either between-trial or within-trial interactions, depending on the availability of data. Prespecified treatment characteristics included (1) ICI timing (concurrent with CRT plus consolidation versus consolidation alone), (2) platinum agent (carboplatin versus cisplatin), (3) thoracic radiation schedule (twice daily versus once daily) and (4) use of prophylactic cranial irradiation (PCI). The risk of bias for individual studies was assessed using the Cochrane Risk of Bias 2 tool. This study is registered with PROSPERO (CRD420251020544).

Results: Four eligible RCTs (n = 1,291 participants) were identified. Three RCTs used consolidation ICI alone, while one RCT employed concurrent ICI with CRT followed by consolidation ICI. The overall risk of bias was assessed as low in two published RCTs, and unclear in two others as the evaluation was limited to the conference abstracts. Overall, the meta-analysis showed no significant OS benefit with the addition of ICIs to CRT (hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.76-1.05, P = 0.16, I2 = 43%). However, prespecified subgroup analyses revealed significant effect modification. The relative effect of incorporating ICIs to CRT on OS was more favorable when used as consolidation alone (HR, 0.78, 95% CI 0.63-0.96) compared to concurrent plus consolidation therapy (HR 1.11, 95% CI 0.85-1.45; interaction P = 0.04). Furthermore, carboplatin-based regimen showed a greater OS benefit (HR, 0.68; 95% CI, 0.51-0.90) compared to cisplatin-based regimen (HR, 1.04; 95% CI, 0.82-1.30; interaction P = 0.02). Thoracic radiation dose schedule (twice daily: HR 0.80, 95% CI 0.59-1.07 versus one daily: HR 0.91, 95% CI 0.74-1.10; interaction P = 0.49) and PCI use (PCI: HR 0.90, 95% CI 0.69-1.17 versus no PCI: HR 0.86, 95% CI 0.68-1.09; interaction P = 0.82) did not significantly modify the overall effect.

Conclusions: For patients with LS-SCLC intended for definitive CRT, the optimal integration of ICIs might be most beneficial when two criteria are met: (1) ICIs are administered exclusively as consolidation therapy following completion of CRT, and (2) carboplatin serves as the platinum backbone in CRT. The effect of ICIs was not influenced by the thoracic radiation dose fractionation schedule or the use of PCI. These findings raise hypotheses for optimising treatment strategies in LS-SCLC.

Keywords: Limited-stage small cell lung cancer, Immune checkpoint inhibitors, Meta-analysis

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.38 Real-World Comparison of Carboplatin-Etoposide vs Cisplatin-Etoposide in ES-SCLC

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Introduction: Combination chemoimmunotherapy with either a cisplatin-etoposide (CisE) or carboplatin-etoposide (CarboE) backbone is the established first-line (1L) treatment for extensive stage small cell lung cancer (ES-SCLC). A 2012 meta-analysis of four RCTs showed equivalence in terms of PFS, OS, and ORR with either doublet. A real-world analysis which included patients with both limited and ES-SCLC showed similar findings. A real-world comparison of CisE to CarboE in ES-SCLC has not been done and has treatment implications given the importance of chemotherapy in 1L treatment.

Methods: Patient data was obtained from the Canadian Small Cell Lung Cancer Database (CASCaDe), a Canadian database of patient-level clinicopathologic and treatment data from cancer centres throughout the country. Eligible patients were diagnosed between 2000 - 2022; had ES-SCLC at diagnosis; and received either CisE or CarboE as 1L treatment. Primary outcomes were overall survival (OS) and real-world progression-free survival (rwPFS). Secondary outcomes included: rates of treatment completion and discontinuation due to toxicity; receipt of consolidative radiation therapy (RT); and receipt of second-line (2L) therapy. Survival outcomes were evaluated via Kaplan-Meier (KM) curves, multivariable and inverse propensity score weighted Cox proportional hazards models. Weighting utilized the ATE scheme. Covariates included age, sex, and ECOG at diagnosis.

Results: Of 1339 eligible patients, 553 (41%) were treated with CisE and 786 (59%) with CarboE. Compared to those who received CarboE, patients treated with CisE: were younger (median 64.0 (58.0 to 69.0) years versus 69.0 (63.0 to 74.0) years, p<0.01); had better performance status (ECOG 0-1: 65% CisE versus 51% CarboE, p<0.01); and were less likely to have liver metastases at diagnosis (38% CisE versus 47% CarboE, p<0.01). Median OS was slightly longer with CisE compared to CarboE (8.9 (95% CI: 8.2 - 9.5) versus 7.8 months (95% CI: 7.4 - 8.3), p = 0.004). However, in the multivariate Cox proportional hazards model, type of first-line systemic therapy was not significantly associated with OS (HR=1.06; 95% CI: 0.94-1.20, p = 0.31) after adjustment. Median rwPFS was comparable between the two regimens (5.8 (95% CI: 5.5 - 6.2) months CisE versus 5.1 (95% CI: 4.9 - 5.5) months CarboE, p = 0.04), adjusted HR=1.07; 95% CI: 0.95-1.21, p=0.23. The weight-adjusted model yielded consistent results. Patients who received CisE received more cycles of treatment than those who received CarboE (% receiving > 3 cycles of treatment: 71% CisE versus 61% CarboE, p <0.01) but rates of discontinuation due to progression or toxicity were similar (10% CisE versus 11% CarboE, p=0.05). Rates of consolidative thoracic RT were similar between the two groups (39% CisE versus 45% CarboE, p = 0.21), but patients receiving 1L CisE were more likely to receive 2L therapy (30% CisE versus 22% CarboE, p <0.01).

Conclusions: In this large retrospective study, choice of 1L platinum agent in the treatment of de novo ES-SCLC did not significantly impact OS or rwPFS when controlling for confounders such as age and baseline performance status. Choice of CisE or CarboE should be individualized based on patient and disease characteristics.

Keywords: ES-SCLC, Real World Evidence

EP.13.39 Factors Associated With Refusal of Chemoradiotherapy in Stage I-III Small Cell Lung Cancer and Their Effect on Survival

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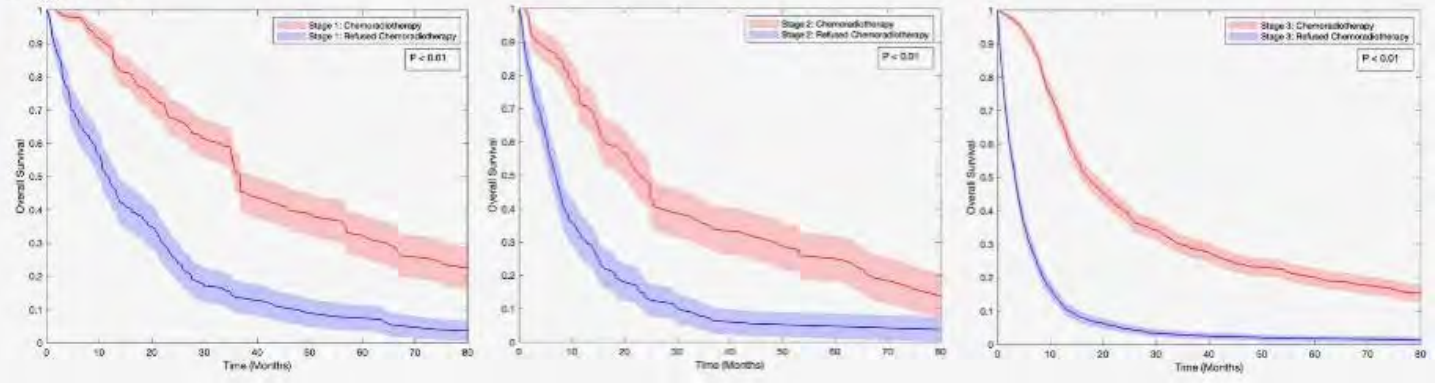
ntroduction: While treatment for small-cell lung cancer (SCLC) is highly dependent on its stage, chemoradiotherapy in stage I-III small-cell lung cancer (SCLC) has been associated with improved survival. Yet, some patients refuse chemoradiotherapy. We examined the factors associated with chemoradiotherapy refusal and its effect on median overall survival (OS).

Methods: The NCDB (National Cancer Database) (2004-2019) was queried for patients in the United States with stage I-III SCLC who were recommended chemoradiotherapy. Patients who underwent chemoradiotherapy were compared to those who refused it. Logistic regression was used to identify predictors of chemoradiotherapy refusal. Propensity scored matching (PSM) was implemented to produce comparable groups in terms of demographics, disease characteristics, and treatment. Kaplan-Meir and Log-Rank analysis were used to determine the effect of chemoradiotherapy refusal on OS. A Cox-Proportional Hazard Model was implemented to investigate factors influencing OS.

Results: Out of 68,764 patients with stage I-III SCLC recommended for chemoradiotherapy, 1,493(2.2%) patients refused it. Factors associated with an increased probability of chemoradiotherapy refusal from the multivariate logistic regression were age 50+ (OR=2.43), female sex (OR=1.19), Charleson Deyo comorbidity score (CDCS) of 1 (OR=1.38) and 2+ (OR=1.89), Medicare insurance (OR=1.81), facility location in the West (OR=1.47), tumor size 2-4cm (OR=1.28) and 4cm+ (OR=1.40), patients agreeing to palliative care (OR=1.41), and surgery refusal (OR=93.84). Factors associated with a decreased probability of chemoradiotherapy refusal was having private insurance (OR=0.52). Kaplan-Meir and Log-Rank analysis of PSM groups showed a decrease in median overall survival in those who refused chemoradiotherapy across all stages (Figure-1): Stage-1 [36.72 vs 11.69 mos. HR=3.67, P<0.01], Stage-2 [22.89 vs 6.89 mos. HR=2.89, P<0.01], and Stage-3 [17.07 vs 3.37 mos. HR=5.65, P<0.01]. On multivariate analysis of survival in patients who refused chemoradiotherapy, factors that were associated with decreased survival were CDCS 1 (HR=1.18) and CDCS2+ (HR=1.49), facility location in Southern (HR=1.20) and Midwestern states (HR=1.31), treatment in non-academic centers (HR=1.01), stage 3 disease (HR=1.94), tumor size 4cm+ (HR=1.60), and surgery refusal (HR=2.73). Factors associated with increased survival were Non-Hispanic Black race (HR=0.57) and median income $50,354-$63,332 (HR=0.84). All variables met statistical significance (P<0.01).

Conclusions: Chemoradiotherapy is associated with improved survival in stage I-III SCLC. Targeted counseling and interventions can help mitigate the identified factors associated with chemoradiotherapy refusal to improve outcomes.

Figure 1:



Keywords: small-cell lung cancer, chemoradiotherapy refusal, survival outcomes

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.40 Trial of Chemotherapy in Patients With Relapsed Small Cell Lung Cancer Combined With Allopurinol and Mycophenolate (CLAMP)

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Introduction: The prognosis for patients with extensive stage small cell lung cancer (ES-SCLC) who progress on front-line chemoimmunotherapy is poor. Relapsed SCLC frequently upregulates MYC expression and guanosine biosynthesis through the inosine monophosphate dehydrogenase enzymes (IMPDH1 and 2). Pre-clinical data suggests a potential synergistic effect of IMPDH inhibition when combined with chemotherapy. Mycophenolate mofetil (MMF) directly inhibits purine synthesis via IMPDH inhibition and allopurinol limits purine salvage via inhibition of xanthine oxidase. In this phase I trial, we evaluated the safety and efficacy of irinotecan in combination with MMF and allopurinol in relapsed SCLC.

Methods: In this single-center phase I study, patients with previously treated ES-SCLC who had progressed on prior chemoimmunotherapy were enrolled. A 3 + 3 dose de-escalation design was used. Irinotecan was administered on days 1 and 8 of a 21-day cycle while MMF and allopurinol were given daily. The doses of irinotecan, MMF, and allopurinol respectively at various dose levels (DL) were as follows: DL1 (100 mg/m2, 1 g TID and 300 mg/day), DL0 (80 mg/m2, 0.5 g TID, and 200 mg/day), and DL-1 (60 mg/m2, 0.5 g BID, and 100 mg/day). Key objectives were to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and antitumor activity using RECIST 1.1.

Results: From 3/1/2023 to 8/6/24, 28 patients were screened for eligibility, and 17 patients were enrolled. Twelve of 17 patients (71%) were female, 7 (41%) had brain metastases at baseline, 13 (76%) had a platinum-free interval of <180 days prior to progression, and the median number of prior therapies was 1 (range 1 - 5). All patients had an adverse event (AE) at least possibly related to treatment (TRAE), most commonly anemia and diarrhea occurring in 12 patients (70%). Grade 3 or higher TRAEs occurred in 12 (70%) patients, including 3 (18%) patients with G3+ lymphopenia and 2 (12%) patients each with G3+ diarrhea, neutropenia, and hypokalemia. There were no G5 TRAEs; 5 (29%) of patients discontinued treatment due to TRAE or intolerance, most commonly diarrhea. A protocol amendment was created after the first 6 patients were enrolled (due to 4 patients requiring dose reduction and 1 discontinuation) to lower the irinotecan dose to 90 mg/m2 (DL1a). Six patients were enrolled at DL1, 5 at DL1a, 3 at DL0, and 3 at DL-1. Two DLTs occurred at DL0 (G3 hypokalemia and G3 diarrhea), and the study was subsequently discontinued due to overall poor tolerance at DL-1, without identification of the MTD. One (6%) patient had a complete response, and 6 (35%) patients had a partial response, with an overall response rate of 41%. The disease control rate was 71%, and the median progression free survival of 2.7 months (95% CI 1.3 - 4.4 mo).

Conclusions: Despite the preliminary evidence of encouraging activity, the combination of irinotecan, MMF, and allopurinol in patients with relapsed ES-SCLC was associated with increased toxicity, most commonly diarrhea. Future studies should explore a more tolerable cytotoxic drug to synergize with inhibitors of purine metabolism.

Keywords: small cell lung cancer, phase 1, clinical trial

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.41 Expression of PD-L1 and Alternative Immune Checkpoints (ICs) and Their Impact on Outcomes in Small Cell Lung Cancer (SCLC)

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Introduction: SCLC is an aggressive malignancy with rapid growth and poor prognosis. Recent molecular profiling has highlighted the potential role of IC genes (PD-L1, B7-H3, B7x, and HHLA2) in the treatment of lung cancer, although the relationship between their expression and patient outcomes in aggressive SCLC remains unclear. This study aims to evaluate the expression of these ICs across various SCLC subtypes and their link to clinical outcomes.

Methods: NextGen sequencing of DNA (592-gene/whole exome) and RNA [(whole transcriptome sequencing (WTS)) were performed for 2,187 SCLC samples at Caris Life Sciences. PD-L1 expression was assessed by IHC (22C3 assay, +: TPS ≥1%). RNA expression of IC genes was evaluated across SCLC molecular subtypes (ASCL1, A; POU2F3, P; NEUROD1, N; and inflamed, I) and specimen sites. Insurance claims data were to calculate overall survival (OS) and time on treatment (TOT, from initiation of immunotherapy (IO) to cessation). Cox models and log rank test were used to calculate HR and statistical significance, respectively.

Results: PD-L1 IHC positive tumors had a median PD-L1 gene expression of 6.9 transcript per million (TPM), compared to 4.6 TPM in PD-L1 negative cases (p<0.05). Immune cell fractions positively correlated with the expression of PD-L1 and alternative IC genes. Table 1 summarizes gene expression across the molecular subtypes of SCLC. SCLC-P subtype had the lowest frequency of PD-L1 positivity, while the highest was observed in SCLC-I (26.5% vs 52.1%, p=0.07). Compared to lung-derived samples, lymph node metastases had lower B7-H3 (16.5 vs. 20.8 TPM, p<0.05) and reduced PD-L1 positivity (32.2% vs. 43.3%, p<0.05). Higher PD-L1 expression was associated with improved OS from time of biopsy until last contact/death, at both RNA (HR 1.59, 95% CI: 1.337-1.894, p<0.001) and IHC protein levels (HR 1.49, p<0.001). Similarly, patients with higher PD-L1 expression had better OS from the start of IO, at both RNA (HR 1.52, p<0.001) and IHC (HR 1.38; p=0.003). No significant survival differences were associated with B7x, HHLA2, or B7-H3 expression.

Conclusions: These data suggest a potential impact of PD-L1 expression in SCLC, particularly its association with improved OS following immunotherapy. Gene expression by WTS has clinical utility independent of IHC. These findings provide valuable insights into the molecular landscape of SCLC and the differential expression of ICs across different subtypes. Further studies are needed to explore the broader implications of ICs expression in the management of SCLC.

Table 1: Expression of ICs Across Molecular Subtypes of SCLC and their association with OS and TOT.

	PD-L1		B7-H3		B7x		HHLA2		Statistically significant results **vs other subtypes** (*P<0.05)
	% Positive by IHC	TPM by WTS	TPM by WTS		TPM by WTS		TPM by WTS		
SCLC-A	43.8	3.1	13.6*		0.5		1.2		*high B7-H3
SCLC-P	26.5	3.3	9.8*		1.9*		1.4		*low B7-H3, high B7x
SCLC-N	34.1	2.4*	12.7		0.5		1.0		*low PD-L1
SCLC-I	52.1	3.8*	14.7*		0.7		1.1		*high PD-L1 and B7-H3
	HR	p	HR	p	HR	p	HR	p	HR	p	
OS (from start of IO)	1.38	**0.003**	1.52	**<0.001**	1.27	0.06	0.84	0.17	1.07	0.63	
TOT	1.12	0.21	1.32	0.013	0.97	0.76	0.85	0.16	0.99	0.93	

Keywords: Small Cell Lung Cancer, Immunotherapy, Alternative Immune Checkpoints

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.42 Self-Oxygenating PROTAC Microneedles for Spatiotemporally-Tunable Protein Degradation and Enhanced Small Cell Lung Cancer Therapy

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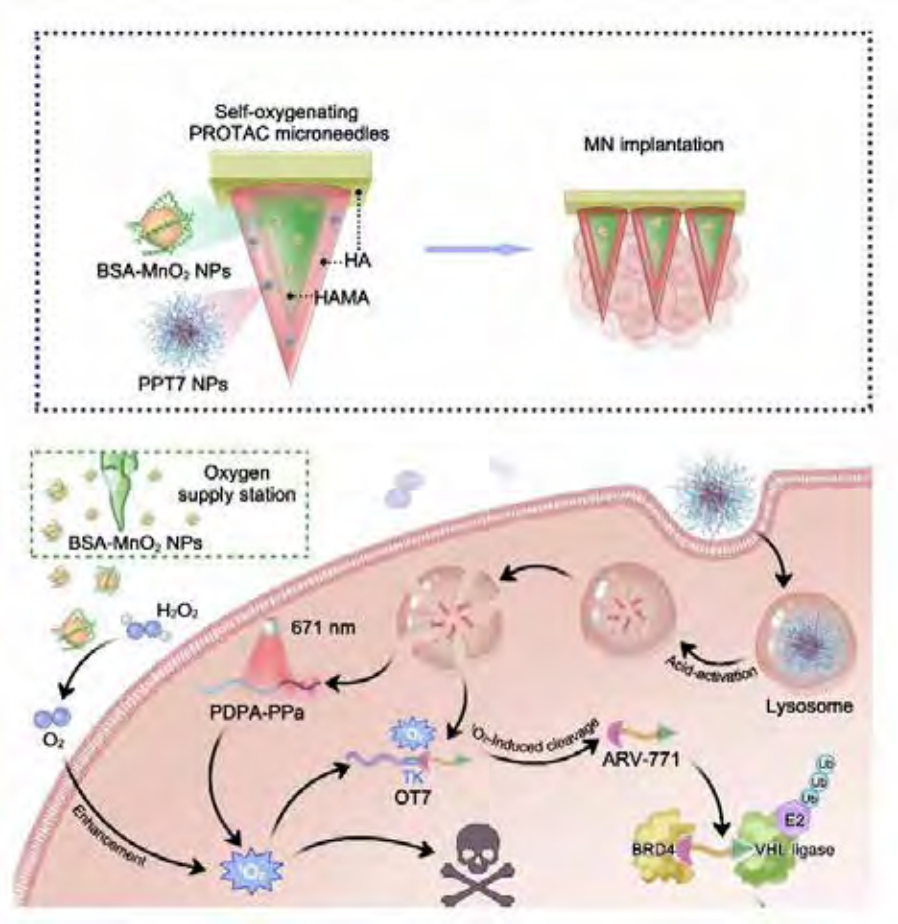
Introduction: Small cell lung cancer (SCLC) characterized by its invasive and infiltrative growth, presents significant challenges for clinical therapy. Proteolysis Targeting Chimera (PROTAC) shows promise in SCLC therapy by diminishing targeted proteins traditionally resistant to small molecular inhibitors. Yet, their effectiveness is limited by the tumor resistance and lack of tumor specificity.

Methods: We innovatively engineered a double-layered microneedle (MN) patch by integrating acid and ROS dual-activatable PROTAC nanoparticles and self-oxygenating BSA-MnO2 nanoparticles into one nanoplatform to overcome the tumor resistance. The microneedle patch were administrated locally at the tumor site to penetrate the tumor and enhance photodynamic therapy (PDT), thus precisely induced bromodomain and extraterminal protein 4 (BRD4) degradation for effective tumor eradication.

Results: Upon administration, the outer layer of the microneedle swiftly releases the PROTAC nanoparticles quickly, which can be specifically activated in the intracellular acidic environment of tumor cells for performing PDT and restored PROTAC prodrug for precise BRD4 degradation. Simultaneously, the BSA-MnO2 nanoparticles loaded inside the inner layer of the MNs acted as an oxygen supply station to counteract tumor hypoxia, and thus promoted PDT and PROTAC activation. This PROTAC-delivered MNs significantly inhibited tumor growth in both subcutaneous and orthotopic SCLC tumor models.

Conclusions: Self-oxygenating PROTAC MNs successfully circumvented the tumor tissue, inducing enhanced BRD4 degradation and PDT for SCLC treatment. This multifunctional MNs might provide a robust nanoplatform for precise protein degradation and highly efficient SCLC therapy.



Keywords: Small cell lung cancer, Proteolysis Targeting Chimera treatment, Microneedle

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP.13.43 The Prognostic Factors Related With the Organ Spesific Metastasis on Survival in ES-SCLC; TROD 08-16 Study

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Introduction: We aimed to assess prognostic factors and the effect of initial location of distant metastases on overall survival (OS) in extensive-stage small cell lung cancer and to compare the results of results with the predictions from Wu et al.'s nomogram based on SEER data.

Methods: A multicenter retrospective analysis comprised 579 patients with metastatic ES-SCLC identified between 2001 and 2023. The data of 9 centers are evaluated. Survival rates were assessed using the Kaplan-Meier method, and prognostic factors were analyzed using Cox regression and Mann-Whitney U tests. Estimated OS rates were calculated utilizing the nomogram developed by Wu et al.

Results: All of the patients had 4-6 courses of chemotherapy, 20 had maintenance atezolizumab. Thoracic radiotherapy (TRT) was administered to 416 (71,8%) patients, while prophilactic cranial radiotherapy (PCI) was performed on 241 (41,6%) patients. Among 579 patients at diagnosis: 302 had bone, 171 had liver, 134 had adrenal, 102 had pleural, 66 had contralateral lung, 164 had brain and 125 had other metastasis. The median OS was 11 months (0-103). 6 months, 1 year, and 2 years OS were 48%, 24%, and 2%, respectively. While patients with brain metastases (p=0.036) has improved survival, liver metastases (p=0.003), bone metastases (p=0.001), pleural metastases (p=0.002), and ECOG performance level (p=0.001) were all significantly related to lower survival in univariate analysis. Additionally, the number of metastases, TRT (p=0.000), PCI (p=0.003), atezolizumab treatment(p=0.038), smoking, marriage, gender, and T and N stages all had an effect on OS. Multivariate studies revealed that pleural metastases (HR:1,41(1,13-1,76)p:0,002), liver metastases (HR:1,41 (1,16-1,7) p:0,001), and ECOG performance status (HR:1,92 (1,12-3,28) p:0,016) were all detrimental prognostic factors. Furhtermore the risk of death is 1,79 (p:0,001) times higher in patients who do not recieve TRT , while the risk of death increases 1,97(p:0,001) times higher in patients who do not recieve PCI. When we compare the predictions of Wu et al.'s nomogram; the results of our data were similar for the patients with liver, bone and brain metastases .

Conclusions: Liver, bone, pleural metastases negatively affected OS in patients with ES-SCLC. TRT and the administration of more than 30 Gy doses demonstrated a positive impact on OS. Moreover, TRT, Atezolizumab treatment, and PCI have survival advantages of 7, 7, and 9 months, respectively. Survival rates of our cohort with liver, bone and brain is correlated with the nomogram of Wu et al..

Keywords: Small cell lung cancer, Metastasis, Radiotherapy

EP.13.44 Real-World Treatment Patterns and Clinical Outcomes in Patients With Metastatic Neuroendocrine Neoplasms of the Lung (NEN-L)

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Introduction: NEN-L is a type of lung cancer originating from pulmonary neuroendocrine cells. One subtype of NEN-L is large-cell neuroendocrine carcinoma of the lung (LCNEC), a rare, aggressive disease with a poor prognosis. Due to disease rarity and heterogeneity, there is no consensus on standard of care for metastatic LCNEC. This study aims to evaluate real-world treatment patterns and clinical outcomes in a sample of patients with metastatic NEN-L in which most patients were expected to have LCNEC with some typical and atypical carcinoid cases.

Methods: This retrospective cohort study used the US-based, electronic health record-derived deidentified Flatiron Health Research Database. Included patients had a chart-confirmed diagnosis of metastatic NEN-L (excluding small-cell lung cancer, a subtype of NEN-L) between October 1, 2018, and April 1, 2023, and initiated systemic anticancer treatment. The index event was the initiation of first-line (1L) treatment. Summary statistics were generated for demographics, baseline clinical characteristics, and treatment patterns. Real-world time to next treatment (rwTTNT) by line of therapy (LOT) was estimated by the Kaplan-Meier method. Analyses were conducted in the overall study population and stratified by LOT (1L, 2L, and 3L), treatment class, and disease stage at initial diagnosis.

Results: At database cutoff (March 31, 2024), 154 patients with metastatic NEN-L were included in the analysis. Patients had a median age of 68 years at 1L treatment initiation, 53.9% were female, and 65.6% had an ECOG PS of 0/1. Median follow-up duration was 8.4 (interquartile range, 3.1-17.1) months. Regardless of disease stage at initial diagnosis, platinum-based chemotherapy (either alone or with an immune checkpoint inhibitor [ICI]) was the most common 1L treatment, while "other" treatment options including mostly nonplatinum chemotherapy drugs were most common for subsequent LOTs (Table). Following 1L treatment, 49.4% and 22.7% of patients initiated 2L and 3L treatment, respectively. Median rwTTNT (95% CI) was 5.3 (4.1-6.4) months for 1L treatment, 5.0 (3.5-7.1) months for 2L treatment, and 4.0 (3.3-10.0) months for 3L treatment.

Conclusions: Patients with metastatic NEN-L were primarily treated with platinum-based chemotherapy with or without ICIs as the frontline treatment. In 2L and beyond, diverse treatment options were used, most of which included nonplatinum chemotherapy drugs. The heterogeneity in treatment strategies is accompanied by suboptimal clinical outcomes across LOTs. These results suggest there is a high unmet need among patients with metastatic NEN-L, including LCNEC.

	Overall
1L treatment patterns, n	154
Median time from metastatic diagnosis to 1L treatment initiation (interquartile range), mo	1.3 (0.7–2.5)
Treatment ongoing at database cutoff, n (%)	9 (5.8)
Therapy class, n (%)	
ICI therapy only	16 (10.4)
Somatostatin-analogue or everolimus monotherapy	37 (24.0)
Platinum-based chemotherapy + ICI	54 (35.1)
Platinum-based chemotherapy	29 (18.8)
Other therapies	18 (11.7)
2L treatment patterns, n	76
Median time from 1L to 2L treatment initiation (interquartile range), mo	4.1 (2.7–7.0)
Treatment ongoing at database cutoff, n (%)	7 (9.2)
Therapy class, n (%)	
ICI therapy only	10 (13.2)
Somatostatin-analogue or everolimus monotherapy	14 (18.4)
Platinum-based chemotherapy + ICI	13 (17.1)
Platinum-based chemotherapy	9 (11.8)
Other therapies	30 (39.5)
3L treatment patterns, n	35
Median time from 2L to 3L treatment initiation (interquartile range), mo	5.3 (3.0–9.0)
Treatment ongoing at database cutoff, n (%)	4 (11.4)
Therapy class, n (%)	
ICI therapy only	4 (11.4)
Somatostatin-analogue or everolimus monotherapy	3 (8.6)
Platinum-based chemotherapy + ICI	3 (8.6)
Platinum-based chemotherapy	2 (5.7)
Other therapies	23 (65.7)

Keywords: Retrospective cohort, metastatic neuroendocrine neoplasms of the lung, real-world outcomes

EP.13.45 Efficacy and Prognostic Significance of Immunotherapy in Postoperative Recurrent and Advanced Large Cell Neuroendocrine Carcinoma

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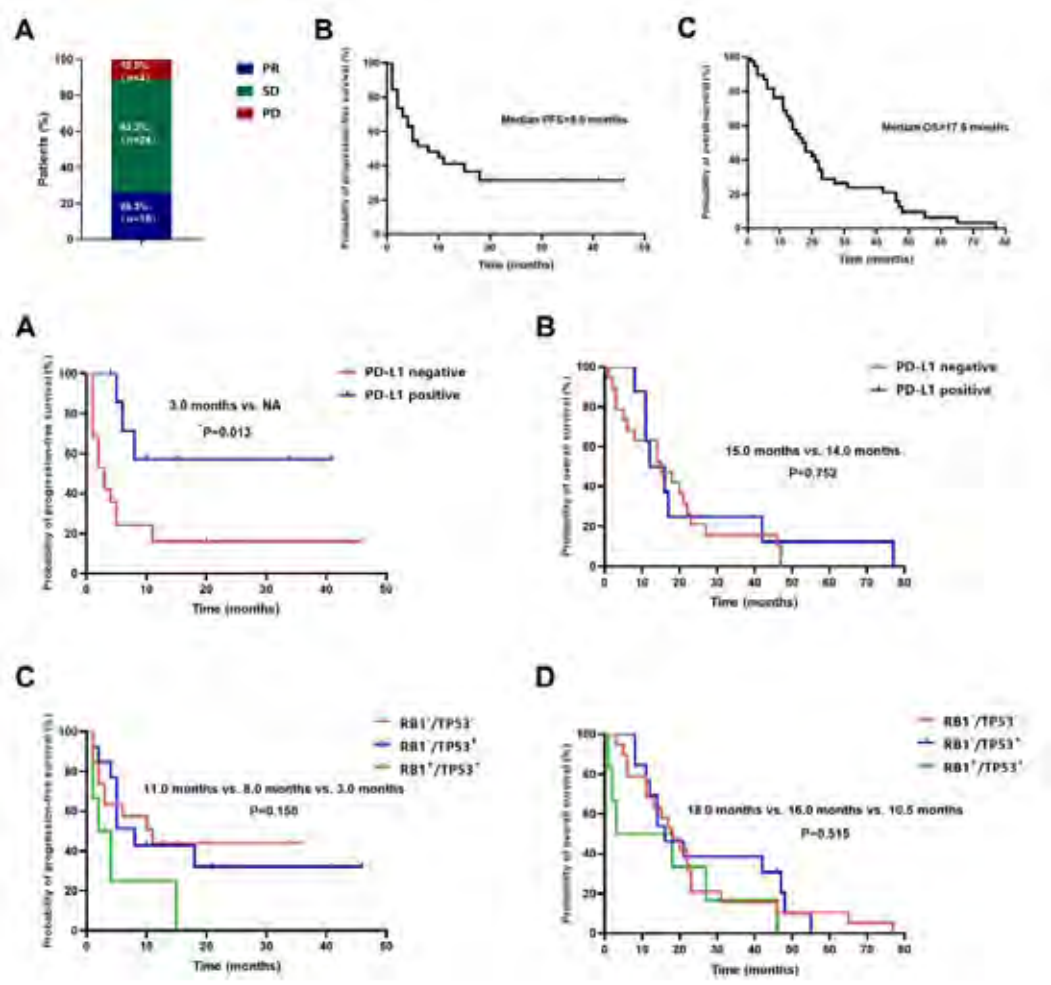
Introduction: Large cell neuroendocrine carcinoma (LCNEC), representing 2-3% of primary lung cancers, is characterized by aggressive behavior and dismal prognosis. While immune checkpoint inhibitors have transformed outcomes in advanced non-small cell lung cancer (NSCLC), therapeutic standards for LCNEC remain undefined, with limited evidence supporting immunotherapy in this rare histologic subtype.

Methods: This retrospective analysis included 47 patients with postoperative recurrent or advanced LCNEC diagnosed between 2018-2024 from a cohort of 526 lung cancer cases. Clinical parameters including treatment line, PD-L1 expression, RB1/TP53 mutational status, and histologic combinations were analyzed for associations with progression-free survival (PFS) and overall survival (OS). Immunotherapy regimens encompassed PD-1/PD-L1 inhibitors as monotherapy or combined with chemotherapy.

Results: Among 38 immunotherapy-treated patients, the objective response rate (ORR) was 89.5% with median progression-free survival (mPFS) of 8.0 months, and median overall survival (mOS) of 17.5 months. First-line immunotherapy demonstrated superior efficacy compared to later-line therapy, significantly prolonging mPFS (15.0 vs. 5.0 months, p=0.038). PD-L1-positive tumors (≥1% tumor proportion score) exhibited markedly improved mPFS compared to PD-L1-negative counterparts (not reached vs. 3.0 months, p=0.013). Patients with combined LCNEC-NSCLC histology derived substantial survival benefits from immunotherapy, showing significantly extended mOS versus non-combined subtypes (19.0 vs. 8.0 months, p=0.0004). While not statistically significant, wild-type RB1/TP53 tumors trended toward improved survival outcomes compared to mutant variants (mPFS: 11.0 vs. 8.0 vs. 3.0 months, p=0.150; mOS: 18.0 vs. 16.0 vs. 10.5 months, p=0.515).

Conclusions: First-line immunotherapy demonstrates clinically meaningful efficacy in advanced LCNEC, particularly in PD-L1-positive tumors and combined histology subtypes. While RB1/TP53 wild-type status showed favorable trends, larger cohorts are needed to validate genetic predictors. These findings support prioritization of PD-1/PD-L1 inhibitors in the frontline setting for this aggressive malignancy.



Keywords: Large cell neuroendocrine carcinoma, Immunotherapy, PD-L1

EP.13.46 Novel Prognostic Markers in Pulmonary Neuroendocrine Tumors (Carcinoid Tumors)

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Introduction: Pulmonary neuroendocrine tumors include Typical (TC) and Atypical(AC) carcinoids, classified based on mitotic count and presence/absence of necrosis. However, this classification remains subjective and often fails to accurately predict recurrence risk or guide surveillance. Unlike gastrointestinal and pancreatic NETs, Ki-67 labeling index is not part of pulmonary carcinoid grading due to lack of consensus on cut-offs. Recent molecular studies (Laddha et al., 2019; Alcala et al., 2019) have identified transcriptomic subgroups with distinct prognostic outcomes. These are defined by expression of markers like OTP, S100, CD1a, CD44, and ASCL1. We hypothesize that immunohistochemistry (IHC)-based stratification using selected markers may correlate with proliferation indices and histologic grade, thereby providing additional prognostic value.

Methods: An ambispective study(2013-2024) was conducted using the tissue microarray. Formalin-fixed paraffin-embedded pulmonary carcinoid samples were used for IHC using primary antibodies against OTP, S100, CD1a, CD44 and ASCL1. Each case was classified per the 2021 WHO criteria into TC or AC. Ki-67 labeling index and mitotic counts were recorded. Correlation analyses (Spearman's rho, Mann-Whitney U tests) were performed between IHC expression, Ki-67, mitotic index, and histological subtype.

Results: Among TC(n=42), OTP is positive in 88.1% cases, S100 is positive in 9.5%,CD44 is strongly positive in 88.1%, CD1a is strongly positive in 7.1% and ASCL1 is negative in all cases. S100 and CD44 showed negative correlation with ki-67, with spearman's rho -0.089 and -0.116 respectively. OTP and CD1a showed weak positive correlation and ASCL1 is unanalyzable due to no variation in data. With mitotic index, S100 and CD1a showed very weak positive correlation and OTP, ASCL1 being unanalyzable due to no variation in data.Among AC(n=11), OTP is positive in 100% cases, S100 is positive in 18%, CD44 is strongly positive in 82%, CD1a is strongly positive in 9% and ASCL1 is negative in all cases. There is moderate positive correlation between mitotic figures and the ki-67 index with S100 but statistically insignificant. No other correlations found due to no variability of data pertaining to other biomarkers.OTP is diffusely expressed in NETs, irrespective of grade showing a good diagnostic value. Although CD44 and S100 correlated with a lower proliferation index, they are not statistically significant from this study limited by sample size.

Conclusions: Our study tried to depict the utility of using IHC biomarkers- OTP, S100,CD44, CD1a and ASCL1 for effective subgrouping of carcinoids. S100 and CD44 showed negative correlation with ki-67 in TC, although statistically not significant, limited by small sample size. OTP and ASCL1 have come out to be independent prognostic markers irrespective of WHO classification. Future evaluations with a larger sample size and detailed survival analysis may aid in better subclassifying carcinoids in cases with ambiguous mitotic counts and assessing prognostic values improving management strategies.

Keywords: Biomarkers, Immunohistochemistry, Pulmonary NETs

EP.13.47 The Subtle Signals of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH): A Clinical Characterization

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Introduction: Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is an underdiagnosed, indolent, pre-malignant pulmonary disease that presents as dyspnea and non-productive cough. Mosaicism and bilateral pulmonary nodules are seen on imaging, and pulmonary function tests (PFTs) show obstructive lung disease. Data guiding clinical management is limited, but treatment typically includes inhalers plus somatostatin analogues or everolimus. Symptom progression can result in a decline of quality of life; thus, better understanding of its pathogenesis and prognosis is needed.

Methods: This IRB-approved retrospective cohort study identified 34 patients with DIPNECH at two institutions (MGH, UCMC). DIPNECH diagnoses were confirmed by histologic or radiologic evidence plus clinician evaluation. Baseline characteristics and clinical outcomes were collected; symptom grading was per CTCAE v5.0 guidelines.

Results: Most patients were elderly (median age 69), white (82%), and never smokers (65%) (Table 1). Baseline symptoms included dyspnea (56%) and cough (56%) in most patients. Most patients had normal or restrictive (32%) PFTs at baseline and did not participate in pulmonary rehabilitation. On imaging, the majority had bilateral pulmonary nodules (97%) and mosaic attenuation (65%). Half of patients had biopsy-proven DIPNECH versus clinical diagnosis. Twenty-one patients (62%) had concurrent carcinoid tumors.

Table 1: Baseline Characteristics

Characteristic	All patients (n=34) # (% of pts)
Median age at diagnosis (range)	69 (41-89)
Race	
White	28 (82%)
Black	5 (15%)
Asian	1 (3%)
History of smoking	
Never	22 (65%)
Former	11 (32%)
Current	1 (3%)
Median pack-years among smokers (range)	17 (1.25-50)
Baseline symptoms	
Asymptomatic	21 (7%)
Dyspneu	
Grade 1	10 (29%)
Grade 2	7 (21%)
Grade 3	2 (6%)
Cough	
Grade 1	8 (24%)
Grade 2	11 (35%)
Baseline FEV1/FVC ratio	
>70%	11 (32%)
≤70%	4 (12%)
Pulmonary rehab	
Yes	5 (15%)
No	29 (85%)
Bilateral Pulm Nodules on CT	
Yes	33 (97%)
No	1 (3%)
Mosaic attenuation on CT	
Yes	22 (65%)
No	12 (35%)
Biopsy-proven DIPNECH	
Yes	17 (50%)
No	17 (50%)
Carcinoid Tumor Present	
Yes	21 (62%)
No	13 (38%)
Type of Carcinoid[1]	
Typical	16 (76%)
Atypical	3 (14%)
NOS	3 (14%)
Dotatate scan	
Yes	7 (34%)
No	27 (66%)
Dotatate with avidity of nodule	
Yes	3 (43%)
No	4 57%)

[1] patient had an atypical and NOS carcinoid tumor

While 23 patients were observed without intervention, 10 were treated with octreotide alone and one with octreotide and everolimus (Table 2). Among those treated, 9 patients (82%) reported symptomatic improvement. Common side effects from octreotide were gastrointestinal-related; one patient developed stomatitis from everolimus. Four patients stopped treatment. Co-management with pulmonology occurred for 23 patients. Additional supportive care included opioids (n=2) and supplemental oxygen (n=5).

Table 2. Treatment Characteristics

Characteristic	All patients (n=34) # (% of pts)
Observation	23 (67%)
Treatment[1]	11 (33%)
Octreotide	11 (33%)
Everolimus	1 (3%)
Symptomatic improvement w/ treatment	
Yes	9 (81%)
No	2 (19%)
Octreotide adverse effects	
None	6 (55%)
Grade 1 nausea, abdominal pain, or diarrhea	4 (80%)
Grade 1 pruritus	1 (20%)
Grade 2 fatigue	1 (20%)
Grade 3 hypertension	1 (20%)
Everolimus adverse effects	
Grade 2 stomatitis	1 (100%)
Stopped octreotide/everolimus	
Yes	4 (36%)
No	7 (64%)
Concurrent pulmonary management	
Yes	23 (68%)
No	11 (32%)
Inhalers used	
SABA	13 (38%)
ICS/LABA	10 (29%)
LABA/LAMA	4 (12%)
LAMA	4 (12%)
ICS.LABA/LAMA	3 (9%)
SAMA	1 (3%)
Opioids used	
Yes	2 (6%)
No	32 (94%)
Supplemental oxygen	
Yes	5 (15%)
No	29 (85%)
Deceased	
Yes	3 (9%)
No	31 (91%)

Legend: SABA=short-acting beta agonist; ICS=inhaled corticosteroid; LABA=long-acting beta agonist; LAMA=long-acting muscarinic antagonist; SAMA=short-acting muscarinic antagonist
[1]1 received treatment with sequential octreotide and everolimus, respectively.

Conclusions: DIPNECH is a rare, underdiagnosed and likely undertreated condition for which consensus guidelines and highly effective treatment options are lacking. Patients with DIPNECH benefit from comprehensive evaluation and multi-disciplinary management, and future standardization of diagnostic and therapeutic approach to this disease is needed.

Keywords: DIPNECH, Neuroendocrine Tumor

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP13.48 Natural Killer (NK) Cell Heterogeneity in Small Cell Lung Cancer: Implications for Chemo-Immunotherapy Response

Chemo-Immunotherapy Response

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Introduction: Small cell lung cancer (SCLC) is an aggressive cancer treated with chemo-immunotherapy, but responses vary. Recent data indicate an "inflamed" SCLC subtype shows improved immunotherapy outcomes, suggesting a role for innate immunity, particularly NK cells. Recently, Rebuffet et al. (Nature Immunology, 2024) identified three prominent NK cell subsets in human blood: NK1, NK2 and NK3, further differentiated into six distinct subgroups. This study investigates differential transcriptional profiles of NK cells from SCLC patients undergoing chemo-immunotherapy, classified as Best Responders (BR) or Non-responders (NR), based on progression-free survival (PFS). It further explores the impact of sequential treatment with cisplatin and a DNA damage repair inhibitor (DNA-PKi) on NK cells, aiming to understand NK cell function in mediating therapeutic efficacy.

Methods: Blood samples were collected from SCLC patients (n=20) at baseline and after chemo-immunotherapy. NK cells were isolated using a Miltenyi NK cell Isolation kit and FACS sorting. Total RNA was extracted for bulk RNA-seq analysis. FACS was used to characterize NK cells subsets. In vitro experiments involved treating NK cells with cisplatin, followed by DNA-PKi for 24 hours. Quantitative RT-PCR was performed to measure the expression of innate immune signaling molecules, and cytotoxicity assays using the SCLC cell lines were conducted using an LDH assay.

Results: Transcriptomic profiling revealed 1,621 downregulated genes in NR NK cells and 1,836 upregulated genes in BR NK cells. Gene Set Enrichment Analysis (GSEA) showed significant upregulation of IFN-related pathways and enrichment in lung proliferating NK cells and DNA repair pathways in BR NK cells. BR patients exhibited increased expression of genes associated with the NK3 phenotype and upregulation of NK1B subtype-related genes. ISMARA analysis demonstrated a higher presence of the IRF3-binding motif in BR NK cells. Treatment with cisplatin alone did not alter the transcriptomic landscape of NR NK cells but induced significant changes in BR NK cells. Sequential treatment with cisplatin and DNA-PKi led to an increase in NK3 and NK1B subtypes in BR patients, while NR patients showed a predominance of the NK intermediate (NKint) subtype. Quantitative RT-PCR revealed upregulation of innate immune signaling molecules (STING, MAVS, CCL5, CXCL10) in BR NK cells following sequential treatment. LDH assay results showed that BR NK cells exhibited higher baseline cytotoxicity against SCLC cells. Sequential treatment enhanced cytotoxicity in both NR and BR NK cells, with BR cells showing superior performance.

Conclusions: The study highlights the importance of understanding NK cells heterogeneity in SCLC, showing a differential response of NK cells from BR and NR SCLC patients to chemo-immunotherapy and sequential cisplatin/DNA-PKi treatment. BR patients' NK cells demonstrated a shift towards more cytotoxic subtypes (NK3 and NK1B) and enhanced immune functionality, contributing to improved treatment outcomes. Finally, the activation of innate immune signaling pathways in BR patients' NK cells suggests potential mechanisms for enhanced therapeutic efficacy.

Keywords: SCLC, Chemotherapy, NK cells

EP.13 SMALL CELL LUNG CANCER AND NEUROENDOCRINE TUMORS

EP13.49 Prognosis of Perioperative Therapy in Primary Limited-Stage Small-Cell Lung Cancer

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Introduction: For limited-stage SCLC (LS-SCLC), synchronous chemoradiotherapy is the recommended treatment options,as surgical resection was only recommended for I-IIA SCLC. However, the majority of these patients experience tumor recurrence or metastasis rapidly. Immunotherapy has achieved good efficacy in extensive-stage SCLC and improved survival in resected non-SCLC. Simultaneously, the use of neoadjuvant immunotherapy in limited- stage SCLC is still unknown but promising.

Methods: Patients diagnosed with LS-SCLC spanning stage I to IIIB who underwent surgical resection at our center were included from May 2015 to July 2025. Survival outcomes were identified in patients received neoadjuvant treatment and adjuvant treatment. Meanwhile, Comprehensive analyses encompassed pathological response [major pathological response (MPR) and pathological complete remission (pCR)], downstaging rate, event free survival (EFS) and treatment-related adverse events (trAEs) were compared in neoadjuvant immunotherapy and chemotherapy patients.

Results: A total of 204 surgical resected SCLC with stage I-IIIB were included in the study, 175(85.8%) patients treated with adjuvant therapy and 29(14.2%) received neoadjuvant therapy. Compared to patients underwent adjuvant therapy, neoadjuvant was associated with longer median overall survival (mOS) (42 months vs Not reach(NR), HR=2.03, P=0.02). Among the 29 neoadjuvant patients, 51.7%(N=15) received immunotherapy and 48.3%(N=14) received chemotherapy. The pCR and MPR of the immunochemotherapy group both were significantly higher than those in chemotherapy group (57.1% vs 0%, P<0.001 and 71.4% vs 20% , P=0.009). 22(75.8%) neoadjuvant patients with lymph node metastasis (N+) at baseline. Downstaging of T and N occurred in 14 (100%) and 9(81.8%) patients in the immunochemotherapy group, respectively, which were also higher than ones in chemotherapy group (66.6%, P=0.042 and 18.2%, P=0.009). Meanwhile, the median EFS of the immunochemotherapy group was not reach, which was 19.1months (P=0.302, HR=2.03). There was no significant difference in the incidence of trAEs between the immunochemotherapy group and the chemotherapy group.

Conclusions: For patients with LC-SCLC, neoadjuvant therapy was associated with improved survival than adjuvant therapy, especially for those with neoadjuvant immunochemotherapy. Compared to neoadjuvant chemotherapy, neoadjuvant immunochemotherapy was related to significantly higher pathological response and can produce significant downstaging to increase the possibility of surgery with similar safety. Therefore, neoadjuvant immunotherapy might be a promising treatment modality for resectable SCLC.

Keywords: Small cell lung cancer, Neoadjuvant systemic therapy, immunotherapy

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.01 Chemotherapy Plus Bevacizumab and Immunotherapy Prolonged the Survival of Unresectable Malignant Mesothelioma Patients in First-Line

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Introduction: Malignant pleural mesothelioma (MPM) is a kind of rare malignant thoracic tumor with poor prognosis. Pemetrexed-platinum regimen with or without bevacizumab regimen and immunotherapy with nivolumab and ipilimumab are currently standard first-line therapies for MPM patients who are medically inoperable. Recently, a phase III study revealed that pemetrexed-platinum-bevacizumab plus atezolizumab prolonged the progression-free survival (PFS), while it did not translate into overall survival (OS) benefit. So far there are few studies explored the efficacy of chemotherapy combined with bevacizumab and immune checkpoint inhibitors in the real-world cohort.

Methods: We retrospectively analyzed unresectable MPM patients who were administered with standard pemetrexed-platinum chemotherapy with or without angiogenesis inhibitors and immunotherapy in first-line treatment. Patients' baseline demographic characteristics, survival time and adverse events (AEs) during treatment were collected. We then divided the enrolled patients into three groups: group A was defined as patients received first-line chemotherapy alone; group B, chemotherapy plus bevacizumab; group C, chemotherapy plus angiogenesis inhibitors and immunotherapy. Kaplan-Meier methodology was used to compare survival difference among three groups.

Results: 128 patients were enrolled between January 2010 and September 2024 with a median age of 59.5 years. The cohort was predominantly male (78 out of 128, 60.9%) and the median follow-up was 37.3 months. 95.3% had ECOG performance status 0-1. Epithelioid histology was the most frequently reported histological subtype (55 of 128; 43.0%), 7.8% had sarcomatoid histology, 4.7% had biphasic histology, the other 44.5% were unknown. 46 out of 128 had distant metastasis, while 35.9% patients were confined to the thoracic cavity. Both group B and group C showed a better PFS compared with group A (median PFS, group A 8.6 months [5.7-11.7], group B 9.7 months [7.4-12.0], group C 16.4 months [7.0-25.7]; p=0.101). There were no significant differences in OS among the 3 groups (median OS, group A 24.9 months [16.3-33.5], group B 26.4 months [14.9-37.5], group C not reached; p=0.326). After adjusting confounding factors include gender, age, clinical stage, pathological type and ECOG performance status in COX multivariate regression analysis, we found that the four drug-regimen which combined chemotherapy, anti-angiogenic therapy and immunotherapy significantly prolonged PFS and OS compared to chemotherapy alone (PFS: HR 0.29, 95% CI 0.12-0.72, p=0.007, OS: HR 0.27, 95% CI 0.08-0.88, p=0.029). However, there was no statistically significant difference in PFS and OS when compared to the three-drug chemotherapy plus bevacizumab group (PFS: HR 0.47, 95% CI 0.19-1.18, p=0.11, OS: HR 0.31, 95% CI 0.09-1.12, p=0.074). No significant difference in the incidence of grade≥3 AEs were observed among the three groups (group A: 7.6%, 9.8%, 18.2%, respectively, p=0.68).

Conclusions: In our real-world cohort, we found that unresectable MPM patients benefited from the combination of chemotherapy, anti-angiogenic therapy and immunotherapy with tolerable toxicity. Both PFS and OS was significantly longer than chemotherapy alone group. And there was a trend that four-drug therapy prolonged survival than chemotherapy plus anti-angiogenic agent group which was consistent with the latest published ETOP 13-18 trial data and more data is needed to confirm.

Keywords: malignant mesothelioma, anti-angiogenic therapy, immunotherapy

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.02 Overall Survival and PD-L1 Expression Analysis of Patients With Pulmonary Mesothelioma

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Introduction: Immunotherapy has become an important treatment option in patients with mesothelioma.The binding of programmed death ligand-1 (PD-L1) to its receptor PD-1, on the surface of activated T cells, inhibits cytotoxic T cell responses. Immune checkpoint inhibitors target this mechanism, improving outcomes for patients with mesothelioma. Stratifying patients based on their PD-L1 IHC (immunohistochemistry) expression score informs response rates. We investigated the prevalence of PD-L1 IHC expression in a Japanese single center setting, retrospectively collecting patient clinical and pathological data.

Methods: On 38 cases of mesothelioma diagnosed between 2004 and 2024 at our institution, immunohistochemistry was performed to detect PD-L1 expression using clone 22C3. Slides were reviewed for pathological analysis, and clinical data was obtained from medical records. The Kaplan-Meier model was adopted for calculating OS was applied to assess the results.

Results: The cohort included 35 males and 3 females, with a median age of 72 years (range 58-82) . Twenty-three 23 cases were epithelioid mesothelioma (approximately 60%), with the remaining cases being biphasic mesothelioma and sarcomatoid mesothelioma. As for treatment, one case underwent surgery, and all cases received drug therapy (chemotherapy and immune checkpoint inhibitors). Chemotherapy was administered in 25 cases (65.8%). Two immune checkpoint inhibitors (Nivolumab + Ipilimumab) were administered in 11 cases (28.9%), one case was administered a single immune checkpoint inhibitor in 11 cases (28.9%), and 16 cases were not administered any immune checkpoint inhibitors at all. Twenty-three cases (approximately 60%) had a PD-L1 CPS of less than 1, followed by 6 cases of 1 to less than 10. 6 cases of 10 to less than 50, and 3 cases of 50 or more.The median survival time for all 34 patients included in the survival analysis was 17.5 months (95% confidence interval: 9.63-35.5 months).In the histological type study, sarcomatoid was statistically significant for the poorest prognosis, followed by biphasic and epithelioid. Patients with a history of combined immune checkpoint inhibitor treatment or monotherapy showed a significantly longer survival time than those without a history of immune checkpoint inhibitor treatment, but in this exploratory study, the presence or absence of CPS was not statistically related to prognosis. The degree of CPS expression was not statistically related to prognosis.

Conclusions: Although this study only examined a small number of cases, there was no association between anticancer drug treatment and the relationship between treatment and prognosis, but patients with a history of immune checkpoint inhibitor treatment had a better outcome than those without a history of treatment.

Keywords: PD-L1, pulmonary mesothelioma

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.03 Glutamine Dependency of Pleural Mesothelioma

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Introduction: Pleural Mesothelioma (PM) is an insidious and very aggressive neoplasm of the mesothelial surface involving the pleura, which is associated with occupational or environmental exposure to asbestos. Metabolism in tumors differs from that in parental tissues to favor maximal use of resources with an adequate energy balance to allow cancer cells to survive and proliferate in a competitive tumor microenvironment. This metabolic rewiring can result in metabolic dependencies and a subsequent change in the cell's energetic profile that has the potential to be exploited therapeutically.

Methods: Publicly available transcriptome data were analyzed from different PM studies to determine the prognostic value of genes involved in glutamine metabolism. Cell viability and cell death were examined in distinct preclinical in vitro models of PM, including commercial cell lines and in-house patient-derived cell lines. Cells were treated with 2-deoxy-D-glucose (2-DG) at 0-5 mM and the glutaminase 1 (GLS1) inhibitor CB-839 at 0-1 µM, which target glucose and glutamine metabolism, respectively. Cell viability was determined by cell counting, while apoptotic death and cell cycle analyses were measured using propidium iodide by flow cytometry. We assessed the adaptive energetic response upon metabolic inhibitor treatment by assessing Oxygen Consumption Rate (OCR) by Seahorse and evaluating mTORC1 pathway dysregulation by Western blot.

Results: Using publicly available transcriptome data, we observed that overexpression of a glutamine metabolism signature, SLC2A1 and GLS1 are significantly associated with shorter overall survival, after adjusting for other clinical covariates (HR = 1.42 [1.11-1.8]). Viability and cell death analysis showed that cell numbers were reduced in several PM lines when treated with 2-DG. Strikingly, PM cells that showed less sensitivity for 2-DG were the most sensitive to CB-839, which reduced proliferation both in 2D and 3D cultures. CB-839 treatment did not arrest cells in any particular phase of the cell cycle. However, in the two most sensitive cell lines, CB-839 treatment resulted in apoptosis at 72h. Supplementation with dimethyl α-ketoglutarate (α-KG) rescued the effect in cell growth and apoptosis seen in 2D mesothelioma cell cultures upon CB-839 treatment. In addition, α-KG supplementation rescued 3D spheroid size in a patient-derived PM cell line. OCR and mTORC1 are significantly reduced upon glutaminase inhibition treatment.

Conclusions: CB-839 reduces cell viability in nine PM cell lines. For the two most sensitive cell lines, CB-839 treatment reduces OCR, mTORC1 and induces cell death, which are rescued by α-KG. These results suggest that glutamine is necessary for PM cell lines to sustain the TCA cycle and maintain energy requirements. Therefore, GLS1 might be a potential new therapeutic target in mesothelioma.

Keywords: Glutamine, metabolism, mesothelioma

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.04 Mapping the Pleural Mesothelioma: Incidence, Treatment Patterns and Outcomes From Endemic Pocket in Southern Rajasthan, India

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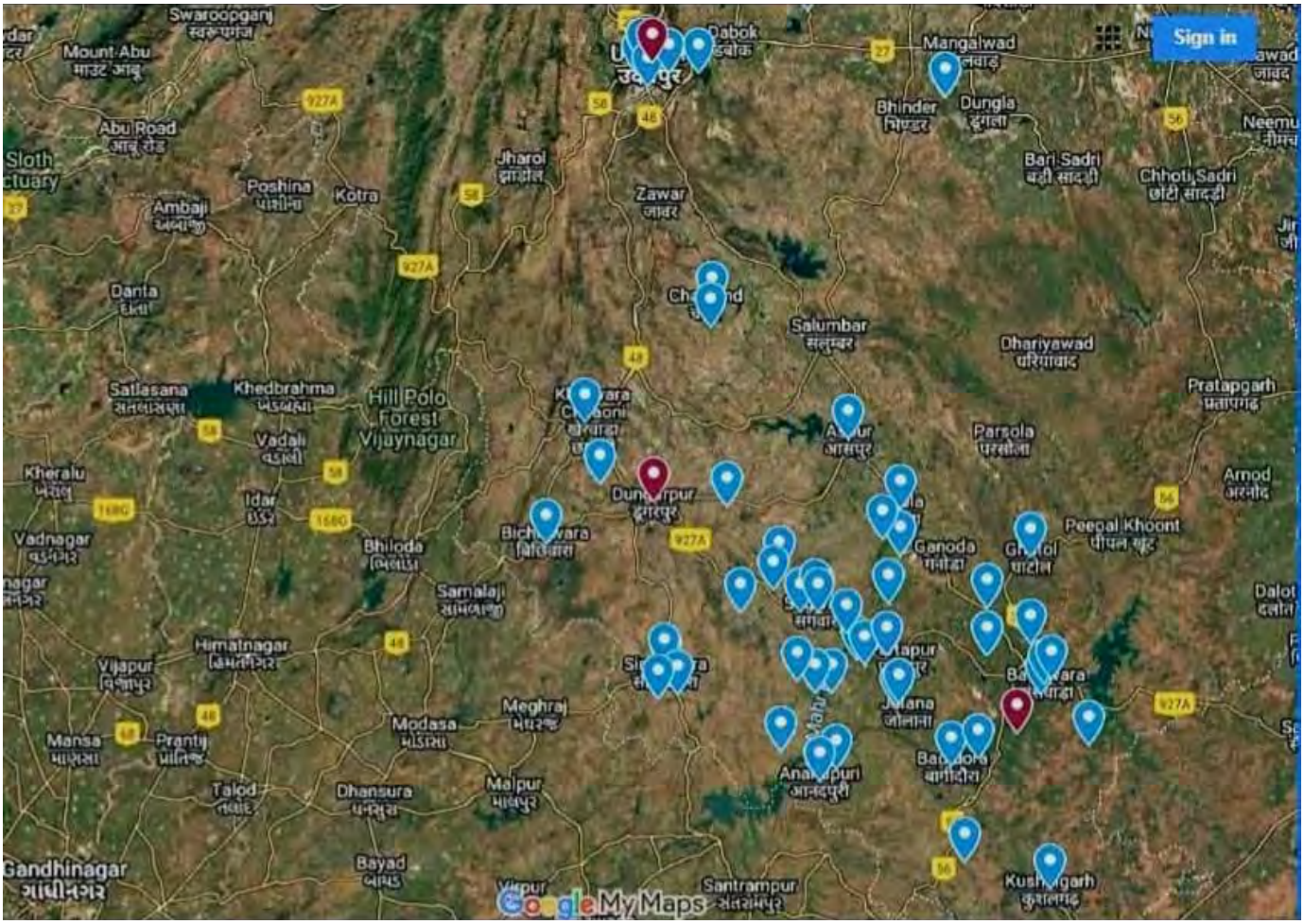
Introduction: The malignant pleural mesothelioma (MPM) is a rare and aggressive cancer with epidemiological linkage to asbestos. While many countries banned the asbestos still China and India are estimated to consume about 50% of global asbestos. Low literacy, ignorance and poor data collection leads to underreporting in India. In last five years we have seen significant cases coming from one area of Rajasthan state in India. Here we analyzed the data of this rare malignancy treated at our center situated in this endemic zone.

Methods: A retrospective analysis of prospectively maintained database of pleural mesothelioma in department of surgical oncology was performed. All the cases treated between May 2018 to December 2024 were identified. A total of 88 cases were treated and as per Pin code districts and villages were mapped to identify the hot spot. Apart from demography, treatment protocols, relapse patterns were also identified.

Results: Out of 88, total 64 cases were localized within a radius of 150 km and three major districts identified as hotspot (image 1). Age range varied from 26 -88 years with male: female ratio of 1.8:1. Majority (56%) were treated with empirical antitubercular treatment (ATT) at peripheral centers. Median duration of symptoms was six months, dyspnea was most common symptom (66%). Tissue diagnosis was done by thoracoscopy in 63 patients followed by CT guided biopsy in 25. Among histological variants Epithelioid was most common (62%) variant followed by sarcomatoid (17%) and Biphasic (10%). Majority received neoadjuvant chemo/immunotherapy (73%), however only 23 patients underwent surgery and in remaining treatment intent was converted to palliative. Out of 23 patients, 12 underwent Extended pleurectomy (EP) and seven underwent extrapleural pneumonectomy, remaining four underwent partial pleurectomy (palliative) in view of extensive disease. After median follow up of 22 months 55 died (62%), 22 were alive and disease free (25%) and 11 were alive with disease (13%).

Conclusions: MPM remains rare and aggressive cancer with poor outcomes despite Tri modality treatment. Due to endemicity of tuberculosis most of the patients are still treated with empirical ATT leading to delay in starting the treatment for this deadly disease. This newly identified hotspot in southern Rajasthan needs more attention to identify the causative factors to further take preventive and curative measures.



Keywords: Malignant pleural mesothelioma, endemic zone, India

EP.14.05 Predictive Factors of Postoperative Long-Term Survival in Patient With Pleural Mesothelioma

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Introduction: To investigate the predictive factors of long-term survival (more than 5 years) in patients with pleural mesothelioma (PM) undergoing curative-intent surgery.

Methods: A total of 255 patients who underwent curative-intent surgery for MPM between January 2006 and December 2019 in two high-volume centers were enrolled in this retrospective cohort study. Long-term survivor was defined as a patient surviving more than 5 years from the date of diagnosis. We analyzed the predictive factor of long-term survival using regression analyses. The data cut-off date was December 31, 2024.

Results: Of 255 patients, 77 (30.2%) survived more than 5 years from the date of diagnosis. Of 77 long-term survivors, the median age was 63-year old, the male was 64(83.1%), the epithelioid type was 75 (97.4%), c-T1(ver.8) and c-T1(ver.9) were 46(59.7%) and 52(67.5%), respectively. Undergoing pleurectomy/decortication was 57 (74.0%) and severe postoperative complication (Clavien-Dindo classification grade 3 or more) was observed in 5 (6.5%).Univariate analysis revealed that PS0, age less than 70 years, blood loss less than 1465g, c-T1(ver.9) and Clavien-Dindo classification adverse effect grade < 3 were significantly associated with long-term survival. Multivariate analysis with regression analyses revealed that age < 70 years (p < .01, 95% CI 1.51-9.38, OR 3.76), Clavien-Dindo classification adverse effect grade < 3 (p < .001, 95%CI 2.27-18.04, OR 6.34), c-T1(ver.9) (p < .001, 95%CI 2.45-8.90, OR 4.67) and blood loss less than 1465g (p=0.04, 95%CI 1.03-3.76, OR 1.97) were significant predictive factors of long-term survival.

Conclusions: Younger age, uneventful peri and post operative course and c-T1(ver.9) were independent predictive factors of long-term survival in PM patient undergoing curative-intent surgery.

Table: Univariate and multivariate analyses

		univariate analyses			multivariate analyses		
		OS≧5Y	OS<5Y	p-value	OR	95%CI	p-value
age	**70>**	69	126	**<.001**	3.76	1.51-9.38	**<.01**
	70≦	8	52				
sex	male	64	147	1.00			
	female	13	31				
PS	0	75	160	0.04	1.67	0.31-8.96	0.55
	1	2	18				
side	right	39	101	0.41			
	left	38	77				
histological type	epithelioid	75	161	0.07	2.11	0.40-10.96	0.38
	non-epithelioid	2	17				
surgical procedure	EPP	20	68	0.06	0.76	0.38-1.55	0.45
	P/D	57	110				
MCR	ahieved	75	165	0.24			
	not achieved	2	13				
c-T factor ver8	T1	46	92	0.27			
	T2-4	31	86				
c-T factor ver9	**T1**	52	49	**<.001**	4.67	2.45-8.90	**<.001**
	T2-4	25	129				
postoperative complication	none	39	65	0.04			
	present	38	113				
severe postoperative complication	**none**	72	122	**<.001**	6.34	2.27-18.04	**<.001**
	present	5	56				
operation time	467min>	40	87	0.68			
	466min	37	91				
blood loss	**1465g>**	51	77	**<.001**	1.97	1.03-3.76	**0.04**
	1465g≦	26	101				

Keywords: pleural mesothelioma, long-term survival, prognostic factor

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.06 Survival Analysis in Malignant Pleural Mesothelioma

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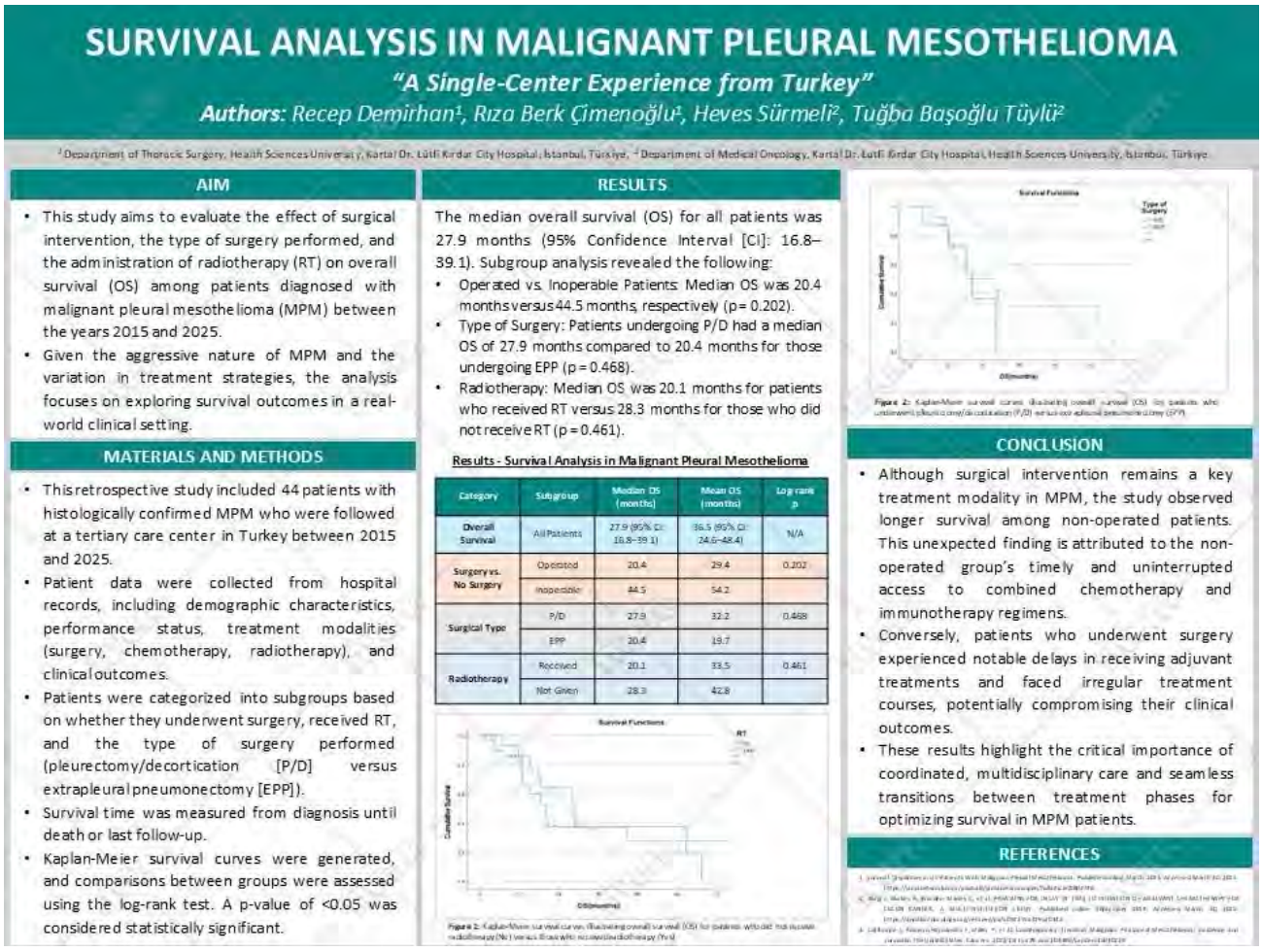
Introduction: This study aims to evaluate the effect of surgical intervention, the type of surgery performed, and the administration of radiotherapy (RT) on overall survival (OS) among patients diagnosed with malignant pleural mesothelioma (MPM) between the years 2015 and 2025. Given the aggressive nature of MPM and the variation in treatment strategies, the analysis focuses on exploring survival outcomes in a real-world clinical setting.

Methods: This retrospective study included 44 patients with histologically confirmed MPM who were followed at a tertiary care center in Turkey between 2015 and 2025. Patient data were collected from hospital records, including demographic characteristics, performance status, treatment modalities (surgery, chemotherapy, radiotherapy), and clinical outcomes. Patients were categorized into subgroups based on whether they underwent surgery, received RT, and the type of surgery performed (pleurectomy/decortication [P/D] versus extrapleural pneumonectomy [EPP]). Survival time was measured from diagnosis until death or last follow-up. Kaplan-Meier survival curves were generated, and comparisons between groups were assessed using the log-rank test. A p-value of <0.05 was considered statistically significant.

Results: The median overall survival (OS) for all patients was 27.9 months (95% Confidence Interval [CI]: 16.8-39.1). Subgroup analysis revealed the following:• Operated vs. Inoperable Patients: Median OS was 20.4months versus 44.5 months, respectively (p = 0.202).• Type of Surgery: Patients undergoing P/D had a medianOS of 27.9 months compared to 20.4 months for thoseundergoing EPP (p = 0.468).• Radiotherapy: Median OS was 20.1 months for patientswho received RT versus 28.3 months for those who didnot receive RT (p = 0.461).

Conclusions: Although surgical intervention remains a key treatment modality in MPM, the study observed longer survival among non-operated patients. This unexpected finding is attributed to the non-operated group's timely and uninterrupted access to combined chemotherapy and immunotherapy regimens. Conversely, patients who underwent surgery experienced notable delays in receiving adjuvant treatments and faced irregular treatment courses, potentially compromising their clinical outcomes. These results highlight the critical importance of coordinated, multidisciplinary care and seamless transitions between treatment phases for optimizing survival in MPM patients.



Keywords: Pleural Mesothelioma, Surgery, Overall Survival

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.07 Applying Multi Criteria Decision Analysis in Health Care Decision Making in Egypt

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Introduction: Multi Criteria Decision Analysis (MCDA) is an evidence based HTA methodology that has the capacity to assess simultaneously a set of criteria that meet the standards of MCDA process (i.e. Completeness, non-redundancy, and mutual independence) for choosing between the different drug alternatives.

Methods: An MCDA framework was developed using multiple chosen criteria for the evaluation of both pemetrexed and gemcitabine, using a numerical scoring system on a scale ranging from 1 to 3 for each criterion. A Delphi study was then used to discuss a final list of criteria with very clear definitions and a potential scoring scale. An appraisal group was formed and participants were invited to express their individual perspectives, by assigning weights to each criterion of the MCDA model. Participants then assigned individual performance scores for each medication. MCDA estimates of perceived value were then calculated by using a combination of normalized weights and scores.

Results: The present study has resulted in a preliminary rating tool for assessing mesothelioma management in Egypt. The tool is made up of 11 criteria covering context of medications, outcomes of drugs, economics and quality of evidence. The next step was determining the total aggregate score by using average weight and average score allocated to pemetrexed and gemcitabine on each of the decision criteria of the MCDA model. Pemetrexed got the highest total aggregate score (2.05) compared to gemcitabine (1.99).

Conclusions: Applying MCDA in the care of mesothelioma favours the use of pemetrexed rather than gemcitabine.

Keywords: mesothelioma, cancer, Egypt

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.08 Gender Difference as a Prognostic Factor in Non-Epithelioid Pleural Mesothelioma: Survival Analysis in the Retrospective SONET Study

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Introduction: Pleural mesothelioma (MP) is a rare, aggressive neoplasm with an unfavourable prognosis, the onset of which is a direct consequence, in about 80% of cases and after a long latency phase, of asbestos exposure. In Alessandria area, which was characterized in the past by the presence in Casale Monferrato of a large factory producing asbestos-cement products, the standardized incidence rates (per 100,000) of MP in the 2017-2021 period are 8.4 for women and 12.1 for men. MP is classified into three subtypes: the most frequent is the epithelioid, which is associated with better prognosis and survival, while the non-epithelioid subtypes (biphasic and sarcomatoid) have a very poor prognosis. While it is known that in patients with epithelioid MP women have better survival, less is known about the effect of gender in non-epithelioid MP. The aim of the study was to evaluate the effect of gender on survival in a cohort of patients with non-epithelioid MP who were diagnosed and treated at Alessandria University Hospital and Casale Monferrato Hospital.

Methods: A retrospective cohort study was conducted, including patients diagnosed with non-epithelioid MP between 2012 and 2020. Survival analysis was conducted using the Kaplan-Meier estimator. Hazard Ratios (HRs) and respective 95% confidence intervals (95% CIs), estimated by Cox regression model, were used to assess the effect of gender on survival, adjusting for other factors including age, histotype and treatment. In Cox models, the type of treatment was considered as a time-dependent variable.

Results: One-hundred seventeen patients were enrolled, 76% of whom were male, with a mean age of 71.5 ± 8.3 years; the biphasic histotype was the most frequently diagnosed (58%). The median overall survival time was 8.46 months (95% CI: 6.90-10.5). Log-rank test for the comparison of survival curves did not show a statistically significant difference between genders (p=0.21). Multivariate analysis confirmed the absence of a statistically significant difference in mortality between men and women, although female gender seemed to have a better survival (HR=0.94; 95% CI: 0.67-1.33). There was not a significant impact of gender on mortality neither in the group of patients with a sarcomatoid histotype nor in the one with a biphasic histotype. In the overall sample, the biphasic histotype was also found to have a better survival than the sarcomatoid one, but not statistically significant (HR=0.91; 95% CI: 0.67-1.24). Chemotherapies different from standard platinum-based and Pemetrexed are associated with a mortality decrease compared to standard chemotherapy, which was not statistically significant (HR=0.80; 95% CI: 0.50-1.30).

Conclusions: There is no evidence of a statistically significant difference on survival in non-epithelioid MPs between the genders, although the results obtained show an apparent protective effect on mortality in female gender. This relationship needs to be further explored by considering a larger sample in order to improve knowledge on these more aggressive forms of MP.

Keywords: non-epithelioid mesothelioma, survival, gender difference

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.09 Comparison Between Epithelioid Type and Biphasic Type in Pleurectomy/Decortication for Pleural Mesothelioma

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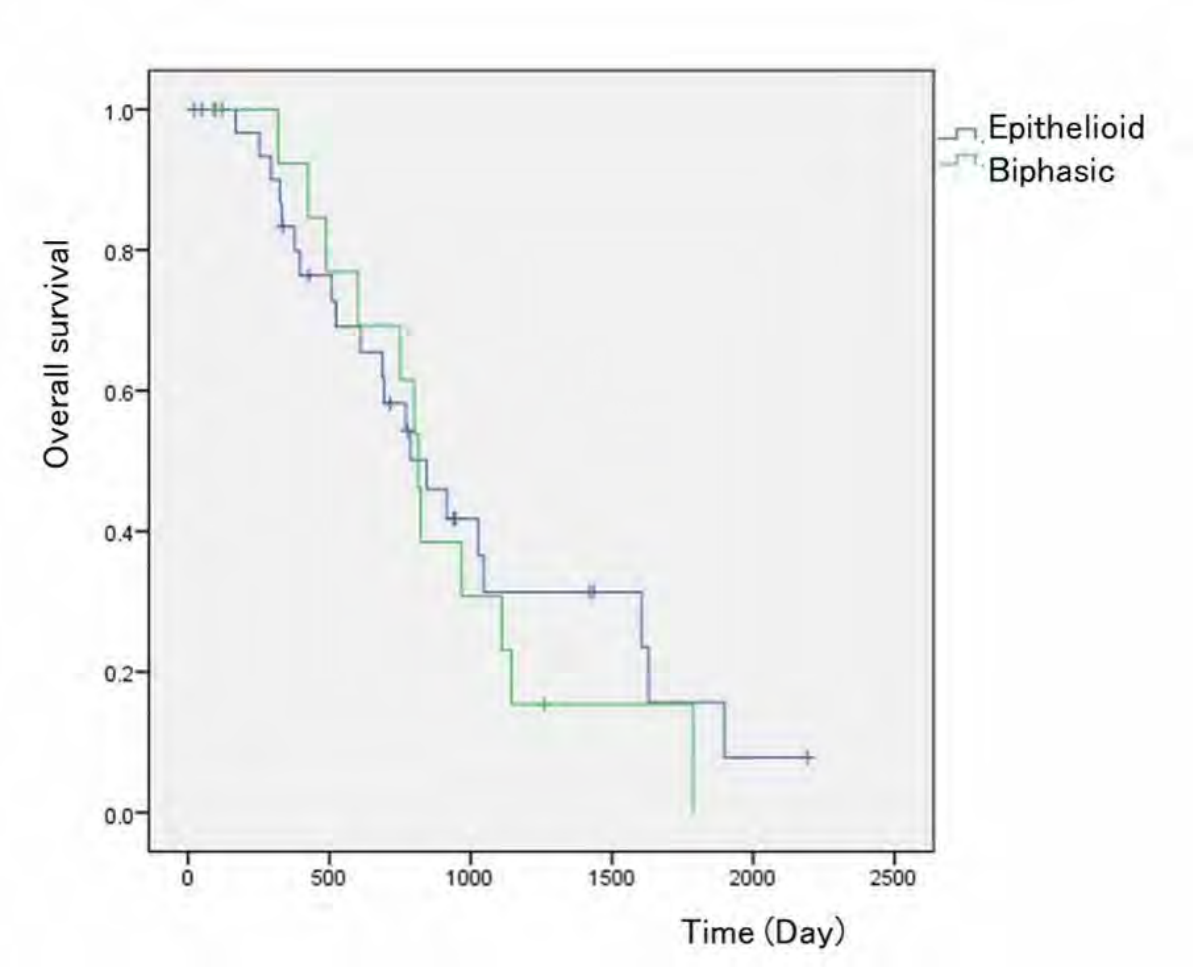
Introduction: Immediately after the presentation of the Mesothelioma and Radical Surgery (MARS) 2 trial, it was met with harsh criticism based on a high 90-day mortality rate of 9% and a big number of serious complications after Pleurectomy/Decortication (P/D). It is said that the significance of the MARS 2 trial is that the median survival of 24.8 months in the chemotherapy-only arm is the only possible guideline for treatment. We report a comparison of the epithelioid type and biphasic type in P/D for patients with pleural mesothelioma for whom Extrapleural Pneumonectomy (EPP) is inappropriate due to past medical history, comorbidities, or advanced age.

Methods: Age, sex, affected side, operative time, blood loss, International Mesothelioma Interest Group (IMIG) pStage, and prognosis were compared in 34 cases of epithelioid type and 14 cases of biphasic type between May 2013 and February 2025. Survival analysis was performed using the Kaplan-Meier method with the Log Rank test.

Results: Median age was 72 years for epithelioid type and 68 years for biphasic type. The sex was 28 males and 6 females for epithelioid type and 14 males and 0 female for biphasic type. The affected side was 24 right and 10 left for epithelioid type and 13 right and 1 left for biphasic type. Median operative time was 8 hours 35 minutes for epithelioid type and 8 hours 43 minutes for biphasic type. Median bleeding volume was 1,655 ml in epithelioid type and 2,055 ml in biphasic type. IMIG pStage was: epithelioid type (IV+III 62%): IV 3, III 18, II 7, I 5, 6 cm in size localized type 1; biphasic type (IV+III 71%): IV 1, III 9,II 3,I 1. Epithelioid type: 2-year survival 58%, 5-year survival 16%, median survival 28 months. Biphasic type: 2-year survival 69%, 5-year survival 0%, median survival 27 months. The Kaplan-Meier survival curves (Figure) for epithelioid type and biphasic type overlapped and were not significantly different with a Log Rank test of p=0.615. 90-day mortality was 0% for both epithelioid and biphasic types, lower than the 9% in the MARS 2 trial.

Conclusions: Despite the majority of advanced cases, the median survival time for epithelioid type and biphasic type was 28 and 27 months, respectively, exceeding the median survival time of 24.8 months for the chemotherapy-only group in the MARS 2 trial. The survival curves for epithelioid type and biphasic type (Figure) overlapped, and there was no significant difference in prognosis.



Keywords: Pleural mesothelioma, Pleurectomy/Decortication, Prognosis

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.10 Role of CT Assessed in the Evaluation of Sarcopenia in Patient With Malignant Pleural Mesothelioma. Results From an Observational Study

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Introduction: Sarcopenia is a condition characterized by skeletal muscle loss associated and it has been associated with poor clinical outcomes in oncology. Computed Tomography based assessment of sarcopenia is a non-invasive method leading to a quantitative assessment of muscle mass. The goal of this study is to explore the prognostic value of CT-assessed sarcopenia in a cohort of patients with Pleuric Mesothelioma .

Methods: 48 Patients underwent a CT scan as part of their oncologic evaluation. For each patient, total muscle area (TMA) was defined as the total area of muscle with density > 30 HU at L3 level . Sarcopenia was defined as a skeletal muscle index (SMI: TMA/Height^2) at L3 lower than 39 for female and lower than 52 for male. A survival analysis was performed using the Kaplan-Meier method.

Results: Patients were mostly male (38/48) with a median age of 72 years and a median BMI of 24. Mean TMA was 128,6 cm2 ±32.5 and mean SMI was 43,5 cm2/m2 ±9.4. 33 patients were sarcopenic. Median OS was 13 months in sarcopenic patients and wasn't reached in non-sarcopenic, but survival curves clearly separated. Median PFS was 6.4 (95%CI 2.9-22.7) months in non-sarcopenic and 6.5 months (95%CI 4.5-7.8) in sarcopenic patients. OS and PFS didn't statistically differ in patient treated with immunotherapy (p=0.8 and 0.4) or ChT (p=0.13 and 0.28).

Conclusions: Sarcopenic patient, especially those ChT treated, showed a tendency towards worse OS, though not statistically significative. Further investigation into the role of sarcopenia in PM patients in a wider prospective population is warranted.

Keywords: mesothelioma, sarcopenia, CT

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.11 Comparison of Short Term Surgical Outcomes for Thymectomy With Various Minimally Invasive Approaches : A Single Center Exper

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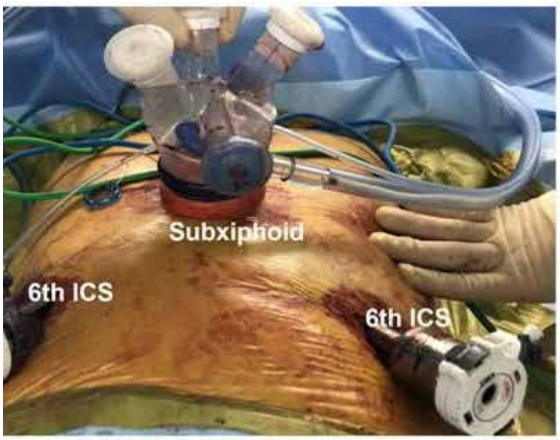
Introduction: Minimally invasive thymectomy, including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS), has gained popularity as an alternative to traditional sternotomy. However, limited studies have compared the short-term surgical outcomes of different minimally invasive approaches. This study aimed to compare the early surgical outcomes of three techniques: VATS lateral, RATS lateral, and RATS subxiphoid.

Methods: We retrospectively analyzed patients who underwent thymectomy with minimally invasive approach for anterior mediastinal mass between October 2020 and April 2024. Patients were categorized into three groups based on the surgical approach: VATS lateral, RATS lateral, and RATS subxiphoid. Baseline characteristics and perioperative outcomes were compared among the groups.

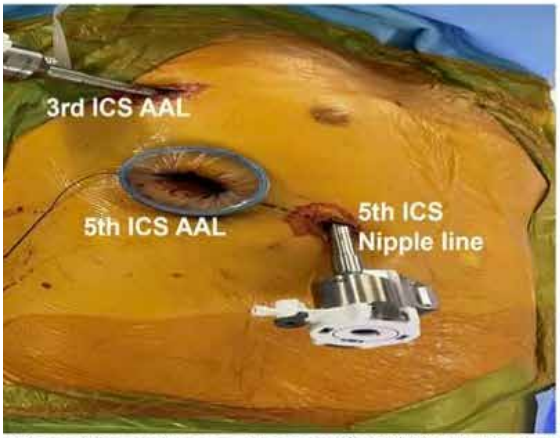
Results: A total of 292 patients were included in this study, of whom 70 (24.0%) with RATS lateral, 67 (22.9%) with RATS subxiphoid, and 155 (53.1%) with VATS lateral. Operation time was significantly longer in the RATS groups than in the VATS group (118.7 ± 42.4 min for RATS lateral, 116.7 ± 33.3 min for RATS subxiphoid, and 93.5 ± 30.2 min for VATS lateral; $P < 0.001$). No significant differences were observed in postoperative pain scores ($P = 0.154$), chest tube duration ($P = 0.165$), hospital stay ($P = 0.059$), or complication rates ($P = 0.424$) among the three groups. The rates of open conversion, R0 resection, and complications (Clavien-Dindo classification ≥ III) were comparable. No in-hospital mortality occurred in any group.

Conclusions: In this study, short-term surgical outcomes for thymectomy via three minimally invasive approaches were comparable and acceptable. These findings indicate that all three approaches are effective and adaptable options for thymectomy, enabling surgeons to select the most appropriate technique based on patient-specific factors and surgical expertise.



nt's position and trocar placement in RATS subxiphoid approach

Fig 3. Patient's position and trocar placement in VATS lateral appro



nt's position and trocar placement in RATS lateral appraoch

Keywords: Thymectomy, Minimal invasive surgery, Robot assisted thoracic surgery

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.12 Immune Profiles and Clinicopathological Insights in Thymomas: A Comprehensive Analysis

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Introduction: Thymic epithelial tumors (TETs) are the most common neoplasms of the anterior mediastinum, with thymomas comprising the majority. The immune microenvironment of thymomas mirrors that of the normal thymus, varying by histological subtype. Active thymomas (AB, B1, and B2) are frequently associated with myasthenia gravis (MG), an autoimmune disorder. However, the functional significance of immune cell populations within thymomas and their prognostic implications remain unclear. This study aims to elucidate the immune landscape of thymomas, its relationship to clinicopathological factors, and potential implications for immunotherapy.

Methods: This retrospective-prospective study analyzed 55 resected thymoma cases (Type A, AB, B1, B2, B3) and 15 control thymuses from the archives of the Department of Pathology, AIIMS New Delhi. Clinical and histopathological parameters were evaluated. Immunohistochemistry was performed using 12 antibodies, with eight assessed via dual staining (DAB+ALP). Whole Slide Imaging (WSI) at 40x magnification was utilized for digital slide analysis. Three consistent regions (outer, middle, and inner) per IHC slide were selected for manual cell counting, annotated with designated color codes, and analyzed for cell density. Markers assessed included CD34, TdT, CD3, CD20, CD4, CD8, CD68, CD163, S100, FOXP3, and IDO1. PD-L1 expression was evaluated using tumor proportion scoring. The same methodology was applied to control samples.

Results: Thymomas exhibited distinct immune profiles based on histological subtype. Type AB, B1, and B2 thymomas displayed high-density immune infiltrates, predominantly immature lymphocytes, while Type A and B3 thymomas had lower immune cell density, enriched in mature lymphocytes. B1 thymomas showed a higher proportion of mature immune cells compared to B2 thymomas. Notably, AB, B1, and B2 thymomas demonstrated significantly higher TdT+, CD3+, double-positive, and CD4+ cell densities compared to Type A and B3 thymomas. PD-L1 expression increased with tumor grade, exhibiting diffuse expression in high-grade thymomas but showing no correlation with immune infiltrates or clinical outcomes. IDO1 expression was significantly higher in AB, B1, B2, and B3 thymomas compared to Type A but did not correlate with PD-L1 expression, stage, or prognosis. Thymoma-associated myasthenia gravis (TAMG) cases exhibited lower immune cell densities, except for FOXP3+ cells, though these differences were not statistically significant. In 15 control thymuses, cortical regions were enriched with immature immune cells, while medullary regions contained mature immune cells. Non-myasthenic controls had higher CD3+ and FOXP3+ cell densities, whereas myasthenic cases displayed more S100+ dendritic and IDO1+ cells. Significant differences in CD20+, double-positive lymphocytes, and IDO1+ cells were observed between thymomatous and non-thymomatous controls.

Conclusions: This study, utilizing double immunostaining and digital analysis, identified unique immunological profiles for each thymoma subtype in the Indian population. Type A thymomas resembled medullary thymus, whereas AB, B1, and B2 resembled cortical thymus. PD-L1 expression was predominantly observed in non-A subtypes and pT1b or higher-stage thymomas, indicating a potential role in immunotherapy response. IDO1 expression, absent in Type A, suggests a therapeutic target in other subtypes. Variations in immune infiltrates between TAMG and non-TAMG cases warrant further investigation for clinical implications.

Keywords: Thymoma, Immune profile, WSI

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.13 Utility of Visual Assessment of PET/CT for Differentiating Malignancy in Thymic Epithelial Tumors

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Introduction: In thymic epithelial tumors, maximum standardized uptake values (SUVmax) derived from 18F-fluorodeoxyglucose(18F-FDG)PET/CT have been reported to correlate with WHO histological classification. However, since the SUVmax value varies depending on the imaging device, the reliability of quantitative evaluation is low. In contrast, the Deauville score is a five-point visual assessment scale widely used in hematologic malignancies for evaluating treatment response. It compares FDG uptake in lesions with that in the liver and mediastinum. Unlike SUVmax, the Deauville score enables consistent evaluation across multiple institutions. While the Deauville score has been reported to be useful for evaluating tumor malignancy in lung cancer, its relevance in thymic tumors remains unclear. This study investigated the relationship between the Deauville score and pathological findings in thymic epithelial tumors.

Methods: We retrospectively analyzed 126 patients with thymic epithelial tumors who underwent PET/CT and surgical resection at our institution between 2005 and 2024. To evaluate the association with the Deauville score, WHO histological classifications were categorized into the thymoma and thymic carcinoma groups. We also assessed the correlation between pathological staging using Masaoka classification and the Deauville score. Associations between variables were analyzed using Fisher's exact test.

Results: Among the 126 cases, 101 were thymomas, and 25 were thymic carcinomas. According to the Masaoka classification, 111 cases were stage I-II, and 15 were stage III-IV. There were 71 patients (56.3%) with the Deauville score ≤3 and 55 patients (43.7%) with a score ≥4. The proportion of thymic carcinoma was 2.82% in patients with Deauville scores ≤3 and 41.8% in those with scores ≥4 ($p<0.001$). The proportions of Masaoka classification III or higher were 2.82% and 24.5%, respectively ($p<0.001$). Deauville scores ≥4 were significantly more frequent in cases of thymic carcinoma and Masaoka stage III or higher.

Conclusions: In thymic epithelial tumors, the Deauville score of ≥4 was associated with thymic carcinoma and advanced Masaoka classification, suggesting its potential utility in evaluating tumor malignancy and invasiveness.

Keywords: Deauville score, Thymic epithelial tumor, Thymic carcinoma

EP.14.14 Cyclophosphamide/Pegylated Liposomal Doxorubicin/Cisplatin as First-Line Treatment for Patients With Advanced Thymic Epithelial Tumors

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Introduction: Thymic epithelial tumors (TETs) are rare tumors including thymoma and thymic carcinoma. Cyclophosphamide/Doxorubicin/Cisplatin (CAP) is the preferred first-line chemotherapy for thymoma and optional first-line chemotherapy regimen for thymic carcinoma. As a substitute for traditional doxorubicin, pegylated liposomal doxorubicin (PLD) has been widely recognized for its efficacy and safety in other malignancies. Due to the rarity of TETs, it is difficult to conduct prospective randomized controlled studies. We conducted this retrospective study to evaluate the activity and safety of Cyclophosphamide/Pegylated liposomal doxorubicin/Cisplatin (CDP) combination as the first-line treatment for patients with advanced TETs.

Methods: This study retrospectively analyzed a total of 57 patients with advanced TETs who received CDP regimen as first-line chemotherapy at Sun Yat-sen University Cancer Center from July 2013 to January 2024. Treatment consisted of intravenous cyclophosphamide (500 mg/m2 on day 1), PLD (30 mg/m2 on day 1) and cisplatin (50 mg/m2 divided into 3 days) every 3 weeks.

Results: Characteristics of the patients are shown in Table 1. A total of 57 patients were involved in this study, including 43 cases of thymoma and 14 cases of thymic carcinoma. As of the last follow-up, 43 patients with thymoma received a total of 177 cycles (median: 4, range: 2-6) , and 14 patients with thymic carcinoma received a total of 75 cycles (median: 5, range: 2-6) of the CDP regimen. Among 43 patients with thymoma, there were 0 CR, 17 PR(39.53%), 26 SD(60.47%) and 0 PD. The ORR was 39.53%, and DCR was 100%. At a median follow-up of 61 months, median PFS was 25 months [95%CI: 5.09-44.91 months], and median OS was 79 months [95%CI: 60.35-97.66 months]. Among 14 patients with thymic carcinoma, there were 0 CR, 9 PR(64.29%), 5 SD(35.71%), and 0 PD, The ORR was 64.29%, and DCR was 100%. At a median follow-up of 71 months, median PFS was 13 months [95%CI: 8.25-17.75 months], and median OS was 24 months (95%CI cannot be calculated). All patients were evaluated for toxicity. Twelve cases (21.05%) experienced grade 3/4 leukopenia, 3 cases (5.26%) experienced grade 3/4 anemia, 1 case (1.75%) experienced grade 3 thrombocytopenia, 1 case (1.75%) experienced grade 3 vomiting, and 1 case (1.75%) experienced grade 3 transaminase elevation. There was no treatment-related death.

Conclusions: This retrospective study demonstrated that the Cyclophosphamide/Pegylated liposomal doxorubicin/Cisplatin regimen exhibited both favorable efficacy and good tolerability as first-line treatment for patients with advanced thymic epithelial tumors.

Characteristics	Thymoma (N=43)		Thymic carcinoma (N=14)		Total (N=57)	
	Number	%	Number	%	Number	%
Age (years)						
Median	49		51		48	
Range	23-69		23-74		23-74	
Sex						
Male	24	55.81	9	64.29	33	57.89
Female	19	44.19	5	35.71	24	42.11
ECOG PS						
0	33	76.74	7	50.00	42	73.68
1	10	23.26	7	50.00	15	26.32
Stage						
III	18	41.86	3	21.43	21	36.84
IVa	11	25.58	4	28.57	15	26.32
IVb	14	32.56	7	50.00	21	36.84

Keywords: pegylated liposomal doxorubicin, thymic epithelial tumors, chemotherapy

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.15 Patterns of Failure and Long-Term Outcomes in Patients With Thymoma Treated With Surgery and Radiation Therapy

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Introduction: Thymic malignancies are rare tumors typically treated with surgical resection followed by postoperative radiation therapy (RT). While long-term outcomes are generally favorable, a subset of patients experience disease recurrence. This study aimed to characterize patterns of failure and identify clinicopathologic predictors of recurrence among patients treated with surgery and RT.

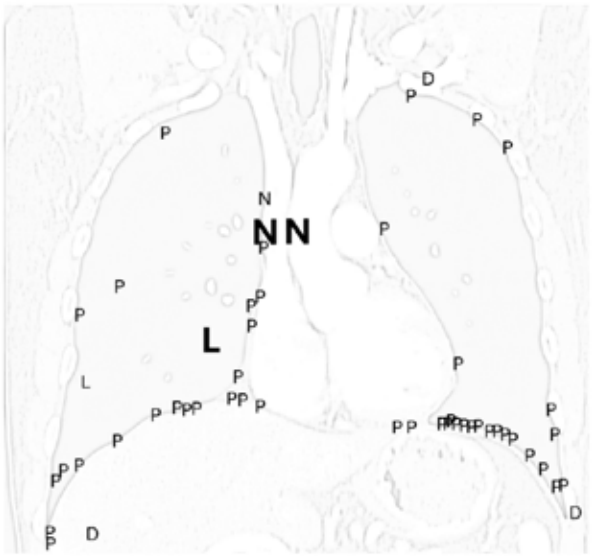
Methods: We conducted a retrospective cohort study of 175 consecutive patients with thymic malignancies treated with curative-intent surgery and RT between 2004-2024 at a single center. Collected data encompassed clinical characteristics, histopathology, treatment parameters, and imaging used to assess recurrence. Survival outcomes were estimated using the Kaplan-Meier method. Recurrence was defined radiographically, with location confirmed by imaging review. A univariate logistic regression model was used to assess predictors of recurrence.

Results: The cohort included patients with Masaoka stage I (4.7%), II (43%), III (33%), and IV (19.4%) disease. Histologic subtypes were type A/AB thymoma (19%), type B (60%), and thymic carcinoma (type C; 15%). Positive resection margins were present in one-third of cases. Most patients (75%) received adjuvant RT, while the remaining 25% were treated with neoadjuvant RT.

With a median follow-up of 9.7 years, the median overall survival (mOS) was not reached. The 5-, 10-, and 15-year OS rates were 92.4%, 78.8%, and 65.8%, respectively. Recurrence occurred in 62 patients (35%), with a median time to recurrence of 3.2 years. Among those with recurrence, mOS was 13.4 years; the 5-, 10-, and 15-year OS rates were 85.0%, 56.3%, and 43.6%, respectively. Recurrence was significantly associated with vessel invasion (OR 6, (2.3-15.6)), pleural invasion (OR 5.4, (CI: 2.7-10.9)), and pericardial invasion (OR 3.6, (1.8-7.3)). Positive surgical margins were also associated with recurrence (OR 2.2, (1.1-4.4)), while histologic subtype was not (OR 1.6, (0.7-3.9)). The most common site of recurrence was the pleura (76%), followed by mediastinal lymph nodes (6.5%), lung parenchyma (5%), and distant sites (5%). Only 5% of recurrences occurred within the radiation field (Image 1).

Conclusions: Patients with thymic malignancies treated with a curative intent surgery and RT demonstrate excellent long-term outcomes, with low rates of in-field recurrence. Most recurrences were pleural and occurred outside the radiation field, underscoring the effectiveness of current treatment approaches. Recurrence was associated with clinicopathologic features of local invasion rather than histologic subtype. While current RT strategies appear effective, further study is needed to define optimal management approaches for patients with high-risk invasive features.

Image 1: Recurrence map. Site of recurrence: Pleural (P); Lung parenchyma (L); Lymph nodes (N)
Distant (D); Letters in **bold** represent in-field recurrences. four distant bone recurrences are not displayed.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EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.16 Clinical Characteristics, Surgical Risks, and Long-Term Prognosis of Good's Syndrome: A Retrospective Analysis of 108 Thymoma Cases

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Introduction: Good's Syndrome (GS) is a rare disorder involving thymoma and hypogammaglobulinemia, leading to a poorer prognosis due to severe infections. Complete tumor resection and appropriate management of infectious diseases have been reported to be essential for long-term survival. Advances in surgical procedure, particularly robotic-assisted thoracic surgery (RATS) and video-assisted thoracic surgery (VATS) can offer lower risks of perioperative infections and ensure complete tumor resection. However, there have been no reports on the association among surgical procedures for GS, complications, and long-term prognosis. Since 2007, we have performed thymectomies for seven patients with GS including three RATS cases. Based on data from all thymectomy cases, including those not associated with GS, we investigated peri- and postoperative outcomes, evaluating the role of surgical intervention for GS patients.

Methods: Data were retrospectively collected from patients who underwent curative surgery for thymoma at Hokkaido University Hospital between July 2007 and January 2024. Background characteristics of the patients, laboratory data, and data on surgery were collected from medical records. The pathological stage was evaluated according to both 8th and 9th editions of TNM classifications. Continuous variables were compared using the Mann-Whitney U test, and categorical data were compared with Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method, and compared using the log-rank test.

Results: Out of the total 104 patients who underwent thymectomy, seven had GS. There were no significant differences in age (p=0.94), sex (p=0.07), and pathological stage (p=0.62 for TNM 8th, p=0.64 for TNM 9th) between non-GS and GS cases. All GS cases were diagnosed as type AB thymoma, whereas only 29% were type AB in non-GS group, indicating a significant difference in histological type (p=0.04). Among the patients with GS, two had median sternotomy (MS), two had VATS, and three had RATS. On the other hand, 31 underwent MS, 35 underwent VATS, and 31 underwent RATS in non-GS thymoma patients. When categorized by surgical procedure, although there was a significant bias in the number of cases, no tendency for greater blood loss or longer operation times, and no significant perioperative complications were observed in GS patients. However, no cases showed improvement in immunodeficiency, and five cases developed severe infections late postoperatively, including one patient with RATS. Two patients died with infectious disease. Furthermore, two GS cases developed extrathymic malignancies more than five years after surgery and subsequently died due to these cancers. While perioperative management could be safely achieved, the long-term risk of severe infections and developing extrathymic malignancies possibly remained. Additionally, three cases developed pure red cell aplasia one to two years following thymectomy. In survival analysis, GS patients had significantly worse prognosis (p=0.002).

Conclusions: The risk of surgery itself for GS patients is possibly not particularly high. However, regardless of the surgical procedures, even if perioperative management proceeds uneventful, there remains a risk of severe infections and development of new malignancies late postoperatively, resulting in a poor prognosis.

Keywords: Good's syndrome, thymoma, thymectomy

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.17 Clinical Outcomes of Patients With Advanced Thymic Malignancies Treated With Carboplatin/Pemetrexed Vs. Pemetrexed Alone

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Introduction: Thymoma (T) and thymic carcinoma (TC) are rare malignancies with limited systemic treatment options. Pemetrexed (pem) is approved as a single agent for advanced and metastatic T and TC. In practice, pem is often given in combination with carboplatin (carbo), but the safety and efficacy of this combination has not been established in either T or TC.

Methods: We identified patients with a diagnosis of unresectable, recurrent, or metastatic T or TC who were treated with carbo/pem or pem alone at the University of Pennsylvania's Abramson Cancer Center from 2011-2024. Time to disease progression and objective response rate (ORR) were determined retrospectively using RECIST 1.1. Median progression-free survival (mPFS) and median overall survival (mOS) were estimated using Kaplan-Meier methodology and compared using the log-rank test.

Results: We identified 24 patients (n=14 T; n=10 TC). Overall, 8 patients were treated with carbo/pem and 16 with pem alone. Carbo/pem was most often used in the first-line setting for patients with T vs in later lines for patients with TC. For our total study population, mPFS was not reached (NR) with carbo/pem and 14.7m with pem (p=0.27). Among patients with T, mPFS was numerically improved with carbo/pem compared to pem (NR vs 15.6m, p=0.09). Among patients with TC, mPFS was 10.9m with carbo/pem vs 14.7m with pem alone (p=0.88). At a median follow up of 49.0m (37m for carbo/pem; 107m for pem), mOS was NR in any group. With carbo/pem, ORR was 1/8 (12.5%) with 1 partial response (PR) observed in a patient with T. With pem, ORR was 5/16 (31%) (3 PRs in T; 2 in TC). Stable disease (SD) was observed in 6/8 (75%) patients treated with carbo/pem (4 with T; 2 with TC) and in 8/16 (50%) treated with pem (6 with T; 2 with TC). The most common AEs in both groups were hematologic: 62.5% experienced hematologic toxicity of any grade with carbo/pem vs 43.8% with pem. 1 patient (12.5%) receiving carbo/pem experienced a grade 3 adverse event (AE) vs 3 patients (18.8%) receiving pem.

Conclusions: Carbo/pem was well tolerated and associated with promising PFS and OS compared to pem monotherapy, especially in patients with T. While more research is needed to determine which patients are likely to derive benefit from the addition of carbo to pem, this combination should be considered an option in the treatment of thymic malignancies.

Table 1: Patient characteristics

	Carbo/pem n=8	Pem n=16
Diagnosis		
Thymoma	5 (63%)	9 (56%)
Thymic carcinoma	3 (38%)	7 (44%)
Median age	56 (range 31-78)	61 (range 27-82)
ECOG		
Thymoma		
0	2 (40%)	3 (33%)
1	1 (20%)	6 (67%)
2	1 (20%)	0
3	1 (20%)	0
Thymic carcinoma		
0	1 (33%)	3 (43%)
1	1 (33%)	4 (57%)
2	1 (33%)	0
Sex, n (%)		
Male	3 (38%)	8 (50%)
Female	5 (62.5%)	8 (50%)
Race		
White	4 (50%)	9 (56%)
Black	4 (50%)	4 (25%)
Asian	0	3 (19%)
Stage		
I-III, recurrent	4 (50%)	7 (44%)
IVA	3 (38%)	6 (38%)
IVB	1 (13%)	3 (19%)
Line of systemic therapy		
Thymoma		
1	4 (80%)	1 (11%)
2	1 (20%)	6 (67%)
3	0	2 (22%)
Thymic carcinoma		
1	1 (33%)	2 (29%)
2	0	1 (14%)
3	0	3 (43%)
4+	2 (67%)	1 (14%)

Keywords: Thymoma, Thymic Carcinoma, Thymic Malignancies

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.18 Post-Thymectomy Myasthenia Gravis: A Multicenter Retrospective Study on Clinical Characteristics and Outcomes

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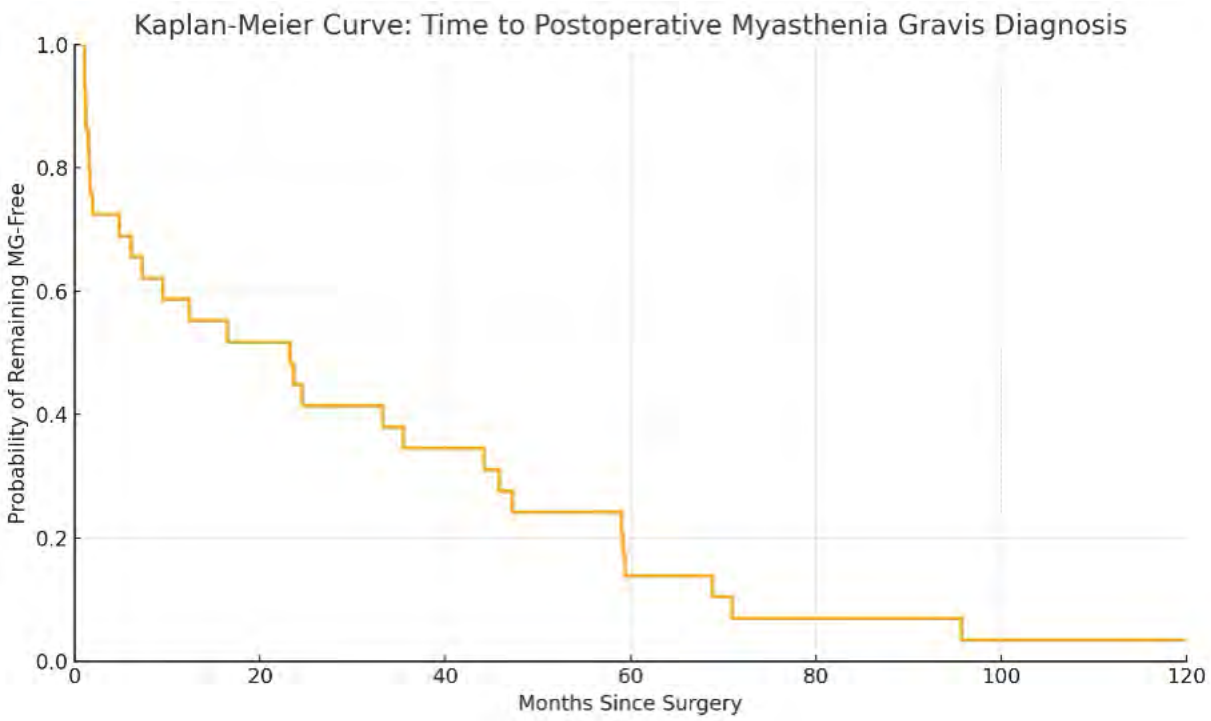
Introduction: Myasthenia gravis (MG) associated with thymoma is a rare but serious autoimmune disorder that may arise after thymectomy, including in patients without preoperative symptoms. This study aims to explore the clinical, pathological, and therapeutic features of patients who developed MG following thymectomy.

Methods: A retrospective analysis was conducted across five national referral centers, involving patients who underwent thymectomy for thymoma. Data collected included demographics, ASA and ECOG status, TNM staging, histological subtype, surgical approach, MGFA classification, antibody status at MG onset, treatment modalities, and remission outcomes. MG-free survival was estimated using the Kaplan-Meier method.

Results: The study included 30 patients, predominantly male (60%), with a median age of 51 years at surgery. Most patients had mild systemic disease (ASA II, 43.3%) and good performance status (ECOG 0-1, 83.3%). The most common pathological stage was T1a (40%), followed by T1b and T3. Lymphadenectomy was performed in 83.3% of cases, all N0, with M0 status in 96.7%. The most frequent histological subtypes were B2 (33.3%), B1 (26.7%), and B3 (20%). Median tumor size was 6.5 cm (range: 1.0-11.5 cm). Surgical approaches included sternotomy (80%), thoracotomy (13.3%), and robotic techniques (6.7%). Median follow-up was 88.9 months (range: 6.0-294.8 months). MG developed at a median of 20.2 months after surgery (range: 1.5-197.9 months). MGFA classification showed class IIa in 23.3% and IIb in 16.7% of patients. Anti-AChR antibodies were positive in 56.7% at diagnosis. The most common treatment regimen included corticosteroids and acetylcholinesterase inhibitors. Complete remission was achieved in 13.3% of patients; the majority had persistent symptoms.

Conclusions: MG after thymectomy is an important postoperative complication with diverse clinical presentations. These findings emphasize the need for long-term follow-up and a multidisciplinary approach to management.



Keywords: Thymoma, Myasthenia, Thymectomy

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.19 A Single Institution Retrospective Analysis of Mediastinal Tumor Resections Utilizing Robotic-Assisted Surgery

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Introduction: Robotic-assisted thoracoscopic surgery (RATS) for mediastinal tumors has been covered by insurance in Japan since 2018 and is increasingly adopted as a standard practice. Our institution has three distinct robotic surgical systems: da Vinci™, Saroa™, and hinotori™. This study evaluates the feasibility and efficacy of robotic-assisted surgery, including emerging robotic platforms, for mediastinal tumor resections.

Methods: A retrospective analysis was conducted at our institution, examining patients who underwent mediastinal tumor resections utilizing the da Vinci™, Saroa™, and hinotori™ surgical systems from April 2019 to March 2025. Short-term outcomes were assessed, including intraoperative complications, operative duration, estimated blood loss, and overall feasibility and safety of robotic-assisted thoracic surgery for mediastinal tumors.

Results: Among 94 patients, robotic resections were performed using the da Vinci™ system in 85 cases, the Saroa™ system in 6 cases, and the hinotori™ system in 3 cases. Procedurally, 25 patients underwent tumor resection, while 69 underwent thymectomy. Histopathological analysis revealed 43 cases of thymoma, 31 cases of thymic cyst, 10 cases of neurogenic tumors, and additional cases of metastatic tumors, thymic hyperplasia, thymic carcinoma, and teratoma. Four patients required conversion to sternotomy due to vascular adhesions. Postoperative complications classified as Clavien-Dindo grade II or higher were not observed, except for two patients requiring intervention for arrhythmia and prolonged air leakage. No intraoperative adverse events were reported. There was no statistically significant difference in console time among the three robotic systems: 133.2 minutes for the da Vinci™, 167.5 minutes for the Saroa™, and 172.3 minutes for the hinotori™ ($p = 0.604$). Similarly, no significant differences were observed in postoperative hospital stay (6.74 days vs. 7 days vs. 5.3 days, $p = 0.412$), total operative time (208.7 minutes vs. 218.7 minutes vs. 327.7 minutes, $p = 0.474$), or intraoperative blood loss (43 mL vs. 14 mL vs. 13 mL, $p = 0.818$).

Conclusions: Our findings suggest that robotic-assisted mediastinal tumor resection is a safe and viable surgical approach. Further investigations are warranted to assess long-term oncological and functional outcomes.

Keywords: Mediastinal tumor, Robotic-assisted thoracoscopic surgery, Thymoma

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.20 Whole-Exome Sequencing Study of Thymic Epithelial Tumors

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Introduction: There is a lack of effective clinical treatment options for patients with unresectable metastatic and recurrent thymic epithelial tumors (TETs). Moreover, patients with TETs often have other comorbidities associated with various paraneoplastic syndromes, including autoimmune diseases, which severely affect their survival. Advances in whole-exome sequencing (WES) technology can help understand the mechanisms of TETs at the genetic level to explore the genetic alterations that play a key role in the pathogenesis of TETs, which could facilitate the reliable diagnosis and treatment of TETs.

Methods: From 2019 to 2024, 24 patients diagnosed to have TETs (18 patients with thymic carcinomas and 6 patients with thymomas) at the Jiangsu Province Hospital underwent WES.

Results: RHPN2 was the most mutated gene in TETs, with a mutation rate of 45.8% (n = 11), and TETs with RHPN2 mutation showed greater upregulation of the oncogenic pathways such as the Notch and WNT signaling pathways as well as a trend toward shorter survival of the patients. Twenty-one peak regions were detected in the focal copy number variation region (q-value < 0.15), which were associated with various tumors. Mutated genes in TETs were enriched in several classical tumor-associated pathways, including cAMP, Notch, PI3K-Akt, and WNT signaling pathway, as well as multiple hormone-associated pathways such as insulin secretion; Cushing syndrome; parathyroid hormone synthesis, secretion, and action; and thyroid hormone signaling pathway. Immune-related pathways, including cytokine receptors and cytokines, were also altered in patients with TETs.

Conclusions: This study indicated that RHPN2 could be a potentially valuable gene associated with the development of TETs. We also elucidated the possible key factors related to TETs development and high prevalence of paraneoplastic syndromes at multiple levels, including tumor-related signaling pathways, hormones, and cytokines. These findings could help further enhance the knowledge and research on TETs.

Keywords: Thymic epithelial tumor, Exome Sequencing, Paraneoplastic Syndromes

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.21 Real-World Clinical Outcomes of Patients With Masaoka Stage Iv Thymic Carcinoma Treated With Carboplatin and Paclitaxel

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Introduction: Thymic carcinoma is rare and there are few phase III trials in thymic carcinoma due to its rarity. The treatment of advanced thymic carcinoma is based on the results of phase II trials, and the carboplatin and paclitaxel (CP) regimen is widely used worldwide. Since there were few real-world data on advanced thymic carcinoma treated with CP, we evaluated the treatment efficacy and the subsequent course of CP for Masaoka stage IV patients.

Methods: We retrospectively identified 107 patients diagnosed with thymic carcinoma between September 2002 and August 2024 at Shizuoka Cancer Center. Thirteen patients with neuroendocrine tumor were excluded. Fifty-eight were Masaoka stage IV patients. Treatment efficacy was evaluated based on overall survival (OS) and progression-free survival (PFS).

Results: The treatment details of 58 patients with Masaoka stage IV were as follows; 3 patients underwent surgery, 4 received chemoradiotherapy, 7 received radiotherapy, 37 received chemotherapy, and 7 received best supportive care (BSC) alone. The time from diagnosis to death in the BSC alone group was 15.5 months (95%CI: 0.2 months-not reached (NR)). The CP regimen was administered in 30 patients (81%). Baseline characteristics in the CP group were as follows; median age was 64.5 years, 63.3% were male, 90.0% had performance status 0-1, 86.7% had squamous cell carcinoma, and 73.3% were Masaoka stage IVB. The median PFS and OS in the CP group were 5.8 months (95%CI: 4.8-8.3 months) and 28.2 months (95%CI: 22.3-63.5 months). Twenty-six patients had disease progression and 24 patients received chemotherapy. As second-line chemotherapy, lenvatinib was administered in 5 patients, amrubicin in 6, S-1 in 3, and other regimens in 10. The median PFS of lenvatinib, amrubicin, and S-1 group were 25.3 months (95%CI 3.3 months-NR), 6.4 months (95%CI: 6.2 months-NR), and 33.6 months (95%CI: 6.4 months-NR), respectively. There was no significant difference in PFS among those groups (p=0.20). The median OS of lenvatinib, amrubicin, and S-1 group were 26.3 months (95%CI: 5.9 months-NR), 18.3 months (95%CI: 12.0 months-NR), and NR (95%CI: 14.9 months-NR), respectively. There was no significant difference in OS among those groups (p=0.35).

Conclusions: This study demonstrated the CP regimen is relatively effective for Masaoka IV stage thymic carcinoma patients. Among the patients who relapsed after the CP regimen, a high proportion of the patients (92%) were able to proceed the subsequent chemotherapy.

Table: Clinical outcomes of patients with Masaoka stage IV thymic carcinoma

	The median PFS	The median OS *BSC group: the time from diagnosis to the death
First line chemotherapy Carboplatin+paclitaxel (N=30)	5.8 months (95%CI: 4.8-8.3 months)	28.2 months (95%CI: 22.3-63.5 months)
BSC (N=7)	—	15.5 months (95%CI: 0.2 months-NR)
Subsequent treatment after relapse		
Lenvatinib (N=5)	25.3 months (95%CI: 3.3 months-NR)	26.3 months (95%CI: 5.9 months-NR)
Amrubicin (N=6)	6.4 months (95%CI: 6.2 months-NR)	18.3 months (95%CI: 12.0 months-NR)
S-1 (N=3)	33.6 months (95%CI: 6.4 months-NR)	NR (95%CI: 14.9 months-NR)

Keywords: Thymic carcinoma, Masaoka Stage IV, prognosis

EP.14.22 Intrathoracic Radiotherapy in the Treatment of Human Papillomavirus-Associated Head and Neck Squamous Cell Carcinoma Metastases

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Introduction: There is no clear consensus on optimal management of intrathoracic metastases from HPV-positive head and neck squamous cell carcinoma (HPV+ HNSCC). Furthermore, patients receive different systemic therapies, including immunotherapy, at the time of metastases. Given the diversity in treatment strategies and radiation therapy (RT) fractionation schemes and timing, we evaluated outcomes in this patient population.

Methods: This is a single-institution retrospective review of selected patients who received intrathoracic RT to gross disease from 2020-2024 for biopsy-proven parenchymal or lymph node metastases from HPV+ HNSCC. Univariable (UVA) and multivariable (MVA) logistic regression analyses were performed to identify predictors of in-field failure on both a patient level and lesion level.

Results: Patient and treatment characteristics are listed in Table 1. We identified 35 patients receiving 52 RT courses to intrathoracic metastases. The majority (31 patients; 89%) had no other sites of disease at the time of intrathoracic RT. In-field failure occurred in 6 cases (11.5%) with a median time of 42.4 months (IQR 27.2, 43.8) after RT, and 42 patients (81%) were alive at last follow-up.On UVA, patients with lung-only metastases had significantly lower odds of in-field failure (OR: 0.095, 95% CI: 0.01-0.64, p=0.015). Higher BED (≥100 Gy) trended toward lower in-field failure (OR: 0.26, 95% CI: 0.03-2.41, p=0.24). In MVA, lung-only disease (OR: 0.17, 95% CI: 0.02-1.55, p=0.12) was the only variable that remained associated with lower odds of failure, though not statistically significant. Of the 6 in-field failures, five of these lesions received a BED <100Gy. Of the 5 in-field failures with BED <100 Gy, 3 lesions were treated with 27Gy in 3 fractions, one with 45-60Gy in 15 fractions, and one with 30Gy in 5 fractions. The one in-field failure with BED ≥100 was treated with 50Gy in 5 fractions. No patient-level predictors (age, KPS), tumor size, RT dose, or systemic therapy within 3 months post-RT were significantly associated with in-field failure.

Conclusions: In this small retrospective cohort, in-field failure was infrequent and appeared less commonly among patients with lung-only metastases and those treated with higher BED. However, these trends did not reach statistical significance in MVA. These results warrant further prospective study in a larger, uniform cohort in order to guide thoracic treatment strategies for HPV+ metastatic HNSCC.

Patient Characteristic	N (%)
Male Sex	34 (94%)
Median Age	68 (IQR 60-79)
Median KPS	90 (IQR 80, 90)
Median Tumor Size	1.6 cm (IQR 1.0, 2.8)
RT Indication	
Oligometastatic	44 (85%)
Oligoprogressive	3 (6%)
Palliative	5 (10%)
Radiation Technique	
SBRT (27-50G y in 3-5 fractions)	36 (69%)
IMRT (45-60 Gy in 8-15 fractions)	11 (21%)
Quad Shot (44.4 Gy / 12 fractions)	5 (10%)
Radiation Details	
Median Total Dose	48Gy (IQR 30, 50)
Median Fractionation	5 (IQR 4-5)
Median BED	72 (IQR 58.5-100)
Radiation Biologically Effective Dose (BED) ≥100	21 (39%)
Systemic Therapy within 3 months post-RT	32 (62%)
Systemic Agent within 3 months post-RT	
Cetuximab-based regimen	12
Chemo-Immunotherapy	10
Immunotherapy alone	9
Chemotherapy alone	5
Clinical trial	2
Status at Last Follow-up	
Active Treatment	22 (63%)
Surveillance with No Evidence of Disease (NED)	9 (26%)
Best Supportive Care	4 (11%)
Median Time from HN CRT to Lung RT	27.7 months (IQR 13.8, 53.0)
Median Follow-Up	1.3 years (IQR 0.9, 2.2)

Table 1. Patient Demographics and Treatment Characteristics.

Keywords: lung metastases, HPV, radiation

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.23 Distinct Mechanical Responses in Psp Reveal AKT1 Mutation and Mechanical Tension Synergy in EMT

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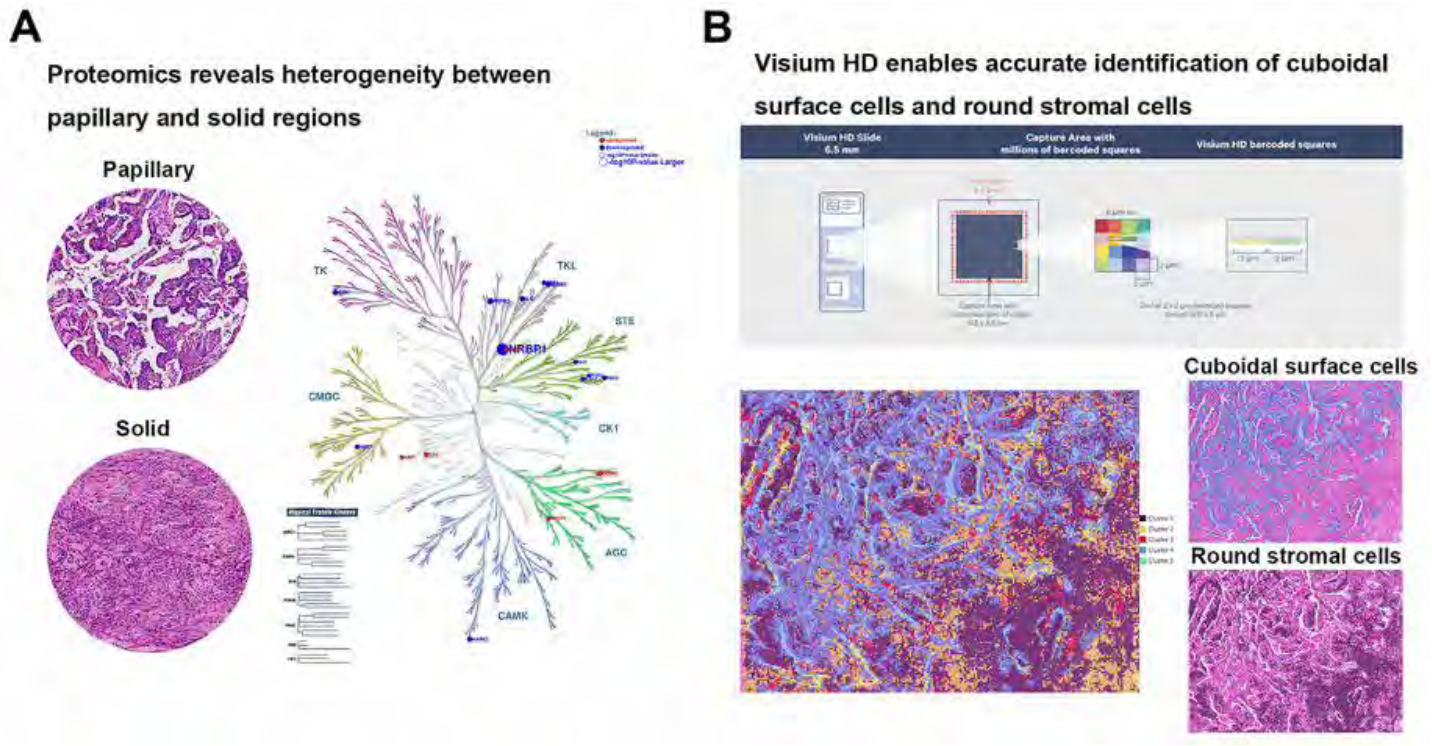
Introduction: Pulmonary sclerosing pneumocytoma (PSP) is a benign lung tumor composed mainly of cuboidal surface cells (CSCs) and round stromal cells (RSCs). Despite its favorable prognosis, it may still metastasize to lymph nodes and distant sites. Studies have shown that PSP originates from primitive lung epithelium, and almost all patients carry AKT1 gene mutations. However, the mechanisms underlying PSP development and progression, particularly the characteristics and interactions between CSCs and RSCs, remain poorly understood.

Methods: In this study, formalin-fixed paraffin-embedded (FFPE) tumor and matched adjacent tissue samples from 31 PSP patients were collected, and the molecular characteristics of CSCs and RSCs were systematically analyzed using a combination of proteomic analysis and Visium HD spatial transcriptomics. We first observed significant differences between CSCs and RSCs in their responses to mechanical stimulation, a finding that led us to further investigate the biological significance of PSPs being commonly located in the lung periphery, where they may be exposed to high mechanical tension over time. To explore this, we constructed a Beas-2b cell line harboring the AKT1_E17K mutation and applied a cyclic stretch model to examine the effects of AKT1 mutation and mechanical tension on the PSP cell phenotype.

Results: Our study revealed distinct molecular characteristics of CSCs and RSCs, along with their differential responses to mechanical stimulation. Additionally, we found that the combination of AKT1 mutation and mechanical tension promoted the epithelial-mesenchymal transition (EMT) process in PSP cells, suggesting that this mechanism may play a key role in PSP progression and potential metastasis.

Conclusions: This study systematically analyzed PSP cellular heterogeneity for the first time and identified differences between CSCs and RSCs in their responses to mechanical stimulation. This observation prompted further investigation into the synergistic effects of mechanical tension and AKT1 mutation, ultimately revealing a potential mechanism for shaping the EMT phenotype in PSP. These findings not only deepen our understanding of PSP development and progression but also provide potential therapeutic implications for other lung tumors harboring AKT1 mutations.



Keywords: Pulmonary sclerosing pneumocytoma, Proteomic, Mechanical tension

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.24 Report of Four Cases of Primary Pulmonary Sarcoma Experienced at Our Hospital

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Introduction: Primary pulmonary sarcomas are very rare, accounting for about 0.5% of all primary lung malignancies, and are one of the most difficult to diagnose and treat and have a poor prognosis. The clinicopathological findings of each case are reviewed.

Methods: Over the past 26 years from 1999 to 2024, 2480 operations for lung malignancies were performed at our institution, of which 4 (0.16%) were for sarcoma. The clinicopathological findings of each case are reviewed.

Results: 1.Female(age29) with no history of smoking. She presented to her previous physician with complaints of left chest pain and bloody sputum. Chest CT scan revealed a nodular shadow on the mediastinal side of the left lower lobe and a left hematogenous pleural effusion. The patient was diagnosed as having a respiratory infection and treated with antibiotics. The nodule was subsequently reduced in size, and internal cavitation was observed. There was no elevation of tumor markers, and FDG accumulation was very slight (SUVmax=1.21) on PET-CT. The patient was followed up for about two years, and no malignant lesion was actively suspected, considering the above examination results and the fact that he was a young non-smoker. After repeated enlargement and shrinkage, he was referred to our hospital for diagnosis and treatment of malignant lesions. In addition to a nodule 30 mm in diameter, an increased pleural effusion (CT values: 30-50 HU) was observed. Intraoperative findings revealed a large amount of hematogenous pleural effusion and a tumor that had already self-destructed with persistent hemorrhage. The tumor was directly invasive to the lingual region, the left diaphragmatic nerve, and the pericardium. Rapid diagnosis suggested a non-epithelial malignant tumor, sarcoma. A left lower lobectomy was performed for hemostasis. The pathological diagnosis was synovial sarcoma, and although there was no metastasis in the accessory lymph nodes, the extension to the resection margin could not be evaluated. 2. Male(age65), SI=900, underwent total left pneumonectomy plus pulmonary angioplasty for a left hilar mass. Postoperative pathology revealed an intimal sarcoma in the main trunk of the left pulmonary artery. The patient died of tumor embolism the day after surgery. 3. Male(age55), SI=640, blood sputum, left upper lobe resection for left upper lobe lung mass.The postoperative pathological diagnosis was synovial sarcoma. The patient survived for more than 10 years after surgery. 4. Male(age65), SI=900, blood sputum, partial right lower lobe resection for right lower lobe lung mass.The pathological diagnosis was liposarcoma. Five months after surgery, local recurrence was found in the lower lobe of the right lung, and resection of the remaining right lower lobe was performed. The patient survived 7.5 years postoperatively without recurrence.

Conclusions: Pulmonary sarcoma is an extremely rare disease and has a low priority in differential diagnosis. It is also reported to be poorly sensitive to chemotherapy and radiation. In the present study, some patients achieved long-term survival after complete resection. Early detection of disease and awareness of differential diagnosis, including rare malignancies, are considered to be of utmost importance.

Keywords: Primary pulmonary sarcoma, Pulmonary sarcoma, Synovial sarcoma

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.25 The Initial Outcome of Single Port Robotic Surgery for Mediastinal Tumors With 16 Cases

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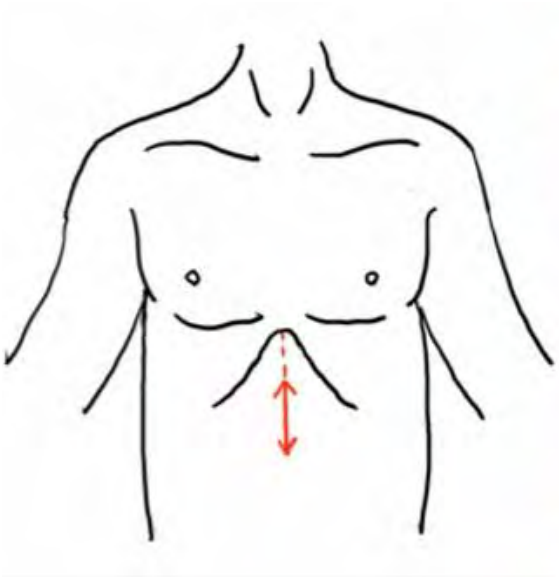
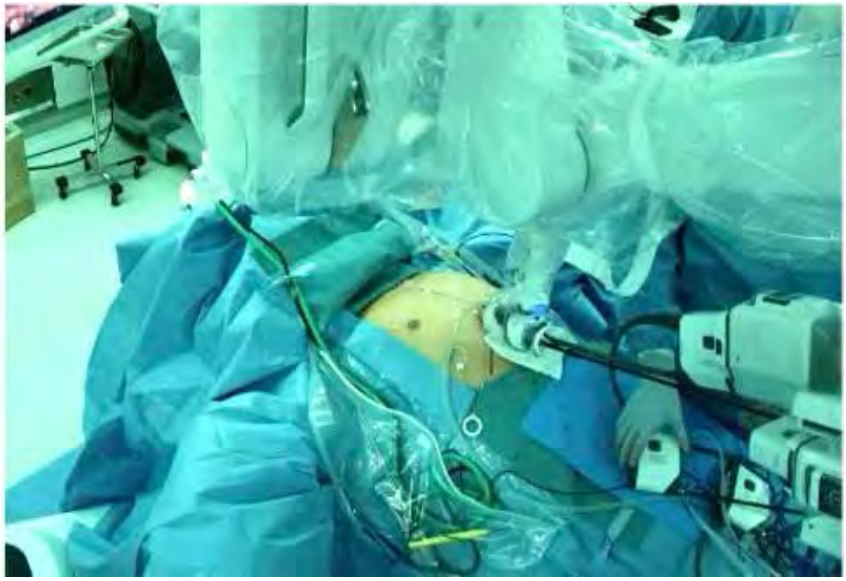
Introduction: Since February 2024, our institution has adopted the da Vinci SP® single-port robotic system for robot-assisted mediastinal tumor resection. This subxiphoid or subcostal approach demonstrates reduced invasiveness compared to conventional methods, potentially lowering postoperative pain and shortening hospital stays. The subxiphoid approach for anterior mediastinal tumors offers enhanced maneuverability over standard thoracoscopic techniques, warranting further evaluation of its safety and efficacy.

Methods: We analyzed perioperative outcomes of 16 consecutive patients undergoing SP robot-assisted mediastinal tumor resection (February 2024-March 2025). Lesion distribution included 14 anterior, 1 middle, and 1 posterior mediastinal tumors. Anterior tumors utilized a subxiphoid approach with a 3-cm midline incision 2 cm caudal to the xiphoid process. Other lesions employed a subcostal approach via a 3-cm incision along the costal margin at the 8th intercostal level. All procedures were performed through a single dedicated access port.

Results: The cohort (10 male, 6 female) had a median age of 58 years (range: 8-75). Median operative and console times were 120 minutes (85-246) and 84 minutes (48-212), respectively, with a mean blood loss of 10g. No perioperative complications occurred. Drain removal was achieved by postoperative day 1 in 15 cases and day 2 in 1 case. The median postoperative hospital stay was 5 days (5-8).Pathological examination revealed: thymoma (6 cases: 3 Masaoka stage I, 3 stage II; including 3 myasthenia gravis cases [1 MGFA class I, 2 class IIa]), thymic cysts (3 cases), neurogenic cyst (1 case), bronchogenic cyst (1 case), mature teratoma (1 case), cholesterol granuloma (1 case). All achieved R0 resection.

Conclusions: In this study, we performed mediastinal tumor resection using a single-port robotic system in 16 cases. Although the safety and efficacy of single-port robotic surgery have not yet been fully established, we were able to conduct these procedures safely at the current stage. Particularly for anterior mediastinal tumors, the approach facilitates surgery without connecting both pleural cavities, potentially reducing the risk of recurrence-related seeding and bilateral pneumothorax. Furthermore, da Vinci SP was indicated for an 8-year-old child with a posterior mediastinal tumor over 10 cm in size, and no intercostal dissection was needed. He was discharged 3 days after surgery and was able to run the same day. Da Vinci SP is also expected to make it a good indication for pediatric surgery. Accumulating further clinical cases will allow us to evaluate the effectiveness of this surgical method comprehensively.





Keywords: da Vinci SP, mediastinal tumor, single port

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.26 Novel Bioengineered Drugs With Immunotherapies for Malignant Pleural Effusion

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Introduction: Malignant pleural effusion (MPE), a hallmark of advanced cancers, portends poor survival due to its immunosuppressive tumor microenvironment (TME) and limited drug penetration. Conventional approaches (e.g., thoracentesis) palliate symptoms but fail to restore antitumor immunity or prolong survival. Emerging bioengineered platforms—integrating nanotechnology, gene editing, and immunotherapy—offer a paradigm shift by dual-targeting TME remodeling and immune activation. This review deciphers the molecular basis of MPE immunosuppression and evaluates novel bioengineering strategies (e.g., cytokine-loaded nanoparticles, oncolytic viruses) to overcome immune tolerance. We further discuss risks, clinical translation challenges, and future directions toward precision MPE therapy.

Methods: 1. Literature Search

Databases: PubMed, Web of Science, ClinicalTrials.gov, IEEE Xplore (2015-2024).

Keywords: “malignant pleural effusion” + (“bioengineering” OR “nanoparticle” OR “oncolytic virus”) + (“immunotherapy” OR “TME remodeling”).

Screening: PRISMA-guided selection (n=XXX studies; Fig 1).

2. Data Synthesis

Focus:

Bioengineering platforms: Nanoparticles (lipid/polymer), CRISPR-edited CAR-T, oncolytic viruses.

Immune metrics: Treg/MDSC suppression, IFN-γ/IL-12 levels, M1/M2 macrophage ratio.

Efficacy: MPE volume reduction, survival benefit.

Safety: Cytokine release syndrome, local fibrosis.

Quality Assessment: SYRCLE (preclinical), Cochrane Risk of Bias (clinical trials).

Results: 1. Bioengineering Strategies

Nanoparticles: pH-responsive carriers enhanced drug penetration (e.g., paclitaxel-loaded liposomes: 60% MPE reduction in murine models). Oncolytic Viruses: Local delivery of IL-12 boosted $CD8^+$ T-cell infiltration (3-fold vs. controls).Combinatorial Therapies: Anti-PD-1 + STING agonists doubled survival in preclinical trials.

2. Challenges

TME Barriers: Fibrosis reduced nanoparticle diffusion (efficacy dropped by 40% in high-collagen models).Safety: Grade 3 cytokine storms reported in 15% of early-phase trials.

3. Clinical Translation

Level 1 Evidence: Nanoparticle-albumin-bound paclitaxel + pembrolizumab (Phase II: 12-month survival in 55% MPE patients).Emerging Tools: AI-designed smart hydrogels enabled sustained cytokine release (preclinical validation).

Conclusions: Bioengineered immunotherapy synergizes TME reprogramming and immune reactivation, showing promise in MPE management. Key advances include nanoparticle-mediated targeted delivery and combinatorial regimens. However, clinical translation requires overcoming fibrosis barriers and cytokine toxicity. Future priorities:

Cross-disciplinary Innovation: Integrate AI, biomaterials, and immune profiling.Precision Biomarkers: Stratify patients for optimal bioengineering platform selection.

This paradigm may herald a new era of curative-intent MPE therapy.

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.27 mTOr Inhibitor as Treatment Inpulmonary Epithelioid Hemangioendothelioma, a Case Series

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Introduction: Pulmonary epithelioid hemangioendothelioma (P-EHE) is an extremely rare vascular tumor originating from the endothelial cells of the lung. It often appears as multiple bilateral nodules, occasionally accompanied by pleural effusion, and can remain asymptomatic until advanced stages. Histologically, it is characterized by epithelioid cells positive for endothelial markers such as CD31, CD34, and ERG, commonly driven by the WWTR1-CAMTA1 fusion gene. Management strategies vary due to its low incidence and heterogeneous behavior. In some asymptomatic patients with indolent disease, watchful waiting is a viable option, whereas symptomatic or more aggressive cases may require systemic therapies like chemotherapy, immunotherapy, or antiangiogenic agents. Sirolimus has emerged as a potential additional treatment approach, exploiting its antiproliferative properties.

Methods: Three cases of patients from the National Thoracic Institute are presented. Their medical history and evaluation were collected in oncology committees over the last five years. The clinical presentation of patients and their treatments are characterized.

Results: First case: male patient, 21 years old, with back pain of two years of evolution. CT scans of the spine revealed multiple pulmonary nodules from 1-22 mm size. Suspecting disseminated tuberculosis, a biopsy of the lesion was performed, showing neoplasm CD34+, FL1+, VEGF- compatible with P-EHE. Staging show several bone metastasis. Began treatment with Pazopanib for two years. Sirolimus treatment was initiated due to poor tolerance and has successfully continued for 18 months, patient remaining asymptomatic thus far. Second case: female patient, 31 years old. Consulted for pain in the left hemithorax, but due to pregnancy, the imaging study was delayed. With persistence of symptoms, a complete study was completed 11 months after the onset of pain. CT scans showed a large mediastinal mass involving large vessels and the left bronchus, associated with adenopathic involvement and bone metastasis. The biopsy was CK AE1/AE3+, CD31+, FLI1+, confirming P-EHE. Receive mediastinal radiotherapy, followed by Carboplatin/Paclitaxel. She was referred to our center where Sirolimus was started, completing 30 months of treatment and remaining asymptomatic thus far. Third case: female patient, 80 years old, with progressive dyspnea associated with massive pleural effusion and cardiorespiratory arrest. After extubation and recovery from cardiac arrest, a pleura biopsy was taken via VTC. The biopsy showed D2-40+, CD31+, ERG+, GATA+. Reviewed in pathological anatomy, P-EHE was confirmed. She presented to the committee for the initiation of Sirolimus, however, the patient refused to start treatment.

Conclusions: The occurrence of only three cases in five years highlights the rarity of this tumor. The advanced stage at diagnosis and the symptoms resulting from its progression are consistent with previously reported cases. Treatment with chemotherapy or antiangiogenic therapies are the most described in case reports. Notably, our series demonstrates an excellent response and high tolerance to the administration of Sirolimus as a second-line treatment. Given the presentation in young patients in two of these three cases, this response facilitates the chronic management of this pathology with this drug. The question remains about how to proceed in the event of progression and observe the survival time of these patients.

Keywords: Pulmonary epithelioid hemangioendothelioma, Sirolimus, Case series

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.28 Three-Dimensional Reconstruction of the Sternum: A Novel Approach for Improved Surgical Outcomes

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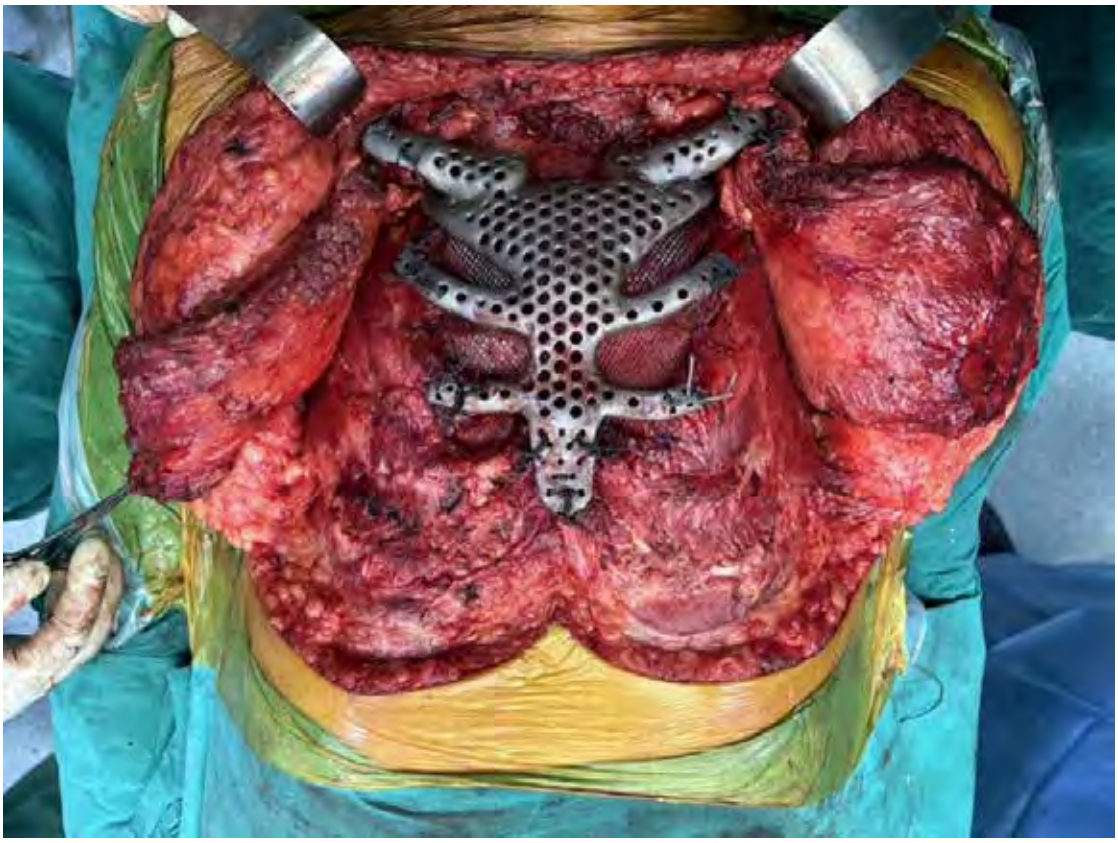
Introduction: The sternum plays a crucial role in chest stability and protection of vital organs. Sternal defects resulting from tumour resection pose significant challenges for reconstructive surgery. Traditional techniques using autologous tissue or synthetic materials have limitations in achieving optimal functional and aesthetic outcomes. Three-dimensional (3D) printing technology offers a promising solution for personalized sternal reconstruction. Here we present a case series of patients with complex sternal defects who underwent 3D-printed sternum reconstruction. We describe the preoperative planning process, surgical technique, and postoperative outcomes.

Methods: The records retrieved from a prospectively maintained database at our institute. A total of three patients were included that underwent curative surgical resection followed by reconstruction using 3D titanium implant between May 2022 and April 2024. All patients underwent preoperative contrast CT scan for preoperative planning and resection margins. Virtual 3D implant was created and after approval from operative team final customized 3D implant was prepared.

Results: The mean age was 44 years, two patients were male and one female. Two patients had chondrosarcoma and one had solitary plasmacytoma of sternum. All three underwent oncological resection with adequate margins. Customized titanium implant was used for all three. Mean duration of surgery was 240 minutes. Implant was covered with pectoralis major muscle in all cases. Mean duration of hospital stay was five days. One patient received post operative radiotherapy and tolerated well. No implant related complications observed and after median follow up of 15 months all three are alive and disease free.

Conclusions: Our results demonstrate that 3D-printed sternum reconstruction provides a customized, anatomically accurate solution with improved surgical precision and patient satisfaction compared to traditional methods. Further studies are warranted to evaluate long-term outcomes and cost-effectiveness of this innovative approach.



Keywords: Sternum, 3D reconstruction, Titanium implant

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.29 A Case Study of Multiple Nodular Lesions in the Anterior Mediastinum Detected on Preoperative Imaging

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Introduction: Multiple nodular lesions in the anterior mediastinum, either solid or cystic, are occasionally encountered on CT or MRI. We retrospectively reviewed the clinicopathological features of surgical cases with such findings identified on preoperative imaging.

Methods: Among 143 patients who underwent surgical resection for anterior mediastinal tumors at our institution between 2011 and 2023, 7 cases with multiple solid and/or cystic nodular lesions in the anterior mediastinum on preoperative imaging were included in this study.

Results: The median age was 56 years (range, 50-64), and the cohort consisted of 1 male and 6 females. CT and MRI findings were reviewed in collaboration with radiologists, and lesions were categorized as cystic type (2 cases), mixed type (3 cases), and solid type (2 cases), depending on their radiologic appearance.Six patients had underlying autoimmune diseases, including Sjögren's syndrome (n=4), rheumatoid arthritis (n=1), and systemic sclerosis (n=1). Bronchial asthma was observed in 3 patients, and one patient had a history of parotid MALT lymphoma.Surgical procedures included extended thymectomy in 5 cases and thymic and perithymic fat resection in 2 cases. Histopathological diagnoses were multilocular thymic cyst (MTC) with MALT lymphoma in 4 cases and MTC with follicular hyperplasia (FH) in 3 cases. One patient with MTC and FH experienced regrowth of residual lesions and underwent reoperation approximately 3 years and 2 months after the initial surgery. As of the most recent follow-up, which was more than 4 years after the reoperation, the patient remains recurrence-free. All four patients diagnosed with MTC and MALT lymphoma showed no recurrence during long-term postoperative follow-up. Postoperative adjuvant therapy with rituximab monotherapy was administered in one case of MALT lymphoma.

Conclusions: All patients with multiple anterior mediastinal nodules—regardless of whether they appeared cystic or solid—were pathologically diagnosed with MTC and further classified as either MALT lymphoma or FH. Notably, all cases associated with Sjögren's syndrome were diagnosed with MTC and MALT lymphoma, indicating a potential relationship.In one patient with FH, recurrence occurred even though extended thymectomy was performed as the initial surgery. The residual lesion likely remained due to anatomical constraints related to the patient's body habitus. MTC was also identified in the tissue removed during the reoperation.This case suggests that complete resection may be important to prevent recurrence when MTC is suspected. Accordingly, extended thymectomy may be a reasonable surgical option in such cases to reduce the risk of residual disease.Although differentiation between MTC, cystic thymoma, and other anterior mediastinal tumors was difficult based on preoperative CT and MRI, surgical resection provided both diagnostic and therapeutic value and was considered an appropriate approach.

Keywords: multilocular thymic cyst, MALT lymphoma, Follicular hyperplasia

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.30 Clinicopathological Features and Diagnostic Challenges of Pulmonary Lymphoma: A Retrospective Review of 21 Cases

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Introduction: Pulmonary involvement of lymphoma can manifest in various clinical contexts, including primary pulmonary lymphoma (PPL), relapse of previously treated lymphoma, or secondary involvement from systemic lymphoma. Given the rarity and nonspecific presentation of lymphoma in the lung, accurate diagnosis is often delayed. This study aims to review cases of lymphoma diagnosed in the lung and to analyze the clinicopathological features, diagnostic approaches, and differential diagnoses, with particular emphasis on cases of PPL.

Methods: A retrospective analysis was conducted on 21 cases in which lymphoma was diagnosed in the lung at Yeouido St. Mary's Hospital, The Catholic University of Korea, between 2019 and 2025. Of these, 15 cases were classified as primary pulmonary lymphoma (PPL), while 4 cases represented relapsed lymphoma involving the lung, and 2 cases were systemic lymphomas with secondary pulmonary infiltration. Among the PPL cases, histologic subtypes included mucosa-associated lymphoid tissue (MALT) lymphoma (n=10), extranodal NK/T-cell lymphoma (n=1), classic Hodgkin lymphoma (n=1), follicular lymphoma (n=1), plasmablastic lymphoma (n=1), and T-cell/histiocyte-rich large B-cell lymphoma (n=1). The diagnoses were established via wedge resection (n=9), segmentectomy (n=2), lobectomy (n=1), and biopsy (n=3).

Results: Radiologic findings in cases of relapse or systemic involvement were often suggestive of lymphoma. In contrast, primary pulmonary lymphomas frequently mimicked benign or other malignant conditions. Among PPL cases, initial clinical or radiologic impressions included organizing pneumonia (n=6), differential diagnoses between sarcoidosis and lymphoma (n=2), suspicion of lymphoma (n=4), IgG4-related disease (n=1), and adenocarcinoma in situ (n=1). MALT lymphoma cases showed favorable outcomes, with 90% of patients achieving and maintaining complete remission following chemotherapy (mean follow-up: 34 months). In contrast, other PPL subtypes showed a more aggressive course with progressive disease.

Conclusions: Lymphomas involving the lung encompass a heterogeneous group of diseases, with primary pulmonary lymphoma being particularly prone to misdiagnosis due to nonspecific imaging and clinical features. Careful correlation of clinical, radiologic, and pathologic data is essential. When imaging findings do not align with the clinical picture or expected response to treatment, timely and adequate tissue sampling should be pursued to ensure accurate diagnosis, especially given the prognostic differences between MALT and non-MALT PPL subtypes.

Keywords: Lymphoma, Lung, MALT lymphoma

EP.14 MESOTHELIOMA, THYMOMA, AND OTHER THORACIC TUMORS

EP.14.31 Incidence Trends and Survival Outcomes of Pulmonary Langerhans Cell Histiocytosis: A National Cancer Study Using SEER

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Introduction: Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, smoking-related neoplastic lung disease arising from clonal proliferation of dendritic cells. Initially considered a reactive disorder, the discovery of recurrent BRAF V600E mutations has led to its reclassification as a neoplasm. PLCH typically presents with nonspecific respiratory symptoms or may be incidentally detected on imaging. Diagnosis is based on high-resolution computed tomography, with histologic confirmation via biopsy. Smoking cessation remains the cornerstone of treatment, although glucocorticoids and BRAF-targeted therapies are used in selected cases. This study aims to characterize the incidence trends and survival outcomes of PLCH using a large population-based dataset in the U.S.

Methods: We performed a retrospective analysis using SEER (Surveillance, Epidemiology, and End Results) Research Plus (17 registries, 2010-2021). Patients with histologically confirmed Langerhans cell histiocytosis (ICD code 9751/3) with a primary site in the lung (C34) were included. Demographic and clinical data collected included age at diagnosis, sex, race/ethnicity, stage at presentation, treatment modality, and county of residence (metropolitan vs. non-metropolitan). Incidence rates (IRs) per 100,000 were calculated using SEER*Stat and age-adjusted to the 2000 U.S. standard population. Kaplan-Meier survival analysis was performed using GraphPad Prism to evaluate overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 253 patients with PLCH were identified. The cohort was 57% female and 43% male, with 73% White, 15% Black, 6% Hispanic, 3.5% Asian/Pacific Islander, and 1% American Indian/Alaska Native. At diagnosis, 73% had localized disease and 20% presented with metastases. The overall age-adjusted IR was 0.0132 per 100,000, with the highest annual IR observed in 2016 (0.0493), followed by a decline. Females had a 33% higher IR than males (0.01509 vs. 0.01138; $p = 0.028$). While Black patients had a higher incidence (0.0190) compared to White patients (0.0160), the difference was not statistically significant ($p = 0.37$). The highest IR was observed in the 55-59 age group (IR = 0.03840), which was significantly higher than in the 40-44 (IR = 0.01419; $p = 0.0004$) and 35-39 (IR = 0.01261; $p = 0.0001$) groups, though not significantly different from those aged 45-54. Nonmetropolitan counties had a significantly higher IR (0.02507) compared to metropolitan counties (0.01185; $p = 0.0004$). The 5- and 10-year OS rates were 84.38% and 60.08%, respectively, while CSS rates were 96.25% and 93.39%. Adults aged ≥60 years had a significantly shorter median OS (mOS) of 81 months compared to younger patients ($p < 0.0001$; HR 4.19, 95% CI 2.20-7.99).

Conclusions: PLCH is an extremely rare pulmonary neoplasm with excellent cancer-specific survival but modest overall outcomes, likely reflecting comorbidities or delayed diagnosis. Incidence was highest in females, adults aged 55-59, and residents of nonmetropolitan areas, suggesting demographic and geographic disparities. These findings highlight the importance of early diagnosis and smoking cessation. The potential for disease stabilization or regression following smoking cessation differentiates PLCH from other lung neoplasms and underscores the need for timely recognition and intervention. Further investigation is warranted into the molecular framework and development of targeted therapies for this rare disease.

Keywords: Pulmonary Langerhans cell histiocytosis, Smoking related lung cancer, Epidemiology

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.01 Anorexia, an Underreported Adverse Event, Predicts Mortality in Lung Cancer Patients

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Introduction: Lung cancer (LC) is often diagnosed at advanced stage. Anorexia, an underreported condition, is defined by loss of appetite, a phenotypic characteristic of cachexia, a common condition in advanced disease that affects clinical outcomes. Anorexia is graded according to changes in eating habits and weight loss following the Common Terminology Criteria for Adverse Events (CTCAE). This study aimed to assess whether the occurrence of anorexia predicts mortality in LC patients.

Methods: This is a prospective study of LC patients treated between May 2023 and December 2024 at an oncology center in Rio de Janeiro, Brazil. Clinical and demographic characteristics, and the Patient Self-Generated Global Assessment (PG-SGA) were collected to identify patients who reported anorexia on first nutritional assessment, recommended within 60 days. The chi-square test (χ^2) was used to compare categorical variables and the student's t-test for continuous variables. Overall survival was estimated using the Kaplan-Meier method and compared between groups using the Log-Rank test.

Results: A total of 134 patients with LC were included, and 49% had the first nutritional appointment before the start of treatment and 30% within 60 days after. The sample total was made up of 58% females, 90% older than 60 years, 76% advanced stage, eutrophic BMI (26 ± 4,5kg/m with a predominant treatment modality of chemotherapy combined with immunotherapy (30%), chemotherapy (25%) and targeted therapy (22%). The anorexic group (32%) was older (74.6 ± 8.7 years, p=0.03), 91% had advanced stage (n=39, p=0,041), eutrophic, but with a lower BMI (24.8 ± 3.5 kg/m, p=0.008), with a greater weight loss in the last 6 months 7.6 ± 7.7% (p<0.00), an indicator of anorexia severity, and a higher nutritional risk (PG-SGA: 12.7 ± 5.1, p=0.00). Overall survival was clinically significantly lower in the anorexia group (23.7 vs. 45.2 months, p=0.002)(Figure 1).

Conclusions: The occurrence of anorexia at the first visit was associated with lower survival, reinforcing the importance of early anorexia screening and nutritional interventions to improve clinical outcomes of advanced LC.

Anorexia	N Patients	Median Overall Survival (95% CI)
No	91	42.5 (37.7-47.2)
Yes	43	23.7 (19.8-27.5)

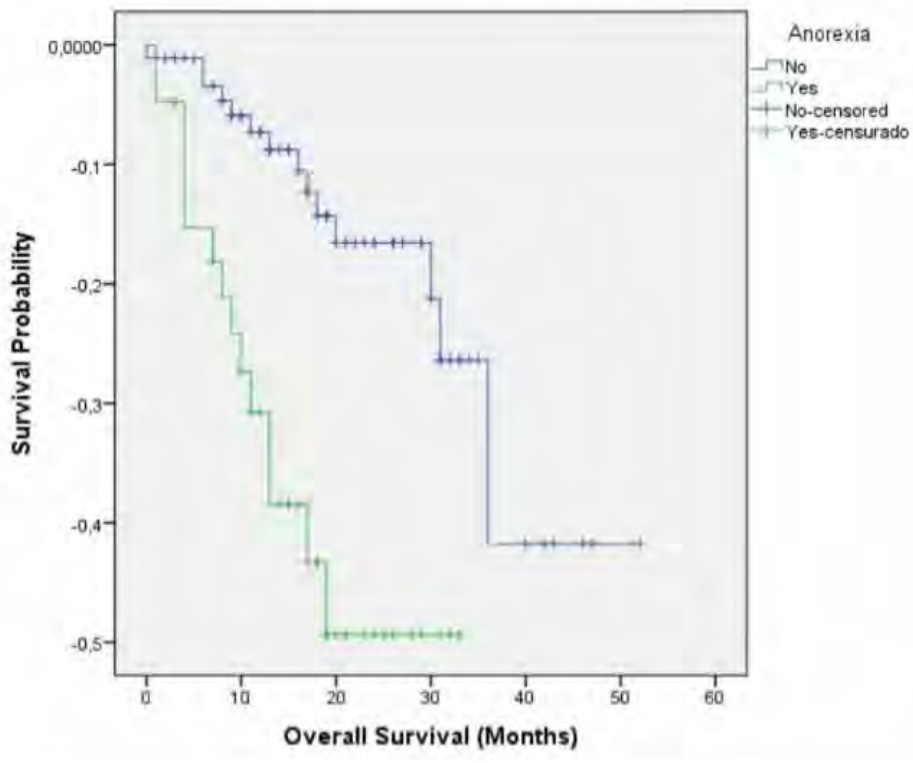

Figure 1. Overall Survival in lung cancer patients according to the anorexia occurrence

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.02 Therapeutic Efficacy of Traditional Chinese Medicine Heat Patch Therapy for People With Lung Cancer

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Introduction: Lung cancer remains a leading cause of cancer-related mortality worldwide, with complex pathogenesis involving environmental, genetic, and molecular interactions. While modern medicine focuses on targeting specific mutations (EGFR, KRAS) and signaling pathways (PI3K/AKT/mTOR), Traditional Chinese Medicine (TCM) conceptualizes lung cancer as "lung accumulation," characterized by deficiency in origin and excess in manifestation. Heat patch therapy, an external TCM treatment, combines warming properties with acupoint stimulation to regulate the tumor microenvironment through local thermal effects and transdermal drug delivery. This study investigates the antitumor effects, immunomodulatory functions, and clinical applications of heat patch therapy in the management of lung cancer.

Methods: This randomized controlled trial enrolled 60 people with stage III-IV non-small cell lung cancer, randomly assigned to either the heat patch group (n=30) or control group (n=30). Inclusion criteria included pathological diagnosis and TCM pattern differentiation of "phlegm-dampness accumulating in the lung" or "yang deficiency with cold coagulation." The treatment group received daily application of medicinal patches on acupoints BL13 (Feishu), CV17 (Shanzhong), and BL43 (Gaohuang) for eight weeks, in addition to conventional chemotherapy. The herbal composition included Cinnamomi Ramulus (15g), Sinapis Albae Semen (12g), Curcumae Rhizoma (10g), and Astragali Radix (20g). Evaluation metrics included tumor response (RECIST 1.1 criteria), serum biomarkers (CEA, PD-L1), T-cell subsets, TCM symptom scores, and safety parameters.

Results: The heat patch group demonstrated significantly higher objective response rate (36.7%) compared to the control group (30.0%, $p<0.05$). In vitro experiments revealed that herbal extracts inhibited A549 lung cancer cell proliferation (IC50=32μg/mL) and downregulated PI3K/AKT pathway phosphorylation. Immunologically, the treatment group showed improved CD4+/CD8+ ratio (from 1.5 to 1.8, $p<0.01$), 18% reduction in serum PD-L1 levels, and 25% decrease in tumor lactate concentration, suggesting reversal of the Warburg effect. Clinically, cough and shortness of breath scores decreased by 40% and 35% respectively in the treatment group ($p<0.01$), with Karnofsky Performance Status improving by 15 points and chemotherapy-related nausea reduced by 50%. Only three participants developed mild skin rash, with no hepatorenal abnormalities observed.

Conclusions: TCM heat patch therapy achieves integrated therapeutic effects through a triple mechanism of "medicinal-acupoint-thermal" action, demonstrating both local tumor-suppressing and systemic regulatory functions. This approach not only inhibits tumor proliferation and angiogenesis but also modulates the immune-metabolic microenvironment and reverses T-cell exhaustion. Clinical data confirms improved tolerance to chemoradiotherapy and significant amelioration of cancer-related fatigue and respiratory distress. This study establishes an evidence-based foundation for incorporating external TCM therapies into multidisciplinary lung cancer management, highlighting the unique value of integrating disease and pattern differentiation in precision medicine.

Keywords: Heat Patch Therapy, Traditional Chinese Medicine, Tumor Microenvironment

EP.15.03 Why Are Patients With Non-Small Cell Lung Cancer in Stage I-IIIA Considered Inoperable? A Registry Study From Denmark

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Introduction: : Surgical resection is the first-line treatment for patients with stage I-IIIA non-small cell lung cancer (NSCLC) when feasible, offering the best chance for long-term survival. However, a significant proportion of patients are deemed inoperable despite technically resectable tumors. The decision to withhold surgery is influenced by multiple factors, including tumor burden, mediastinal lymph node involvement, and patient-specific factors, necessitating a multidisciplinary team (MDT) evaluation to determine the most appropriate strategy.

Methods: This retrospective registry-based cohort study included patients diagnosed with NSCLC in stage I-IIIA in the Capital Region of Denmark between January and December 2022. Patients were stratified into "Surgery" and "No Surgery" groups based on treatment records. Data on demographic variables, comorbidities, pulmonary function, performance status, and MDT decisions were extracted from the Danish Lung Cancer Registry and medical records. Logistic regression analyses identified predictors of non-surgical management. The one-year overall survival (OS) rate was estimated using the Kaplan-Meier method. Additionally, preoperative exercise testing was documented.

Results: Among 524 patients with NSCLC in stage I-IIIA, 178 (34%) did not undergo surgery. Advanced age (≥ 80 years, OR 1.298), poor performance status (ECOG-PS ≥ 2, OR 1.443), comorbidities (OR 1.116), and stage IIIA disease (OR 1.181) were significantly associated with non-surgical management. The primary reasons for non-operative management in MDT decisions were low pulmonary function or poor performance status (29.2%) and comorbidities (18.0%). Notably, in 19.7% of cases, no justification for "No Surgery" was recorded. Furthermore, preoperative exercise testing was not documented for any patient. One-year OS was 95.7% in the "Surgery" group versus 82.0% in the "No Surgery" group.

Conclusions: The findings of this study align with previous research, indicating that patients with stage I-IIIA NSCLC are often deemed inoperable due to comorbidities, poor performance status, or advanced age. A novel insight from this study is its documentation of the rationale for non-operative treatment, as recorded in the MDT decision-making process. Additionally, our findings indicate that exercise testing is not utilized in the assessment process, despite being recommended in current guidelines. The study also suggests a difference in overall survival between operative and non-operative treatment; however, these results should be interpreted with caution due to study limitations. Further research is needed to explore the underlying reasons for treatment decisions. Moreover, future studies could examine whether the implementation of exercise testing, as recommended, may improve the assessment of patients with lung cancer and their surgical eligibility.

Written justification in the journal notes from the MDT conference

Justification	N=178
Low lung function or poor PS	52 (29,2)
No clear justification	35 (19,7)
Comoroidities	32 (18,0)
Cancer in lymph nodes (N2)	21 (11,8)
Other cancer	15 (8,4)
Multiple tumors	11 (6,2)
Technical reasons	8 (4,5)
Patient chooses not to undergo surgery	4 (2,2)

Frequencies and percentages of patients in the group

Keywords: Resectable non-small cell lung cancer, inoperability, overall survival

EP.15.04 Lung Function Before and After Development of Checkpoint Inhibitor Pneumonitis: Insights for Risk Assessment and Recovery

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Introduction: Checkpoint inhibitor pneumonitis (CIP) presents with highly heterogenous clinical manifestations and disease trajectories, with severe cases linked to increased morbidity and mortality. Lung function testing offers a non-invasive approach to assessing the risk of CIP-related complications and potential long-term respiratory sequelae. This study investigates the relationship between lung function parameters before and after CIP diagnosis to determine their predictive and prognostic value.

Methods: A retrospective analysis was conducted of patients who received immune checkpoint inhibitors (ICIs) between 2015 and 2024 at Austin Health, Melbourne. Patients diagnosed with CIP were identified alongside a comparator cohort without CIP. Those with available pre-diagnosis lung function testing were included in the final analysis. Lung function parameters, including spirometry and diffusion capacity, were assessed in relation to CIP severity. Post-diagnosis lung function was analysed to evaluate recovery following CIP treatment.

Results: A total of 46 patients were included (21 CIP cases, 25 non-CIP cases), with a mean age of 75 years (95% CI: 69-74) and a predominance of males (n=25). Most patients had an Easter Cooperative Oncology Group (ECOG) performance status of 1 (n=30, 65.2%) prior to developing CIP. Among CIP cases, 11 patients (23.9%) developed grade 2 pneumonitis, while 6 (13%) and 4 (8.7%) developed grades 3 and 4, respectively. No significant difference in baseline lung function or diffusion capacity were observed between CIP and non-CIP cohorts. Regression modelling indicated that abnormal diffusion capacity (β = -3.273 95%CI: -5.951,-0.594; p=0.017) and ECOG performance status (ECOG 1 β= -3.625 95%CI: -6.146,-1.104); p=0.005) were predictive of increased severity of CIP. In a subset of patients with post-diagnosis lung function assessments (n=7), a significant decline in Forced Expiratory Volume in one second (FEV1) % predicted and diffusing capacity of the lungs for carbon monoxide (DLCO)% predicted was observed within the first 18 months (Figure 1).

Conclusions: CIP is associated with substantial morbidity and mortality. Within the limitations of this small retrospective study, we demonstrated that pre-diagnosis gas transfer and ECOG performance status was predictive of progression to severe forms of CIP. Persistent reduction in FEV1 and DLCO were observed in some patients , several months following initial CIP diagnosis. Larger prospective studies are required to better assess the role of lung function testing in CIP risk assessment and management.

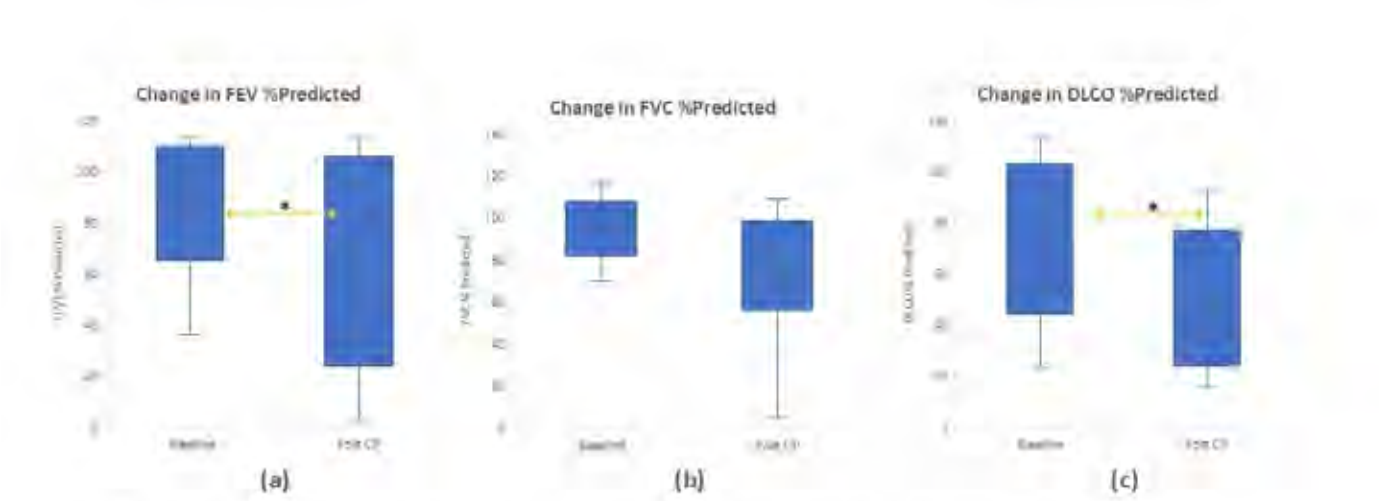

Figure 1. Box and whisker plot depicting the changes in lung function and gas transfer before and after development of CIP:

a) FEV1 %predicted: mean difference = 16.48 (95% CI: -3.69-36.64), p value of 0.046; b) FVC %predicted: mean difference = 23.35 (95% CI: -7.23-53.92), p value of 0.055; c) DLCO %predicted: mean difference = 17.33 (95% CI: -2.13-36.79), p value of 0.036.

FEV1: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide

Keywords: Checkpoint inhibitor pneumonitis, lung function, immunotherapy

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.05 Wearable Devices and ePROs for Perioperative Continuous Monitoring in Thoracic Surgery

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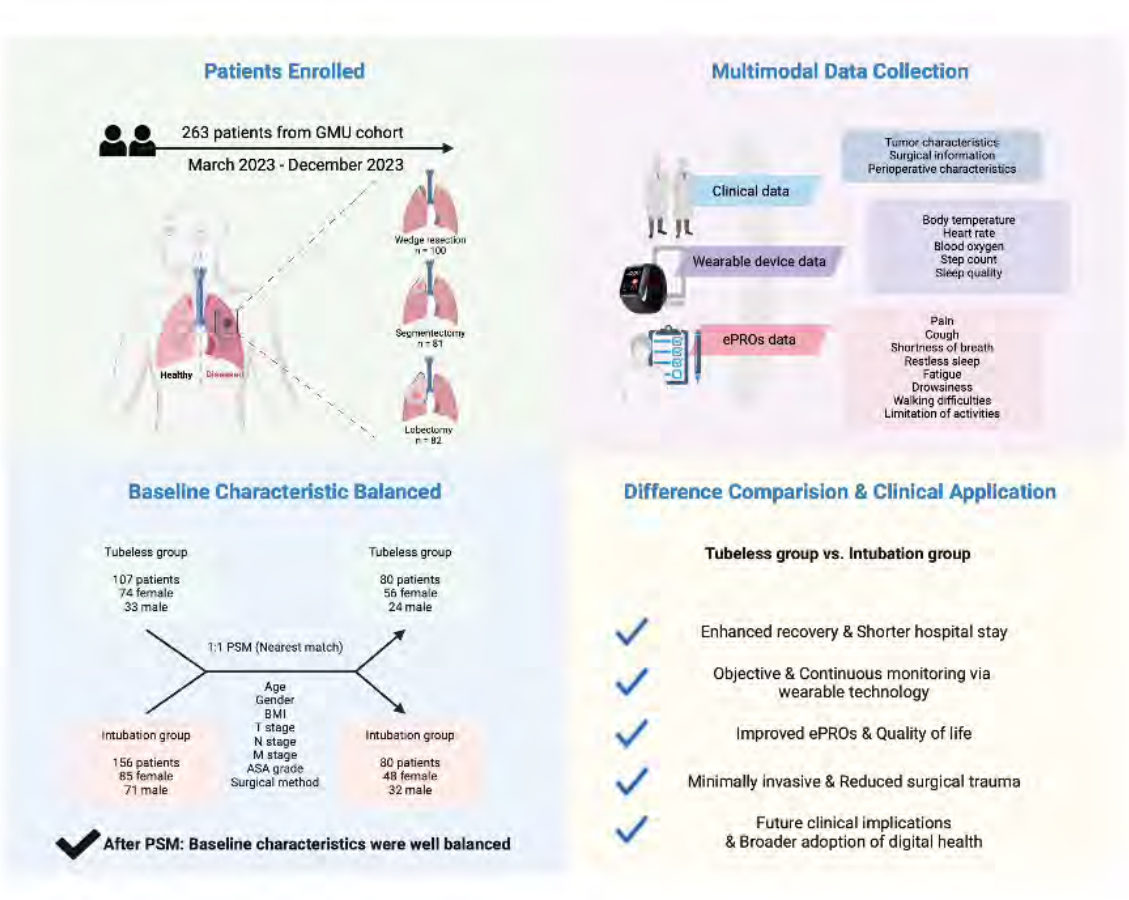
Introduction: Minimally invasive thoracic surgery (MITS) has improved lung cancer outcomes but requires enhanced postoperative care. Traditionally episodic care model has limited timely and multi-dimensional monitoring of patients. Recent technological advances in multimodal digital devices, including wearable device and electronic patient reported outcomes (ePROs), offer a promising solution to these challenges. However, current studies focus on only a few parameters and limited application in thoracic surgery.

Methods: We included 288 non-small cell lung cancer (NSCLC) patients from the GMU cohort, which includes 2,757 participants with various lung diseases. Digital data were collected during hospitalization using a commercial smartwatch combined an electronic patient-reported outcomes (ePROs) questionnaire, while clinical data was obtained from electronic health record (EHR). Agreement between the digital device and EHR was evaluated via Bland-Altman analysis. Time-series data were normalized for continuous outlier monitoring and threshold analysis of ePROs scores was used to explore associations across different modules.

Results: Throughout hospitalization, digital devices provided a subjective overview of the patients' recovery trajectories. Agreement analysis confirmed that wearable devices deliver accurate and clinically relevant measurement. Meanwhile, wearable devices demonstrate significant potential in outlier detection compared to episodic care model, offering accurate and sensitive monitoring of outliers between traditional measurement intervals. Using a thresholding method, we found that wearable metrics was correlated with the severity of ePROs.

Conclusions: These findings highlight the reliability and clinical potential of digital device-based multimodal system within the enhanced recovery after surgery (ERAS) framework, offering a novel approach for continuous perioperative monitoring.



Keywords: Lung cancer, digital device, patients reported outcomes

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.06 Bridging the Gap: Co-Designing Tools to Improve Equity in Lung Cancer Screening Care Pathways

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Introduction: Lung cancer remains the leading cause of cancer-related death in Canada due to late-stage diagnosis. Although low-dose computed tomography (LDCT) screening can reduce mortality by up to 20% among high-risk individuals, uptake remains low—especially among underserved populations facing systemic barriers, incomplete smoking history documentation, and fragmented referral pathways. In Ontario, the Ontario Lung Cancer Screening Program (OLSP) provides a pathway for LDCT screening to those at high risk, but systematic identification of eligible individuals is lacking, representing a missed opportunity for early diagnosis and timely care. The Smoking Cessation Treatment for Ontario Patients (STOP) program is Canada's largest smoking cessation initiative, with over 416,000 participants and comprehensive demographic and smoking-related data contained within an Electronic Medical Record (EMR). Leveraging STOP data to identify and refer high-risk individuals to OLSP through decision-support prompts could streamline referral workflows, improve documentation, facilitate timely care, and reduce inequities. In this study, we will leverage STOP's infrastructure to streamline the process of connecting high-risk individuals to LCS in the OLSP, thereby enhancing early detection, promoting equitable access and improving patient care pathways with a focus on structurally underserved populations.

Methods: This is a patient-partnered, interdisciplinary study that employs qualitative methods using interpretive description to co-design and implement practical screening tools. Guided by Trauma and Violence Informed (TVIC) principles, the project team will recruit and engage three stakeholder groups: healthcare providers (10), patients (10), and key informants (10) in 1:1 semi-structured interviews and virtual co-design sessions. Our research questions are: (1) What are the perspectives and needs of providers and patients regarding systematic LCS referrals initiated by the STOP smoking cessation program? (2) What patient, provider and system-level barriers and facilitators must be addressed to ensure tools are practical, equitable, and user-friendly? (3) How can a systems-level implementation plan be designed to integrate co-designed tools into the STOP program and support broader adoption across LCS and smoking cessation programs in Canada?

The project team will de-identify and analyze interview data thematically using NVivo software. Themes will focus on barriers, facilitators, and actionable insights for integrating support for LCS referrals into the STOP program. Interview findings will be presented and collaboratively analyzed during the virtual workshop sessions with the stakeholder committee and patient partner panel to refine emerging themes and co-create provider-facing prompts, patient-facing scripts, an implementation plan outlining how to integrate the tools into STOP workflows, and training requirements and scalability considerations.

Results: This study will produce co-designed trauma-informed referral tools, including provider prompts embedded within the STOP EMR, patient-facing scripts to guide the referral process in a patient-centric and accessible way, and a comprehensive implementation plan that is feasible and ready for implementation into the STOP program.

Conclusions: This project promotes timely and equitable access to LCS for high-risk individuals by bridging gaps between smoking cessation and lung cancer care. The project can improve provider workflows, patient-provider communication, and referral processes. It can also directly increase LCS access among underserved populations and potentially reduce lung cancer mortality and treatment burden by facilitating earlier diagnosis.

Keywords: Smoking Cessation, Lung Cancer Screening, Co-design

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.07 Living With Lung Cancer-A Qualitative Exploration of Its Psychosocial Impact

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Introduction: In India , Lung cancer is the most common cancer in men and the most common cause of cancer related deaths. A recent study reported that Lung cancer contributes significantly to the global cancer burden, with tracheal, bronchus, and lung(TBL) cancer accounting for approximately 20.4% of total cancer related deaths and 18.3% of disability adjusted life years(DALY). Beyond its physical burden, the patients are prone to psychological, social and emotional stress; thus, negatively affecting their quality of life. Given these complexities, individuals with lung cancer often struggle with uncertainty, lifestyle adjustements,stigma associated with the disease and burden of managing a long -term illness. The main objectives of the study are to assess the psychological experiences and challenges faced, to understand how the disease impacts daily life and the financial burden imposed.

Methods: Study setting was in a tertiary care hospital where patients came for admission due to complications, follow-up or those who participated in clinical trails. Study design is a qualitative study which was conducted through in-depth interviews through a semi-structured questionnaire which consisted of questions related to demographic information and social, emotional and mental aspects of the disease. After obtaining informed consent, the interviews were conducted and audio-recorded. Initially 6 patients were interviewed, data saturation was observed as most of the themes were repititive. Additionally, 2 interviews were conducted to confirm the data saturation. Each interview lasted for about 25-30 minutes and was transcribed in the local language. After identifying the quotations, it was translated to English. Codes and then later themes were developed by deductive thematic analysis method.

Results: After analysis, 4 main themes and 10 sub themes were developed. The first theme was psychological turmoil and emotional impact which had the sub-themes: " why me", fear of future and uncertainty, persistant stress. The second theme developed was socioeconomic impact which had the sub-themes: financial burden, embarrassment, isolation. The third theme was lifestyle disruption which had the sub-themes: change in body image perception, changes in sleep pattern. The fourth theme was support systems and coping strategies which had support from friends and family, coping mechanisms as sub-themes.

Conclusions: This study highlights the multidimensional psychosocial burden of lung cancer. Understanding this is essential for developing comprehensive strategies that provide holistic support including mental health care, patient education and emapthetic healthcare interactions. Some of the strategies we propose are patient education and self empowerment, promoting positive outlook, enhancing healthcare provider support, community and policy level interventions, peer mentorship and group therapy and psychological support.

Keywords: LUNG CANCER, PSYCHOSOCIAL IMPACT, QUALITATIVE STUDY

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.08 The Lived Experience of Dyspnea and Quality of Life Before and After Lung-Sparing Surgery

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Introduction: Pleural Mesothelioma (PM) is a rare, incurable malignancy of the pleura. The most common symptoms experienced include dyspnea, pain, fatigue, anorexia, early satiety and anxiety. Lung-sparing surgery for PM is considered investigational and involves resection of pleura, pericardium, diaphragm, depending upon the extent of disease. While the primary goal of surgery is to prolong survival, palliation of symptoms and improvement in quality of life (QOL) are taken into consideration when offering surgery. Beyond the standard quantitative measures used to determine successful surgical outcomes, an understanding of an individual's perception of the impact surgery has had on their symptom burden and QOL has not been reported in the literature. The primary aim of this study was to explore the lived experience of dyspnea and QOL before and after lung-sparing surgery.

Methods: The philosophical approach to this study was grounded in hermeneutical phenomenology which combines the interpretive focus of hermeneutics with the exploration of lived experiences and consciousness of phenomenology. Participants underwent in-depth semi-structures interviews, before and 3-4 months after surgery. Interviews were transcribed using NVivo and transcripts were analyzed according to Interpretive Phenomenological Analysis, focusing on detailed examinations of lived experience, the meaning of the experience to participants and how participants make sense of and describe that experience.

Results: The Group Experiential Themes (GETs) before and after surgery included Psychological: Mind supports body in the world; Physiological: Body fighting, enduring, adjusting and adapting in the world; Social: Others sharing and supporting body in the world; Existential: Facing an uncertain future of body living in the world. The emotional impact a diagnosis of PM has on a person is multidimensional and involves elements of time, internal psychological struggles and learning to deal with the reality of the diagnosis. The physical impact of living with mesothelioma can disrupt a person's normal routine and interactions with the world as they perceive it. An individual's interaction with others during an illness experience such as PM can influence the perception of the lived experience for both the individual and others in their world. Facing a serious illness such as PM was disruptive to individual normal bodily routines and interactions with the world.

Conclusions: The results of this study provide valuable insight regarding the essence of the experience of living with mesothelioma, enduring lung sparing surgery and coping with the symptom of dyspnea. This enriched understanding of the experience comes from the voice of the experiencer, not from the usual measures used to determine success of surgery, mitigation of symptoms and optimization of QOL. The lived experience of dyspnea and QOL before and after lung-sparing surgery is a continuum influenced and impacted by physical, psychological, social and existential factors that vary for each individual but are most certainly present at some level. This study provides qualitative evidence that perceptions of dyspnea and QOL play an impactful role in the patient experience, before and after surgery. Healthcare teams must look beyond what is measurable and visible and consider what patients are experiencing physically, emotionally, socially and existentially.

Keywords: pleural mesothelioma, quality of life, dyspnea

EP.15.09 Clinical Decision Flowchart for Optimizing the Use of EGFR Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer: Real-World Data

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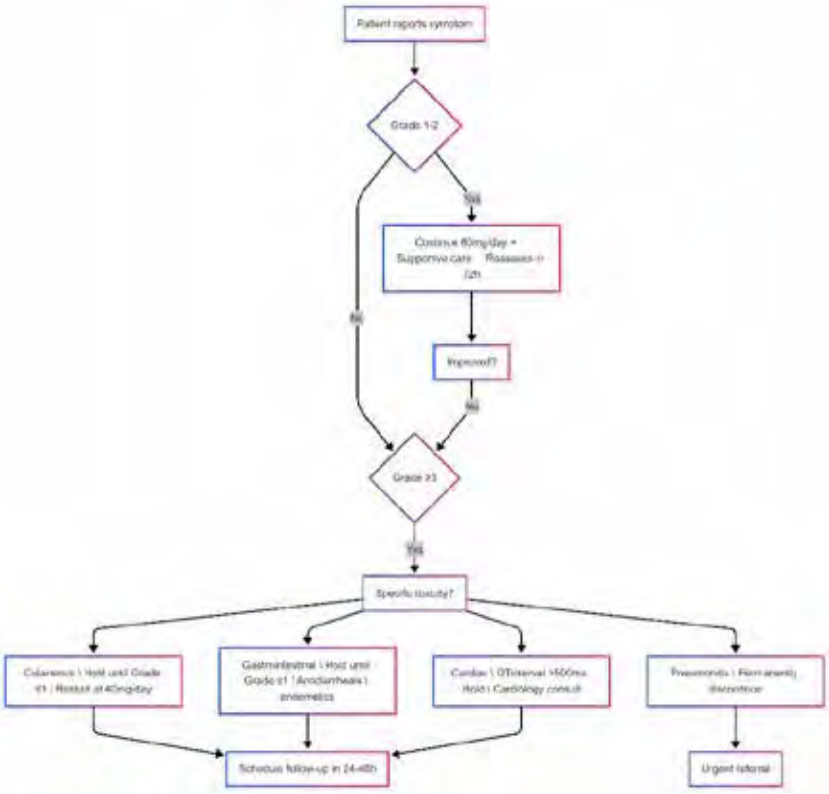
Introduction: Osimertinib represents a significant advance in the treatment of non-small cell lung cancer (NSCLC) with EGFR mutations. The management of related toxicities remains a complex challenge in oncology practice, requiring innovative approaches that combine technology and patient-centered care. While osimertinib has significantly improved outcomes for EGFR-mutated lung adenocarcinoma patients, its toxicity profile often leads to treatment interruptions and reduced quality of life. Current care models frequently lack efficient systems for early toxicity detection and intervention, highlighting the need for more integrated and innovative approaches, incorporating telemonitoring and the role of the multidisciplinary team.

Methods: This is a retrospective cross-sectional study carried out in a private cancer center in Brazil. The data consisted of clinical and epidemiological variables, as well as the detection and intervention of AEs by the multidisciplinary team. AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), and the data were presented descriptively.

Results: We retrospectively analyzed data from 24 patients with NSCLC and EGFR mutations, 84% of whom were stage III-IV, treated with osimertinib at a dose of 80 mg/day for an average of 19 months. The population was predominantly female (83%), with a mean age of 64 years. AEs occurred in 54% of cases, with 37.5% requiring dose adjustment. The most frequent toxicities were cutaneous (44.4%), gastrointestinal (33.3%), hepatic (11.1%), and pneumonitis (11.1%). Management included a dose reduction to 40 mg, which was effective in 100% of cutaneous cases and 66.7% of gastrointestinal cases. Discontinuation was necessary in one case of grade 3 pneumonitis. Patients over 70 experienced severe gastrointestinal toxicities, while cardiac comorbidities increased cardiovascular risk. Symptom management was carried out by a nurse navigator. AEs were grade 1-2 (20%) and 80% of patients had grade 3, with only 4% requiring hospitalization (due to pneumonitis). A flowchart was created to design the management (Figure 1).

Conclusions: The study proposes a clinical decision flowchart integrated into a telemonitoring model, with nursing associated with a multidisciplinary team, allowing for early identification and intervention, thereby reducing the time between symptom manifestation and intervention. The results reinforce the need for active telemonitoring, particularly in the elderly and patients with comorbidities, and highlight the crucial role of advanced practice nursing in patient navigation and the timely implementation of osimertinib treatment adjustments.

PS: We use AI with Mermaid Live Editor to build the flowchart.



Keywords: Telemonitoring, Oncology Nursing, Osimertinib

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.10 Do Enhanced Recovery After Lung Cancer Surgery Programs Risk Putting Primacy of Caring at Stake?

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Introduction: Since nurses play a key role in overcoming implementation barriers in enhanced recovery after surgery programs, successful implementation depends on their care approach during the surgery pathway. To gain insight into nursing in an enhanced recovery after surgery program for lung cancer, we explored its meaning for nurses in a thoracic surgery unit.

Methods: A hermeneutic approach inspired by Gadamer guided the research. Sixteen thoracic surgery nurses participated in focus group interviews. Benner's primacy of caring theory enhanced understanding of the findings.

Results: The thoracic surgery nurses compared the streamlined trajectory in the lung cancer program to working in a factory. Shifting focus away from a dialogue-based, situated care practice compromised their professional nursing identity. The program made combining scientific evidence with lung cancer patients' lifeworld perspectives challenging. Although the nurses recognized that the physiological processes and positive outcomes promoted recovery, they felt each patient's life situation was not sufficiently considered. To meet the program's professional nursing responsibilities and provide comprehensive lung cancer care, specialized thoracic nursing should continue after discharge to allow professional care while meaningfully engaging with the patient's situatedness and lifeworld.

Conclusions: Primacy of caring risks being compromised if accelerated treatment is implemented uncritically. If care is based on the dominant rational justifications underpinning thoracic surgical nursing, living conditions, and patient values might be overlooked, affecting how disease, illness, and health are managed. Our findings focus on obvious unintended consequences of enhanced recovery after surgery programs. To avoid dehumanizing patients, surgical lung cancer programs must adopt a humanistic attitude in a caring practice guided by the moral art and ethics of care and responsibility.

Keywords: NSCLC, Surgery, Nursing

EP.15.11 Patterns of Care and Outcomes in Patients With Advanced Lung Cancer in a Hospital Palliative Care Unit: A Single-Center Retrospective Study

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Introduction: Palliative care is essential for managing patients with advanced lung cancer, yet real-world data on their end-of-life care are scarce. This study evaluates patient characteristics, treatment approaches, and clinical outcomes in a specialized palliative care unit within a university hospital, an uncommon setting that allows for a detailed analysis of hospice care. Patients were assessed using the Palliative Prognostic (PaP) score, Edmonton Symptom Assessment System (ESAS), and PERSONS tool to systematically evaluate symptom burden and palliative needs.

Methods: A retrospective analysis was conducted on patients with advanced thoracic malignancies admitted to the Palliative Care Ward of Modena University Hospital between January 2022 and September 2024. Clinical and demographic data, prior oncologic treatments, symptom burden, palliative interventions, and overall survival from admission were collected. Descriptive statistics summarized patient characteristics, and Kaplan-Meier analysis estimated survival.

Results: A total of 144 patients (42.4% female, median age 75 years) were included, representing 20% of all admissions during the study period. The majority had non-small-cell lung cancer (68.1%), followed by small-cell lung cancer (15.3%) and mesothelioma (2.1%). Seventeen patients (11.8%) lacked a histological diagnosis due to clinical deterioration and non suitability for active treatments. All had stage IV disease, with a median of three metastatic sites. In the 30 days before admission, 79 patients (54.9%) had not received oncologic treatments. Among the 65 treated patients, 45 (31.3%) received systemic therapy, 9 (6.3%) had radiation therapy, and 5 (3.5%) received both. Of note, 72% of patients were not receiving active home-based palliative care at the time of admission. The median time from diagnosis to palliative care admission was 4.8 months, and from the first oncology referral to admission was 4.1 months. Most patients (73.6%) were transferred from other hospital wards, while 22.2% were admitted from home or residential care. The most common reasons for admission were dyspnea (50%), pain (24.3%), and neurological symptoms (19.4%). Median hospitalization duration was 14 days (range 1-73). By discharge, 34% of patients returned home or to other facilities, while 66% died in the unit. PaP scores indicated high (>70%) mortality risk in 26.8% of patients, intermediate (30-70%) in 41.3%, and low (<30%) in 31.2%. The mean ESAS score was 30.7, with dyspnea (38.2%) and pain (13.2%) being the most frequently reported symptoms. Palliative sedation was necessary in 38.9% of cases, primarily for refractory dyspnea (62.2%) and agitation (56.8%).

Conclusions: This study highlights the role of hospital-based palliative care units in managing patients with advanced thoracic malignancies. Despite late referrals, multidisciplinary care provided effective symptom management and dignified end-of-life support. The fact that 31% of patients received systemic therapy within one month of admission raises concerns about the appropriateness of late-line treatments in this population. Notably, 11.8% of patients lacked a histological diagnosis, underscoring the need to better identify those presenting at an advanced stage who are unable to receive oncologic treatment. Strengthening early palliative care integration and timely patient identification can improve quality of care and ensure that even those without a formal diagnosis receive appropriate symptom management and support.

Keywords: lung cancer, palliative care, hospital-based palliative care unit

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.12 Virtual Personalized Exercise Program for Subjects With Lung Cancer: A Feasibility Study

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Introduction: With improved outcomes, cancer is increasingly viewed as a chronic disease, highlighting the need for exercise programs to enhance survivors' quality of life (QOL). Unlike heart disease, diabetes, and pulmonary disease, where exercise has long been recommended, guidance for cancer patients has lagged. Exercise and rehabilitation interventions clearly benefit cancer survivors by improving outcomes, treatment tolerance, delaying progression, and reducing new primary cancer risk. Despite support from societies such as IASLC, exercise programs remain underutilized in lung cancer treatment plans.

Methods: This single-arm, investigator-initiated feasibility study evaluates a virtual exercise platform for patients with non-small cell lung cancer (NSCLC) undergoing surgery with or without peri-operative chemoimmunotherapy (cohort A); radiation ± chemo (cohort B); or systemic treatment only (cohort C). Potentially eligible subjects are referred to physiatry for evaluation, enrollment, and individualized virtual exercise prescription, accessible via personal electronic devices. The primary objective is feasibility, targeting 50% program completion at 12 months. Secondary objectives include satisfaction, measured via patient and provider questionnaires [i.e., System Usability Scores (SUS), Technology Acceptance Model (TAM) Perceived Usefulness (PU) and Perceived Ease of Use (PEOU), and Net Promoter Score (NPS)]. Exploratory outcomes include Pulmonary Function Test (PFT), Six Minute Walk Test (6MWT), and Sit to Stand Test (STS) obtained at the start and 12 months, and QOL changes, measured by FACT-L at baseline and every three months. Descriptive statistics (mean, SD, median, IQR, minimum, maximum for continuous variables; frequencies/percentages for categorical variables) were calculated at months 1, 3, and 6.

Results: Twenty-one patients have consented to the study to date. Two (9%) were subsequently deemed ineligible by PM&R, and eight have withdrawn consent or missed deadlines, leaving ten active patients in the study. Retention among those seen by PM&R was 80%. Compliance increased significantly after a study navigator was recruited in late November. Since then, nine new patients have consented, and the average monthly compliance of all enrolled patients has increased from ~10% to ~40%. The average time from oncology referral to PM&R visit was 11 days. The two eldest participants both aged 77 have shown the highest engagement. SUS suggested fair usability at 100%, 80%, and 75% at months 1, 3, and 6, respectfully. Median TAM PU scores were 4.39, 5.57, and 4.32 at months 1, 3, and 6; PEOU remained 4.07 throughout and NPS was 75 at month 3, which is an excellent rating.

Conclusions: This pilot study demonstrates that a virtual exercise platform is feasible in a lung cancer population. Larger validation studies are needed to demonstrate impacts on QoL and treatment outcomes. Clinicaltrials.gov ID: NCT06540495

Keywords: Non-Small Cell Lung Cancer, Exercise, quality of life

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.13 Pilot Study of Exercise Program and Monitoring by a Lung Cancer Patient Navigator During Chemoradiotherapy for Stage III Lung Cancer

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Introduction: Stage III locally advanced non-small cell cancers (NSCLC) patients are treated with definitive chemoradiation (chemoRT) followed by maintenance immunotherapy (durvalumab). Specialized multidisciplinary approach combining medical oncology management with symptom management, nutritional support and exercise plans to improve physical functioning in lung cancer patients are increasingly explored and shown to be beneficial. The use of patient navigators may help patients with the necessary support throughout their cancer journey to connect the patient with the necessary community and hospital resources. We conducted a feasibility study incorporating supervised exercise program in lung cancer patients receiving definitive chemoRT with the assistance of lung cancer patient navigator throughout the program.

Methods: Patients≥ 21 years old, diagnosed with stage III NSCLC seen at the Tan Tock Seng Hospital oncology clinic who will be initiated on definitive chemoRT between June 2023 to August 2024 were eligible. The exercise program will span 8 weeks duration. On the first visit, the patient will be assessed by the exercise physiotherapist and cancer rehabilitation physician (6 mins. walk test). Patients will be taught exercises that they can self-administer at home. A care navigator will contact patient weekly to check for compliance and discuss any difficulties faced by patient with the exercises. The patient will continue with self-administered home exercises with the care navigator contacting patient weekly until the last week 8 where patient will return for review assessment by physiotherapist and rehabilitation physician.

Results: We screened and invited 28 stage III lung cancer patients who are planned for definitive chemoRT and only 5 patients agree to participate and are recruited to the pilot exercise study (acceptance rate of only 17.9%). There is high screened fail rate, and the common factors include high dyspnoea score, comorbidities unsuitable for exercise, presence of thrombosis, sequential chemo then radiation and falls history. Two patients have withdrawn midway through the exercise program in view of inability to complete the exercises due to prolonged admissions and medical issues. 6MWT improved with the program albeit not statistically significant. All of patients had experienced fatigue and breathlessness during the exercises and had to reduce their exercise duration/intensity; however, they managed to continue some physical activity during the chemoRT period. Patients shared subjectively that it improved their well-being and helped them to relax during the chemoRT treatment.

Conclusions: The low uptake of exercise program in stage III lung cancer patient in this single institution in Singapore has shown a huge discrepancy in level of acceptance for exercise during chemoRT compared to the prior reported literature in Caucasian populations. Many of the stage III lung cancer patients are already having difficulty adjusting to the chemotherapy and daily RT, leading to a low uptake despite active screening by the nurse coordinator during this 1-year period. The study provides insight into the barriers to recruitment for exercise programs in Asian patients who may have different concerns and physical capacities for ongoing physical workout during their treatment course. This will inform future trial designs concerning rehabilitation programs peri-chemoRT period for lung cancer patients.

Keywords: Exercise program, lung cancer nurse navigator, stage III lung cancer

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.14 Empowering Lung Cancer Care: The Role of AI Chatbots to Promote Exercise Oncology

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Introduction: Exercise oncology has demonstrated significant benefits in improving the physical and psychological well-being of patients with lung cancer. Involving patients in personalized exercise programs can improve their quality of life, minimize the side effects related to treatment, and improve general resilience during the lung cancer journey. Limited information and adherence of cancer patients to physical exercise is a significant concern in cancer care. Despite the well-documented benefits of exercise, such as improved quality of life and general resilience, enhanced physical function, and potentially better treatment outcomes, there remains a gap in awareness and understanding among patients regarding the importance of incorporating exercise into their treatment regimen. Simultaneously, AI chatbots have emerged as a transforming tool in oncological care, providing immediate access to credible information, facilitating communication and support for behaviour change. These chatbots can also monitor the physical activity levels of patients, offering feedback and motivation in real time, which can reinforce adherence to exercise regimes. The objective of this research is to evaluate and compare the accuracy of several popular free AI chatbots when responding to specific questions concerning the impact of exercise on lung cancer patients.

Methods: We reviewed a range of commonly available tools for patients and selected the most frequently used free chatbots for our analysis: ChatGPT, Google Gemini, Microsoft Copilot, and Claude. We therefore posed five questions to AI chatbots regarding the role of physical exercise in patients with lung cancer, the anticipated benefits, and the timing and methods involved in performing physical exercise.

Results: The results of our analysis are summarized in Table 1.

	Google Gemini	Microsoft Copilot	Claude	Chat GPT
Is exercise contraindicated in lung cancer patients?	Exercise is not contraindicated for lung cancer patients	Exercise is not universally contraindicated for lung cancer patients. However, there are specific situations where exercise might need to be modified or avoided	The relationship between exercise and lung cancer patients is complex, and the recommendations can vary depending on the type and stage of cancer	Exercise is generally not contraindicated for most lung cancer patients and can offer many benefits
How can exercise improve the quality of life for lung cancer patients?	Reducing cancer-related fatigue; enhancing mental wellness; increasing muscle strength and improving management of specific side effects	Reducing fatigue, and enhancing physical function during cancer treatment	Improving physical function and quality of life, reducing fatigue and depression	Reducing fatigue, depression, anxiety; increasing muscle strength, cardiovascular fitness and immune function
How many times a week should a lung cancer patient exercise?	Both aerobic and resistance exercise 2-3 times a week is a good general guideline	3-5 times a week, depending on the individual's energy levels and treatment stage. Additionally, incorporating resistance training at least 2 days a week and stretching exercises is recommended	2-3 times per week of moderate-intensity exercise. This can be gradually increased as the patient tolerates it	At least 3-5 times a week of physical activity, with adjustments made based on how they feel and their specific treatment or recovery needs
What type of exercise is recommended for a lung cancer patient?	A combination of aerobic, resistance, flexibility, and balance exercises	A combination of walking, yoga, swimming, tai chi, stretching	A combination of aerobic exercise like walking and cycling, flexibility like yoga and Tai Chi and balance exercises	Low-impact activities like walking, swimming, cycling, or yoga

Although the positive impacts of exercise on the well-being of oncology patients are well-documented, the responses indicate the limited information about how tailored exercise regimens can be effectively implemented with adapted physical activity programs. The absence of specific indications related to the expertise of kinesiologists in this setting suggests that their contributions to developing individualized exercise plans are not sufficiently recognized or understood within the context of cancer care.

Conclusions: As research continues to explore the effectiveness of these integrations, it is crucial to evaluate the precision and reliability of AI chatbots' responses. By incorporating more specific exercise recommendations in chatbot functionalities, patients could receive more specific information about exercise oncology. These evaluations will be vital to ensure that improved services with AIs align with evidence-based oncology practices.

Keywords: Exercise oncology, AI chatbots information, supportive care

EP.15.15 Lived Experiences and Needs of People Living Long-Term With Metastatic Non-Small Cell Cancer: A Qualitative Study

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Introduction: Until recently, persons diagnosed with metastatic non-small-cell lung cancer (mNSCLC) faced a dire prognosis. In 2016, the IASLC Lung Cancer Staging Project reported a worldwide 5-year overall survival of about 6% for persons with mNSCLC. However, advances in precision oncology have substantially improved the prognosis for specific subtypes of mNSCLC patients. For example, people with anaplastic lymphoma kinase (ALK)-translocations have achieved a 5-year overall survival of 62.5% with first line targeted therapy. Yet, beyond the view of cancer-directed treatment, we have a limited understanding of how to support and care for this growing population. Worldwide, less than a handful of studies have explored the lived experiences of persons with mNSCLC who are on targeted or immunotherapies. In the care setting, the services and supports designed for persons post-treatment without active disease may not be well suited for people living long-term with disease. Given this context, we sought to: (1) explore the lived experiences and needs of persons receiving targeted therapy agents or immunotherapies for mNSCLC and (2) identify key components of ongoing care and supports to design future interventions.

Methods: Guided by qualitative description, we conducted semi-structured, one-on-one interviews with persons with mNSCLC who are receiving long-term targeted therapy agents or immunotherapies. Recruitment occurred via community-based approaches. Interviews explored participants' experiences living with mNSCLC, including their physical, emotional, and practical needs, and their views on services and supports that would help meet their needs and optimize their quality of life. All interviews were conducted by the same researcher experienced in qualitative methods, audiotaped, and transcribed verbatim by an experienced transcriptionist. Data analysis involved constant comparative analysis, a technique commonly used in descriptive qualitative research. Team meetings were held to review, question, and clarify findings.

Results: Nine individuals (3 male, 6 female) participated in this study. Participants identified significant gaps in care, including delays in biomarker testing, limited disease-specific information, and concerns about accessing treatment beyond first line therapies. Physical challenges included fatigue, cognitive issues, and pain, while emotional needs centered on anxiety, stigma, finding meaning, and uncertainty about the future. Practical barriers, such as financial strain, travelling for treatments, and insurance limitations, complicate the long-term management of one's disease. Participants emphasized the need for improved provider communication and collaboration, automated referrals to supportive care services, and ongoing, multidisciplinary care (versus the short-term, fragmented, and episodic services many participants described experiencing). Suggested interventions included accessible and trustworthy informational resources and integrated healthcare services and programs tailored for persons living long-term with metastatic cancer.

Conclusions: Existing cancer survivorship services were designed for persons without active disease and may not meet the needs of persons living with metastatic cancer, a growing population worldwide. One example is the short-term nature of many survivorship services, which are less suitable for people living with persistent symptom burden and uncertain prognosis. The information gained from this study is informing the co-design of services to better support persons with mNSCLC who are living long-term in the era of targeted and immunotherapies.

Keywords: metastatic cancer, qualitative inquiry, lived experiences

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.16 Patient's Understanding of Follow-Up Post Curative Primary Lung Cancer Surgery

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Introduction: Follow up is an important part of patient care post primary lung cancer resection due to the possibility of cancer recurrence or the development of a new primary lung cancer. We aim to explore post operative patient's with a lung cancer understanding of follow-up and how we can implement and support this practice.

Methods: Between 01/08/2023 and 31/08/2023 every curative intent surgical patient was given a questionnaire to complete whilst attending follow-up clinics. This was rolled out over three UK thoracic surgical centers/Diagnostic centers and targeted patients with lung cancer undergoing follow-up post curative primary lung cancer surgery (excluding carcinoids, recurrence). 148/155 questionnaires were returned, collecting information on demographics, smoking status, operation performed, follow-up period post-surgery and patient understanding of follow-up. The responses were collated, compared and interpreted by the authors

Results: 148/155 (96%) patients responded. 62% female, 36% male. 80% Ex-smokers, Lobectomy most common operation 64%. 97% of patients' aware follow-up was required, and 72% identified that this would be for 5 years. 68% knew their diagnosis prior to surgery and 58% their final staging, 9% understood TNM. 58% knew their lung cancer nurse specialist (LCNS) and 54% when radiological investigations would be performed. 57% recall being given advice on improving their health and wellbeing, from (LCNS) 30%. 45% recalled a healthcare professional discussing recurrence. 34% knew the potential signs and symptoms of recurrence.

Conclusions: This study has identified a gap in patients' knowledge and understanding of follow-up: The necessity of follow-up; TNM stage relevant to individuals; Schedule and frequency of radiological tests; Signs and symptoms suggestive of lung cancer recurrence. The development of a information leaflet patients with lung cancer by LCNS aims to address this need.

Keywords: Surgery, Follow-up, Communication

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.17 The Role of Pneumonia in Mortality Among Hospitalized Patients With Advanced Lung Cancer

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Introduction: Patients with lung cancer are are at high risk of developing pneumonia, particularly those with advanced and terminal-stage disease. Analyzing the occurrence of pneumonia in deceased hospitalized lung cancer patients would deepen the understanding of prognostic characteristics in advanced lung cancer, refine the treatment strategies, and ultimately improve the quality of life and extend survival time for these patients.

Methods: A retrospective analysis was conducted on hospitalized patients with primary lung cancer who died in the Lung Cancer Department of Beijing Arion Cancer Center from February 2021 to February 2025. Demographic and clinical variables were extracted from the electronic medical record system.

Results: 52 patients met the inclusion criteria, including 43 males and 9 females, with a mean age at death of 66.36±11.23 years. Pathological types included adenocarcinoma (26, 50%), squamous cell carcinoma (18, 34.61%), small cell carcinoma (5, 9.61%), large cell carcinoma (1, 1.92%), and mixed type (2, 3.84%). At the final hospitalization, 43 patients (82.69%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score >2. Metastases were present in one or more sites in 91.2% of the patients, and 82.3% had received second-line or subsequent treatment. A total of 36 patients (69.23%) died directly or indirectly from pneumonia. Sputum samples from these patients underwent microbiological testing, yielding 103 isolated strains. Gram-negative bacilli accounted for 59 strains (57.28%), predominantly Pseudomonas aeruginosa (22.03%), followed by Klebsiella pneumoniae, Escherichia coli, and Acinetobacter baumannii, which showed sensitivity to third-generation cephalosporins, aminoglycosides, and carbapenems. Gram-positive cocci comprised 16 strains (15.53%), primarily coagulase-negative staphylococci (10.08%), followed by Staphylococcus aureus and Enterococcus faecium, with sensitivity to vancomycin and linezolid. Fungi constituted 28 strains (27.18%), predominantly Candida albicans (14.23%), followed by Candida tropicalis and Candida glabrata, which were sensitive to voriconazole and amphotericin B. Antibiotic therapy was administered to all 36 patients with pneumonia. Among them, pneumonia was temporarily controlled in 7 patients (19.44%), with a duration from the last pulmonary infection to death exceeding 30 days. For the remaining 29 patients (80.55%), the mean duration to death was only 9.86±7.71 days, with the shortest interval being 1 day.

Conclusions: Pneumonia is a major complication and leading cause of death in patients with advanced lung cancer. Gram-negative bacilli are the primary pathogens, but fungal infections require vigilant monitoring. Early detection of pneumonia and integration of pneumonia-specific effective therapy into palliative care would systematically improve outcomes for advanced lung cancer patients.

Keywords: Pneumonia, Advanced lung cancer, Mortality

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.18 Characteristics and Clinical Outcomes of Hispanic Patients With Thoracic Malignancies Requiring ICU Admission: A Single Center Experie

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Introduction: Patients with thoracic malignancies (TMs) admitted to the intensive care unit (ICU) face challenges owing to advanced disease, comorbidities, and organ failure risk. Lung cancer (LC) is the leading cause of cancer-related mortality worldwide and often requires ICU admission. Recent therapeutic advancements have improved survival rates but increased complication risks. This study aims to delineate the clinical characteristics, comorbidities, interventions, and outcomes of TM patients admitted to the ICU while examining differences based on cancer subtype and mutation status.

Methods: This retrospective study included patients diagnosed with TMs who were admitted to the ICU of a Latin America reference hospital between July 2022 and December 2024. Demographic, clinical, treatment, and hospital outcome data were extracted from the medical records. Statistical analysis, including bivariate analysis, was conducted to evaluate the associations between clinical features, lung cancer subtypes, mutations, and outcomes, with significance set at $P < 0.05$.

Results: We analyzed 41 patients with TM admitted to the ICU (57 ICU admissions). The median age was 65 years (r, 45-80), with 60% male. Predominant LC subtypes were non-small cell lung cancer (NSCLC) (70%) and small cell lung cancer (SCLC) (30%), followed by pleural mesothelioma (MPM) (9.8%), thymic tumors (TT) (7.3%), and neuroendocrine thoracic tumors (NETs) (7.3%). Molecular testing found EGFR mutations (20%), KRAS mutations (15%), and ALK rearrangements (10%) among the subgroup of patients with adenocarcinoma. NSCLC patients had lower ICU mortality (55%) than SCLC (70%). Among NSCLC patients, EGFR mutations showed lower mortality (40%) than KRAS (65%) and ALK (60%). The 30-day mortality rate was 30%, varying by subtype: SCLC (100%), NSCLC (40%), NET (20%), and TT (0%). For the general population, the post-ICU overall survival (OS) was 11.7 months (95%CI 3.7-18) and 8.7 months (95%CI 3.3-24.3) for NSCLC patients. Comorbidities were observed in 78% of the patients with cardiovascular diseases (45%) and chronic lung conditions (33%). Invasive ventilation was needed in 65% of cases, and 60% required vasoactive support. Primary complications were respiratory failure (50%) and sepsis (30%), which were caused by respiratory infections in 60% of cases. Higher mortality was significantly associated with infections of any origin ($P = 0.0027$), sepsis ($P = 0.00079$), and the requirement of a high-flow nasal cannula ($P = 0.0056$) or vasoactive agents ($P = 0.02$).

Conclusions: Hispanic patients with lung cancer admitted to the ICU experienced high mortality, particularly those with SCLC and NSCLC-harboring KRAS mutations. Conversely, patients with EGFR mutations and ALK rearrangements exhibit better outcomes. Identifying the clinical and molecular factors associated with a poor prognosis can inform tailored ICU care and early palliative interventions. Further research is warranted to optimize management strategies for high-risk patients.

Keywords: Thoracic malignancies, Intensive Care Unit, Clinical outcomes

EP.15 MULTIDISCIPLINARY CARE: NURSING, ALLIED HEALTH AND PALLIATIVE CARE

EP.15.19 Patients With Advanced-Stage Lung Cancer in Intensive Care Unit, a Retrospective Observational Study Assessing Their Prognosis

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Introduction: The admission of patients with advanced-stage lung cancer to the intensive care unit (ICU) is often a matter of debate. However, little is known about their prognosis since the era of immune checkpoint inhibitors (ICIs) and targeted therapies. In this study, we aimed to evaluate the mortality rate of patients with advanced-stage lung cancer admitted to ICU and the characteristics of those who died in ICU.

Methods: We conducted a retrospective monocentric study which included patients with metastatic or locoregionally-advanced-stage lung cancer (according to UICC eighth edition) admitted to ICU of CHU UCL Namur (Godinne) (academic institution) from August 2018 to August 2023, aiming to evaluate their mortality rate and characteristics of those who died in ICU in an era with availability of ICIs and targeted therapies. Following patient data were collected : general clinico-pathological characteristics, reasons for admission to ICU, and delivery of intensive care. The study was approved by the Ethical Comittee of CHU UCL Namur (Godinne).

Results: Over this period, 82 patients with a metastatic or locally-advanced-stage lung cancer were urgently admitted to ICU. Majority of patients were admitted to ICU for respiratory issues (57%) and cancer-related reasons (44%). Median age was 72 years. Majority (72%) were men with an ECOG performance status >2 (68%). Non-small cell lung cancer (NSCLC) was observed in 81% and small cell lung cancer (SCLC) in 17% of patients. Majority were receiveing a first-line anti-cancer treatment (59%) or had not yet initiated it (34%). Twenty-nine% died in ICU, 43% died in hospital but outside ICU, and 70% died within a year. Fourty-five% of patients (n=37) received an anti-cancer treatment after their stay in ICU. Average SAPS II and APACHE II scores were respectively 43 and 20 at admission. Half (51%, n=42) of patients had mechanical ventilation, one quarter (24%, n=20) high-flow nasal oxygenation, and one quarter (24%, n=20) non-invasive ventilation. Half (48%, n=39) of patients received vasoactive or inotropic support and 35% developed acute renal failure, but only two patients were hemofiltered. Main factors for mortality in ICU were severity scores (APACHE II median score at 17 in the ICU survival group (SG) versus 25 in the ICU mortality group (MG) and SAPS II median score at 38 in the ICU SG versus 59 in the ICU MG, p-value<0,01), mechanical ventilation (38% in the ICU SG versus 83% in the ICU MG, p-valu<0,01), and acute renal failure (24% in the ICU SG versus 63% in the ICU MG, p-value<0,01). However, in a one-year analysis, only the ECOG performance status at baseline, before admission in ICU, was identified as a poor prognosis factor (84% of patients who died at 1 year had an ECOG > 2 versus 32% in the group still alive at 1 year, p-value<0,01).

Conclusions: In this study ICU mortality was linked to the severity of the illness bringing them to ICU, while long-term mortality was related to the performance status. Further studies, prospective and involving a larger number of patients, are warranted.

Keywords: Lung cancer, Critically ill patients, Management

EP.16 PATIENT ADVOCACY

EP.16.01 Is Follow Up for Lung Cancer Surgery Evidence Based Within the UK - a Critical Review of Protocols

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Introduction: Our aim is to look at surgical follow-up protocols in different UK trusts to critically review and see if follow up varies post-surgical patient with lung cancer.

Methods: A literature review around this topic was conducted to establish if there was an evidence-based approach. We collected follow up protocols from 10 trusts in the UK and applied 6 questions to each to allow us to compare the results. Responses were collated, compared and interpreted by the authors.

Results: Our literature review highlighted there is limited evidence to support how lung cancer patients should be followed up post-surgery. Overall, the literature supports CT based imaging although no specific period is supported. From the protocols reviewed there were common themes identified. Post-surgical follow-up was predominantly nurse led, face to face appointments or mixed with virtual were more common. Frequency of follow-up varied between 3 and 8 months, but apart from one site was consistently over 5 years. Similarly, radiology modality predominantly used CT scan either solely or mixed with chest x-rays. Only one site only used chest x-rays to follow up patients

Conclusions: Both the literature review and critical review of protocols highlight that further research would be beneficial, looking at a wider population of protocols could help encourage a more standardised approach across the UK to ensure optimum care for patients.

Keywords: Surgery, Protocols, Follow-up

EP.16 PATIENT ADVOCACY

EP.16.02 Lung Cancer Patients' Involvement and Support Preferences and Needs: Insights From a Global Patient Experience Survey

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Introduction: The Global Lung Cancer Coalition (GLCC), a partnership of 43 patient organisations across 31 nations, reaffirms in its charter the right of all lung cancer patients to be treated with dignity and respect and to have informed self-determination. Understanding patients' preferences and needs for involvement and support is essential to ensure that their physical, emotional and practical needs are met. This survey examines patients' preferences for involvement with their treatment and support teams in different situations. It also aims to explore where lung cancer patients currently seek support, where they would prefer to receive support and what kind of assistance they need most.

Methods: For its sixth annual survey, GLCC commissioned Censuswide to conduct a global survey of lung cancer patients. The survey is currently in the field across 18 countries (Australia, Argentina, Brazil, Canada, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Portugal, South Africa, Spain, Taiwan, UK, USA). As part of this survey, the GLCC included questions about patients' preferred method of involvement with their treatment and support teams at different points in their care journey. Additionally, the survey assesses where patients are currently seeking help to cope with their disease, where they would prefer to receive support, and the most important type of support patients need at the current stage of their journey.

Results: Results will be available for presentation. The results will provide insights into how lung cancer patients worldwide would like to communicate with their care teams, and whether their preferences vary by country, age, or gender. The survey also assesses the sources of support patients currently rely on and how these match or differ from their preferred sources of support. Finally, the survey results will include insights into the most pressing support needs of lung cancer patients.

Conclusions: It is anticipated that this survey will provide valuable insights for healthcare providers, patient organisations, and policy makers by identifying where patients seek help, their preferred methods of involvement with their treatment teams, and their most pressing support needs. The findings can help tailor care and support services to better meet the needs of lung cancer patients, ultimately improving their experience of care and quality of life.

Questions	Answer options															
What do you think is the best way to have a conversation with your treatment and support team in the following situations? (Matrix. Rows provided are: • Finding out the diagnosis • The first consultation • Regular check ups • If there is a change to treatment • If there is a change in my disease • If I'm worried about something	Video	Telephone	Face-to-face	Not sure												
a) Where do you get help to cope with your disease? b) Where would you like to get help to cope with your disease? Please tick all that apply:	Family and Friends	Healthcare Professionals (Doctors, Nurses, etc.)	Patient organisations	In-person support groups	Virtual support groups	Online support groups /social media communities	Peer matching services / one-to-one peer support	Helplines/chats /text services for support, information and referral	Education programme (for example chemo education)	Counselling or therapy	Spiritual or religious communities	Work colleagues	Physical therapy	Respiratory therapy	Other [open text box]	Nowhere/I do not do this
What is the most important help you need at the moment? [Ranking scale]	Emotional support – I need counselling, mental health support, or someone to talk to	Medical care – I need better access to doctors, treatments, or pain management	Financial assistance – I need help covering medical costs, travel expenses, or daily living costs	Information and education – I need clearer information about my condition, my treatment, side effects, or what to expect	Practical support – I need help with transportation, childcare, or other daily tasks	Social support – I need connection with support groups, family, or community	Carers support – I need support in looking after my children/parents/o their family members while dealing with my diagnosis and/or treatment	Other [open text box]	Nowhere/I would not want this							

Keywords: Patient support, Patient communication, Coping mechanisms

EP.16 PATIENT ADVOCACY

EP.16.03 Characterization of a Real-World Data Set of EGFR+ NSCLC Patients

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Introduction: Since the introduction of the first targeted therapy for thoracic malignancy, the field of personalized medicine and oncologic genetics has undergone rapid expansion. Though great strides have been made, there is still much we do not know about the different subgroups of people impacted by genetic drivers and personalized medicine. While mutations in the Epidermal Growth Factor Receptor (EGFR) gene are reported as the driver mutation in approximately 32% of non-small cell lung cancer (NSCLC) cases represent a larger proportion in the GO2 for Lung Cancer LungMATCH database, at about 60%. Using patient and caregiver-reported data, we sought to better understand characteristics shared amongst these individuals.

Methods: GO2 for Lung Cancer, a non-for-profit organization, runs a concierge-style treatment and clinical trial navigation service (LungMATCH) for people affected by lung cancer and their loved ones. LungMATCH collects self-reported data from patients/caregivers utilizing the service. For this analysis, we examined all contacts from the period of 01/01/2018 to 09/30/2024 to identify individuals with an EGFR driver mutation who had reported receipt of targeted therapy, and, after removing duplicate entries, analyzed their health and demographic data for commonalities and outliers.

Results: Between 01/01/2018 and 09/30/2024, 113 unique EGFR-positive (EGFR Exon 19 deletions, L858R mutation, L861Q, L718Q, or Exon 20 insertions) individuals who had received targeted therapy (or their loved ones) contacted the LungMATCH program. Patients contacted GO2 after a median of 2 lines of therapy and the median age at diagnosis was 58. Most patients (79%) were female, which aligns with the current literature, highlighting the prevalence of EGFR mutations in women. Cases were predominately adenocarcinoma (97%) and the most common co-mutations in this population were EGFR T790M (14%) and TP53 (12%). Other than targeted therapy, the most common treatments received were chemotherapy (46%) and radiation (32%). A third-generation TKI (tyrosine kinase inhibitor) was the most common first-line treatment (49%), followed by surgery (14%). Prevalent second-line treatments were third-generation TKIs (31%) or radiation (16%). Of note, 98.1% of patients presented with late-stage (stage IV) disease at the time of first LungMATCH contact. The most frequently reported sites of lung cancer metastasis were bones (30%), brain (26%), and lymph nodes (16%). For navigation services, 4% requested biomarker testing navigation, 49% requested treatment navigation, and 29% sought clinical trial navigation. 82% of calls regarded the next steps after progression on a 3rd generation EGFR-targeted therapy.

Conclusions: People diagnosed with EGFR-positive lung cancer represent a distinct subset of the NSCLC population. This real-world data analysis highlights the pervasiveness of third-generation EGFR inhibitor resistance. Once progression occurs, patients and their loved ones are unsure of how to proceed, and what options remain. Providing an individualized support service, such as the treatment and trial navigation offered through LungMATCH, can help to bridge this gap. In addition, using platforms such as LungMATCH to gather real-world, patient-reported data can help to broaden our understanding of what these groups require and how we can adapt to their changing needs.

Keywords: NSCLC, EGFR, Patient Reported Data

EP.16 PATIENT ADVOCACY

EP.16.04 Relationship Between Telomere Length and Pulmonary Toxicity in Patients With Locally Advanced Unresectable Lung Cancer

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Introduction: Telomere length (TL) is involved in tissue repair. Pulmonary toxicity (PT)due to radiotherapy (RT) is a complication of non-small cell lung cancer (NSCLC)treatment, being a risk factor under study.Our objective is to analyze the relationship between TL and PT due to RT in patients with locally advanced unresectable NSCLC treated with concurrent chemoradiotherapy and immunotherapy (IT) in PDL-1 positive patients.

Methods: A unicenter prospective study of 90 patients enrolled between 2018and 2021. Clinical, analytical, tumor, treatment data and TL were collected. TL was obtained from buccal samples. Patients were classified in percentiles according to z-score and were divided into two groups according to the severity of PT: G1-G2 (mild)/G3-G5 (severe).

Results: Ninety (90%) were men with a mean age of 72 years (SD 6.3). Predominanthistology was squamous (54%) and 40% received IT. In relation to PT, 81% developed G1-G2 toxicity and 19% G3-G5 with significant differences between groups only in dosimetric variables; V20: 20Gy vs. 26Gy (p=0.002) and in V5: 46Gy vs. 54Gy (p=0.006). No significant difference was observed between PT and TL, according to the univariate analysis. In the subgroup analysis by IT treatment, lower PT was observed in patients with TL above the 25th percentile (Figure 1). TL was shorter in our population compared to general population, done by indirect comparation.

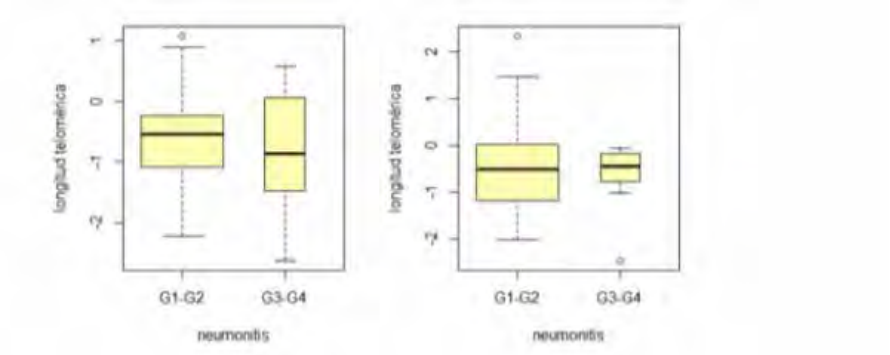

Figure 1. Boxplot of pneumonitis and telomere length in both groups (Left, without IT. Right, with IT). p-value 0.045.

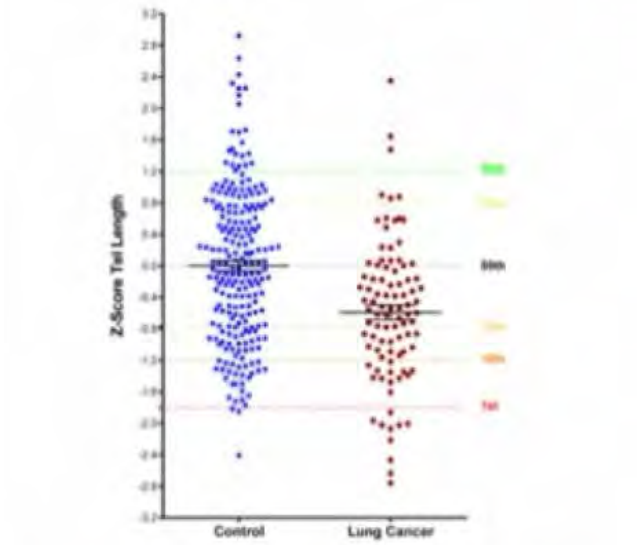

Figure 2 TL Distribution in our series compared to general population

Conclusions: No relation was found between LT and PT development. However,patients with TL above 25 th percentile treated with IT had lower risk of developing severe PT. Further studies are needed to validate the findings and think about therapeutic implications.

Keywords: Cancer, Pneumonitis, Telomere

EP.16 PATIENT ADVOCACY

EP.16.05 Expectations and Quality of Life of Lung Cancer Patients During the Care Process

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Introduction: Lung cancer affects an increasing number ofpeople worldwide. Mortality and incidence rates are traditional public healthindicators, but these indicators are difficult to interpret at the individuallevel. The experiences of those affected in the care system and during thepatient journey can provide important feedback.

Methods: A quantitative questionnaire-basedcross-sectional study examining patients' self-reported clinical data and theirexperiences during the patient journey, in two selected institutions (in total,n=122). The qualitative method focuses on feedback on personal experiences(focus groups n=7).

Results: The patients average age was 66.8 years,and their general health was good according to their self-reporting. In termsof stage: 51% of the patients were in stage I-II, 20% in stage III. and 29% instage IV. Over 90% wereunaware of biomarker positivity, although it was at the base of subsequenttreatments.Half of thepatients were identified through screening, 10% were included in the LDCTprogram.In terms of transparency in the patientjourney, public information on early symptom recognition, improving therelationship between primary care physicians and patients, and more in-deptheducation about lung cancer were considered useful by 85%. Reducing waitingtimes was considered important by 60%, and clear information about diagnosticprocesses was considered particularly important by 77%.In theirsuggestions, 91% of patients identified the accessibility of the medical teamand 86% of professionals' communication skills as areas for improvement. Intotal, 89% found the communication reassuring.

Conclusions: Patients willtrust clinical decisions when they are provided with sufficient information andunderstanding during treatment so that their overall quality of life issatisfactory regardless of the outcome of treatment. Clearcommunication with patients during the whole examination and treatment promotesthe quality of life and sence of security.Patientsexperience difficulties in accessing primary care and early information at thebeginning of their journey, and the time to diagnosis seems long, which ispartly a justified observation. The feedback on the work of the care teamand the information received and the quality of care is satisfactory. However,the quantity and quality of communication is not entirely reassuring. This maybe due to the known capacity and staff shortage, which means that the team isoverloaded.

Keywords: QoL, Communicaton, patient perspective

EP.16 PATIENT ADVOCACY

EP.16.06 Health Literacy Leads to Health Equity; a Best Practice Approach From a Lung Cancer Organization

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Introduction: Health literacy is defined as the ability to find, understand, and use information to make health-related decisions. In the US, health literacy is a stronger predictor of health outcomes than income, employment status, education level, and racial or ethnic background. With nearly 9 out of 10 Americans experiencing limited health literacy and lung cancer being the leading cause of cancer deaths, addressing this issue is critical. Recognizing this, health literacy guidelines were integrated into all educational materials and the Lung Cancer Registry (LCR) with the goal of improving health outcomes, and supporting health equity within lung cancer communities.

Methods: After extensive research and advanced training in health literacy best practices, the content and design features of all educational materials were reviewed and revised to align with these guidelines. The same best practices were also integrated into the Lung Cancer Registry (LCR), an online platform where individuals with lung cancer and caregivers can provide updates on treatment and disease status. Created to track the journey from diagnosis through treatment and survivorship, the LCR helps researchers assess treatment effectiveness, side effects, quality of life, outcomes, and quality of care.

Adaptations to the LCR included making it easier for individuals to understand the informed consent, survey descriptions, and registry questions. Feedback was gathered from community members living with lung cancer to ensure the registry platform and educational materials were clear, easy to understand and accessible.

Results: Along with the language and design of the LCR, nearly 50 individual educational materials were reviewed and revised with input from multiple audiences, including people living with lung cancer, healthcare professionals, and the general public. Valuable feedback was gathered, including the need for the LCR to avoid the phrase 'Advance lung cancer research,' as it closely resembles 'advanced lung cancer,' which could unintentionally exclude some individuals. Once feedback and health literacy guidelines were incorporated, lung cancer community members confirmed that the information was clearer and more engaging. By incorporating health literacy guidelines such as plain, person-first language, shorter sentences and structuring content with bullet points and other design elements - the accessibility and readability of lung cancer materials were significantly improved to best meet the needs of the population.

Conclusions: Integrating consistent health literacy best practices fosters equitable health outcomes. With significant advances in lung cancer, vital information has grown increasingly complex, making clear communication about lung cancer more urgent than ever. Engaging a multidisciplinary group to provide feedback and confirming the final draft with lung cancer community members, was highly effective in improving the health literacy of our content. Additionally, using shorter sentences, bullet points, and person-first language are simple strategies that others can implement in order to positively impact health outcomes and survivability.

Established in 2021, the IASLC Language Guide reminds us that thoughtful language "respects the dignity of those diagnosed with lung cancer and their families." We have created a model for improving health literacy across all aspects of lung cancer care that can be replicated anywhere around the world.

Keywords: Health Literacy, Patient Education, Health Equity

EP.16 PATIENT ADVOCACY

EP.16.07 Addressing Unmet Needs of the Lung Cancer Community: The Journey to Find and Implement Mind Over Matter

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Introduction: People with lung cancer experience high levels of distress and have great unmet psychological and physical needs. Their loved ones often also have high rates of distress, anxiety, and depression. Many cancer centers lack comprehensive psychosocial programs, and where services are offered, there are often barriers to participation such as waitlists, ill health, and transportation issues. Research confirms the effectiveness of psycho-oncology interventions to address these needs. Specifically, studies have found benefits of mindfulness- and cognitive behavioral-based group interventions for those impacted by lung cancer, Implementation of interventions from research to practice is rare, and can take up to 17 years. In a quest to help address the psychosocial needs of the US lung cancer community, we began the search for an intervention to implement.

Methods: From October 2022 to June 2023, our efforts were three-fold. As we completed a literature review, we conducted five key formal and informal interviews with behavioral researchers, providers of psychosocial services, and an implementation scientist. We then formulated six key requirements for the intervention: 1. suitable for both those diagnosed and their loved ones; 2 the participant burden needed to be low, to allow those in active treatment and busy caregivers to join; 3. licensing constraints meant that it had to be skills based, not therapeutic; 4. as stress and anxiety affect those across the continuum, it needed to be relevant at any point in the journey, including for long-term survivors; 5. for anyone in the US to join, it had to be virtual; and 6. we needed assurance that it was evidence-based.

Results: Mind Over Matter (MOM), is a five-week group psychosocial coping skills training developed by Inova Peterson Life with Cancer™. MOM teaches “ tips and tools to deal with the fears, worries, and sadness that can come with a cancer diagnosis.” We discovered MOM in June 2023 and found it met our requirements. We attended facilitator training in November 2023, hired a MOM-specialist social worker in May 2024, and began recruitment that June. We “soft” launched MOM in August 2024, marking the first time it was offered at the national level and the first exclusive to the lung cancer community. At the end of 2024, two full classes had been completed, with post-attendance surveys indicating that MOM provided helpful information to change behaviors and learn coping skills. We are expanding our recruitment efforts and expect to have data from three additional classes by September. We are also initiating an enhanced intake process and plan to offer a MOM class just for lung cancer caregivers.

Conclusions: In under two years, we researched, identified, and launched a unique virtual psychosocial intervention, available to anyone affected by lung cancer in the United States. MOM has the potential to meet the global need for coping skills as well. Thus far, it has been adapted and translated into Spanish and the feasibility and acceptability of MOM is under study with African American/Black women. Interestingly, providers from Latvia joined Life with Cancer’s most recent facilitator’s training.

Keywords: Psychosocial, Anxiety, Intervention

EP.16 PATIENT ADVOCACY

EP.16.08 Preliminary Study of Culturally Adapted Approaches to Enhance Lung Cancer Education for Hispanic/Latino Population

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Introduction: Effective lung cancer education for Hispanic/Latino populations requires a strategic adaptation to address cultural preferences in material engagement, an understanding of the barriers to care access within the community and insight into how this population interacts with medical information in daily life. Nuestra Gente, a health education initiative from GO2 for Lung Cancer, developed a series of videos designed to bridge linguistic and cultural gaps in lung cancer education for Hispanic/Latino communities in the U.S. This qualitative review examines the perceptions, knowledge, and relevance of these audiovisual materials, assessing their effectiveness in conveying critical lung cancer information and their ability to address health communication disparities.

Methods: Our qualitative analysis is based on responses from an in-person, structured focus group conducted in February 2024 with Spanish-speaking Hispanic/Latino adults (ages 30-60 years, n=4). Participants engaged in a structured discussion of the Nuestra Gente video library to assess the knowledge gained and effectiveness of the Spanish-language materials developed by GO2 for Lung Cancer. The analysis also examined participant engagement, accessibility of media format, and comprehension of the medical information presented.

Results: Preliminary findings revealed that while the information was considered useful, there is a need for visual reinforcements within the videos and improved accessibility measures for video distribution. Specifically, the use of traditional medical terminology without sufficient context posed a challenge. Focus group analysis also indicated that language, pacing, and the integration of supplementary educational materials (such as infographics) significantly influenced participants' comprehension and retention of information.

Conclusions: Leveraging a more deliberate approach towards lung cancer education is essential to ensure that the information is both accessible and culturally relevant for Hispanic/Latino populations. Future efforts should focus on refining educational tools to better align with the cultural, linguistic, and health literacy needs of the community. Enhancing engagement, incorporating visual reinforcements, and improving accessibility can help ensure that members of the Hispanic/Latino community receive information in meaningful and actionable ways. Our analysis highlights the need for clear explanations of medical terminology, improved pacing, and the integration of supplementary materials to support comprehension and retention. Applying these insights can help healthcare organizations develop new, more effective materials that not only inform but also empower individuals to make more confident decisions about their care. To further guide best practices and the development of educational resources, additional data collection and a larger-scale analysis are needed to confirm these findings and assess the long-term impact of culturally tailored lung cancer education initiatives.

Keywords: Hispanic/Latino, Education, Lung Cancer

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.01 Identifying Barriers to Timely Initiation of Oral Anti-Cancer Medication in Patients With Non-Small Cell Lung Cancer

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Introduction: Delays in initiating therapy in patients diagnosed with non-small cell lung cancer (NSCLC) can worsen outcomes. Therefore, the timely initiation of oral anti-cancer medication (OAM) is paramount. A previous study demonstrated that time to treatment initiation (TTI) of less than 45 days was associated with improved outcomes, and 37.2% of patients experienced treatment delays. The cost of OAMs, requirements of prior authorization (PA), and need of patient assistance programs (PAP) can all contribute to delays. This study aims to evaluate the timeliness of OAM initiation in patients with advanced NSCLC with EGFR mutations or ALK translocations.

Methods: A retrospective observational cohort study was conducted at the Memorial Cancer Institute (MCI), a large multi-site community cancer center. Medical records were reviewed for patients diagnosed with advanced NSCLC prescribed preferred first-line therapy between January 1, 2020, and December 31, 2023. TTI was defined as the number of days from initial diagnosis to the first dose of OAM. A delay in TTI was defined as initiation occurring more than 45 days after diagnosis. Descriptive statistics were used to summarize patient demographics, insurance status, type of specialty pharmacy, and quantify the duration of each step in the medication access process. The Mann-Whitney U test was used to compare TTI between patients who received PAP support and those who did not.

Results: Of the 150 patients identified, 34 were included in the analysis. The mean age was 64.8 years (SD 13), and the majority were female (n=23, 67.6%), White (n=27, 79.4%), Hispanic (n=18, 52.9%), and had stage IV NSCLC (n=33, 97%). A total of 24 patients (70.6%) obtained their medication through an internal specialty pharmacy, and 31 patients (91.2%) had insurance coverage. Overall, 52.9% of participants utilized PAP support, while 47.1% did not. The mean processing times for each step were as follows: 2.2 days (SD 2.4) from prescription to PA submission, 2.9 days (SD 3) for PA approval, 1.1 days (SD 1.5) for PAP approval, and 9.7 days (SD 5.6) from written prescription to patient receipt. Overall, the mean TTI—from diagnosis to patient receipt of medication—was 26.5 days (SD 15.5), with 11.76% (n=4) of patients experiencing a delay defined as TTI exceeding 45 days.

Conclusions: Majority of patients with NSCLC receiving OAM from MCI received timely treatment from diagnosis, and the use of PAP was not associated with delays in treatment. These findings may reflect the efficiencies of coordinated medication access processes at MCI. Given the impact of delayed diagnosis and treatment initiation on clinical outcomes, future research should assess generalizability and evaluate both patient-specific and system-level contributors to treatment delays across diverse care environments.

Keywords: Timeliness, Access, Outcomes

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.02 Treatment and Survival Outcomes for Indigenous Australians Within the Victorian Lung Cancer Registry

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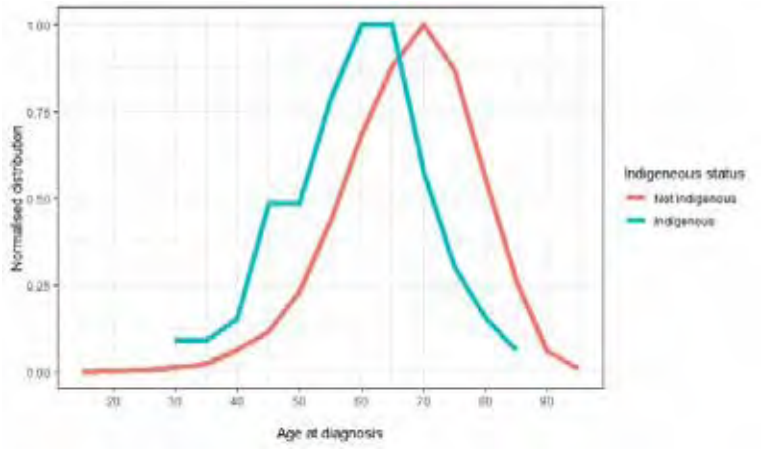
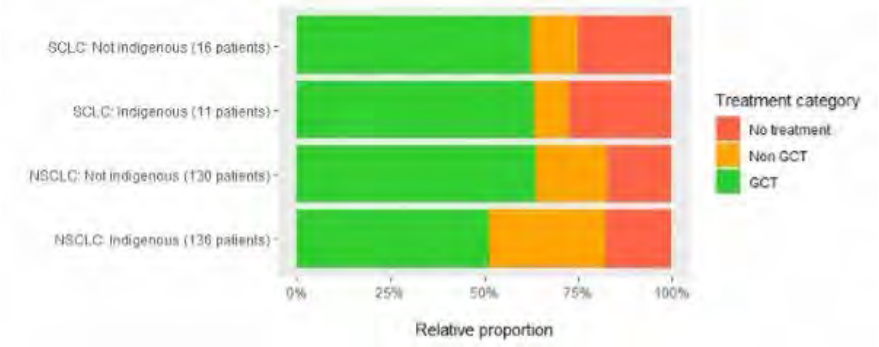
Introduction: Indigenous Australian lung cancer patients are known to have poorer survival outcomes, later stage at diagnosis, and significant comorbidities. Socioeconomic disadvantage, cultural awareness and access to healthcare are key factors that impact outcomes of indigenous populations. Our goal was to explore risk factors, patterns of management and survival outcomes in Indigenous compared to non- Indigenous Australian patients using the Victorian Lung Cancer Registry (VLCR).

Methods: A retrospective observational cohort study, using data collected on primary lung cancer patients in the VLCR between January 2011 and January 2024. Multivariate Cox regression and propensity matched survival analysis was performed to assess impacts of patient and clinical variables on survival.

Results: We included 171 Indigenous and 17,343 non-Indigenous Australian patients. Indigenous lung cancer patients were younger in age (<60 years: 41% vs 17.2%, p<0.001), had lower socioeconomic status, were more likely to be current smokers (99% vs 87%, p<0.001) and had higher levels of respiratory comorbidity (36% vs 23%, p<0.001) Figure 1. Indigenous patients had lower receipt of guideline concordant treatment (53% vs 59%, p=0.084) Figure 2. Survival outcomes were not statistically significant but slightly lower for Indigenous compared to non-Indigenous Australian lung cancer patients (median survival 1.3 vs 1.6 years, HR=1.13, p=0.2).

Conclusions: We found lung cancer patients of Indigenous status were more likely to have demographic disadvantage and clinical risk factors that contributed to poorer management and survival outcomes compared to patients of non-Indigenous status. 16% of the Indigenous population were aged <50 at diagnosis posing eligibility concerns for the upcoming National Lung Cancer Screening Program. Identifying barriers to healthcare and treatment in the Indigenous Australian population is an important research priority to improve disparities between the two populations.





Keywords: Indigenous population, Lung cancer registry, Disparity and inequity

EP.17.03 Disparities in Lung Cancer Treatment for Older Adults

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Introduction: Older adults are disproportionately affected by non-small cell (NSCLC) and small cell lung cancers (SCLC), with most patients diagnosed over age 65. Treatment depends in part on functional status, generally measured by ECOG performance status, however other factors associated with treatment receipt are less clear. Here, we investigate whether differences in treatment exist for older adults with lung cancer, and explore factors associated with receipt of frontline treatment.

Methods: Clinical data was obtained from an institutional cancer registry (including academic and community sites) for patients with stage IV lung cancer diagnosed between 2018-2022. Social determinants of health data were obtained from the national LexisNexis database. Older adults were defined as ≥65years. Chi-square and Fisher's exact tests were used to evaluate associations between categorical variables, including treatment receipt and baseline characteristics across age groups and subgroups. For continuous or ordinal variables, the Wilcoxon rank-sum test was used for assessing normality and comparing differences between groups for skewed distributions.

Results: For younger and older adults, there were no differences in baseline features (Table 1) or receipt of any systemic treatment (p=0.49). Older adults were more likely to be treated with immunotherapy alone (p=0.006). Younger adults survived longer than older adults (p<0.01, median survival 352 vs 217 days). For all patients, ECOG 0-2 was associated with increased likelihood of treatment; for older adults only ECOG 0-1 showed this association (p<0.01). For all patients (p=0.005) and older adults specifically (p=0.013), having SCLC was associated with increased likelihood of treatment compared to NSCLC. There was no difference in hospitalizations between younger and older adults, although the proportion of patients hospitalized after diagnosis was high in both groups (76 vs 67%, p=0.80). There were no differences in treatment receipt based on wealth index or college attendance. There were significant differences in the household structures of older and younger adults, suggesting potential differences in caregiving dynamics and family support structures by age, however total household members, and their age, were not associated with receipt of treatment.

Conclusions: Older adults are as likely to receive frontline systemic therapy for stage IV lung cancer as younger adults, but more likely to receive immunotherapy alone and less likely to receive treatment if ECOG 2. Younger adults have longer survival times after diagnosis compared to older adults. Household support structures vary by age, with future research to be focused on personalizing support for older adults based on their unique needs.

Table 1: Baseline Demographics

	Younger Adults (n = 120)	Older Adults (n = 188)	p-value
Median Age in Years (IQR)	59 (56-62)	74 (69-79)	
Sex (%)			
Male	57 (47.5)	93 (49.5%)	0.825
Female	63 (52.5)	95 (50.5%)	
Race/Ethnicity (%)			
White	93 (77.6)	155 (82.4)	0.511
Black	24 (20.0)	28 (14.9)	
Asian	1 (0.8)	2 (1.1)	
American Indian/Alaska Native	1 (0.8)	0 (0.0)	
Other	1 (0.8)	3 (1.6)	
Histology (%)			
NSCLC	96 (80.0)	149 (79.3)	0.724
SCLC	24 (20.0)	38 (20.2)	
Unable to Determine	0 (0.0)	1 (0.5)	
ECOG (%)			
0 (Fully Active)	21 (17.5)	27 (14.4)	0.057
1 (Restricted Activity)	53 (44.2)	67 (35.6)	
2 (Self-Care Only)	21 (17.5)	47 (25.0)	
3 (Limited Self Care)	6 (5.0)	14 (7.4)	
4 (Disabled)	5 (4.2)	1 (0.5)	
Not Reported	14 (11.6)	32 (17.1)	
First Treatment (%)			
Chemotherapy	28 (23.3)	32 (17.0)	0.017
Immunotherapy	11 (9.2)	38 (20.2)	
Chemotherapy and Immunotherapy	39 (32.5)	41 (21.8)	
Oral Chemotherapy	12 (10.0)	22 (11.7)	
No Treatment	30 (25.0)	55 (29.3)	

Keywords: Disparities, Older Adults, Lung Cancer

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.04 Social Vulnerability as a Determinant of Disparities in Lung Cancer Management and Survival

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Introduction: Social vulnerability significantly influences lung cancer outcomes, contributing to disparities in diagnosis, treatment, and survival. This study evaluates the impact of the Índice Paulista de Vulnerabilidade Social (IPVS -São Paulo Index of Social Vulnerability) on clinical characteristics, treatment access, and survival among patients with lung cancer in São Paulo.

Methods: A retrospective cohort of 6,835 treated patients diagnosed with lung cancer (stages I-IV) between 2000-2013 was analyzed. Patients were stratified by IPVS categories, ranging from very low (IPVS 1) to very high (IPVS 4-6) vulnerability. Clinical and demographic disparities across PVS groups were evaluated using ANOVA and chi-square tests. Survival outcomes were assessed using Kaplan-Meier analysis and Cox regression models, adjusted for confounders such as stage at diagnosis and treatment modality.

Results: Significant disparities were observed across IPVS groups. Patients in the most vulnerable categories (IPVS 4-6) were older (27.3% aged ≥70 years), had lower educational attainment (10.4% illiterate; only 2.8% with higher education), and were more frequently diagnosed at advanced stages (33.2% at stage IV). Treatment access also declined with higher IPVS levels, with a treatment rate of 85.5% in IPVS 4-6 versus 89.4% in IPVS 1 ($p<0.001$). Survival outcomes mirrored these disparities: mean survival times were 18 ± 19 months for PVS 1, 15 ± 17.3 months for IPVS 2, and 13.2 ± 15.8 months for IPVS 4-6 ($p<0.001$). In multivariate Cox regression, high social vulnerability independently predicted poorer survival (HR for IPVS 4-6 vs. IPVS 1=1.32, 95% CI: 1.22-1.43, $p<0.001$), even after adjusting for stage and treatment. Advanced clinical stage and non-surgical treatment also contributed to worse outcomes.

Conclusions: The Índice Paulista de Vulnerabilidade Social is a powerful predictor of disparities in lung cancer diagnosis, treatment, and survival. Higher social vulnerability correlates with delayed diagnosis, reduced access to treatment, and significantly worse survival outcomes.

Keywords: Social Vulnerabilities, Lung cancer, Disparities

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.05 Association of Social Vulnerability With Prognosis of Lung Cancer in Japan

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Introduction: Lung cancer remains the leading cause of cancer-related deaths worldwide. Prognosis is often determined by clinical factors such as tumor stage and response to treatment. Outcome of cancer care is also influenced by social and economic factors. Some studies have suggested that social isolation may be associated with an increased risk of mortality in cancer patients, as it can lead to a reduction in treatment intensity and promote behaviors that hinder treatment continuation. However, the impact of social vulnerability on survival outcomes on lung cancer care has not been sufficiently explored. Socially vulnerable populations, including individuals with low socioeconomic status, limited healthcare access, and social isolation, face unique challenges that can detrimentally affect their prognosis. This study aims to investigate the influence of social vulnerability on the survival outcomes of lung cancer patients.

Methods: We performed a retrospective cohort analysis of 71 socially vulnerable lung cancer patients diagnosed between 2021 and 2023. Data were extracted from cancer registries and patients were identified as welfare recipients or extreme elderly (range, 85-98 years) . The primary outcomes evaluated were overall survival (OS), availability of active treatment, and whether they received the treatment plan they desired. Data, including patient demographics, tumor characteristics, treatment details, and clinical outcomes, were collected from medical records. Reasons for not receiving active treatment, such as chemotherapy or molecular targeted therapy, were also examined. Statistical analyses including survival and subgroup analyses were performed to summarize the data.

Results: In socially vulnerable lung cancer patients, median overall survival (mOS) was 14.6 months, considerably worse than historical survival data for lung cancer patients. The prognosis for extreme elderly group had very poor of mOS of 7.1 months. The group that received active treatment, including surgery, chemotherapy, and/or radiotherapy had a better mOS of 20.4 months. Of all patients studied, 65.7% were not eligible for curative therapy, chemotherapy, or molecular targeted therapy. The main reasons for not receiving these treatments were deterioration of general condition in 22.5% and the patient's will in 21.1%. Notably, patients who received early diagnosis and treatment before their performance status (PS) declined significantly had improved survival, underscoring the importance of early diagnosis and timely medical intervention.

Conclusions: Our findings indicate that socially vulnerable lung cancer patients have considerably worse survival outcomes compared to historical data, even after accounting for clinical factors. Addressing the needs of this high-risk group through systems for regular lung cancer screening and facilitating early access to treatment may improve their prognosis. Further research is required to identify the underlying causes of these disparities and develop targeted interventions to enhance survival rates for socially vulnerable populations.

Keywords: Socially vulnerable group, extreme elderly, welfare recipient

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.06 Evolving Trends in Lung Cancer Epidemiology in India: A Shift in Patterns and Clinical Insights

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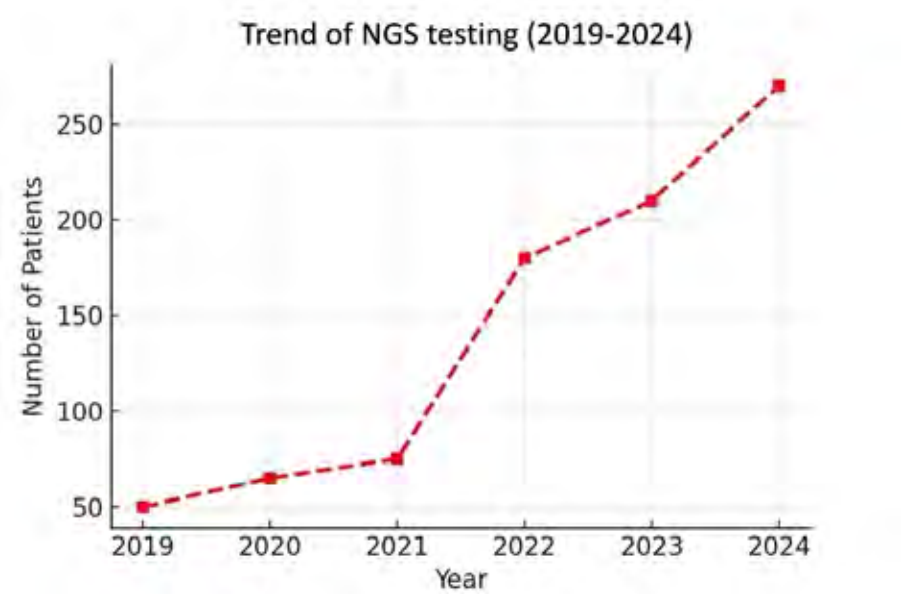
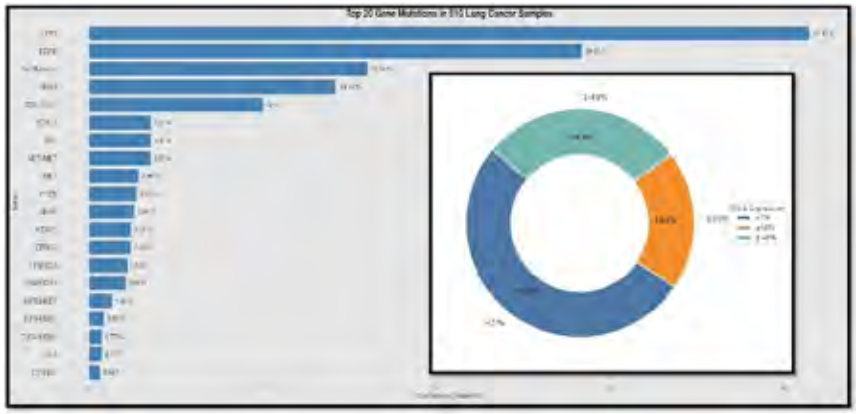
Introduction: Lung cancer in India is rising due to increasing air pollution and lifestyle changes, with more cases among females, non-smokers, and younger patients and a declining co-existing tuberculosis. There exist significant differences in the molecular landscape of NSCLC between the western and Indian population. This study aims to examine the changing epidemiology and molecular profile of lung cancer in India.

Methods: We collected patient data from the Thoracic Oncology OPD at RGCIRC. Relevant clinical and demographic variables including age, gender, histological subtype, tuberculosis status, smoking history, ECOG PS, metastatic disease and NGS/ PDL1 was included. Analysis was conducted using JAMOVI software, version 2.6.

Results: A total of 1,714 patient data was analysed. The findings indicated prevalence of lung cancer was 32.3% in females. Furthermore, only 7.1% of the total cases were empirically treated with ATT in the 6 months prior to diagnosis . However, once diagnosed with NSCLC, high number of patients underwent hot spot NGS and PDL1 testing with a higher NGS positivity in the female group.

Conclusions: This study reveals evolving trends in the epidemiology of lung cancer in India. Our data suggests a rise in trend among nonsmoking, females and decrease in the trend of TB. The PDL1 positivity rates and incidence of EGFR /ALK/Ros mutations is also different from western and far east population. This study highlights the importance of real world data and global participation in clinical trials so as to ensure that treatment strategies are tailored to the unique genetic and epidemiologic characteristics of different populations, ultimately improving patient outcomes.





Keywords: molecular classification, real world data, heterogeneity of cancer

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.07 Using COM-B Behavioural Change Framework to Implement Lung Cancer Pathway for Primary Care Physicians

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Introduction: To improve care of people with suspected lung cancer in Northern Australia, we developed an online 'Health Pathway' called the Townsville lung cancer referral pathway (TLCRP). TLCRP outlines the recommended investigations and appropriate referrals for a person with suspected lung cancer. Implementation of evidence-based practices like the TLCRP depends on successful behavioural change interventions. Here, we describe the implementation of TLCRP using the COM-B behavioural change framework.

Methods: The COM-B model proposes three necessary components for any behaviour (B) to occur. Through assessing capability (C), opportunity (O), and motivation (M), targeted interventions can be created that lead to effective change (figure 1)

Results: Interventions that were useful in TLCRP implementation based on the COM-B framework 1. Education- Team of clinicians who regularly educate local GPs, nurses and medical students about TLCRP.....

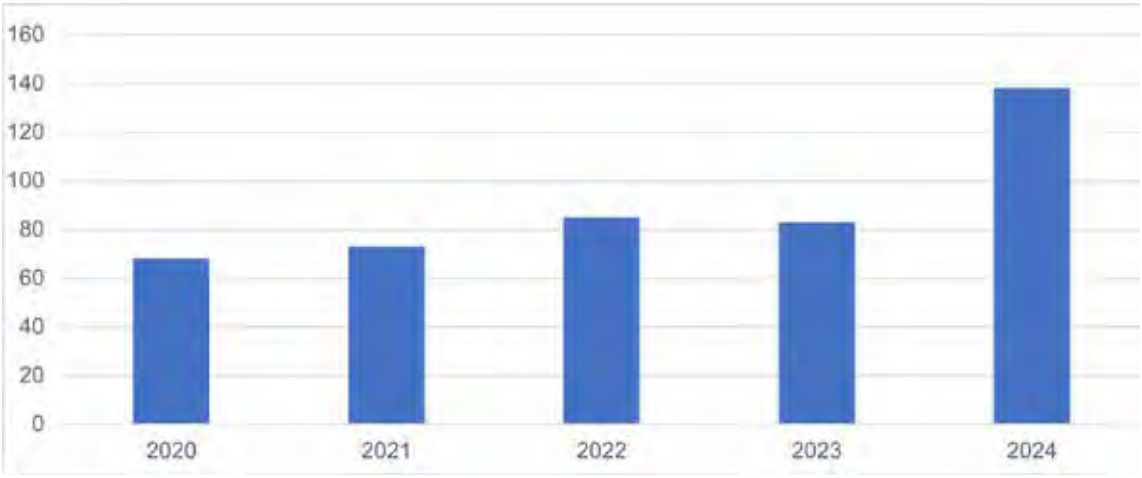
2. Persuasion-Increased engagement with GPs who don't use TLCRP and resolve the barriers for using it.....

3. Incentivisation- RACGP (Royal Australasian College of General Practitioners) provides CPD (continuous professional development) points for using TLCRP.....

4. Training- Training for new GPs and practice managers to use the TLCRP portal.....5. Restriction- Respiratory physicians not accepting referrals that do not include all the required information. ..... 6. environmental restructuring-TLCRP is easily accessible - on the desktop as well as mobile devices. ..... 7. Modelling-Positive feedback from specialists and patients. ..... 8. Enablement- Prompt technical support for use of the website.....

Policy categories that were useful in TLCRP implementation based on the COM-B framework: 1.Communication/ marketing- The local Primary Health Network actively promotes use of TLCRP through flyers and newsletters.....
2. Guidelines- Cancer Australia lung cancer management protocols. .....3. Fiscal- 'Health Pathways' software provided free to all the GP practices. ..... 4. regulation- Establishing agreements on GP specialist referrals.....5. Legislation-Governement policy to encourage the use of Health Pathways and online referrals..... 6.Environmental/social planning- Ensuring adequate clinical staff and diagnostic facities .....7. Service provision- Employing a team of clinicians and administration personnel to implement and support TLCRP.

Conclusions: IThe COM-B model for behavioural change is a useful tool to implement Health Pathways for primary care physicians. use of TLCRP increased from 2020 to 2024 (figure 1).



Keywords: lung cancer, health pathways, COM B framework

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.08 Ready or Not: Assessing Provider and Facility Preparedness for Bispecific Therapy in Extensive Stage-Small Cell Lung Cancer

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Introduction: Small Cell Lung Cancer (SCLC) is aggressive with 94% of cases extending outside the lung (ES-SCLC), leading to poor 5-year survival rates. Until recently, limited therapeutic options were available to treat SCLC and its associated poor outcomes. A new T-cell engager immunotherapy that targets delta-like ligand 3 (DLL3) and CD3 T-cell co-receptors for cytotoxic T-cell activation (bispecific therapy (BT)) has been shown to improve overall survival for ES-SCLC. However, BTs carry an adverse side effect (AE) profile requiring enhanced monitoring after certain doses. This study aimed to define healthcare provider knowledge gaps related to BT and measure their preparedness for its implementation as an effective treatment for ES-SCLC.

Methods: A survey was distributed to assess facility demographics, populations served, and provider characteristics; BT awareness, preparedness, barriers, likelihood of offering or referring, and interest in further education. Emails were sent to GO2 Centers of Excellence (COE; n=94) and non-COE (n=48). Additionally, 435 emails were distributed nationwide, including providers in various geographic locations and health professional shortage areas (HPSAs).

Results: Participant Population Sixty-nine participants completed the survey, representing a diversity of professional roles: physicians (28%), Advanced-Practice Registered Nurses (APRNs; 25%), oncology navigators (16%), nurses (9%), healthcare administrators (4%), and clinical healthcare staff (2%). These participants served Urban (61%) and Suburban (25%) populations, while fewer served Rural (10%) and Healthcare Professional Shortage areas (HPSA; 1%). Of note, 63% of rural or HPSA participants were oncology navigators or nurses. Familiarity with Therapy 74% of participants reported familiarity with BT for SCLC management. However, most nurse and health administrator respondents reported no familiarity, including approximately 25% of APRNs. Only 50% of respondents from rural or HPSA areas reported familiarity. Additionally, all nurse respondents, most healthcare administrators, approximately 40% of oncology navigators, and approximately 30% of APRNs reported no familiarity with the therapy's mechanism of action. Similar patterns appeared for other BT-related topics, including administration route, time-bound AEs, and extended monitoring requirements. Systems Preparedness Overall, 27% of respondents felt their facility was very highly prepared to offer BT for ES-SCLC, and 24% felt highly prepared. In rural or HPSA areas, 25% reported very little and 38% reported no preparedness. Notably, half of rural and HPSA participants reported no confidence in their ability to order or obtain BT or IL-6R antagonist therapy for AE management.

Conclusions: These results show a generally high level of familiarity with BT for ES-SCLC and readiness to offer it. However, they also reveal a pronounced gap in familiarity and preparedness of nurses, oncology navigators, and APRNs (regardless of facility location or type) compared to other professionals. This underscores the need for targeted education and training for nurses, oncology navigators, and APRNs, including those in rural and HPSAs, to ensure equitable readiness across patient-facing roles for optimal and widespread implementation. Further study is needed to examine systemic differences across facility types and better understand gaps in knowledge of BT characteristics and administration by role.

Keywords: ES-SCLC, Bispecific, Implementation

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.09 Pulmonary Nodule Burden in Melbourne: A Snapshot Pre-Australian Lung Cancer Screening Rollout

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Introduction: The Australian National Lung Cancer Screening Program launches on 1st July 2025. It is anticipated that demand for pulmonary nodule diagnostic and management services will increase. To date, there is a lack of understanding of the prevailing pulmonary nodule burden in Australia. Therefore, there is a need to characterise the nodule landscape before the implementation of the screening program so that services can be appropriately upscaled to deliver high-quality, patient-centered and efficient nodule care. This study has commenced at a single large tertiary centre and will expand to involve two further tertiary institutions that will encompass northern, southern and central regions of the state (Victoria).

Methods: This is a retrospective review of electronic and scanned medical records to assess the burden of new pulmonary nodules referred to both the respiratory and thoracic surgery departments in a metropolitan-based, university-affiliated tertiary centre in Melbourne between 1st July 2023 to 1st August 2024. Known pulmonary nodules undergoing surveillance or associated with underlying known malignancy before study duration were excluded.

Results: A total of 1,338 cases were reviewed with 535 new referrals (288 males and 247 females) identified for further evaluation of new pulmonary nodules across the respiratory and thoracic surgery departments. 231 (43.6%) patients were referred by a primary care physician. Within the cohort, 134 (25.1%) patients were current smokers, 215 (40.3%) were former smokers and 170 (31.9%) were lifelong non-smokers. 158 (31.7%) pulmonary nodules were identified in the right upper lobe. 422 nodules (85.6%) had a solid component, 26 (5.3%) were semi-solid whilst 45 (9.1%) nodules were ground glass in nature. 99 (19.9%) nodules were spiculated, 44 (8.9%) were lobulated and 37 (7.4%) nodules had cavitations. 325 (63.9%) patients underwent subsequent positron emission tomography (PET) scans and 159 (29.7%) nodules were biopsied. 113 (21%) nodules were diagnostic for malignancy with 61 (54%) cases being adenocarcinoma. 161 (30%) patients had more than 1 nodule identified.

Conclusions: Based on documented international experience from national lung cancer screening programs, there is an anticipated increase in pulmonary nodule burden which would lead to a proportionate rise in demand in resource utilization and will need adequate planning to ensure delivery of high-quality, timely care to patients and ensure patient adherence to the program.

Keywords: Pulmonary nodule, Lung cancer screening, Lung nodule

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.10 Opportunities and Challenges of Lung Cancer Diagnosis, Care and Treatment in Western Kenya

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Introduction: The incidence of lung cancer generally remains low in Africa despite high mortality. According to the Kenya National Cancer Control Strategy 2017-2022, lung cancer accounted for 794 cases with 729 deaths and a prevalence of 1.75 per 100,000 translating to a case fatality of 92%. Diagnosis, care, and management of lung cancer in the western region have presented disparities in the outcomes due to multiple factors including; unique biological characteristics of patients, socio-economic and health systems factors. This has conferred opportunities and challenges we wish to share.

Methods: The study employed a retrospective review of records of all patients with a histological diagnosis of primary lung cancer at MTRH AMPATH Oncology Clinics from January 2018 to January 2021. Data on demographics, history, signs and symptoms, the outcome of investigations, treatment, and status at the end of the period were analyzed.

Results: Out of 153 patients, 79(51.60%) were male, 74(48,40%) were female (n = 153). The median age at diagnosis was 59 years (range:20-95 years) with 44(29.30%, n = 150) as active smokers. Of the active smokers, 36(81.82%) were males. Majority had non-small cell lung cancer 143(94.10%, n = 152) with 103(74.10%) adenocarcinoma and 36(25.90%, n = 139) squamous cell carcinoma. Most had advanced disease with 130 (89.10%, n = 146) in stage III or IV and 12(8.20%) not stagged. Chemotherapy 149(97.40%, n =153) was the most common treatment modality. 124 (81.04%) deaths were reported.

Conclusions: Lung cancer is a significant Public Health problem in western Kenya that calls for a screening/case-finding program to enable early diagnosis. The majority of patients with Lung Cancer in Western Kenya have never smoked tobacco. Adenocarcinoma is the predominant subtype of non-small cell lung cancer. A referral system with feedback from the community to the facility will improve early referral and prompt diagnostic interventions.

Keywords: Retrospective review of records, Adenocarcinoma, Non-Small Cell Lung Cancer

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.11 Integrating Prevention and Screening of Tobacco-Related Diseases Including Lung Cancer Screening: Results of a Pilot Program

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Introduction: Active smoking and tobacco-related diseases (TOREDI) such as cardiovascular diseases, cancers and chronic obstructive pulmonary diseases (COPD) are limiting the net benefit of lung cancer screening (LCS). The feasibility of an integrated clinical program for transversal prevention and screening of TOREDI has been poorly reported. Our monocentric pilot program includes smoking cessation with brief structured intervention and follow-up, cardiovascular risk factor evaluation, spirometry in case of COPD symptoms, in addition to lung cancer screening in case of eligibility. The objective of the study is to report our monocentric experience in implementing a pilot clinical program for the prevention and screening of TOREDI in addition to LCS in an academic hospital.

Methods: We performed a retrospective analysis of the patients' medical folders that were included in the pilot TOREDI program from 11/2023 to 12/2024. The study was approved by the local Internal Review Board (CSE25-30). We analyzed the number of 1st planned visit, 1st visit, visits per patient, the proportion of visits performed by nurses (vs. physicians) and performed by phone calls (vs. in person). We evaluated smoking cessation after the first visit among smokers, as well as the rate of known, screened and uncontrolled or unknown cardiovascular risk factors and COPD. History of cancer and active cancer were reported as well as the rate of participants undergoing LCS. Age was presented as mean ± standard deviation and categorial variables as median [IQR], ratio were presented as %, while smoking cessation probability was evaluated by Kaplan-Meier analysis.

Results: Among 346 planned 1st visit, 300 were actually performed in person. Mean age was 55 ± 13, sex ratio (men/women) was 148/152. Among 283 available folders for smoking cessation, 244 (86.2%) were active smokers; 965 visits were performed for smoking cessation including 548 (57%) nurse driven visits, 409 (42%) physician driven visits and 8 (1%) unknown; a median of 5 [3; 7] visits was performed per active smoker; 562 (58%) visits were performed in remote by phone. The median delay for smoking cessation was 120 days. Among 300 1st visits, 290 folders were available for TOREDI evaluation, we found known history of atheromatous cardiovascular disease in 82 (28.3%), hypertension in 78 (26.9%), blood pressure evaluation in 173 (59%) identifying untreated or undertreated hypertension in 21 (7.2%); known history of dyslipidemia in 89 (30.7%), dyslipidemia evaluation in 57 (19.7%) identifying 16 (5.5%) untreated or under treated dyslipidemia; known history of diabetes in 30 (10.3%), diabetes evaluation in 64 (22.0%) and untreated or undertreated diabetes in 8 (2.8%). Out of 290, 85 (29.3%) presented history of cancer including, 22 (7.6%) with active cancer; we performed LCS in 139 (47.9%) and 209 had available lung CT (72%); 25 (8.6%) had a diagnosed COPD, 128 (44%) without known COPD presented symptoms and underwent spirometry, 31 (10.6%) presented airway obstruction defined by Tiffeneau index < 70%.

Conclusions: Integrating smoking cessation, cardiovascular risk factors evaluation, COPD screening and lung cancer screening is possible in an integrated transversal program mainly driven by nurses and including remote visits by phone.

Keywords: lung cancer, tobacco, screening

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.12 Utility of CT Scans & Blood Tests After Maintenance Durvalumab Post Chemort in Stage III NSCLC Patients

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Introduction: The phase 3 PACIFIC trial established the benefit of one year of durvalumab maintenance following chemoradiotherapy (chemoRT) in stage III non-small cell lung cancer (NSCLC) patients, with imaging every 8 weeks during treatment and every 12 weeks thereafter. While imaging follow-up is in guidelines, blood test surveillance remains undefined.This retrospective study evaluated the frequency and clinical impact of follow-up CT scans and blood tests in stage III NSCLC patients treated at The Royal Marsden Hospital, London. We analyzed adherence to 3-monthly (3M) CT scans, correlation with progressive disease (PD) or death, and the utility of post-treatment blood tests. Secondary objectives included assesing scan findings´ impact on clinical decisions.

Methods: Patients with stage III NSCLC diagnosed from March 2019, who received ≥1 cycle of adjuvant durvalumab and completed one-year post-treatment, were included. Sixty patients were identified. A >20% rate of CT scans prompting intervention was set as a threshold for maintaining current practice.Adherence to 3M blood tests, including full blood count (FBC), urea and electrolytes (U+E), liver function (LFT), and thyroid function tests (TFTs), was recorded. Seventy-two patients had a complete baseline panel. Clinically significant abnormalities requiring intervention during follow-up were also documented.

Results: Of 60 patients, 4 showed progression on baseline CT, leaving 56 in the 3M follow-up. Compliance was high (92.8%). At 3 months, 14.2% of scans led to further imaging, decreasing to 11.5% at 6 months and 4% at 9 months. PET-CT was the most common additional test. Medication changes and specialist referrals ranged from 4% to 9.6%.

None of the patients with unspecified baseline CT changes progressed, but up to 50% of those with suspected tumor regrowth, pneumonitis, or pleural effusions had PD. At 3 months, 2/4 patients with pneumonitis progressed; at 6 months, 1 patient with suspected tumor growth progressed at 9 months. At 12 months, no patients had PD.

Regarding blood tests, 72 patients had a baseline panel. At 3 months, 79% had follow-up tests, with 45% showing clinically significant results requiring intervention. At 6, 9, and 12 months, follow-up rates dropped to 51%, 32%, and 39%, with 54%, 74%, and 53% of tests showing abnormalities, respectively. In total, 52% of all tests revealed significant abnormalities. Blood test follow-up was irregular (75%), with only 20% receiving routine 3M monitoring.

Conclusions: Adherence to 3M CT scans post-durvalumab was high (93%). The 10% scan pickup rate aligns with PACIFIC trial relapse rates (PFS 12-24 months). As this is below our 20% threshold, scan frequency will be reduced to 6 months. Blood test follow-up was poorly adhered to, yet when performed, it identified significant abnormalities, supporting its continuation.

Keywords: NSCLC, stage III, follow-up

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.13 Healthcare Professionals' Perceived Barriers and Facilitators of Risk-Stratified Follow-Up Care in Lung Cancer

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Introduction: Routine follow-up of lung cancer patients involves thoracic computed tomography (CT) scans every 3-6 months for the first 2 years, followed by yearly CT-scans up to 5 years. This 'one-size-fits-all' approach poses immense pressure on current healthcare facilities. Therefore, a risk-stratified strategy, tailoring follow-up frequency and imaging modality per patient, is needed to reduce the number of unnecessary scans and ensure high-quality follow-up. This study aims to identify healthcare professionals' (HCPs) barriers and facilitators for the implementation of a risk-stratified follow-up in lung cancer care.

Methods: A qualitative study was performed, involving 14 semi-structured interviews with a heterogenous group of HCPs engaged in lung cancer care. Inductive and axial coding of the transcripts was performed to categorize barriers and facilitators using the Grol & Wensing framework.

Results: Overall, HCPs stated that risk-stratified follow-up may help to organize follow-up care more accurately. Key identified barriers included the fear of missing disease progression when extending follow-up intervals for low-risk patients and the potentially increased healthcare burden from more intensive follow-up schedules for high-risk patients. Conversely, a key facilitator was that depicting the most accurate imaging modality and frequency for each patient could reduce the number of necessary follow-up scans. Another identified facilitator was that risk-stratified follow-up may pose an opportunity to increase the involvement of specialized nurses during follow-up.

Conclusions: This study shows that HCPs are generally willing to adopt a risk-stratified follow-up in lung cancer care. Nonetheless, the approach should be feasible and cost-effective, and its safety and effectiveness should be proven before implementation.

Keywords: Risk-stratification, Follow-up care, Lung cancer

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.14 Concordance Between Clinical and Radiological Diagnoses of Pneumonitis: Retrospective Cohort Review From Regional Health Service in Australia

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Introduction: Background:

Pneumonitis is a clinically challenging and potentially life-threatening condition, often presenting with non-specific respiratory symptoms that overlap with other pulmonary diseases. In regional healthcare settings, the limited availability of timely radiological support further complicates diagnostic accuracy. Although clinical guidelines for pneumonitis exist, evidence supporting clinical diagnosis without radiological confirmation remains sparse. This audit investigates the level of diagnostic agreement between clinical assessments and radiological findings in a regional Australian health service and evaluates the impact of imaging on clinical decision-making.

Aims:

- To assess concordance between clinical and radiological diagnoses of suspected pneumonitis.
- To evaluate the necessity of radiological imaging in guiding treatment decisions.
- To inform local clinical protocols for diagnosing pneumonitis when imaging is not readily available.

Methods: This retrospective audit reviewed patient presentations to Central Gippsland Health from 1 January to 31 December 2024. Patients included were those assessed for suspected pneumonitis based on presenting symptoms. Data collected from electronic medical records included demographics, clinician-documented diagnoses, and corresponding radiological interpretations. Diagnostic concordance was defined as agreement between the initial clinical impression and radiological findings and was expressed as a percentage. Data were de-identified and analysed using descriptive statistics.

Results: Thirty-four eligible cases were identified. Clinical and radiological diagnoses aligned in 50% of cases. In 25% of cases, imaging either confirmed or challenged the clinical impression, influencing final diagnosis. However, in the remaining 25%, radiological imaging did not affect patient management, indicating that clinical judgment alone may be adequate in some cases. These findings are particularly relevant in resource-limited settings, where immediate access to radiology is not feasible.

Conclusions: Conclusion:

This study highlights a critical gap in evidence regarding the utility of imaging in diagnosing pneumonitis, particularly in rural and regional contexts. The moderate level of concordance observed suggests that with enhanced clinical criteria and structured assessment tools, diagnosis and initial treatment may be possible without immediate imaging. These findings support the development of localised, evidence-informed diagnostic pathways aimed at improving efficiency without compromising patient care. Further prospective studies are warranted to validate these findings and assess long-term outcomes in settings with constrained access to radiology.

Keywords: pneumonitis, regional, concordance

EP.17.15 Tackling the Lung Cancer Crisis in Canada: Co-Creating a National Strategy to Reduce Lung Cancer Mortality by 30% Action Plan?

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Introduction: Lung cancer is the leading cause of cancer death in Canada, claiming more lives annually than breast, colorectal, and prostate cancers combined. Despite advancements in care, inequities in access, diagnosis, and outcomes persist—especially among underserved populations. To address this, the Canadian Cancer Society (CCS), with guidance from a National Steering Committee of diverse stakeholders, developed the 2025-2035 Pan-Canadian Lung Cancer Action Plan. The plan's overarching goal is to reduce lung cancer deaths by 30% over the next decade through coordinated, equity-focused national action.

Methods: The Action Plan was developed through a multi-phase, community driven process. Inputs were gathered from environmental scans, active engagement, and a national Lung Cancer Summit held in late 2024. The Summit convened over 100 interest holders from across the lung cancer ecosystem, including people with lived experience, cancer charities, clinicians, researchers, advocates, policymakers, and representatives from equity-deserving communities. A modified Delphi approach using an adapted form of the James Lind Alliance priority setting partnership was used. This enabled structured dialogue and consensus-building to identify and validate key priorities across the continuum of lung cancer care, from prevention through to survivorship and research.

Results: The Action Plan is built around four strategic priorities: 1. Reduce exposure to carcinogenic inhalants: National education campaigns will increase awareness of lung cancer risk factors, including radon and occupational exposures. The plan calls for enhanced tobacco control policies, improved product labelling, and advocacy for stricter air quality and workplace safety standards. 2. Detect lung cancer earlier: Actions include the development of national screening guidelines with expanded eligibility, scaling screening programs in all provinces and territories, and improving access to diagnostics, particularly in rural and remote areas and launching culturally competent awareness campaigns. 3. Improve access to timely, best-in-class care: The plan supports equitable access to genomic and molecular testing, faster regulatory approval and reimbursement of new therapies, expanded navigation services, and greater integration of trauma informed and culturally appropriate care. 4. Accelerate lung cancer research: Key actions include advocating for funding proportionate to disease burden, establishing national research priorities with increased investment in clinical trials, supporting early career researchers, and improving health data and biospecimen sharing across jurisdictions.

Each strategic area includes clear progress indicators. By 2035, the plan aims for earlier detection of lung cancer, consistent access to high-quality screening and testing, shorter diagnostic and treatment wait times, and increased research investment and innovation.

Conclusions: The 2025-2035 Pan-Canadian Lung Cancer Action Plan outlines a bold, coordinated path forward to reduce lung cancer mortality and address longstanding inequities in care. Grounded in community engagement, evidence, and a shared commitment to health equity, the plan provides a roadmap to improve outcomes and transform the lung cancer landscape across Canada over the next decade.

Footnote: ChatGPT was used to consolidate the existing original non-AI generated Action Plan in the first draft of this abstract.

Keywords: Action Plan, Strategy, Consensus

EP.17.16 Improved Concordance to Clinical Practice Guideline: Analysis Of Multidisciplinary Team Discussed Patients With Stage III Lung Cancer

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Introduction: China has a vast lung cancer disease burden due to the high incidence of 1.02 million new cases annually, accounting for 40% of the world total. The management of lung cancer - especially stage III - patients is complex due to the tumor severity, patient health status, and treatment feasibility. Meanwhile, guidelines from organizations like ASCO, ESMO, and CSCO are available, yet research on patient guideline concordance post-MDT is limited. This study aims to assess stage III lung cancer patient concordance to CSCO guidelines post-MDT and its impact on diagnosis and treatment outcomes.

Methods: This retrospective study assessed the impact of remote MDT discussions on diagnostic accuracy and treatment guideline concordance for lung cancer. The study included 77 patients from lower-tier hospitals discussed in 20+ remote MDT sessions with Shanghai Chest Hospital (2024-2025). Eligible patients had histologically confirmed lung cancer and underwent CT imaging and biopsy before MDT discussions, with 70% diagnosed at stage III, given the complexity of lung cancer at later stage. Data from electronic medical records and MDT logs included pre-MDT diagnosis and treatment plans, MDT recommendations, and post-MDT decisions. Outcomes analyzed were treatment guideline concordance, diagnostic modifications, genetic testing rates, and treatment changes. Descriptive statistics assessed MDT impact on clinical decision-making in lower-tier hospitals.

Results: Prior to MDT discussions, only 42% of stage III patients had undergone genetic testing. Following MDT recommendations, an additional 20% were advised to complete molecular testing to enable precision diagnostics. Diagnosis was revised in 22% of cases, and 11% of initially deemed unresectable cases were reclassified as potentially resectable. Regarding treatment optimization, 45% of stage III cases had their treatment plans modified post-MDT, leading to better alignment with national guidelines. The most significant adjustments included a shift from systemic therapy alone to multimodal approaches: a). Systemic + radiotherapy increased from 16% to 35%, b). Systemic + radiotherapy + surgery increased from 11% to 20%. These findings highlight the role of MDTs in ensuring more standardized and evidence-based management of stage III lung cancer.

Conclusions: This study demonstrates the significant role of MDT discussions in refining diagnoses and optimizing treatment strategies for stage III lung cancer. MDT participation enhances guideline adherence and promotes evidence-based decision-making, particularly in lower-tier hospitals. Future research should focus on long-term clinical outcomes, patient survival, and quality of life metrics to further assess MDT effectiveness. Additionally, expanding MDT networks and integrating digital platforms could strengthen multidisciplinary collaboration and improve lung cancer care in resource-limited settings.

Keywords: Stage III Lung Cancer, Remote MDT, Guideline concordance

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.17 Availability of PD-L1 and Ngs Results at Initial Medical Oncology Consultation in Patients With Non-Small Cell Lung Cance

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Introduction: PD-L1 and next-generation sequencing (NGS) testing are essential for guiding treatment choices in non-small cell lung cancer (NSCLC), influencing decisions on targeted therapy and immunotherapy. Delays in obtaining these results at the time of initial medical oncology consultation may impact timely treatment initiation and patient care. This quality improvement (QI) project aimed to assess the availability of PD-L1 and NGS results at initial consultation and their effect on patient care and treatment decisions.

Methods: With an ethics board waiver for QI projects, we reviewed 100 consecutive patients with newly diagnosed NSCLC seen in medical oncology consultation at The Ottawa Hospital Cancer Centre, a Canadian tertiary academic cancer centre with an in-house molecular testing laboratory, starting October 1, 2024. Molecular testing is initiated by the pathologist in our institutions workflow policies. PD-L1 is routinely ordered in all cases, and NGS in all non-squamous NSCLC cases. Data collected included patient demographics, staging, PD-L1 and NGS result availability, and treatment decisions.

Results: Among 100 patients (median age 71 years, 51% male), 3% had stage I, 13% stage II, 33% stage III, and 52% stage IV disease. Histological subtypes included 75% adenocarcinoma and 24% squamous cell carcinoma. PD-L1 and NGS testing were ordered reflexively by the pathologist before the initial medical oncology consultation in 96% of cases. PD-L1 testing was performed on 99/100 patients. At the time of consultation, PD-L1 results were available for 80/99 (81%) patients. NGS was performed on 77 patients and only 43/77 (56%) had NGS results at the time of consultation. The time between PD-L1 results becoming available and medical oncology consultation ranged from -150 to +20 days, with a median of 7 days before (IQR -16 to +4). For NGS, this range was -146 to +26 days, with a median of 1.5 days before consultation (IQR -16.6 to -1). Due to unavailable results, 39 patients required additional visits, with 36 needing one extra appointment, 1 requiring two, and 2 needing three additional visits. Despite this, only 5 patients had treatment initiated before obtaining PD-L1 and/or NGS results. No patients required a complete change in treatment upon result availability, though 2 had pembrolizumab added once results were available.

Conclusions: Overall, many NSCLC patients lack complete molecular testing results at their initial medical oncology consultation, particularly NGS. This delay often necessitates additional clinic visits, potentially delaying treatment initiation, although did not result in incorrect treatment in any cases. The efficiency of initial 1 hour consultations and subsequent 15-20 minute follow up appointments is impacted based on clinical discussions reliant on those results. These are complex issues, and oncology wait times and laboratory turn-around-times are also important variables. Given that most patients did not start treatment before results were available, this study helps inform whether scheduling the initial consultation after PD-L1 and NGS results are received may improve efficiency in clinical decision-making and reduce unnecessary visits. Our centre is currently piloting oncologist review of referrals to identify cases that can safely wait for initial consultation until results are ready.

Keywords: NGS, PD-L1, NSCLC

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.18 Refining Lung Cancer Diagnosis Through Multidisciplinary Team Collaboration

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Introduction: Lung cancer remains a leading cause of cancer-related mortality worldwide, in part due to challenges in achieving accurate tumor-node-metastasis (TNM) staging. Multidisciplinary team (MDT) approaches have demonstrated the potential to refine staging accuracy and optimize treatment. In China, the disparity between top-tier Centers of Excellence (CoEs) and resource-limited lower-tier hospitals often hampers comprehensive diagnostic reviews. Remote MDT consultations, facilitated by digital platforms, aim to bridge this gap by enabling real-time collaboration across institutions. This study assesses whether MDT discussions can improve clinical TNM staging and resectability determinations in patients with lung cancer, providing a foundation for broader implementation aligned with established guidelines.

Methods: An observational approach was adopted across a Center of Excellence (CoE) - Henan Cancer Hospital and lower-tier hospitals. 102 real-time patient cases with lung cancer were discussed via remote MDT sessions, among which 99 were patients with Stage III and beyond. During each MDT review, imaging results, pathology findings, and clinical variables were reassessed, and any resulting modifications in TNM classification, clinical staging or resectability status were recorded.

Results: Among the 99 cases, 10% of patients exhibited a change in either their TNM classification or clinical stage after MDT review. Of these, 7% experienced modifications in TNM components, while the remainder had changes in overall clinical staging. In the group with modified TNM classifications, the shift was more frequently downward than upward. Closer analysis indicated that T and N statuses underwent changes more often than M. One example involved downgrading a patient from T3 to T1 following enhanced radiologic assessment; in other instances, N status was revised after comprehensive lymph node evaluations. With respect to clinical staging, alterations were relatively modest overall. Stage IIIA and IIIC decreased, whereas IIIB and IV showed a slight uptick in patient numbers. Collectively, these modifications in TNM components and clinical staging yielded a 9% increase in the proportion of patients deemed resectable. Furthermore, after MDT, 30% of patients have changed their treatment plan, with more people switched from no therapy at all, or chemotherapy only to a combination between radiotherapy, chemotherapy and immuno-therapy. Crucially, these improvements stem from more precise clinical decisions made at lower-tier hospitals once they received valuable remote MDT input from the CoE (Henan Cancer Hospital). By providing specialized diagnostic and treatment insights, the CoE helped align final staging determinations with recognized guidelines and enhanced consistency across diverse clinical settings.

Conclusions: These findings underscore the value of MDT participation—particularly when CoE expertise is combined with remote digital platforms—in refining lung cancer staging and improving resectability and other treatment determinations. While most clinical diagnoses remained unchanged, the observed modifications highlight the importance of thorough, collaborative review. Improved identification of T, N, or M status facilitates more precise treatment planning, which is especially beneficial in lower-tier hospitals that may lack advanced imaging and pathology capabilities. Broadening the reach of MDT frameworks across facilities with vastly different infrastructures can ultimately help standardize guideline-based care and enhance outcomes for patients with lung cancer.

Keywords: Refining TNM Staging, Remote MDT

EP.17.19 Quality Control and Analysis of Standardized Diagnosis and Treatment of Lung Cancer

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Introduction: Lung cancer is the most common malignancy in China in terms of morbidity and mortality. Benefiting from the improvement of etiological prevention awareness, the promotion of screening work and the continuous improvement of comprehensive diagnosis and treatment level, the 5-year survival rate of lung cancer patients in China has been greatly improved, but there are still significant differences in the diagnosis and treatment level of lung cancer in different regions, which is also one of the key factors restricting the further improvement of survival of lung cancer patients. The quality control is conducive to promoting the standardization and homogenization of lung cancer diagnosis and treatment, and improving the level of diagnosis and treatment in primary hospitals, which is of great significance to improve the survival rate and quality of life of lung cancer patients.

Methods: From August 20 to September 20, 2024, a survey was conducted on the diagnosis and treatment status of lung cancer in the department heads of secondary and above medical institutions in Henan Province, and relevant information was collected by questionnaire. SPSS software (23.0 version) was used for statistical analysis.

Results: The quality control of standardized diagnosis and treatment of lung cancer covers 18 cities and 136 districts in the province, including 194 medical institutions; A total of 278 valid questionnaires were collected in this survey. The pathological diagnosis rate of lung cancer patients before the first non-surgical treatment was 100 (81.5-100) %. The average proportion of newly diagnosed and treated NSCLC undergoing genetic testing in 2021-2024 is shown in Table 1. We further investigated the factors affecting the submission of genetic testing, and 86.3% of the participants believed that “patients or family members give up” was the main factor. The average clinical TNM stage diagnosis rate of lung cancer patients before the first anti-tumor treatment was 99 (80-100) %.18.3% of the participants had no MDT team in their hospital, and 22.3% of the participants could not carry out radiotherapy in their hospital.

Table1. The average proportion of newly diagnosed and treated non-small cell lung cancers undergoing genetic testing in 2021-2024.

	2021	2022	2023	2024
LUAD	70 (45-90)	81 (60-95)	90 (70-100)	95 (80-100)
LUSC	17 (5-34)	16.5 (5.25-40)	20 (7-50)	20 (8.25-50)
LUASC	26.5 (7.75-80.00)	40 (10-80.75)	52 (11-89)	61.5 (11.25-95)

LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; LUASC, lung adenosquamous carcinoma.

Conclusions: Thvrough the quality control and analysis of lung cancer diagnosis and treatment, we found that there are still problems including insufficient related equipment and configuration in some primary hospitals, low pre-treatment genetic testing delivery rate, and insufficient evaluation of adverse reactions after treatment: Strengthening standardized training and multidisciplinary cooperation may help to reduce the occurrence of misdiagnosis, missed diagnosis and improper treatment, and ultimately reduce the mortality rate of lung cancer.

Keywords: quality control, lung cancer

EP.17.20 Natural Language Processing in Rapid Evaluation of Suspicious Lung Findings: Impact on Lung Cancer Outcomes

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Introduction: Lung cancer represents the leading cause of cancer-related mortality, making early diagnosis and prompt treatment initiation imperative. This study assessed the Natural Language Processing (NLP)-assisted rapid evaluation protocol, which employs chest CT report analysis as an opportunistic screening tool to identify suspicious lung findings necessitating further investigation, and evaluated its impact on prognosis and diagnostic work-up timelines for patients with lung cancer.

Methods: Consecutive lung cancer patients (n-200) diagnosed at Assuta Medical Centers (AMC) between January 2019 and December 2022 were retrieved from the AMC electronic database using the MDClone platform. The participants were divided into 2 groups: Group A (NLP-assisted rapid evaluation, n=100) and Group B (traditional referral for rapid evaluation by community physicians, n=100). Stage at diagnosis, time from initial imaging to biopsy, - histological verification, - molecular subtype determination, and - treatment initiation were assessed.

Results: The implementation of the NLP-assisted protocol resulted in a significant stage shift, with a higher percentage of patients diagnosed at Stage I (47.5% in Group A vs. 26.8% in Group B, p=0.013, Figure 1). While Group B exhibited a shorter median time to biopsy, this difference was not clinically significant. Other diagnostic work-up timelines were comparable between both groups; however, Group A demonstrated reduced variability in these timelines (Table 1).

Figure 1. Stage distribution at diagnosis by study group

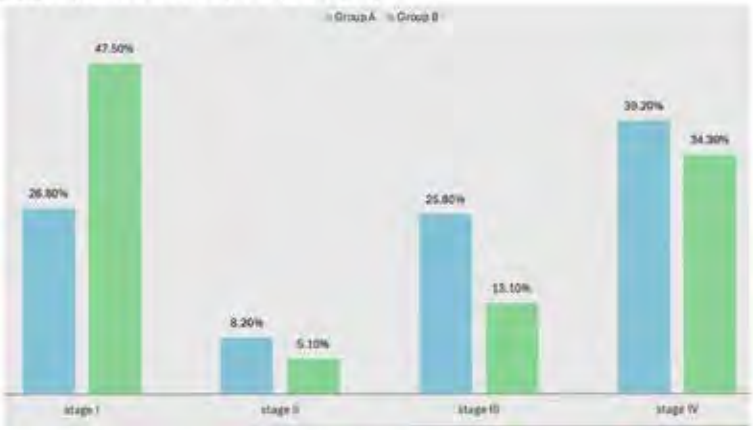

Table 1. Time from performance of the first imaging study demonstrating any cancer-related finding to biopsy, - histological verification, - molecular subtype determination, and - treatment initiation.

	Group A	Group B	P value
Time to biopsy performance, weeks			
Mean ± SD	9.31 ± 7.83	8.89 ± 10.87	0.05
Median, 95% CI	6.428 (1.1-50)	6 (0-54.9)	
Time to histological diagnosis verification, weeks			
Mean ± SD	11.37 ± 10.07	9.87 ± 9.14	0.39
Median	7.142 (2.9-63.4)	7.857 (1.4-55.7)	
Time to molecular subtype determination, weeks			
Mean ± SD	14.75 ± 7.66	20.90 ± 32.44	0.53
Median	13 (5.9-41.9)	11.928 (0-173.4)	
Time to definitive treatment initiation, weeks			
Mean ± SD	15.39 ± 10.73	15.71 ± 17.31	0.08
Median	12.785 (3.1-65.4)	10.571 (1.6-123.6)	

Conclusions: The incorporation of an NLP-assisted diagnostic approach facilitates opportunistic screening, promoting a stage shift towards earlier stages at diagnosis and potentially enhancing diagnostic efficiency along with the timeliness of interventions in lung cancer patients. ChatGPT AI tool was used to finalize the abstract.

Keywords: natural language processing, opportunistic screening, outcomes research

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.21 A Digital Health Solution for Monitoring Pulmonary Symptoms in Cancer Treatment

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Introduction: Pulmonary toxicities such as pneumonitis or interstitial lung disease (ILD), are associated with significant morbidity and can hinder patient outcomes of immunotherapy, chemotherapy, and targeted therapies through required treatment delays, dose reduction, or treatment discontinuation. Clinical providers are expected to monitor for and promptly investigate respiratory signs and symptoms for drugs associated with fatal cases of ILD. A digital application that supports capture, transfer and visualization of patient-reported new or worsening respiratory symptoms is a pragmatic tool for health care providers to meet label or protocol requirements.

Methods: Clinical consensus from a panel of oncologists (n=4), pneumonologists (n=2), and radiologist using a qualitative Delphi methodology, in addition to the review of published literature and AE adjudication charters (n=3) informed the content of this digital application. Interfaces for data collection (patient) and access (clinician) were designed with a focus on user-engagement and clinical relevance to inform the likely occurrence of ILD. Patients receiving anticancer therapies and clinicians (oncologists and nurses) participated in 1:1 qualitative user testing of the overall application's content and design. Prototypes of the patient app were implemented in clinical trials (n=484 patients) to inform patients' engagement.

Results: Based on clinical consensus, the patient app enables reporting of onset or worsening of the cardinal (cough, dyspnea, pain) and secondary symptoms of ILD (fever, fatigue) and the capture of blood oxygenation (SpO2), pulse and respiration rate collected at rest or during mild exertion (walking at normal pace for 3 minutes). Data collection uses a gated approach to foster daily symptom report while minimizing burden. The clinician portal provides easy to access chronological data visualizations in addition to alerts for symptom-worsening. As we could not achieve a consensus on an SpO2 threshold, the solution enables clinical staff to set a threshold adapted to the patient's health status and prompt investigation. Qualitative testing and early quantitative data from trial implementation support sustained patients' engagement (275 patients compliant over at least 5 weeks) to provide relevant data for the monitoring of the risk of ILD.

Conclusions: Leveraging digital interfaces provides a solution for clinicians to monitor patients at risk of ILD in between clinic visits while filling in a gap in evidence to support algorithm development for patient triaging or diagnosis (with added imaging). As both the patient and the clinician interfaces are implemented in 5+ clinical trials in various tumors, data and evidence of clinical validity and utility are expected within the next year or so.

Keywords: Remote Monitoring, ILD, Digital symptom monitoring

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.22 The Burden of Lung Cancer in Nigeria's Capital City: Findings From the Population Based Cancer Registry

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Introduction: Globally, lung cancer is the most frequently diagnosed malignancy responsible for about 2.5 million new cases and a mortality of 1.8 million in 2022. There is a rising incidence in sub-Saharan Africa with Nigeria having about 1,789 new cases and 1,643 deaths annually and projected to increase to 2.4 and 1.4 million respectively by 2040. The causes, types and survival trend vary in different populations. It is important to understand these characteristics in order to proffer plausible interventions for prevention and treatment. This study seeks to describe the lung cancer burden in Nigeria through analyses of data from the Abuja population based cancer registry (PBCR).

Methods: We conducted a retrospective analyses of lung cancer cases recorded in the Abuja Cancer Registry between 2009 and 2024. Key variables analyzed included age, sex, tumor morphology, diagnosis type, marital status, religion, and vital status. Data cleaning and transformation were performed using Python and R. We derived the incident year from the date of diagnosis and categorized age into three groups. Descriptive statistics were computed, and cross-tabulations with chi-square tests and t-tests were used to examine associations between sex and other variables. Trends in lung cancer incidence were visualized by year.

Results: A total of 98 lung cancer cases were reported to the Abuja Cancer Registry. The mean age at diagnosis was 56.8 (SD = 12.4) years, ranging from 29 to 83 years. Majority were married (89.8%), and Christains (77.6%) with a higher proportion of women with lung cancer [54 55.1%]. The morphological verification percent is 98%, the most common morphological type was Bronchio-alveolar carcinoma mucinous, representing 67.3% of cases, followed by Adenocarcinoma NOS (20.4%). Regarding diagnostic type, most cases were diagnosed through asymptomatic presentation (43.9%), symptomatic presentation (41.8%), and screening programs (14.3%). Out of all patients, 88 (89.8%) were alive at the time of data collection, giving a case fatality rate of 10.2%. A year-on-year trend analysis showed fluctuating incidence with no significant consistent increase or decline between the years captured in the dataset.

Conclusions: The data from the PBCRs in Abuja highlights the demographic and clinical characteristics of lung cancer cases. We observed a majority of cases occurring in older adults with a slight female predominance. The high proportion of diagnoses through asymptomatic presentation suggests the lack of early detection efforts. Although a low fatality rate may suggest a high survival of patients with lung cancer, a follow up assessment of vital status is recommended. The findings underscore the need for improved lung cancer surveillance. Research into the early diagnosis, screening, socio-economic and environmental factors that may predispose to lung cancer will prove beneficial. Findings from this registry study will be compared to other PBCRs in Nigeria.

Keywords: Lung Cancer Burden, Population Based Cancer Registry, Case Fatality Rate

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.23 Demographic Profile and Patient Journey of Early-Stage NSCLC Patients in a Brazilian Public Reference Center: A Real-World Study

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Introduction: Early-stage non-small cell lung cancer (NSCLC) poses unique challenges in diagnosis and treatment, particularly in asymptomatic patients. This study describes the demographics, patient journey, and healthcare resource utilization (HCRU) of early-stage NSCLC patients at the Instituto do Câncer do Estado de São Paulo (ICESP), Brazil. Insights into these aspects are vital for improving patient outcomes and resource allocation.

Methods: A retrospective study was conducted on early-stage NSCLC patients treated at ICESP from January 2010 to January 2022. Inclusion criteria encompassed patients with histologically confirmed early-stage NSCLC (stages I, II, and IIIA) who underwent tumor resection, excluding those treated with immunotherapy. Data collection continued until January 2024, with the surgery date as the index date.

Results: Among 606 early-stage NSCLC patients, most were over 65 years old (52%), female (54%), and white (78%), with a median BMI of 26. Most were former or current smokers (74%), with squamous histology in 19%. Stage distribution was 56% stage I, 23% stage II, and 18% stage IIIA (AJCC 8th edition). The mean age at diagnosis was 63 years, with common comorbidities including hypertension (53%), COPD (44%), and previous malignancy (40%). Median time from symptom onset to histological diagnosis was 241 days (SD 391), and from diagnosis to surgery was 145 days (SD 114). Surgery only was predominant in stage I (93%), stage II (67%), and stage IIIA (51%), while surgery combined with adjuvant treatment was received by 4%, 31%, and 47%, respectively. Most patients (84%) underwent lobectomy. Recurrence rates were 19% for stage I, 37% for stage II, and 43% for stage IIIA. Recurrence-free survival (RFS) ranged from 47 months (SD 27) in stage I to 28 months (SD 28) in stage IIIA, with a mean of 39 months (SD 29). Regarding HCRU, non-invasive staging tests were common, including thorax CT (87%) and PET scan (83%). Invasive tests were less frequent, with EBUS performed in 24%: 16% in stage I, 38% in stage II, and 35% in stage III. Molecular exams were conducted in only 28% of patients. Postoperative care involved ICU admissions for 49%, with a median stay of 4 days. Stage IIIA patients had the highest rates (69%) and longest ICU stays (mean: 21 days; SD: 26). The median inpatient stay post-surgery was 4 days, with stage IIIA patients requiring longer stays (mean: 8.0; SD: 9.1).

Conclusions: This real-world study characterizes the demographic and clinical profiles, treatment patterns, and HCRU of early-stage NSCLC patients undergoing curative-intent surgery at a major public cancer center in Brazil. Notably long-time intervals were observed, with a median of over 7 months from symptom onset to diagnosis and nearly 5 months to surgery. Despite surgical treatment being the primary approach, recurrence rates were significant, especially in stages II and IIIA, with diminishing RFS. The variability in staging and molecular tests and high rates of intensive postoperative care underscore the complexities of managing early-stage NSCLC and the need to improve diagnostic timeliness, standardize staging practices, and strengthen postoperative follow-up within the public healthcare system.

Keywords: NSCLC, Patient journey, Real-World Study

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.24 Clinicopathological Features of Lung Cancer: A Study From a Tertiaryreferral Center in Georgia

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Introduction: Lung cancer (LC) is one of the leading causes of mortality in Georgia. This study is first such kind in Georgia aiming to analyze the clinicopathological characteristics of patients with confirmed LC.

Methods: Between 2023 and 2024, data from 255 LC patients, including demographic and clinicopathological characteristics, were analyzed at a tertiary referral center in Tbilisi, Georgia.

Results: The median age was 67 years (range 31-88), with 200 patients (78.4%) older than 60, 86% were male and 88% smokers. Among current smokers, the male-to-female ratio was 2:1 and 47% were heavy smokers (>1 pack/day).Cough and shortness of breath were the most common presenting symptoms (28%), followed by fatigue (22%) and hemoptysis (16%).Bronchoscopy was performed in 125 (49%) patients for diagnosis. Only 40 patients (16%) had a PET-CT for staging, likely due to limited access to this procedure in a resource-limited setting. Non-small cell lung cancer cases (NSCLC) were 82% and small cell lung cancer (SCLC) 18%. Among NSCLC cases, 51% were adenocarcinoma, 38% squamous cell carcinoma, and 11% other subtypes. With biomarker testing, 14.5% of cases were EGFR-positive and 10% ALK/ROS1-positive, with higher rates in nonsmokers and those with non-squamous histology. For PD-L1 expression, 37% had TPS <1%, 35% TPS 1-49%, and 28% TPS >50%.Distant metastases were observed in 171 (67%) patients. Among NSCLC cases, 64.7% (136/210) were stage IV, while 80% of SCLC cases had extensive-stage disease.Bone and contralateral lung (29%) were the most common metastatic sites, followed by brain and pleura. Only 13 (5%) of patients were diagnosed at stage I or II.A family history of cancer was found in 39 patients (15%), and notably, 13 patients (5%) had a family history of LC.We found a significant correlation between smoking and histology, with non-smokers mostly having adenocarcinoma (p=0.009). No correlation was found between PD-L1 status and smoking.

Conclusions: Most LC cases present at advanced stages, leading to poor outcomes. Adenocarcinoma is prevalent in nonsmokers and driver mutations occur in one-quarter of NSCLC cases, which shows the need for biomarker testing. Implementing preventive programs and LC screening could help reduce mortality rates.

Keywords: Lung Cancer, Clinicopathological Characteristics, Georgia

EP.17.25 The Transition of Treatment Choice for First-Line Treatment for Advanced or Recurrent NSCLC and the Patients' Characteristics

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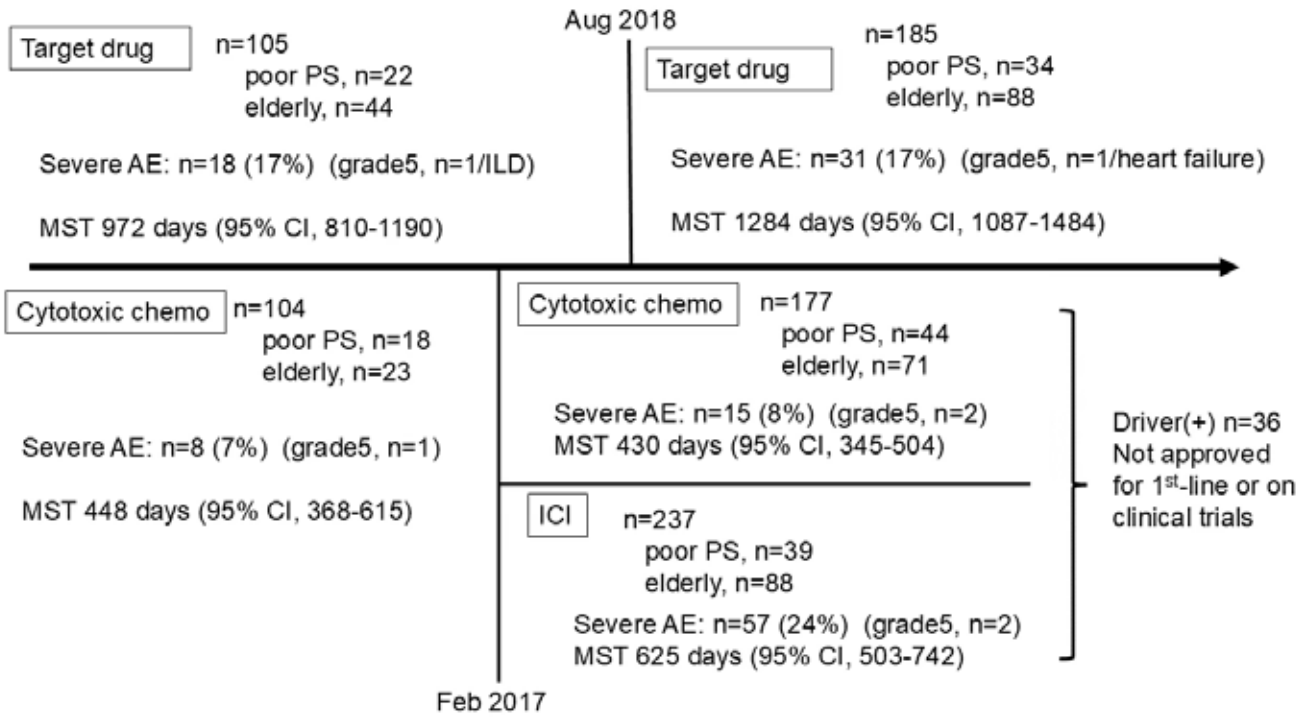
Introduction: The introduction of targeted therapies and immune checkpoint inhibitors (ICIs) has enhanced survival rates for patients with advanced or recurrent NSCLC. However, anticancer medications with new mechanisms of action can sometimes lead to unforeseen adverse events (AEs). In this retrospective analysis, we aimed to assess the efficacy and adverse events associated with anticancer treatments, categorized by treatment era and the types of drugs used.

Methods: In this retrospective single-center analysis, we planned to assess the transitions of treatment strategies for first-line treatment for advanced or postoperative recurrent patients with NSCLC and the incidence of AE stratified by treatment era and drugs. We accessed the data of patients who started first-line therapy in our institute between April 2014 and February 2024. Treatment eras for patients with targeted therapy for first-line treatment were divided into two periods by August 2018, when osimertinib was approved for first-line therapy. Treatment eras for patients who did not receive targeted drug were divided in February 2017, when pembrolizumab was approved for first-line treatment.

Results: The ratio of the patients with poor performance status (PS) score of 2-4 was 16-17% in the target therapy group, the ICI group, and the chemotherapy group prior to the ICI era, whereas the chemotherapy group post ICI era included 25% of poor PS. The incidences of AE were consistent in both periods in the target therapy group (17%) and in the cytotoxic agent group (7-8%). ICI regimen caused the highest incidence of AE (24%), and endocrine disorders were the most common. Six cases of grade 5 occurred (EGFR-TKI, n=1; cytotoxic chemotherapy, n=3; ICI, n=2). Even after the approval of ICI for first-line therapy, patients with ILD as comorbidities, the elderly or poor PS tended to choose a cytotoxic regimen due to the concern of AE.

Conclusions: This research had several limitations due to its retrospective nature. Our data included only the patients who received anticancer drugs, and we did not collect the details of subsequent treatment. However, many patients who received cytotoxic chemotherapy may have reaped the benefit of survival by later-line administration of ICI. Some targeted drugs, e.g., sotorasib and TdX-D, are approved for late-line therapy. Due to the aging society of Japan, the ratio of the elderly has increased. The treatment decision for patients with underlying conditions places more importance for oncologists.



EP.17.26 Survival in Advanced NSCLC Patients With PD-L1 =50% Treated With ICIs : A Multicenter, Retrospective Real-World Study in Georgia

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Introduction: ICIs are standard for aNSCLC with high PD-L1 expression(≥50%) and no genomic aberrations. Real-world survival outcomes often differfrom clinical trial results, with shorter overall survival (OS) reported in severalstudies. This study aimed to assess real-world OS and progression-freesurvival (PFS) in patients with aNSCLC and high PD-L1 expression treatedwith ICIs, comparing outcomes with clinical trials.

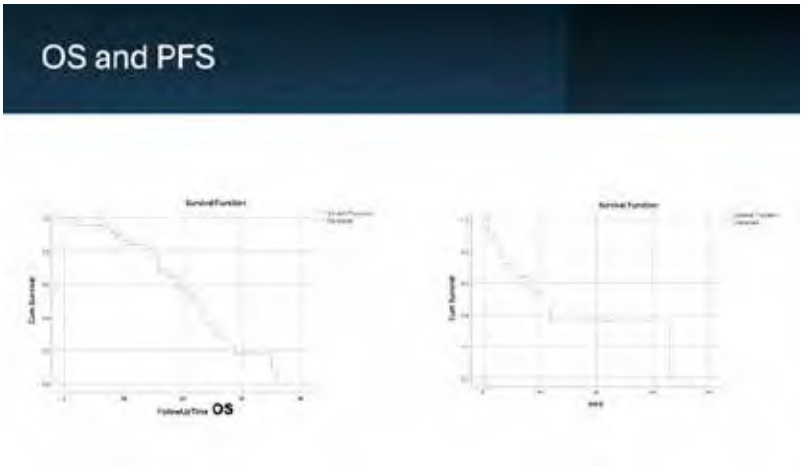
Methods: A retrospective analysis was conducted on 49 patients withaNSCLC, PD-L1 tumor proportion score (TPS) ≥50%, and no drivermutations, treated with ICIs between January 2019 and September 2024 atfour centers in Georgia. All patients received either pembrolizumab oratezolizumab without chemotherapy as first- or second-line treatment. Dataon patients' clinicopathological characteristics (see Table #1). Kaplan-Meierestimates were used to calculate PFS and OS, and treatment responses andadverse events were assessed.

Results: The median age was 69 years (range: 44-84), with 93% male. 26patients (53%) had non-squamous carcinoma, while 23 patients (47%) hadsquamous cell carcinoma. The majority (88%) had stage IV disease, and 92%received pembrolizumab. The median follow-up duration was 16 months (2-36), with a median of 7 (1-37) treatment cycles. The best response waspartial response (46%), disease stabilization (24%), and disease progression(24%). The median PFS was 10.0 months (95% CI: 6.7-13.2 months), andthe median OS was 22.0 months (95% CI: 17.8-26.1 months). Adversereactions were reported in 70% of patients, with 24.4% experiencing grade3-4 events. Two patients had fatal immune-related adverse events (irAEs).

Conclusions: Study shows the effectiveness of using ICIs monotherapy inreal-world setting in patients PD-L1 TPS ≥50% aNSCLC. Our results clearlystate that the overall survival benefit is consistent with clinical trial data,although PFS was slightly lower. It might be useful to briefly acknowledge

limitations (e.g., retrospective design, sample size) or implications for futureresearch.

PATIENTS' CHARACTERISTICS	N (%)
Age, Median (Range)	69 (44 to 84)
Sex	
Male	46 (93%)
Female	3 (7%)
ECOG Performance Status	
0	12 (24%)
1	30 (61%)
2	7 (15%)
NSCLC Histology	
Squamous Cell	23 (47%)
Adenocarcinoma	21 (43%)
Other	5 (10%)
Staging	
IIIA/IIIB/IIIC	2/2/2 (12%)
IV	43 (88%)
Number of Metastatic Sites	
1	21 (49%)
2	16 (37%)
≥3	6 (14%)
Line of IO Therapy	
1	41 (84%)
II	8 (16%)
PDL Status	
50-75%	21 (43%)
>75%	23 (47%)
N/A (≥ 50%)	5 (10%)
Number of IO Cycles, Median (Range)	7 (1 to 37)
Used IO	
Pembrolizumab	45 (92%)
Atezolizumab	4 (8%)



Keywords: immune checkpoint inhibitors, non-small cell lung cancer, PD-L1 expression

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.27 Real-World Impact on Overall Survival of High-Cost Targeted and Immunotherapies in Lung Cancer Patients Under Chile's DAC Program

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Introduction: Lung cancer remains among the leading cancers in incidence and mortality worldwide, including Chile. Advances in cancer therapy, notably immunotherapy and targeted therapies, have substantially improved patient quality of life and overall survival. However, the high cost of these drugs generates significant access disparities, challenging the Chilean public health system's ability to provide them equitably. To address this, in 2019, Chile's Ministry of Health established the High-Cost Drugs Program (DAC), which evaluates and finances selected high-cost oncologic therapies for public health patients. This study assesses the survival impact of treatments funded by DAC among lung cancer patients treated at Instituto Nacional del Tórax (INT).

Methods: We retrospectively analyzed survival data of lung cancer patients enrolled in the DAC program at INT. Patients were evaluated according to the medication received (immunotherapies: Pembrolizumab, Nivolumab; and tyrosine kinase inhibitors: Osimertinib, Alectinib, Crizotinib). Mean survival with 95% confidence intervals, median follow-up, overall mortality rate, and survival rates at 12 and 24 months were calculated. Time of survival consider from indication of therapy from oncology committee. This analysis did not stratify by histology, cancer stage, age, or other relevant clinical variables.

Results: A total of 76 patients were included. Overall, patients showed a mean survival of 16.41 months (95% CI: 13.68 - 19.13 months) and a median follow-up of 13.5 months. The observed mortality rate was 32.9%.Survival rates at specific intervals indicated that 51.3% of patients remained alive at 12 months, decreasing to 23.7%at 24 months. Treatment-specific mean survival results were:• Alectinib: 19.16 months (95% CI: 14.59 - 23.73 months)• Osimertinib: 20.20 months (95% CI: 11.36 - 29.04 months)• Nivolumab: 15.67 months (95% CI: 7.86 - 23.47 months)• Pembrolizumab: 13.59 months (95% CI: 9.78 - 17.39 months)• Crizotinib: 43.00 months (single patient; no CI available)

Conclusions: The analysis demonstrates improved survival outcomes for patients enrolled in the DAC program compared to historical survival rates for lung cancer in Chile. However, important limitations must be acknowledged. Notably, this analysis did not adjust survival outcomes for crucial prognostic factors such as tumor histology (e.g., adenocarcinoma versus squamous cell carcinoma), clinical stage, patient age, or comorbidities, all of which significantly influence survival outcomes. This limitation may partially explain variations observed in survival between immunotherapy-treated patient groups and should be considered when interpreting these results.The presence of heterogeneous histologies (adenocarcinoma and squamous cell carcinoma) among patients treated with immunotherapy could influence differential responses and survival outcomes, highlighting the need for future, more detailed subgroup analyses. Additionally, age and cancer staging are critical factors known to influence survival significantly and should be included in subsequent analyses to provide a clearer interpretation of the impact of DAC-funded treatments.Despite these limitations, the data confirm the clinical relevance of DAC by facilitating access to high-cost drugs and underscore the importance of conducting comprehensive, locally-relevant cost-effectiveness and clinical studies to guide future policy decisions.

Keywords: High-cost drugs programs, lung cancer survival, real world data

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.28 Duration of Systemic Therapy in Patients With Metastatic EGFR-Mutated NSCLC and Brain Metastases: First vs Third Generation TKIs

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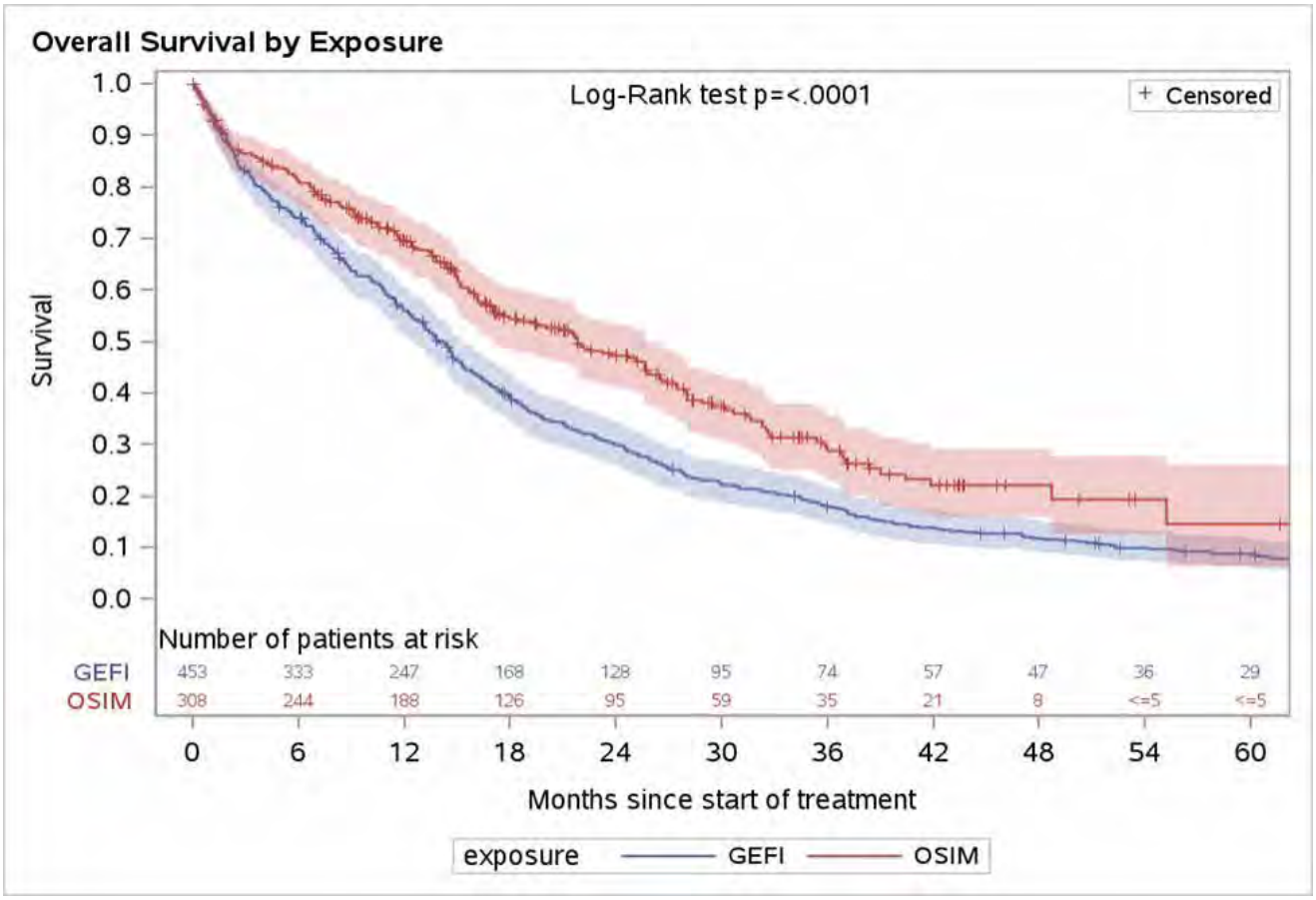
Introduction: New-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as Osimertinib, demonstrate high central nervous system (CNS) activity in EGFR-mutated non-small cell lung cancer (NSCLC). Clinical guidelines recommend TKI monotherapy as an effective option for small, asymptomatic brain metastases (BM). We hypothesize that patients receiving Osimertinib remain on therapy longer than those on first- or second-generation TKIs. This study evaluates treatment duration in a real-world setting using a healthcare administrative database.

Methods: We analyzed data from the Institute for Clinical Evaluative Sciences (ICES), a provincial health administrative database, identifying patients diagnosed with non-squamous NSCLC from 2002 to 2022. Eligible patients received first-line EGFR-targeted therapy with either Gefitinib or Osimertinib. Brain radiotherapy receipt was used as a surrogate for BM presence. Patients under 18 or those with a prior cancer diagnosis within five years were excluded. The primary outcome was the duration of first-line systemic therapy. Overall survival (OS) was estimated using the Kaplan-Meier method. Propensity score matching adjusted for baseline factors influencing systemic therapy duration, including age, sex, rurality index, Charlson and Elixhauser comorbidity indices, income quintile, and treatment year.

Results: Among 3,088 screened patients with EGFR-mutated NSCLC, 1,243 received Osimertinib and 1,845 received Gefitinib as first-line therapy. A total of 761 patients had BM while receiving systemic therapy and met inclusion criteria (Osimertinib: 308; Gefitinib: 453). The median first-line systemic therapy duration was significantly longer in the Osimertinib cohort (327 vs. 190 days, $p < 0.001$). Median OS was also higher with Osimertinib (21.8 vs. 14.0 months, $p < 0.001$) (Figure 1). After propensity score matching (n = 168, 84 in each cohort), patients on Osimertinib first line had a median duration of 390 days vs. 154 days per patients receiving Gefitinib. There was no longer a significant difference in OS, with a median OS of 16.2m vs. 14.7m in the same respective cohorts ($p = 0.36$).

Conclusions: Patient with brain metastases treated with Osimertinib remained on this line of systemic therapy longer than patients treated with Gefitinib. These findings remained consistent after propensity score matching. These findings suggest that despite BM, patients on Osimertinib may have sustained efficacy in this patient population.



Keywords: Brain Metastases, Osimertinib, EGFR

EP.17.29 Real-World Effectiveness of Immunotherapy for Advanced Non-Small Cell Lung Cancer (NSCLC) Without Oncogenic Driver Alteration

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Introduction: Immune checkpoint inhibitor (ICI) is the standard of care for non-oncogene-addicted advanced NSCLC. ICIs used either in frontline (1L) or second-line (2L) setting improved patient survival, compared to chemotherapy alone. Unfortunately, ICIs are not reimbursable in many countries due to financial constraints. While the cost of ICIs used in the 1L setting is higher than the 2L one, the comparative effectiveness is unknown.

Methods: Medical records of advanced NSCLC patients receiving ICIs or chemotherapy at Siriraj Hospital, Bangkok, Thailand from 2016 to May 2023 were reviewed. Progression-free survival of 1L treatment (PFS) and overall survival (OS) of patients receiving 1L-ICIs, 2L-ICIs, and chemotherapy alone were compared using Kaplan-Meier method and log-rank test. Hazard ratio (HR) was calculated using Cox proportional hazard model. OS was defined as the duration from 1L treatment initiation until death.

Results: Both 1L-ICIs and 2L-ICIs significantly improved OS, compared to chemotherapy alone. However, no OS difference was observed between 1L-ICIs and 2L-ICIs (p=0.45).

Conclusions: Real-world evidence confirmed that ICIs significantly improved OS compared to chemotherapy alone. However, OS was similar for ICIs used in 1L and 2L settings. These results will be used for cost-utility analysis to identify the most cost-effective scenario for ICI reimbursement.

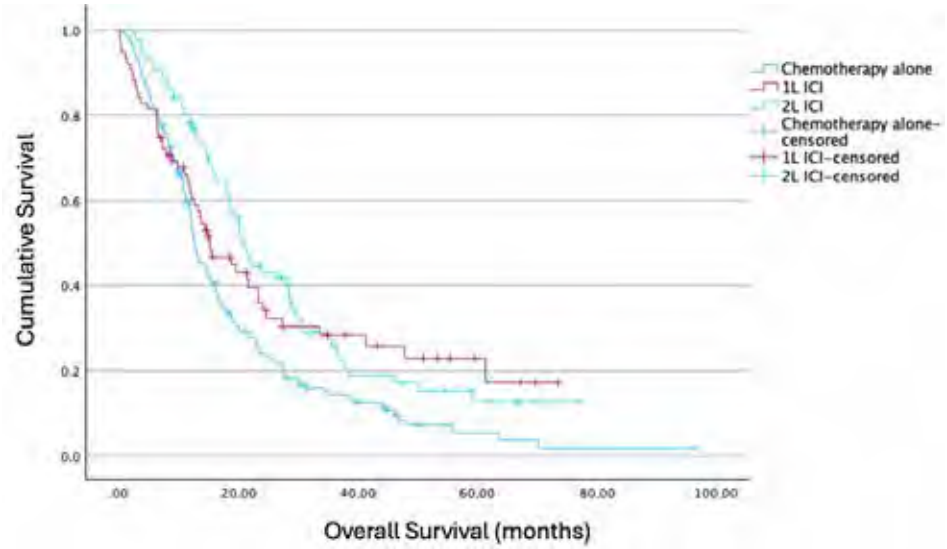

Table 1. Baseline characteristics

	Chemotherapy alone (n=156)	1L-ICIs (n=75)	2L-ICIs (n=87)	p-value
Male (%)	102 (65.4)	54 (72.0)	59 (67.8)	0.60
Age – Mean (SD)	62.7 (10.8)	69.6 (10.4)	64.7 (10.2)	< 0.001
Smoker – n (%)	82 (52.6)	44 (58.7)	53 (60.9)	0.05
Adenocarcinoma – n (%)	127 (81.4)	60 (80)	72 (82.8)	0.14
ECOG 0-1 (%)	137 (87.8)	54 (72.0)	79 (90.8)	0.001
Brain metastasis – n (%)	21 (13.5)	9 (12.0)	13 (14.9)	0.86
PD-L1 – n (%)				< 0.001
Negative	52 (33.3)	15 (20.0)	38 (43.7)	
Low (TPS 1-49%)	15 (9.6)	17 (22.7)	27 (31.0)	
High (TPS ≥ 50%)	9 (5.8)	33 (44.0)	17 (19.5)	
Unknown	80 (51.3)	10 (13.3)	5 (5.7)	

Table 2. Survival outcomes

Treatment	Median PFS (months)	Hazard ratio for PFS [95% CI]	p-value
Chemotherapy alone	8.9	Reference	
1L ICIs	24.6	0.35 [0.24-0.50]	<0.001
2L ICIs	7.2	1.18 [0.90-1.55]	0.23
Treatment	**Median OS (months)**	**Hazard ratio for OS [95% CI]**	**p-value**
Chemotherapy alone	19.4	Reference	
1L ICIs	27.1	0.70 [0.50-0.96]	0.027
2L ICIs	28.7	0.60 [0.45-0.80]	<0.001

Keywords: Advanced non-small cell lung cancer, Immunotherapy, Real-world evidence

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.30 Rising Incidence of Early Onset Thoracic Malignant Tumors: Real-World Data From Two Hospitals in Brazil

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Introduction: A rising number of early onset cancers have been observed worldwide in the last two decades. In lung cancer, the population of early onset cancer has conflicting data as far as risk factors, such as tobacco exposure, family history and female gender. In Brazil, tobacco consumption has decreased over the last two decades, while other lifestyle risks have increased, such as obesity, pollution exposure and use of electronic nicotine delivery systems. Moreover, the increase in early onset cancers holds substantial personal and societal consequences, including greater disease burden, loss of potential working years, and long-term health complications throughout the life course. There has been published data in other populations of this phenomena, however, there is a notable scarcity of data regarding this trend in Brazilian population. This study aims to evaluate the increase of number of early onset thoracic solid malignant tumors in two Hospitals in Brazil.

Methods: Retrospective data from Hospital Israelita Albert Einstein and Hospital Municipal Vila Santa Catarina in Sao Paulo, Brazil were queried from the period of 2018 to 2023. The study assessed patients with the diagnosis of thoracic solid malignancies according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Search included C33 - malignant neoplasm of trachea, C34 - malignant neoplasm of bronchus and lung and C37 - malignant neoplasm of thymus. Early-onset cancer was defined as cases diagnosed in adults between 18 and 49 years. Data extraction was automated, utilizing precision medicine sources to obtain information related to ICD codes, demographics, and medical history.

Results: Our analysis observed 954 cases of malignant solid thoracic neoplasms, divided into 933 cases of lung and bronchus cancer, 20 cases of malignant neoplasm of thymus and 1 case of malignant neoplasm of trachea. From the total, 871 patients (91%) were aged 50 years or older, while 83 (9%) were between 18 and 49 years old. Smokers or former smokers were majority in both populations, but less common in the early onset population (68%) when compared to 50 years or older (82%), with statistical significance (p-value 0.002). In the early onset population, female gender was numerically more prevalent with 58% versus 42% of males and more common when compared to 51% in the 50 years or older, but with no statistical significance (p-value 0.3). Proportion of localized or locally advanced disease was similar in both populations. Incidence in early onset cancer increased from 0.16 cases per 10,000 people in 2018 to 0.49 per 10,000 people (p-value 0.001), with an increase in variation of 200% in the early onset population versus 18% in the 50 years or older.

Conclusions: Rising number of early onset thoracic solid cancers appears to be trend observed worldwide and was also saw in our sample with Brazilian patients. Even though our study does not have the power to fully represent the population, this trend deserves further studies to better understand it, so we can better characterize risk factors and access best screening opportunities for this younger population.

Keywords: early onset cancer, rising incidence, thoracic tumors

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.31 Temporal Trends and Prognostic Factors in Lung Cancer Patients: Analysis Of a 25-Year Cohort of 2,488 Cases

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Introduction: Lung cancer remains the leading cause of cancer-related mortality worldwide. Clinical and epidemiological factors such as sex, smoking, histological type, staging, functional performance (ECOG), and recurrence pattern directly influence patient survival. This study aims to demonstrate temporal changes in the Brazilian patient profile over the past 25 years.

Methods: This is a retrospective cohort study involving 2,488 lung cancer patients at three hospital institutions in São Paulo between 1999 and 2024. Variables analyzed included sex, smoking status, ECOG, histological type, recurrence, and survival. Statistical tests were applied according to data type and distribution (Wilcoxon, Shapiro-Wilk, Kruskal-Wallis, chi-square, and Cochran-Armitage trend tests).

Results: There was a decrease in the proportion of male patients (from 75% in 1999 to 41.7% in 2024) and an increase in the number of women diagnosed with lung cancer. Prevalence of non-smokers rose from 13.6% (2000) to 40.1% (2024), and probability of developing lung cancer as a non-smoker increased from 6.3% to 34.2% during the period. Smoking cessation after diagnosis dropped from 69.3% in 2013 to 38.6% in 2024. Probability of quitting smoking post-diagnosis showed a downward trend (from 57.1% in 1999 to 53.2% in 2024). Men were more frequently former smokers (65.3%), while women predominated among non-smokers (37.3% vs. 12.9%). Proportion of current smokers was similar between sexes (21.3% in men vs. 20.2% in women). Adenocarcinoma increased in prevalence from 62.5% (1999) to 67% (2024), while squamous cell carcinoma decreased from 37.5% to 8.2%. Although there was no statistically significant increase in adenocarcinoma among women ($p = 0.1433$), it was significantly associated with active smoking. A significant increase in the proportion of patients diagnosed at stage I was observed, especially after 2015, reaching 83.5% in 2024 ($z = 22.7$; $p < 0.001$).

Stage IV cases dropped from 50% in 1999 to less than 2% in 2024 ($z = -20.0$; $p < 0.001$). Being diagnosed at stage I increased from 26.9% (before 2010) to 61.2% (2015-2019), reaching 79.4% between 2020-2024, while stage IV diagnosis decreased from 24.6% to 5.2% in the same period ($p < 0.001$). Median survival was 25.3 months in patients with local recurrence, 20.0 months with distant recurrence, and 15.83 months in patients without recurrence overall. Women with local recurrence had the best survival outcomes (33.7 months). ECOG 2-3 associated with smoking correlated with worse survival (1.5 months in men; 1.08 months in women).

Conclusions: There has been a transformation in the profile of lung cancer patients in this Brazilian cohort over the past 25 years, with an increase in cases among non-smokers and a higher proportion of affected women.

There was a decrease in squamous cell carcinoma and a rise in adenocarcinoma.

The percentage of patients diagnosed at stage I increased, while stage IV cases declined over the years.

Survival is influenced by sex, type of recurrence, functional status, and smoking, with women showing more favorable prognoses. Smokers with high ECOG scores have worse survival.

Prospective national-level studies are needed to better understand lung cancer behavior and trends in the coming years.

Keywords: lung cancer, trends in Brazil, lung cancer trends

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.32 Real-World Disease Impact in First-Line Treated Patients With Advanced Non-Small Cell Lung Cancer With PD-L1 Expression =50%

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Introduction: Given the evolving treatment landscape globally in patients with advanced non-small cell lung cancer (aNSCLC), PD-L1 ≥50% and without actionable genomic alterations (AGA), there is a need to better understand impact of symptoms and comorbidities on overall functioning to support treatment choice. This study assessed disease burden in patients prescribed first-line (1L) immunotherapy monotherapy or immunotherapy + chemotherapy across Europe (EU), United States (US), and Asia.

Methods: Data were derived from the Adelphi NSCLC Disease Specific ProgrammeTM: a comprehensive multifaceted systematic approach involving multi-country, cross-sectional surveys of physicians and patients across EU (France, Germany, Spain, Italy, UK), US, and Asia (China, Japan) between Dec 2023-May 2024. This included data from medical charts of patients (alive at the time of the study) on symptoms, comorbidities and patient-reported impairment on activities of daily living during treatment, as well as hospitalizations (excluding routine visits) 12 months prior to data collection (recent). All analyses were descriptive.

Results: Of 512 patients (EU: n=369; US: n=53; Asia: n=90) with PD-L1 expression ≥50% and without AGAs, median (IQR) age across regions was 69 years (64-74) with majority (75%) treated at a public hospital. Overall (n=430), 44% experienced a recent hospitalization. Symptoms were similar for 1L immunotherapy + chemotherapy (n=116) and 1L immunotherapy monotherapy (n=340) across regions, with the most common being cough (66% and 62%), fatigue (53% and 42%), dyspnoea (35% each), loss of appetite (28% each), chest pain (24% and 26%), and persistent cough (30% and 20%). On a severity scale, cough and persistent cough were reported severe by a higher proportion of 1L immunotherapy + chemotherapy patients (11%, n=76 and 9%, n=35) than 1L immunotherapy monotherapy patients (1% each, n=211 and n=67), respectively. A higher proportion of patients with squamous histology, history of smoking, and ECOG 1+ experienced symptoms during 1L treatment than patients with non-squamous histology, never smokers, and ECOG 0, respectively. When examining by duration of 1L treatment (median: 8 months; n=216), a lower proportion of patients with ≥6 months experienced cough (60%), wheezing (23%) and persistent cough (23%), than with <6 months (71%, 38%, and 36%). Chronic pulmonary disease (25% and 23%) and diabetes without chronic complications (17% and 18%) were the most common comorbidities for immunotherapy monotherapy and immunotherapy + chemotherapy, respectively. From patient-reported aNSCLC-related impairment (n=148), patients receiving 1L immunotherapy monotherapy (n=88) and 1L immunotherapy + chemotherapy (n=36), reported moderate-severe impairment of overall general health (38% and 44%), overall level of physical function (33% and 44%), quality of life (33% and 53%), ability to work (50% and 47%), ability to socialize (27% and 28%) and emotional well-being (33%, each), respectively.

Conclusions: Considerable symptom burden and impairment on patient health due to aNSCLC was found during 1L treatment in patients with PD-L1 ≥50% and without AGAs, regardless of treatment received across all regions. This highlights a persistent unmet need in the current treatment landscape over the past decade to reduce symptom burden and understand drivers of treatment choice as combination therapies continue to evolve.

Keywords: NSCLC, Real-world, PD-L1

EP.17.33 Evolving Treatment Patterns in Early-Stage Non-Small Cell Lung Cancer in the United States

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Introduction: The standard of care for patients (pts) with early-stage non-small cell lung cancer (esNSCLC) is surgery combined with systemic therapy. Recent approvals of immunotherapies (IO) and targeted therapies (TT) offer new options for pts with early-stage disease. This study evaluated evolving trends in the adoption of TT and IO among pts with resected esNSCLC in the US.

Methods: This retrospective observational study included pts diagnosed with esNSCLC (stages IB-IIIA) who underwent surgical resection between 1/1/2019 and 12/31/2023, with follow-up through 9/1/2024. Data were extracted from nationwide Flatiron Health electronic health records-derived de-identified database. Demographics, clinical characteristics, neoadjuvant, adjuvant and perioperative treatment patterns, and time to treatment discontinuation (TTD) of adjuvant IO and TT were reported.

Results: Among 14,638 pts who met the eligibility criteria (median age 70 years [IQR: 64, 75]; 53.3% female), 32.1% were diagnosed with stage IB, 39.2% with stage II, and 27.7% with stage IIIA disease, 87.1% had a history of smoking, and 22.9% were treated in an academic setting. From 2019 to 2023, use of platinum-based chemotherapy remained steady, while use of IO and TT increased (Table). Among pts who underwent surgery in 2023 and treated with IO (n=1,024), the majority (72.4%) received IO as adjuvant therapy, 17.1% as neoadjuvant therapy, and 10.6% as perioperative therapy. IO use was observed across all PD-L1 subgroups. In 2023, 28.8% of pts with PD-L1 <1%, 39.7% of pts with PD-L1 1-49%, and 52.8% of pts with PD-L1 ≥ 50% received IO as a component of their curative regimen. Pts without pathologic complete response after neoadjuvant chemotherapy with IO (ChemoIO) received adjuvant IO (33.5%), ChemoIO (7.4%), chemotherapy (6.5%), other treatment (6.2%), or no adjuvant treatment (46.5%). Median TTD for adjuvant IO (pembrolizumab, durvalumab, and atezolizumab) was 10.5-11.4 months. Median TTD for adjuvant osimertinib was 35.1 months.

Table: Systemic therapy in patients with resected esNSCLC from 2019 to 2023*

	Stage IB-IIIA N=3,256	**Stage IB-IIIA** N=2,950	**Subgroup: Stage II/IIIA** N=2,241	**Subgroup: Stage II/IIIA** N=1,947
	2019	**2023**	**2019**	**2023**
Any systemic therapy, %	54.6	63.0	66.1	77.1
Any platinum-based chemotherapy, %	47.9	48.5	60.9	62.9
Any IO, %	6.5	34.7	8.5	48.6
Any TT, %	1.2	7.8	1.2	7.2
Neoadjuvant IO, %	0.2	5.9	0.3	8.5
Adjuvant IO, %	6.1	25.1	8.0	34.8
Perioperative IO, %	0.2	3.7	0.2	5.3

*Treatment patterns were assessed by surgery year.

Conclusions: The clinical landscape in esNSCLC has rapidly evolved following paradigm-changing clinical trials, with growing adoption of adjuvant IO and TT. Approximately half the pts with stage II/IIIA disease received IO in 2023, with adjuvant therapy as the dominant curative paradigm. However, FDA approvals of perioperative IO occurred at the end of the study period; ongoing assessment of uptake is warranted.

Keywords: Early-stage NSCLC, Immunotherapy, Adjuvant therapy

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.34 Real-World Survival Outcomes in Non-Small Cell Lung Cancer: Insights From UK Ehr-Derived Data

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Introduction: Non-small cell lung cancer (NSCLC) treatment has evolved significantly in recent years with the introduction of immune checkpoint inhibitors and targeted therapies. However, understanding real-world testing patterns, treatment patterns, and outcomes remains challenging due to limited availability of comprehensive, longitudinal datasets. We evaluated biomarker testing, treatments, and overall survival (OS) outcomes in the UK health care setting using a novel NSCLC dataset derived from the electronic health records (EHRs) of patients in the UK.

Methods: The study used the UK Flatiron Health Research Database and included anonymised, longitudinal data from patients diagnosed with NSCLC in the UK from January 1, 2016, to September 30, 2024. Structured and unstructured data were curated through technology-enabled abstraction and manual review. Key variables included patient demographics, clinical characteristics, biomarker testing (eg, programmed death-ligand 1 [PD-L1] and epidermal growth factor receptor [EGFR]; anaplastic lymphoma kinase [ALK]; B-Raf proto-oncogene, serine/threonine kinase [BRAF]; and Kirsten rat sarcoma viral oncogene homolog [KRAS] mutations), treatment regimens, and OS. Kaplan-Meier methods were used to estimate OS, stratified by stage of disease at diagnosis.

Results: Of the patients with metastatic disease at diagnosis (n = 946), >50% were tested for standard of care biomarkers (ALK, BRAF, EGFR, KRAS, and PD-L1). Of those tested, the rate of positive tests align with literature findings for patients with NSCLC (ALK, 5%; BRAF, 1%; EGFR, 11%; KRAS, 33%; PD-L1, 57%). The 3 most commonly used drugs in the metastatic setting were carboplatin (31%), pemetrexed (22%), and pembrolizumab (17%). For the entire cohort (n = 2674), OS stratified by stage at diagnosis showed plausible relationships, with higher stage associated with shorter median OS: 5.8 years (Stage I), 3.0 (Stage II), 2.9 (Stage III), 2.2 (IIIA), 0.9 (IIIB), 1.0 (IIIC), and 0.4 (Stage IV).

Conclusions: By addressing gaps in longitudinal data availability, the EHR-derived UK NSCLC dataset offered valuable insights into real-world testing patterns, treatment patterns, and outcomes. Observed biomarker prevalence aligns with established literature and treatment patterns, and survival outcomes align with typical clinical expectations, supporting the reliability, and representativeness of the dataset. Ongoing efforts to expand analyses of treatment patterns and key clinical endpoints, such as disease progression, will further enhance its role in supporting research on real-world patient care and outcomes in the UK.

Keywords: Real-World Data, Biomarker Testing, Treatment patterns

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.35 Treatment-Associated Interstitial Lung Disease in Extensive-Stage Small Cell Lung Cancer

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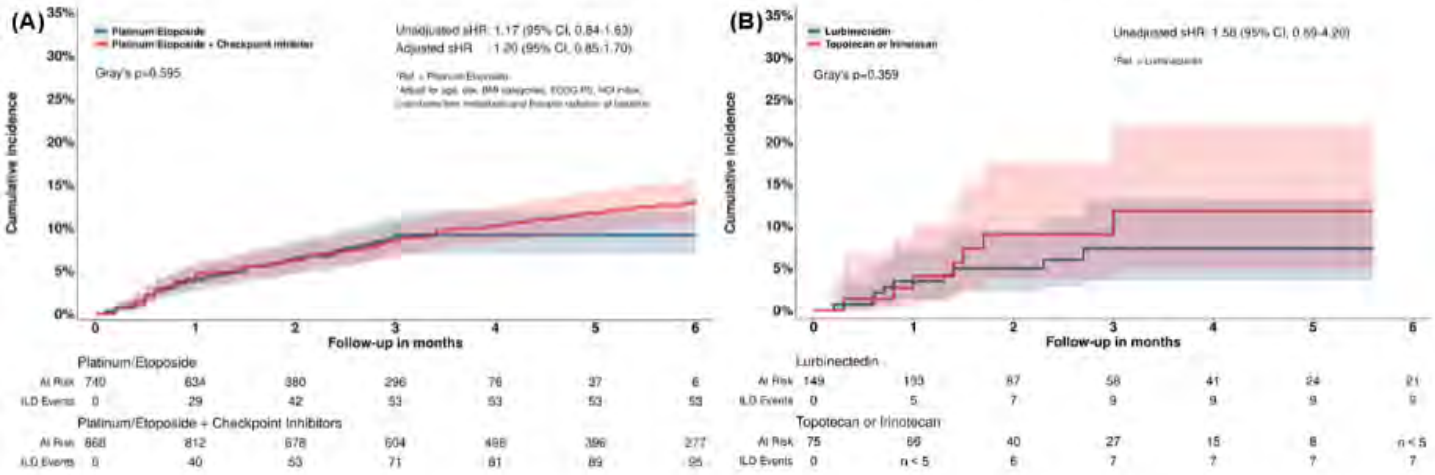
Introduction: Interstitial lung disease (ILD) is a clinically significant adverse event associated with systemic cancer treatment, including chemotherapy and immunotherapy. Our objective was to describe rates of ILD in patients with extensive-stage small cell lung cancer (ES-SCLC) receiving first-line (1L) chemotherapy with and without a checkpoint inhibitor (CPI) and subsequent second-line (2L) monotherapy.

Methods: We conducted a retrospective cohort study using Optum's de-identified Market Clarity Data (Optum® Market Clarity). Patients diagnosed with ES-SCLC between 2019 and 2023 initiating 1L with platinum (cisplatin/carboplatin) and etoposide chemotherapy with and without CPI (atezolizumab/durvalumab) were included. Secondary analyses included patients initiating 2L with lurbinectedin, topotecan, or irinotecan. Cumulative incidence of ILD was estimated using an adapted algorithm of inpatient and outpatient diagnostic codes. Patients were followed from treatment initiation until the first of incident ILD, death, treatment discontinuation or end of study follow-up (June 2024). Fine-Gray regression models were used to calculate multivariable-adjusted sub-distribution hazard ratios (sHR) and 95% confidence intervals (CI).

Results: In a cohort of 1,608 ES-SCLC patients initiating 1L (median age: 67 years; interquartile range 61-73) with median treatment duration of 3.3 months, 740 received platinum/etoposide and 868 received platinum/etoposide plus CPI. Patients that received only platinum/etoposide had greater comorbidity at baseline, including higher prevalence of autoimmune disease, congestive heart failure, and chronic pulmonary disease, whereas those that received platinum/etoposide plus CPI had higher prevalence of brain, bone, and liver metastases and were more likely to receive thoracic radiation. Overall, 158 (9.8%) patients had incident ILD events during 1L treatment. More patients receiving platinum/etoposide plus CPI experienced an ILD event compared to platinum/etoposide alone (12.1% vs. 7.2%, P=0.001). After accounting for greater comorbidity and competing risks of death, platinum/etoposide plus CPI was associated with higher risk of ILD that was not statistically significant overall (sHR 1.20, 95% CI 0.85-1.70) but was consistently elevated throughout CPI maintenance (Figure). Among 224 patients initiating 2L, 23 (10.3%) experienced ILD during follow-up with greater incidence observed with topotecan versus lurbinectedin (18.3% vs. 8.1%, P=0.034), while no events occurred with irinotecan. Prior receipt of thoracic radiation was similar between those that did and did not develop ILD. However, the majority (87.0%) of ILD events during 2L occurred following prior immunotherapy.

Conclusions: In this real-world study of patients with ES-SCLC, more ILD events were observed among patients receiving platinum/etoposide plus CPI versus platinum/etoposide alone, and most ILD events in 2L occurred among those with prior CPI treatment.

Figure 1. Cumulative incidence of ILD among patients with previously untreated ES-SCLC initiating (A) 1L platinum/etoposide or platinum/etoposide plus checkpoint inhibitor and (B) 2L monotherapy with lurbinectedin, topotecan, or irinotecan



Keywords: small cell lung cancer, interstitial lung disease, pneumonitis

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.36 Disparities in Survival Outcomes of Primary Pulmonary Diffuse Large B-Cell Lymphoma: A SEER Database Analysis

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Introduction: Primary pulmonary diffuse large B-cell lymphoma (DLBCL) is a rare extranodal non-Hodgkin lymphoma involving the lung, accounting for only 0.5 - 1% of primary pulmonary malignancies. Given its rarity, survival outcomes and the influence of sociodemographic disparities in this population remain poorly understood. This study aimed to evaluate the impact of age, sex, race/ethnicity, marital status, geographic location, and median household income on survival outcomes in patients with primary pulmonary DLBCL using a national database.

Methods: We conducted a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) Research Plus database (17 registries, 2000-2021). We included adults aged ≥20 years with histologically confirmed DLBCL and a primary tumor site in the lung, identified using ICD codes 9680/3 and C34. Descriptive statistics were used to summarize patient characteristics. Survival outcomes, including median overall survival (mOS) and cancer-specific survival (mCSS), were analyzed using the Kaplan-Meier method. Survival differences were assessed using the log-rank test, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. A p-value of <0.05 was considered statistically significant.

Results: A total of 1,524 patients were identified. At diagnosis, 65% were aged >65 years, 51% were female, and 75% were White, 11% Hispanic, and 7% Black. Most patients (88.5%) lived in metropolitan areas, and 45% had a median household income below $75,000. Metastatic disease was present in 38% at diagnosis. The mOS was 66 months, and mCSS was 220 months. Patients aged >65 had significantly worse mOS (30 months) compared to those aged 20-64 years (171 months; p<0.0001; HR 2.54, 95% CI 2.23-2.89). mOS was 70 months in females and 55 months in males (p=0.09). No significant survival differences were observed across racial and ethnic groups (p=0.62). By stage, mOS was 94 months (regional), 83 months (localized), and 45 months (metastatic) (p=0.0003). Among patients with metastatic disease, those <65 had a mOS of 135 months versus 26 months in those ≥65 (HR 0.45, 95% CI 0.36-0.55; p<0.0001). Rural residents had shorter mOS (47 months) compared to urban residents (67 months), though not statistically significant (p=0.0511). Survival did not differ significantly by income (p=0.1467). Married patients had a mOS of 82 months versus 41 months in unmarried patients (p=0.0001; HR 0.77, 95% CI 0.68 - 0.89).

Conclusions: In this population-based study of primary pulmonary DLBCL, older age, metastatic disease, and unmarried status were associated with significantly worse survival. Race/ethnicity, income, and residence location were not statistically significant predictors. These findings highlight the importance of age and social support as prognostic factors and underscore the need for early psychosocial risk screening and supportive care interventions in this rare population.

Keywords: Primary pulmonary diffuse large B-cell lymphoma, Survival disparities, Rare lung cancers

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.37 Assessing the Hidden Risk From 1990-2021: Radon-Attributable Tbl Cancer Burden Across the European Union

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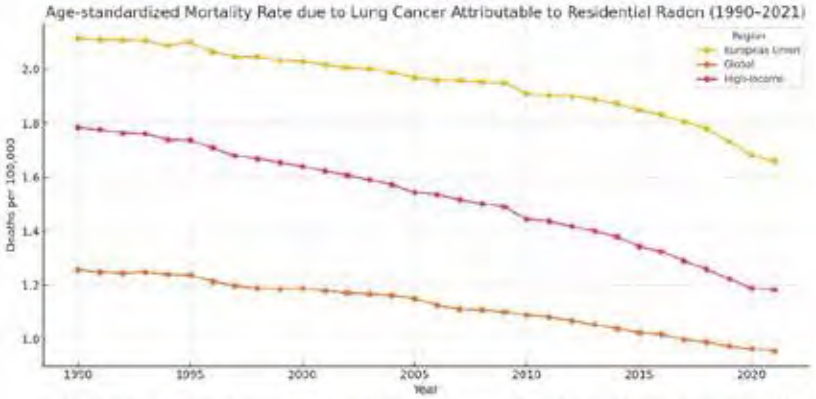
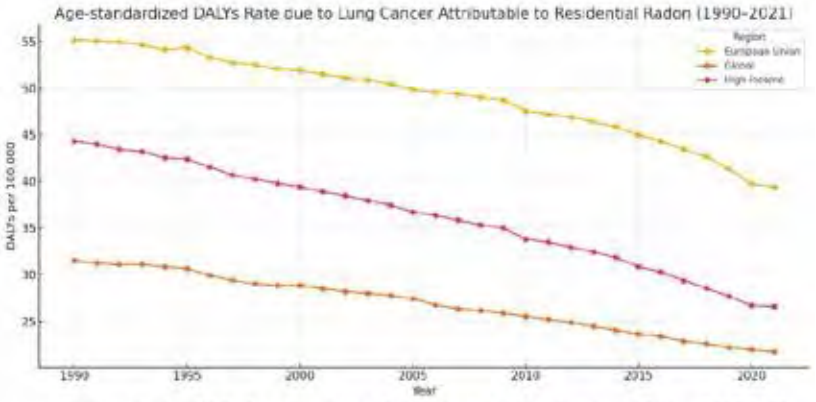
Introduction: Tracheal, bronchus, and lung (TBL) cancer is a leading cause of death in the European Union, with residential radon exposure recognized as a major environmental risk factor. As a radioactive gas that accumulates indoors, radon contributes significantly to the lung cancer burden, especially among non-smokers, underscoring the need for targeted prevention and mitigation efforts.

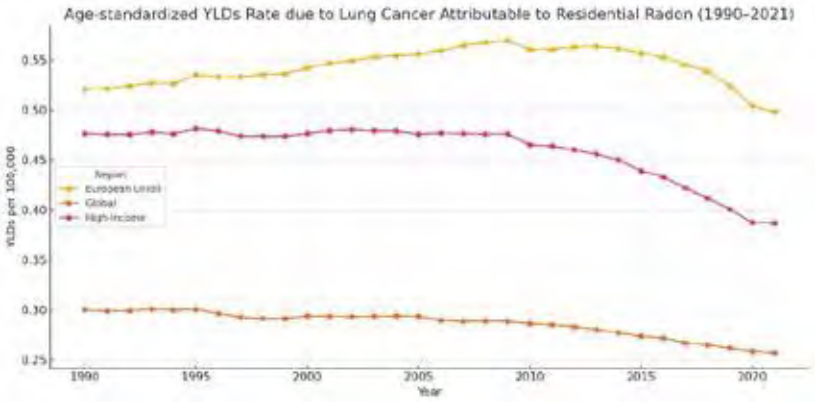
Methods: We estimated deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) due to TBL-cancer attributable to RR across age, sex, year, and location in the European Union from 1990-2021 using the standardized Global Burden of Disease-2021 tool. Temporal trends were assessed using estimated annual percentage change(APC), with results presented as absolute counts and age-standardized rates per 100,000 population.

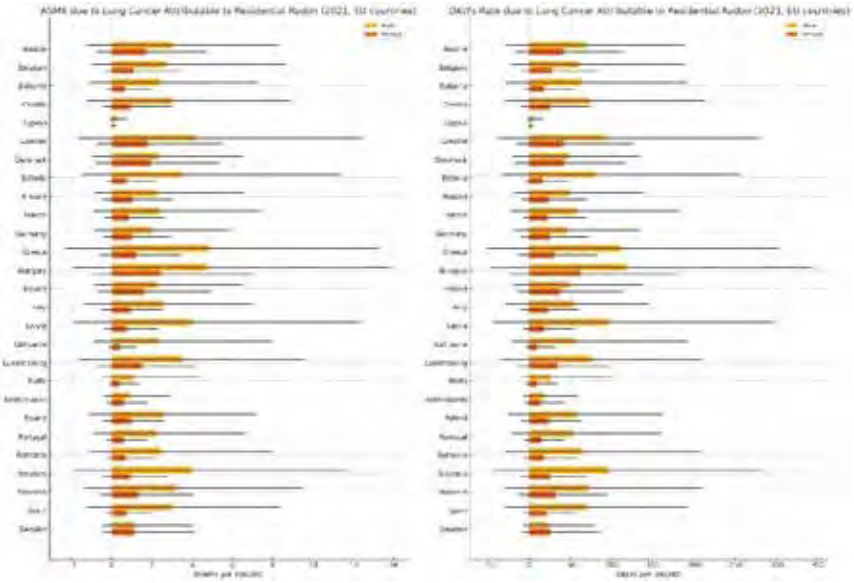
Results: From 1990 to 2021, the total number of deaths increased from 12,635 (95% UI: -6,113 to 33,583) to 15,816 (-7,648 to 41,686). DALYs rose from 317,832(-153,698 to 840,975) to 340,698 (-163,261 to 899,744), while YLDs increased from 3,056(-1,479 to 8,377) to 4,441 (-2,032 to 12,208). The highest APC in age-standardized mortality rate (ASMR) was observed in Romania(0.73%), followed by Bulgaria(0.45%), while the rest of the EU showed a declining trend over the same period. Age-wise, individuals aged 55 and above showed increasing APC in ASMR in Romania(1.33%), Bulgaria(0.9%), Portugal(0.31%), and Greece(0.07%), whereas all countries showed a declining trend in those under 55. Regarding gender, females experienced a greater increase in burden, with ASMR increasing in all countries except Lithuania, Latvia, Denmark, and Estonia; in contrast, most countries saw a declining trend in males, except for Romania(0.5%) and Bulgaria (0.23%).

Conclusions: In 2021, the EU accounted for 19.25% of all global TBL cancer deaths attributable to residential radon, representing 5.84% of all TBL cancer deaths in the region—highlighting the urgent need to implement widespread radon testing and mitigation policies to reduce this preventable burden.









Keywords: Global burden, Lung cancer, residential redon

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.38 Intersecting Determinants of NSCLC Outcomes in Brazil: The Roles of Histology, Socioeconomic Status, and Healthcare Sector Disparities

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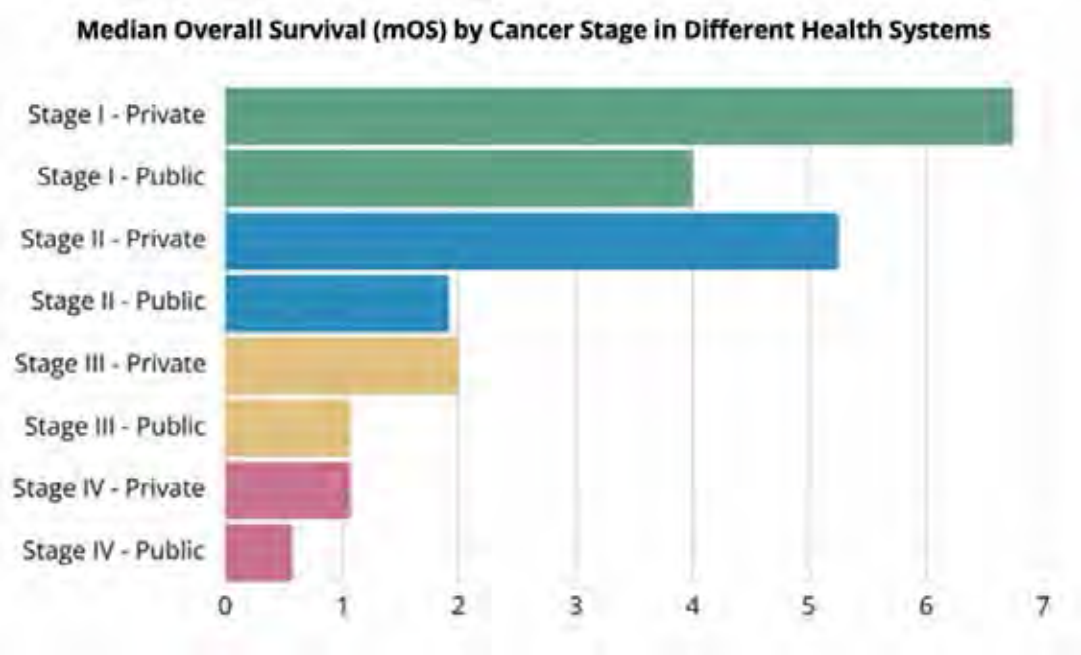
Introduction: While socioeconomic status (SES) is globally linked to cancer outcomes, Brazil's unique healthcare landscape — combining public and private sectors amid stark regional inequities — remains understudied. This study examines how histological subtype, SES, and healthcare coverage influence diagnosis stage, treatment access, and survival in NSCLC over a 20-year period.

Methods: A retrospective cohort of 37,606 adults (≥18 years) with pathologically confirmed NSCLC (2000-2020) was analyzed using data from the Fundação Oncocentro de São Paulo (FOSP). Histology (adenocarcinoma vs. non-adenocarcinoma NSCLC), SES (education level, municipal GDP per capita), and healthcare sector (public vs. private) were evaluated. Trends in diagnosis stage, treatment patterns, and diagnosis-to-treatment intervals were assessed. Survival analyses used Kaplan-Meier curves and log-rank tests.

Results: The cohort comprised 61% males, with 87% treated in the public healthcare system. Most patients (82%) presented with advanced-stage disease (III/IV). Adenocarcinoma (47% of cases) was associated with modestly earlier diagnosis and longer median overall survival (mOS) compared to non-adenocarcinoma NSCLC (53% of cases). Public-sector patients had significantly worse survival than private-sector patients (mOS: 0.83 vs. 2.00 years; p<0.0001), a disparity persisting across all stages (e.g., stage I: 4.00 vs. 6.75 years; p=0.0032). Higher SES correlated with private-sector access (4.4% in lowest GDP regions vs. 8.8% in highest GDP regions), earlier diagnosis (p<0.001), and improved survival: university-educated patients had the highest mOS (0.99 years) versus unschooled patients (0.58 years; p=0.0037).

Variable	Public System	Private System	No Schooling	University Education	Lowest GDP	Highest GDP	Adenocarcinoma	Carcinoma
Median age (yrs)	-	-	-	-	-	-	63	65
% Female	41.4	44.5	36	44	37.7	39.1	45	32
% Stage I	10.9	25.0	7.9	19.7	8.9	11.7	12	9.9
% Stage IV	57.5	50.2	50.1	54.6	54.5	55.6	62.6	48.4
Median OS (yrs)	0.83	2.00	0.58	0.99	0.65	0.76	0.74	0.72
% Waiting >60 days	43.4	26.9	29	21.4	27.5	29.5	29.6	27.0
% Receiving IO	0.43	3.22	0.18	1.42	0.8	0.43	0.60	0.50



Conclusions: NSCLC outcomes in Brazil are shaped by intersecting factors: tumor biology, healthcare infrastructure, and SES. Public-sector patients and those with lower education or income face delayed diagnoses, limited treatment access, and poorer survival — even at early stages. These findings underscore the urgent need for policy reforms to address systemic inequities in cancer care, prioritizing resource allocation and access within Brazil's public health system.

Keywords: Non-small cell lung cancer (NSCLC), Healthcare Disparities, Health System Analysis

EP.17 GLOBAL HEALTH, HEALTH SERVICES, AND HEALTH ECONOMICS

EP.17.39 Carbon Footprint of Lung Cancer Management and Impact of Lung Cancer Screening Implementation

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Introduction: Health care is a key contributor of national greenhouse gas (GHG) emissions in western countries. Climate change directly threatens populations health around the world, undermine the past 50 years of gains in public health and threatens heath system ability to deliver high quality care. Reducing GHG emissions has become an urgent and significant issue to limit climate change, air pollution and health system dependence to fossil energies. Individual benefit of lung cancer (LC) screening is now well established: it reduces LC mortality in a heavy smoker population about 20% and increases the diagnosis rate of localized and treatable stages. The aim of this study was to evaluate LC management carbon footprint across different stages (localized vs metastatic diseases)

Methods: We performed a comparative environmental study to assess the carbon footprint of LC management in a thoracic oncology centre (Toulouse University Hospital) at different stages (localized vs metastatic stages). This project has been made in partnership with Monde Nouveau, a design office specialized in carbon and environmental footprint accounting. The methodology used is based on Bilan Carbone® methodology coupled with the Life Cycle Assessment (LCA) steps principle. The Base Empreinte® database was used to evaluate emission factors and a specific calculator has been made by the design office leaning on a flow mapping for the different health trail. Data from global results of GHG emissions of Toulouse University Hospital (year 2022) and specific data (drugs prescription, medical devices use, and visitors shift) from patients treated for LC in Toulouse University Hospital (year 2022) were used. Direct and indirect GHG emissions (scopes 1, 2 and 3) were taken into account.

Results: A total of 1293 patients treated for LC in 2022 were included. 245 patients underwent thoracic surgery for localized LC and 566 patients were treated for metastatic disease. The carbon footprint of stage I lung cancer patients who have undergone curative thoracic surgery was estimated at 2.7 tCO2e/patient/year (year of surgery). GHG emissions from the systemic treatment of metastatic cancers (stage IV) were estimated at 9.5 tCO2e/patient/year. The uncertainty interval was 22%. A very large majority of the carbon footprint was linked to the purchase and use of medicines and medical devices (respectively 94% and 77% for stage I and IV). GHG emissions due to LC screening were estimated in our institution at 0.02 tCO2e/patient/year.

Conclusions: The management of stage I LC appears to emit 3.5 less atmospheric CO2 in comparison to metastatic diseases. Considering that the majority of operated LC are cured, this difference is likely to increase considerably during follow-up. GHG emissions related to LC screening by low-dose computed tomography appear much lower than emissions related to LC treatment. LC screening could therefore effectively reduce the carbon footprint of LC management, which in turn would be beneficial for the health of the general population.

Keywords: lung cancer, carbon footprint, climate change

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.01 The Beneficial Value of 18F FDG PET/CT in the Follow-Up of Stage III Non-Small Cell Lung Cancer Patients (NVALT31-PET Study)

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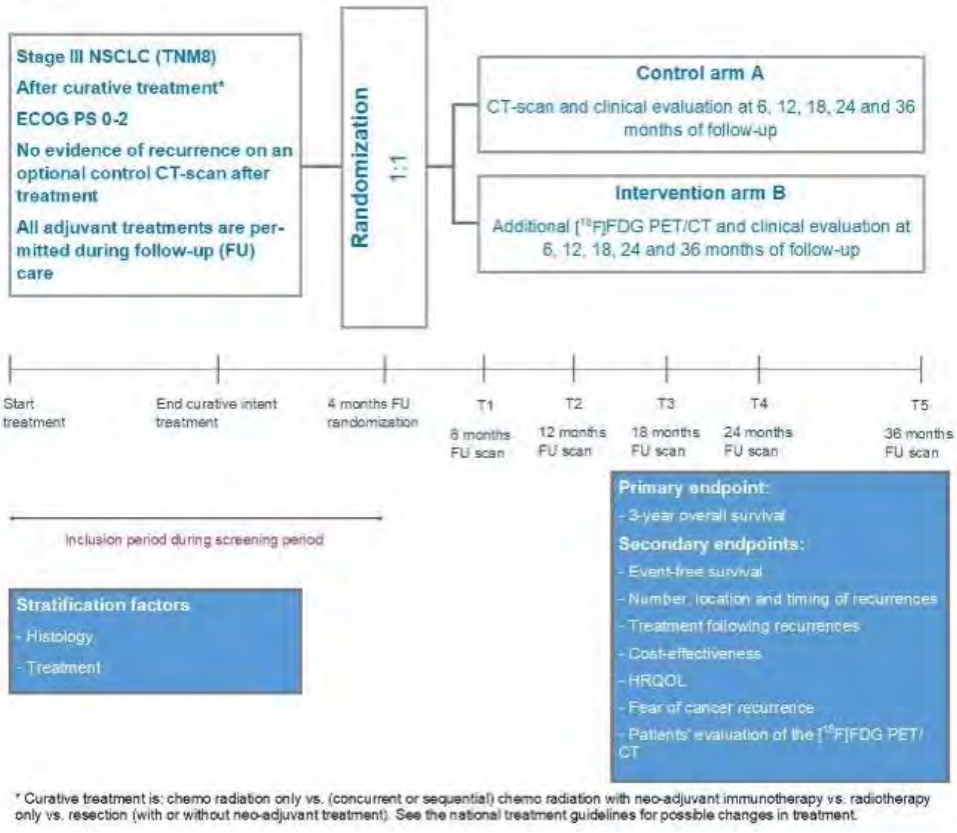
Introduction: Stage III non-small cell lung cancer (NSCLC) patients have a high risk of developing a recurrence after curative-intent treatment. As more effective treatments are now available, especially for patients with oligometastatic disease, earlier detection of recurrences utilizing [18F]FDG PET/CT (PET/CT) may prolong survival and health-related quality of life (HRQOL).

The Dutch multicenter NVALT31-PET randomized controlled trial aims to evaluate the effect of PET/CT versus only CT on 3-year overall survival (OS) in stage III NSCLC patients during FU surveillance. Secondary aims are to compare the rate of detected recurrences, type of treatment following recurrence, event-free survival, cost-effectiveness, HRQOL, patients' fear of cancer recurrence and the role of circulating tumor DNA (ctDNA) in the detection of recurrences during FU surveillance.

Methods: This study randomizes 690 patients at 4 months post curative intent treatment to either the intervention group or the control group. Eligible patients (>18yrs) have stage III NSCLC and are starting FU care, (which may include adjuvant therapies) with an ECOG Performance Status 0-2. The control group (n=345) receives usual care CT-based FU surveillance and HRQOL surveys at 6-, 12-, 18-, 24-, and 36-months FU. The intervention group (n=345) receives usual care, with additional whole-body PET-scans, blood samples and HRQOL surveys at the same intervals (Figure 1). Intention-to-treat analysis will be conducted to assess the intervention effect of PET/CT on 3-year OS using Kaplan-Meier curves.

Figure 1. Flow chart



Results: Patient recruitment and data collection commenced in March 2024. Currently, 27 hospitals have initiated patient recruitment with over 167 patients enrolled as of Apr. '25 (control group n = 85; intervention group n = 82). The mean age is 66.9 years (SD 7.5) and 54.5% is male. See Table 1 for a short overview of the baseline characteristics. The first results are anticipated by the end of 2029..$$graphic_{C8DC5DE5-97B1-44F9-BE3B-23CA1C17B538}$$

Conclusions: -

Keywords: Stage III NSCLC, PET-CT, Recurrences

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.02 Multicenter, Prospective Study on the Precise Diagnosis and Treatment of Shape-Sensing Robotic-Assisted Bronchoscopy

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Introduction: Interventional bronchoscopy is a major tool for airway examination, diagnosis of airway lesions, therapeutic aspiration of airway secretions, and transbronchial needle biopsy for the diagnosis of pulmonary nodules. However, traditional bronchoscopes are too large in outer diameter to reach the peripheral lung, and although transthoracic needle biopsy has a high diagnostic rate, it also has a high risk of pneumothorax. In recent years, robotic bronchoscopes such as shape-sensing robotic-assisted bronchoscopy (e.g. ION system) can perform biopsies on peripheral pulmonary nodules, improving the biopsy diagnostic rate while achieving a low complication rate. Compared with existing technologies (ENB electromagnetic navigation technology, etc.), they have the advantages of high clinical performance and high stability.

Methods: This study intends to be based on the new generation ION system in a multicenter, prospective clinical cohort study to explore the precise diagnosis and treatment plan for thoracic tumors using robotic bronchoscopes. We aim to enroll 327 patients with pulmonary nodules who will undergo robotic bronchoscopy in three medical centers and conduct a follow-up for no less than 6 months. For patients with pulmonary nodules, the navigation success rate, biopsy success rate, diagnostic sensitivity for malignant tumors, and overall complication rate will be statistically analyzed and compared with the performance of existing technologies. For patients with malignant tumors who are intolerant of surgery or refuse to surgery for various reasons, a new microwave ablation technology using robotic bronchoscopes will be carried out and optimized in 32 patients.

Keywords: shape-sensing robotic-assisted bronchoscopy, Ion system, pulmonary nodules

EP.18.03 Neoadjuvant Toripalimab for Stage Ii-Iiib Resectable NSCLC With EGFR Mutation and PD-L1 Positive Expression (TOPLINE)

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Introduction: The optimal neoadjuvant treatment strategy for EGFR-mutant (EGFRm+) non-small cell lung cancer (NSCLC) remains unclear. Current strategies using either chemotherapy or EGFR tyrosine kinase inhibitors (TKIs) demonstrate modest efficacy, with major pathological response (MPR) rates approximating 10%. Preliminary data suggest neoadjuvant chemoimmunotherapy can achieve MPR rates exceeding 40% in EGFRm+ and PD-L1-positive (PD-L1+) NSCLC patients. This study aims to assess the safety, feasibility, and efficacy of neoadjuvant toripalimab (anti-PD-1) in patients with EGFRm+, PD-L1+ resectable stage II-IIIB NSCLC (NCT06269211).

Methods: This open-label, multicenter, prospective single-arm trial will employ Simon's optimal two-stage design, initially enrolling 10 patients with EGFRm+, PD-L1+ stage II-IIIB (N2) NSCLC, with trial continuation to an additional 19 patients upon observing ≥2 MPR cases in the first stage. To ensure balanced representation, patients will be stratified 1:1 based on PD-L1 tumor proportion score (TPS) (1-49% vs. ≥50%). All enrolled participants will receive three cycles of neoadjuvant toripalimab (240mg Q3W) prior to surgical resection. Postoperatively, adjuvant therapy will be determined based on pathology and minimal residual disease (MRD) status, with options including EGFR-TKIs and/or platinum-based doublet chemotherapy. The primary endpoint is the MPR rate. Secondary endpoints include other short-term oncologic outcomes (pathological complete response [pCR] rate, objective response rate [ORR]), as well as safety, feasibility, and long-term oncologic outcomes.

Results: Currently, two patients have been enrolled and have completed neoadjuvant therapy and surgery—one with a PD-L1 TPS of 1% and the other with ≥50%. Both experienced treatment-related hypothyroidism and diarrhea; however, no grade ≥3 treatment-related adverse events were observed. Neither patient achieved an MPR.

Conclusions: No optimal neoadjuvant treatment exists for EGFRm+, PD-L1+ NSCLC, and we hope that the findings of this study will contribute to the development of more effective treatments in this context.

Keywords: NSCLC, EGFR-mutant, neoadjuvant immunotherapy

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.04 CLOG-0004 Clinical Outcomes of Tislelizumab Combined With Chemotherapy as Induction Therapy in Stage III (cTNM-IIIB/IIIC) NSCLC

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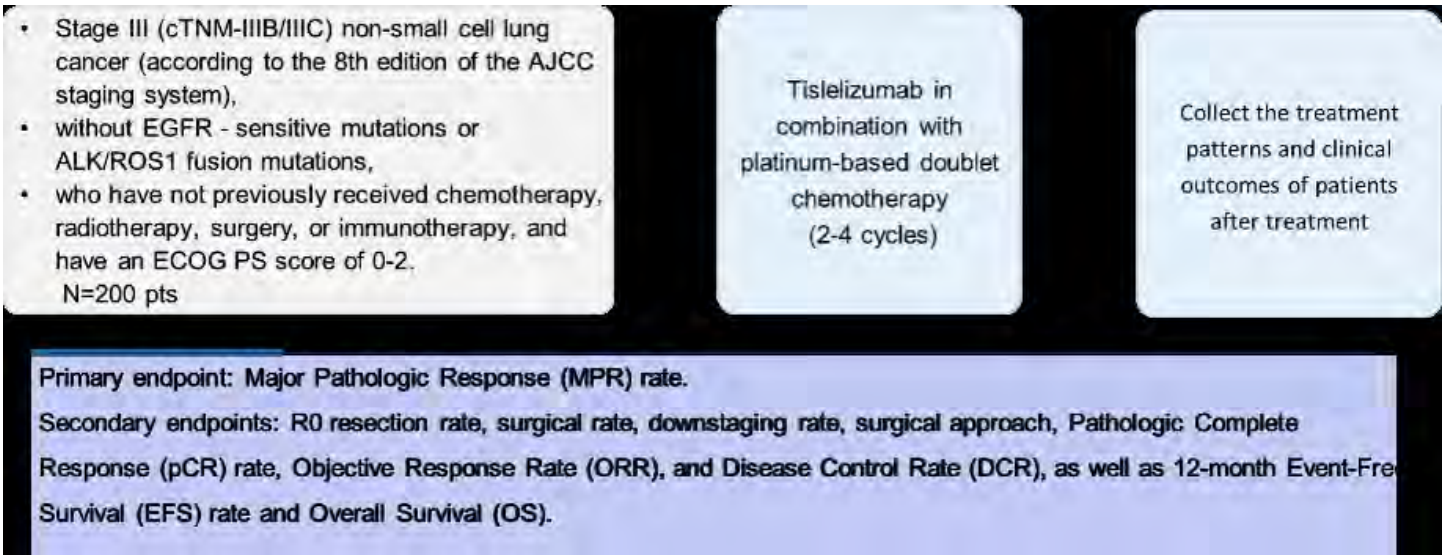
Introduction: In patients with resectable stage II-IIIA non-small cell lung cancer (NSCLC), neoadjuvant tislelizumab plus chemotherapy showed clinically meaningful improvements in major pathological response (MPR) and pathological complete response (pCR) rates compared to chemotherapy alone. However, the clinical benefit of tislelizumab plus chemotherapy for potentially resectable stage IIIB/IIIC NSCLC remains to be determined.

Methods: Participants were recruited from August 2020 to June 2026 from dozens of large tertiary hospitals in China, enrolling patients with Stage III (cTNM-IIIB/IIIC) non-small cell lung cancer (according to the 8th edition of the AJCC staging system). The aim is to assess the Clinical Outcomes of Tislelizumab Combined with Chemotherapy As Induction Therapy in Stage III (cTNM-IIIB/IIIC) NSCLC



Keywords: Stage III (cTNM-IIIB/IIIC) NSCLC, Clinical Outcomes, Tislelizumab

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.05 Tislelizumab Combined With Low-Dose Chemotherapy in Previously Treated Advanced Squamous NSCLC

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Introduction: The standard second-line treatment for advanced squamous non-small cells lung cancer (SQ-NSCLC) typically involves single-agent chemotherapy or single-agent immunotherapy with the median progression-free survival (mPFS) approximately 3 months. Compared to monotherapy, using the combination of immunotherapy and chemotherapy as second-line treatment, may achieve better therapeutic outcomes. Conventional chemotherapies are administered at maximum tolerated doses (MTD) to maximize tumor cytoreduction. However, this high-dose may paradoxically impair treatment efficacy by directly cytotoxic effects on immune cells, leading to immunosuppression. Recent evidence suggests that low-dose chemotherapy may upregulate PD-L1 expression, stimulate an anti-tumor immune response, and enhance immune memory, thereby synergistically enhancing the therapeutic effects of immune checkpoint inhibitors. The aim of this study was to explore the value of low-dose chemotherapy combined with tislelizumab, an anti-PD-1 monoclonal antibody, in the later-line treatment of advanced SQ-NSCLC.

Methods: All eligible patients received low-dose chemotherapy, either nedaplatin (NDP) at 50 mg/m^2 or gemcitabine (GEM, for patients who had prior NDP exposure) at 1000 mg/m^2 on day1, combined with tislelizumab at 200 mg on day 2. The treatment was administered every 3 weeks for 6 cycles, followed by maintenance of tislelizumab for up to 2 years or disease progression. The primary endpoint was the 6-month progression-free survival (PFS) rate. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), 1-year OS rate, and safety.

Results: From August 2022 to June 2024, a total of 13 local advanced or advanced SQ-NSCLC patients who had failed first-line systemic treatment were enrolled in this study. Median age was 65 years(range 51-74), 12 (92.3%) male, 11 (84.6%) stage IV, 8 (61.5%) had previously received immunotherapy. Efficacy was evaluated in 11 patients,with median follow-up for all patients was 27 months. 6-month PFS rate 63.6% met the primary study endpoint; 4 pts achieved PR, 4 pts achieved SD, 3 pts PD, ORR was 36.4%, DCR was 72.7%; median PFS 9.0 months, 1-year PFS rate was 36.4%; median OS had not reached, 1-year OS rate was 72.7%. In safety analysis set, 2 patients occurred ≥ grade 3 adverse events (AEs), including 1 grade 4 thrombocytopenia, and 1 grade 3 thrombocytopenia combined with grade 4 leukopenia.

Conclusions: Low-dose chemotherapy combined with immunotherapy as second-line treatment for SQ-NSCLC was safe and effective, which deserves further investigation.

Keywords: Squamous non-small cells lung cancer, Immunotherapy, Low-dose chemotherapy

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.06 ML44840: A Multicenter Prospective Cohort Study of the Patient-Reported Outcomes in Chinese Patients With ALK+ Advanced NSCLC

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Introduction: The development of tyrosine kinase inhibitors (TKIs) targeting ALK rearrangements has dramatically improved the treatment outcome of patients with ALK-positive Non-Small Cell Lung Cancer (NSCLC). Based on the results of the phase III Alesia study (Zhou et al. 2024), the 7-year overall survival rate in patients treated with Alectinib was 56.0%, which means ALK+ NSCLC gradually became a chronic disease. Poor quality of life is a severe challenge faced by the majority of lung cancer patients. Patients with ALK gene rearrangements usually require longer treatment courses of ALK-TKI, indicating that these patients could be at the highest risk of adverse drug reactions (ADR). The tolerability and toxicity profiles differ considerably between ALK-TKIs. Patient-reported outcomes (PROs) can provide important patient perspectives on the disease and the treatment received, capturing the impact of adverse reactions on patient well-being. ML44840(ALK PRO DCT, NCT06586801) aims to evaluate the PROs and safety profiles of patients with ALK-positive advanced NSCLC who received ALK-TKIs as first-line treatment in China real world practice.

Methods: Decentralized trial (DCT) mode is applied in this study. Approximately 800 patients with ALK-positive locally advanced or metastatic NSCLC will be enrolled into 3 parallel cohorts from both traditional sites and Direct to Patient (DTP) Pharmacies: Alectinib Cohort(n=400), Lorlatinib cohort(n=200) and other approved ALK-TKIs cohort(n=200), by the treating physician's decision. Key eligibility includes locally advanced and metastatic NSCLC, ALK-positive diagnosed by local standard methods, planned to receive ALK-TKIs as 1st line treatment and asymptomatic CNS metastasis allowed. The PRO follow-up will be continued until new anti-cancer therapies start, death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first. The data collection period for an individual patient was approximately 12 months. PRO data will be collected using the instruments of EORTC QLQ-C30,EORTC QLQ-LC13,selected items from the PRO-CTCAE and EORTC-IL46 by APP on the smart phone. Patients are required to report the outcome at Cycle 1, (baseline, Day 1±7days except IL46), Cycle 3(Day 1±7days), Cycle 5(Day 1±7days), Cycle 7(Day 1±7days), Cycle 9(Day 1±7days), Cycle 11(Day 1±7days) and Cycle 13(Day 1±7days). One cycle=28 days. The primary endpoint is PRO related outcome. The secondary endpoint is safety.

Results: NA

Conclusions: NA

Keywords: ALK+ NSCLC, ALK-TKI, Patient Reported Outcome

EP.18.07 Aumolertinib Combined With Lomustine as First-Line Treatment for EGFR-Mutant NSCLC Patients With Brain Metastasis

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Introduction: As is known to all, EGFR-mutant NSCLC patients with brain metastasis are inclined to have worse efficacy and prognosis. According to subgroup analyses from registration clinical trials, the mPFS of the third-generation EGFR-TKI as first-line treatment for NSCLC with brain metastasis was 5.6-7.2 months longer than that of the control group (the first-generation EGFR-TKI). In addition, at least 95% of the enrolled patients of all registration clinical trials were evaluated as ECOG 0-1. How to further improve efficacy of EGFR-mutated NSCLC patients with brain metastasis is of great meaning in clinical practice. Lomustine is a fat-soluble drug that can be delivered effectively across the blood-brain-barrier to the brain and therefore, it has been the standard therapy for primary brain tumors or brain metastasis for its potent intracranial efficacy. Aumolertinib, targeting EGFR mutations, has been proved efficacious and well-tolerated for advanced NSCLC patients, especially with brain metastasis. Consequently, we conducted a phase II, single-arm, prospective study to verify the efficacy and safety of the combined therapy.

Methods: A total of 131 NSCLC patients with brain metastasis harboring EGFR mutation without prior anti-tumor treatment will be continuously recruited in th study. Patients with an ECOG≥3 or estimated survival lifetime less than 12 weeks will be excluded. All the participants will be orally treated with aumolertinib (110mg QD) plus lomustine (100-130/m2 at a draught, every 6 weeks) till disease progression or intolerance. The primary efficacy endpoint is PFS by investigator assessment as defined by RECIST1.1. The secondary endpoints comprise of iPFS, iORR, iDCR, OS and safety. Our study is the first trial to evaluate the efficacy and safety of third-generation EGFR-TKI plus traditional oral chemotherapy drug and the "all-oral" regime will be the key to guarantee compliance of patients resulting in lower admission rate and less hospitalization-related infection.

Keywords: EGFR-mutant NSCLC, brain metastasis, oral regime

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.08 Adebrelimab as Consolidation Therapy in Limited-Stage Small Cell Lung Cancer After Hyperfractionatedradiotherapy Combined With Chemotherapy

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Introduction: Concurrent chemoradiotherapy remains the standard treatment for limited-stage small cell lung cancer (LS-SCLC). However, most patients experience disease relapse within two years of treatment initiation. Hyperfractionated radiotherapy (45 Gy in 30 fractions) has shown improved long-term survival by reducing total treatment time. Adebrelimab, an anti-programmed death ligand-1 (PD-L1) antibody, demonstrated survival benefits in extensive-stage SCLC in the CAPSTONE-1 trial. The proposed study aims to assess the efficacy and tolerability of adebrelimab as consolidation therapy in LS-SCLC patients without disease progression after hyperfractionated radiotherapy combined with chemotherapy.

Methods: In this single arm, open-label, phase II trial, 36 patients with histologically or cytologically confirmed LS-SCLC as per Veterans Administration Lung Study Group staging system and without receiving prior systemic therapy are anticipated to be enrolled. Eligible patients are aged 18-80 years old with an ECOG performance status of 0 or 1, have a life expectancy of at least 12 weeks, and adequate organ function. Patients will be excluded if they have active or previous autoimmune disease, evidence of uncontrolled concomitant diseases or active infection or symptomatic interstitial lung disease. Patients will receive hyperfractionated radiotherapy at a dosage of 45 Gy (1.5 Gy bid, 5 days a week for 3 weeks) in combination with etoposide (100 mg/m2, iv, q3w) and platinum drugs (cisplatin 75 mg/m2 or carboplatin AUC 5, iv, q3w) followed by maintenance with adebrelimab (1200 mg, iv, q3w) and etoposide/platinum drugs for up to 24 months. The chemotherapy consists of a total of four cycles. The primary endpoint is 12-month progress-free survival (12-month PFS) rate, and the secondary endpoints are objective response rate, disease control rate, PFS, overall survival, safety and quality of life. Based on an estimated improvement in 12-month PFS from 42% to 65% (one-sided α=0.05, 80% power) with a 24-month follow-up, a total of 36 evaluable patients are required assuming a 10% dropout rate. The trial is currently recruiting.

Keywords: Adebrelimab, LS-SCLC, Hyperfractionated Radiotherapy

EP.18.09 Adebrelimab Beyond Progression Plus Chemotherapy or Targeted Therapy as Second-Line Treatment for Extensive-Stage Small Cell Lung Cance

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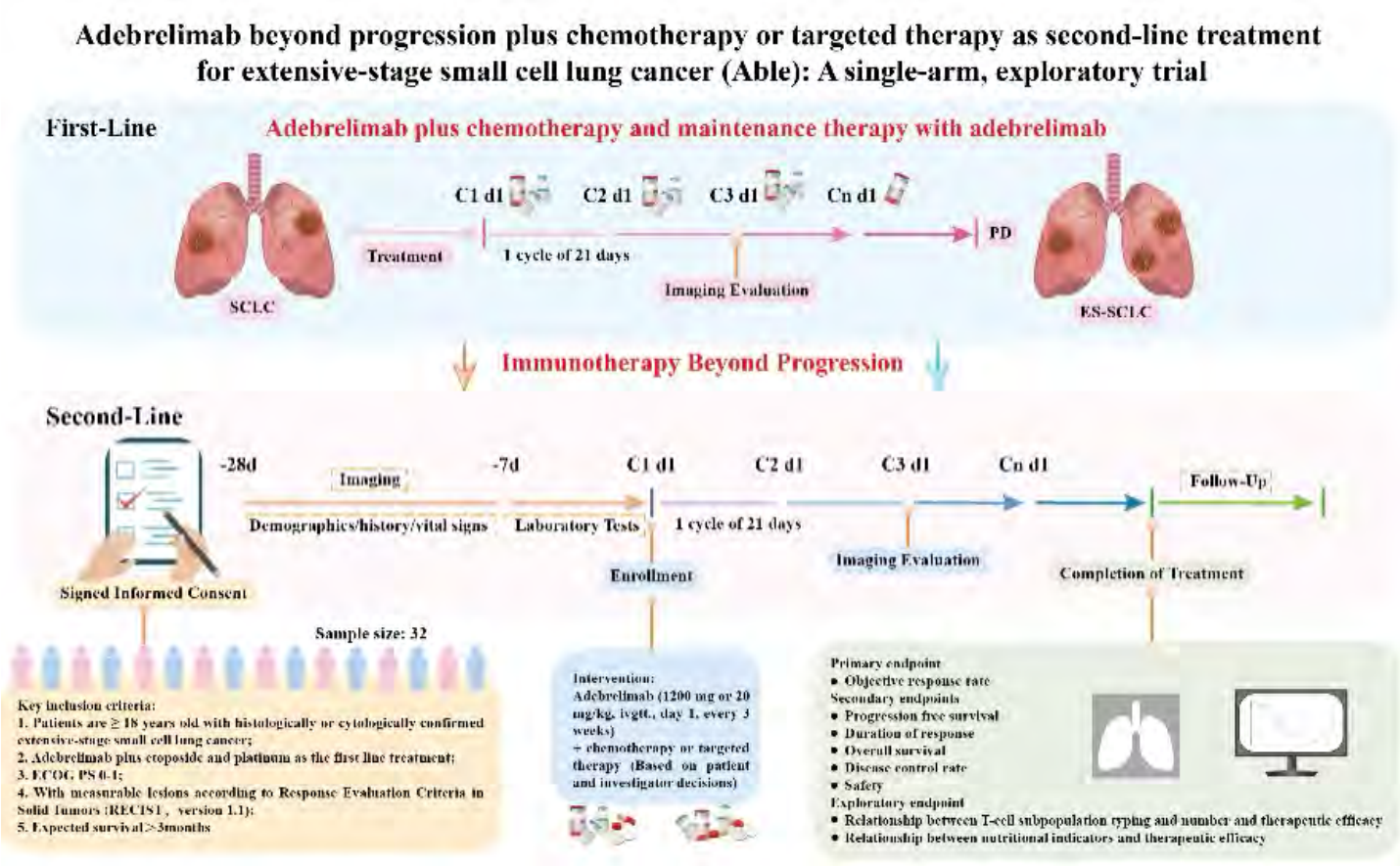
Introduction: The phase III IMfirst study (EudraCT: 2019-002784-10) showed that compared with no follow-up therapy and other treatments, atezolizumab beyond progression tends to prolong overall survival. Twenty-four-point-four percent of patients in the ASTRUM-005 trial continued to receive serplulimab after disease progression, which may be one of the key factors contributing to a lower overall survival hazard ratio (HR) of non-head-to-head comparison to the IMpower133, CASPIAN, and CAPSTONE-1 trials (HR 0.62 vs 0.76, 0.71, 0.73, respectively). According to the Cancer-Immunity Cycle theory, adding immune checkpoint inhibitors to chemotherapy or targeted therapy may enhance anti-tumor efficacy. Currently, the efficacy of second-line monotherapy for ES-SCLC is limited, and there are no clinical studies on combining adebrelimab beyond progression with chemotherapy or targeted therapy as second-line treatment for ES-SCLC.

Methods: This is a prospective, single-arm, exploratory trial. The population included in the study is adult patients with ES-SCLC who have cancer progression after receiving first-line treatment with adebrelimab plus chemotherapy. Patients must meet Eastern Cooperative Oncology Group Performance Status 0-1, have measurable lesions according to Response Evaluation Criteria in Solid Tumors version 1.1, and have adequate organ function. The primary endpoint is the objective response rate. The secondary endpoints include disease control rate, duration of response, progression-free survival, overall survival, and safety. Additional indicators include the relationship between T-cell subpopulation typing and number and therapeutic efficacy and the relationship between nutritional indicators and therapeutic effectiveness.



Keywords: Small cell lung cancer, Beyond progression, Immune checkpoint inhibitor

EP.18 CLINICAL TRIALS IN PROGRESS

EP.18.10 Phase II Study: Efficacy and Biomarker Exploration of Anlotinib Plus Penpulimab in ES-SCLC After Failure of Platinum-Based Chemotherapy

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Introduction: The Phase II ALTER1202 trial demonstrated improved progression-free survival (PFS) and overall survival (OS) in patients receiving anlotinib after failing ≥2 systemic chemotherapy regimens compared to placebo. To further optimize outcomes for extensive-stage small cell lung cancer (ES-SCLC) patients refractory to first-line platinum-based chemotherapy, this study investigated the combination of anlotinib (a multi-target tyrosine kinase inhibitor) and penpulimab (a novel PD-1 inhibitor).

Methods: This open-label, single-arm, multicenter, phase II exploratory trial enrolled ES-SCLC patients with disease progression after platinum-based chemotherapy. Patients received penpulimab (200 mg intravenously every 3 weeks) plus oral anlotinib (10 mg daily, administered in a 2-week-on/1-week-off cycle) until disease progression, unacceptable toxicity, or withdrawal. Primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), PFS, OS, and safety.

07 | AUTHOR INDEX

A

Aarntzen, E. EP.18.01
Aarøe, J. EP.06.42
Aarts, M. J. P3.01.10
Aazzane, O. P2.10.07
Abair, T. EP.12.07
Abalo, L. PT2.15.04
Abate-Daga, L. P3.14.06
Abayomi, O. A. P1.17.76
Abbate, M. I. P3.14.06
Abbott, N. L. PT2.12.01
Abdayem, P. P3.14.15
Abdelhady, K. MA05.03
Abdelhamid, K. EP.09.17, P1.11.03, P3.18.82
Abdel Jalil, R. EP.08.11
Abdeljalil, R. P1.17.39
Abdel Karim, N. P3.01.19
Abdel-Razeq, H. P2.06.09
Abdulwahid, D. OA16.02
Abe, C. P3.18.58
Abe, M. EP.07.35, P1.07.49
Abe, Y. EP.09.16
Abhyankar, A. EP.08.32
Abioye, O. P3.01.18
Abi-Rjeile, J. P3.13.06
Abodunrin, F. OA17.03
Abolfathi, H. MA07.04
Aboubakar Nana, F. P1.17.54, P1.17.55
Aboud, A. OA15.01
Abraham, R. P1.04.18
Abrahami, D. P3.12.34
Abrol, E. P3.01.26
Abu Al-Hial, F. P2.06.89
Abualinin, S. P3.03.31
Abu Hejleh, T. P1.17.54
Abu jazar, H. P1.17.53, P1.17.64
Abu Rous, F. P1.11.56, P2.05.05, P2.06.50, P2.06.62, P2.10.09, P2.10.11, P3.03.31, P3.12.16
Abu-Rous, F. P3.12.42
Acharige, S. M. P3.14.05
Acharki, A. P2.10.07
Achilleos, N. P2.05.17
Achira, M. P3.16.14
Acosta-Plasencia, M. P2.06.32, P3.03.10
Adabi, G. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Adachi, H. EP.07.21
Adachi, K. EP.08.05, P2.08 .08
Adams, A. P3.03.29
Adams, G. EP.04.07
Adams, J. P3.09.02
Adams, M. PT1.04.03
Adamson, B. EP.17.34
Ádány, R. P1.07.22
Adavelly, P. EP.13.24, P2.08 .56
Adcock, B. P1.11.77
Addeo, A. EP.06.83, OA18.01, P1.11.17, P3.18.82
Adebayo, O. W. P2.06.64
Adedewe, N. EP.01.04
Adegbola, A. E. P1.17.76
Ademola, A. EP.17.22
Aden, D. EP.01.27
Adeoti, A. O. P1.17.76
Adewole, M. EP.01.04
Adhikarla, C. EP.07.33, P1.17.27
Adib, E. P1.11.62, PT2.14.05
Adjei, A. P1.11.77
Adler, D. P3.16.08
Adole, P. EP.08.14
Adorni, A. MA02.05
Adusumilli, P. P1.04.17, P3.01.22, P3.18.11
Aerts, J. G. OA01.01, P1.17.54
Aerts, J. EP.13.15
Afanga, K. M. P1.04.45, P2.06.54
Aflatooni, J. P1.17.47
Afonin, G. V. EP.08.25
Agarwa, J. EP.09.08
Agarwal, A. EP.07.37, EP.14.04
Agarwal, A. P3.01.51
Agarwal, J. P. P3.09.01
Agarwal, J. EP.08.14
Agarwal, M. P1.11.50, P3.12.02
Agbarya, A. P1.04.46
Agelaki, S. P2.15 .06
Ågesen, T. EP.01.09
Aggarwal, C. EP.14.17, MA10.02, P2.06.17, P2.06.18, P3.01.19, P3.18.28
Aghera, V. OA05.04
Agkoc, M. EP.03.11, EP.04.23
Agkoç, M. P3.03.04
Aglione, S. P1.11.01
Agne, J. P2.15 .24
Agnelli, L. OA09.02, P1.17.44
Agosta, C. P1.04.51, P1.11.66, P1.17.30, P2.15 .34
Agrawal, A. MA09.08
Agrawal, A. EP.14.15
Agrawal, P. P2.06.12, P3.18.11
Agterhuis, D. P3.18.56
Aguado, R. P3.01.25
Aguado, MD, C. MA01.03
Aguayo, S. EP.04.13
Aguiar, D. P1.11.37, P3.01.25, P3.18.12
Aguiar, I. EP.01.05
Aguiar, R. A. EP.08.16, EP.08.20
Aguiar, R. A. EP.09.03, EP.09.07
Aguiar, R. A. P1.17.72, P2.08 .52
Aguiar, R. B. P1.04.28, P3.01.41
Aguilar , MD, A. MA01.03
Aguiló, R. EP.08.07
Aguirre-Quezada, D. EP.12.18
Agulnik, J. EP.13.38
Agustí, C. EP06.85, P3.03.10
Agustí García-Navarro, C. EP.05.01
Agustoni, F. P1.11.01, P1.11.54, P2.08 .53
Şahin, U. OA13.02
Ahlin, C. EP.12.52, P3.18.66
Ahluwalia, M. MA06.09
Ahluwalia, M. S. P2.06.76
Ahmad, A. P1.17.39
Ahmad, A. EP.06.58
Ahmad, J. I. P1.17.76
Ahmad, S. PL03.19
Ahmadi, M. P3.03.38
Ahmadi, N. EP.07.17
Ahmed, M. PT2.14.01
Ahmed, S. P3.12.65
Ahn, C. P1.07.52
Ahn, H. P3.12.37
Ahn, J. P1.11.73, P3.13.13
Ahn, J. EP.07.46, EP.08.29, P1.11.32, P2.08 .31, PT2.11.04
Ahn, M.-J. EP.07.46, EP.08.22, EP.08.29, MA03.03, OA06.03, OA10.01, OA13.01, P1.11.32, P2.06.102, P2.08 .31, P3.12.40, P3.18.38, P3.18.80, PL02.15, PT2.11.04, PT2.12.03, PT2.12.04
Ahn, Y. P3.13.21
Ahn, Y. P1.07.32
Ahsan, H. EP.01.30, MA06.02
Ahuja, A. EP.01.07, P1.11.21, P1.11.81
Ai, S. P2.06.72
Ai, X. P1.11.83
Ai, X. MA02.07, P3.18.59
Ai, X. EP.14.23
Ai, Y. EP.18.08
Aiba, T. P3.13.14
Aigner, C. MA11.06, P3.13.03
Aijaz, A. P1.07.43, P1.11.17

Aikins, M. PT1.03.01
Ailifeire, A. MA05.07
Aine, M. P2.02.40
Aires Machado, J. PL03.10
Aje, E. EP.01.04
Ajenjo-Bauza, M. P2.06.37
Ajibade, A. F. P1.17.76
Ak, G. P2.05.07
Akagi, K. EP.06.49
Akanni, B. A. P1.17.76
Akazawa, Y. EP.17.25
Akcali, Z. P2.08 .36
Akdemir, E. Y. EP.08.19, P2.06.76
Akerele, O. F. P1.17.76
Akerley, W. MA10.02
Akerman, M. EP.15.12
Akewanlop, C. P3.12.49
Akhmedov, P. P3.01.11
Akinbobola, O. A. EP.07.20, P2.05.02
Akinbobola, MPH, O. OA11.03
Akiyama, T. EP.07.36
Ağkoç, M. EP.05.04
Akpinar, M. EP.04.43
Akpowowo, K. C. P1.17.76
Akram, A. R. EP.03.16, P3.03.46, P3.03.48
Akurang, D. P2.10.06
AKYUREK, S. EP.13.43, P2.08 .15
Al-Agha, F. EP.13.38, P1.17.08, P1.17.09
Alahmadi, A. P2.08 .47, PT2.12.01
Alajlouni, Y. M. P2.05.05
Alaluf, L. EP.06.50
Alamgeer, M. EP.11.11
Alawa, F. B. P1.17.76
Alay, A. EP.14.03, P2.06.37
Al Baghdadi, T. P3.12.42
Albarrán Gómez, A. P2.15 .03
Al-Batsh, T. P1.17.39, P2.06.09
Albayaty, M. P3.12.62, P3.12.65, PL02.06
Albert Ribera, M. EP.05.01
Albinet, V. P3.18.60
Albliwi, M. P1.11.77
Albrecht, F. EP.08.19, P2.06.76
Al Bzour, A. P2.06.62, P2.10.09, P2.10.11
Al Bzour, N. P2.10.11
Al Bzour, N. P2.06.62, P2.10.09
Al-Bzour, A. P3.03.31
Al-Bzour, A. N. P2.05.05, P2.06.50
Al-Bzour, N. P3.03.31
Al-Bzour, N. N. P2.06.50
Al-Bzour, N. N. P2.05.05
Alcaide Córdoba, P. EP.07.43
Alcaide Cordoba, P. P2.08 .48
Alcala, K. OA01.03
Alcaraz, J. P2.06.56
Alchiarazi, M. P1.11.77
Aldana, C. F. MA07.02
Aldea, M. MA01.04, P1.07.43, P1.11.56, P3.12.63, P3.14.22, PT2.11.01
Alder, L. P1.11.75, P3.01.18, P3.01.53
Aleem, A. EP.17.37, P3.01.14, P3.01.15, P3.01.16, P3.01.17
Alejandro, L. P3.12.34
Alencar, R. L. P3.01.06, PT1.04.02
Alencar, T. EP.15.09
AlEnizi, F. EP.12.50
Aleshin, A. MA03.02
Alesi, E. MA10.02
Alessandra, B. EP.11.20
Alessandrini, G. P1.07.07, P3.14.17
Alessi, J. V. P1.11.42
Alessio, L. EP.06.24
Alessio, N. L. P1.11.54
Alexander, L. PT2.14.01
Alexander, M. P3.18.74
Alexander, M. EP.13.33, EP.17.02, MA06.06, P1.17.18, P1.17.61, P1.17.62, P2.06.89, P3.01.13
Alexandrov, L. OA14.05
Alfieri, R. P3.03.15
Alghabban, A. EP.06.75
Alhadab, A. MA08.03, MA08.05
Alharbi, M. EP.08.32
Alhushki, S. P2.06.27
Ali, A. P3.03.15
Ali, G. P2.08 .03, P3.14.06, PT2.14.02
Ali, M. K. P1.11.77
Ali, M. S. PT1.03.01
Ali, S. P3.14.08
Aliagas, E. P3.14.12
Al-Ibraheem, A. P1.17.39, P1.17.53, P2.06.09
Alifano, M. P2.05.10, P3.18.60
Alioke, I. I. P1.17.76
Alisanant, C. EP.04.37
Alizadeh, A. MA03.01
AlJassim, A. EP.12.50
Alkapalan, D. P1.04.01
Al-Kasasbeh, M. P2.06.09
Alkrekshi, A. P3.12.02
Alkurdi, E. P1.07.16
Allakhverdiev, A. P3.01.11
ALLALI, R. P2.10.07
AL Lawati, A. S. EP.06.54
Allegra, M. P2.06.88
Allgäuer, M. EP.01.20, EP.06.29, MA04.06
Alliaume, S. P2.15 .29
Allsworth, M. P1.04.54
Almeida, C. E. EP.08.16, P2.08 .52
Almeida, C. P1.04.28
Almeida PhD, C. E. P3.01.41
Almog, N. P2.06.93
Almquist, D. PL03.06
Almuinas de Armas, S. P2.06.75
Almutawa, A. EP.06.54
Almutrafi, A. EP.06.31
Alnajdawi, Y. P1.07.28
Alnajjar, Q. P1.17.39
AlNassar, M. EP.12.50
Alonso, M. EP.06.43
Alonso, P. EP06.85
Alpert, E. EP.15.12
Al-Rabi, K. P1.17.39, P1.17.64
Al-rabi, K. H. P1.17.53, P2.06.09
Al Rawabdeh, J. P2.06.62, P2.10.09, P2.10.11
Alrawabdeh, J. P2.05.05, P2.06.50, P3.03.31
AlSaleh, T. EP.12.50
Alsarayrah, B. M. P2.05.05
Alsati, R. EP.06.80
Alshobaki, L. P2.06.09
Alt, J. P3.12.14
Alt, J. MA01.07
Altan, M. EP.04.31, MA10.05, OA05.04, OA07.01, P1.11.60
Altenburg, H. P1.17.47
Altenburg, J. P3.12.42
Altoe, M. P1.11.59
Altorki, N. OA09.01
Altuna-Coy, A. P2.06.32, P3.03.10
Altundag, O. P2.08 .36
Álvarez, A. MA01.01
Alvarez, L. P2.08 .49
Alvarez, R. OA01.02
Alvarez, S. OA01.02
Álvarez González, L. EP.08.47
Álvarez Gracia, A. EP.08.47
Alwon, MS, E. EP06.86, P2.06.20
Aly, R. OA12.01

Alzaher, T. E. P2.05.05
Amadi, C. E. P1.17.76
Amano, A. P1.11.40
Amano, Y. PT2.14.03
Amato, L. EP13.48
Ambi, I. EP.17.22
Ambrogi, M. P2.08 .03
Ambrogi, V. P3.14.17
Ambrogio, C. P3.03.17
Ambrosi, F. EP.08.03, P2.06.81
Ambrosini, E. P1.04.51
Ambrosini, P. MA06.07, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34, P3.12.30
Ambrosio, F. EP.11.03, P3.18.18
Amenu, B. EP.15.06
Ameri, A. EP.13.25
Amerl Šakić, V. OA15.01
Amino, Y. EP.08.42, EP.13.11, P3.12.54
Aminu, M. P1.11.55, P1.11.70
Ammakkanavar, N. R. OA08.02
Amorim, P. P. P1.17.11
Amos, C. PT1.04.04
Amos, C. I. MA05.06
Ampollini, L. P1.07.04
An, J. EP.12.08
AN, S. P3.12.74
An, S. MA05.08
Anadon Galindo, C. P3.03.20
Anagnostou, V. OA12.03, P1.11.72, P3.18.40, PL03.06
Anand, S. EP.13.25
Anantham, D. OA15.02
Anastasiou, M. EP.01.19
Anastasiou, Z. MA07.07
Anazodo, U. EP.01.04
Andersen, B. L. OA04.04
Andersen, S. P1.11.62
Anderson, A. P1.17.20
Anderson, B. G. P3.12.46
Anderson, K. P1.04.08
Anderson, M. P3.03.29
Anderson, R. MA05.01, P2.15 .01
Ando, Y. EP.04.36
Ando, Y. P3.13.14
Andrasina, I. P3.12.62, P3.12.65
Andreas, V. P3.18.82
Andrei, A. M. EP.05.08, P2.05.06
Andreo, F. P3.03.44
Andrew, A. S. P1.04.29
Andriatte, G. M. EP.17.30
Ang, Y. P2.06.14
Angelicola, S. P1.11.54
Angra, N. P3.18.38
Angrisani, A. P3.18.82
Anichini, A. P1.17.44
Anne, T. P1.11.70
Anosike, C. P1.17.76
Anoze, A. EP.06.73
Ansari, M. P2.06.64
Anselmo, P. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Antao, H. P2.15 .22
Antelo, M. G. EP.13.19
Anthony, L. EP.13.29
Anton, A. P3.03.34
Antoñanzas, M. P3.01.25
Antoñanzas, M. P3.12.30
Antoñanzas, M. P3.18.12
Antonia, S. P1.11.75, P3.03.20
Antoniak, S. MA11.05, P3.13.02
Antonissen, N. J. OA01.01
Antonoff, M. P2.02.36, P3.18.84, PT1.01.03, PT1.04.03
Antonoff, M. B. EP.04.31, OA07.01, P1.11.60
Antonuzzo, L. MA08.01, OA08.03, P1.11.66
Aokage, K. EP.07.01, EP.07.10, P1.07.03
Aoki, H. EP.07.32
Aoki, T. P3.18.04
Aoyama, J. EP.11.07
Aoyama, Y. EP.06.26
Appel, H. P2.06.76
Appel, S. EP.09.01
Appenzeller, T. P2.06.56
Aprile, V. EP.14.18, P2.05.10, P2.08 .03
Arabadjiev, J. P1.17.29, P2.15 .06
Aragaki, M. EP.04.36, EP.06.84, EP.14.16, P1.07.21
Arai, H. EP.07.04, EP.08.02, EP.14.24
Arai, R. P3.03.42
Arai, S. P1.11.06, P3.03.02
Aramburu, J. EP.14.03
Aranda, E. EP.06.66
Arasanz, H. OA01.02
Arasaratnam, D. MA06.06, P1.17.61
Araújo, A. P1.17.29
Araujo, H. P2.02.36, PT1.01.03
Araujo, H. A. EP.04.31
Araujo, L. OA11.02
Aráujo, R. PT1.03.03
Araya, J. EP.17.05
Arbajian, E. P2.02.40
Arbour, K. C. OA08.01, P2.06.12, P3.18.65, P3.18.71
Arbusa, A. P2.06.65
Arbusà Roca, A. OA09.02
Arcangeli, S. P2.08 .53
Arcidiacono, F. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Arcocha, A. EP06.85, OA01.02, P3.01.46
Ardeshir, F. P3.01.09
Ardeshir- Larijani, F. PT1.06.03
Ardizzoni, A. P1.11.42, P2.06.92
Arellano, M. P2.06.37
Arellano-Vengoechea, M. EP.16.04, P2.08 .60
Aremu, O. EP.01.04
Arena Siqueira, A. C. P3.16.04
Arends, K. P1.11.71
Areses, K. P3.01.25
Areses, M. P3.18.12
Arevalo, J. EP.06.24
Argento, M. EP.15.11
Arguis, M. P2.15 .21
Aris, V. P3.12.41
Aristu, J. PT1.08.05
Aritonang, R. S. EP.04.22
Arivajiagane, A. P3.03.03
Ariyasu, R. EP.08.42, EP.13.11, MA08.04, P3.12.54
Ariyasu, S. EP.05.02
Ariyo, I. EP.01.04
Arizio, F. P3.16.05
Arizpe, A. P1.17.02, P1.17.16
ARMAND, E. EP.04.29, P1.04.39
Armanetti, P. P3.03.15
Armato, S. OA09.02
Armato III, S. G. P3.14.04
Armenta, A. EP.06.66
Armenteros-Monterroso, E. P3.12.62, P3.12.65
Arnold, K. B. P3.18.84
Arnold, P. EP.12.56, P3.12.67
Arnold, S. EP.13.29, P1.17.65
Aroldi, F. P3.18.35
Arrabal, R. MA01.01
Arranz, S. P1.17.80, PT2.17.05
Arrato, N. OA04.04
Arredondo, M. EP.06.45
Arredondo Lasso, M. EP.03.12, P3.18.36

Arribas, L. PT1.08.04
Arriola, E. EP.08.07, P2.06.74, P3.18.38
Arroyo, I. P1.17.80, PT2.17.05
Arroyo de Leon, G. P3.16.15
Arshakyan, M. P2.06.56
Arslan, C. OA13.02
Arslan, Y. P2.08 .15
Artamonova, E. P3.13.29
Artiga, G. EP.01.05
Arulananda, S. EP.11.11, OA03.04, P1.17.62, P2.06.89
Arunachalam, J. EP.14.31, EP.17.36
Arunachalam, J. EP.14.31, EP.17.36
Arya, G. EP.01.07, P1.11.21, P1.11.81
Asami, M. EP.14.13
Asamura, H. EP.07.01, OA11.01, OA11.02, PL03.16
Asano, S. P3.12.35
Asante-Siaw, J. EP.07.47
Asao, T. PT2.14.03
Ascanio, F. MA01.01
Aseem, A. P1.17.13
Aseyev, O. P1.11.36
Ashaye, A. EP.12.35
Ashok Kumar, P. P2.08 .42
Ashoush, N. EP.14.07
Ashtekar, A. P1.17.22
Ashton, M. PT2.14.01
Asiltürk, M. EP.04.28
Aslibekyan, S. EP.01.17
Asna, N. EP.06.73
Aso, S. P2.06.37, PT1.08.04
Aso-Gonzalez, S. EP.07.42
Aso-González, S. EP.16.04, P2.08 .60
Assumpção, L. EP.17.31, PT1.01.02
Assunção, L. B. EP.08.16, EP.08.20
Assunção, L. B. EP.09.03, EP.09.07, P1.04.28, P1.17.72
Assunção, L. B. P2.08 .52
Assunção, L. B. P3.01.41
Atallah, S. P2.06.75
Atashrazm, F. EP.15.04, P1.11.49, P2.06.89
Ates, O. P2.10.02, P3.18.74
Athanasiadis, I. P2.15 .26
Atkar-Khattra, S. MA05.05, P1.04.36
Atkin, N. EP.13.33, EP.17.02, PT2.17.02
Atkinson, D. MA07.02
Atmaca, A. MA01.07
Attili, I. P1.07.51
Atueyi, U. MA05.03
Atwal, T. P2.02.15
Auber, R. P. EP.06.23
Audigier Valette, C. P3.12.29
Audigier-Valette, C. P1.17.21
Auliac, J. P2.06.43
Auliac, J.-B. EP.12.36, EP12.64
Aung, T. N. P2.06.68
Aung, W. P2.06.10
Austin Taylor, M. P1.11.15, P1.11.46
Autheman, M. P1.17.21
Autschbach, F. P3.12.61
Avancini, A. P3.12.08, P3.18.85, PT2.15.01
Avander, M. EP.06.42
Averbuch, I. P3.09.03
Avila, J. OA18.04
Aviles, J. D. EP.04.14
Avilés, P. EP.13.27
Awad, M. MA01.04, P1.11.55
Awad, M. M. MA04.05, OA02.03, P1.07.43, P1.11.42
Awan, A. EP.06.54
Awano, N. PT1.05.02
Awolola, N. A. P1.17.76
Awrey, S. P2.02.15
Aykac, M. EP.03.12, P3.18.36
Aykac-Bicer, M. P3.18.02
Ayoade, O. F. P1.07.31, P2.08 .07
Ayo-Yusuf, L. EP.01.23
Aza, I. P3.12.42
Azad, T. P3.03.38
Azaizeh, A. EP.06.31
Azambuja, A. P3.18.80
Azkárate, A. P3.18.12
Azkona, E. MA06.03
Azmi, A. P3.12.42
Aznar-Garcia, L. P3.09.02
Azuara, D. P2.06.37
Azuma, K. P3.03.42, P3.12.33

B

Baas, P. P1.07.41, P3.14.03, PT1.06.03
Baba, A. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Babiker, H. M. OA08.01
Bacchin, D. P2.08 .03
Backhus, L. M. P1.04.19, P3.01.07, PT1.01.01
Bader, J. M. EP.06.58
Badin, F. P3.13.31
Badiyan, S. P2.08 .23
Bae, B. EP.09.02
bae, y. EP.14.11
Baena, J. P3.12.30
Baena Espinar, J. EP.12.24, P2.10.05
Bafaloukos, D. P2.15 .26
Baffert, K.-A. P3.03.33
Bafunno, D. OA17.01, P3.16.05
Bahce, I. EP.18.01, P1.11.62, P3.13.16, P3.18.16, P3.18.54, PT2.11.02
Bahig, H. P1.17.42, P2.08 .54
Bai, C. EP.03.05, P2.02.09, P2.02.13, P2.15 .33
Bai, H. P3.03.51
Bai, J. MA06.04, MA09.09
Bai, J. MA09.09
Bai, J. P3.12.64
Bai, R. EP.06.56, EP.12.38, P2.06.46
Bai, X. MA07.08, OA14.02
Bai, Y. OA05.01
Bai, Y. P2.10.17
Baig, M. MA07.07, MA08.03, MA08.05
Baik, C. MA03.03, P2.02.37, P3.12.71
Baik, C. S. MA07.07, P1.07.37, PL02.15
Bailey, H. EP.17.32
Baili, P. P2.15 .34
Bain, N. OA03.04
Baine, M. OA13.04, OA14.05
Bains, P. MA08.07
Baio, N. P3.12.38
Baird, A.-M. EP.06.61, EP.06.79, OA17.02, PT2.17.04
Baixeras, N. EP.06.48, P2.06.37
Baiyewu, L. A. P1.17.76
Baker, A. EP.17.09
Baker, C. P2.08 .19
Bakhmach, A. P1.04.39
Bal, A. P1.17.79
Balaji, D. P3.01.09
Balaji, S. P3.01.09
Balamurugan, A. P1.07.22
Balanag, V. M. P1.17.31
Balaramal, N. EP.07.40
Balaraman, R. P3.18.39
Balaratnam, K. EP.13.38
Balata, H. PL03.19
Balázs, D. P2.02.22
Balbi, K. P2.06.08
Balbi, M. P1.04.53, P2.06.22
Baldes, N. EP.04.27, EP.07.22, P2.05.17
Baldini, E. MA02.05

Baldotto, C. EP.13.28, OA18.02
Baldotto, C. S. EP.09.09
Baldwin, D. EP.01.22
Baldwin, D. A. EP.06.15
Balestra, V. P1.07.04
Balladore, E. EP.06.03
Ballantyne, F. P2.06.04
Ballesteros, M. P1.04.35
Balli, S. EP.06.18
Ballinger, M. L. P2.06.61
Ballinger, Z. P1.17.01
Baltimore, S. OA04.04
Balzan, E. EP.08.03
Balzano, V. EP.03.02
Bandaranaike, R. P2.06.27
Bando, J. EP.07.14
Banegas, M. P1.17.17
Banerjee, A. PT1.03.01
Banfill, K. OA16.02
Bang, S.-M. P2.02.11
Bani Mustafa, A. A. EP.01.11
Banini, M. P1.07.51
Banks, E. PT2.14.01
Banna, G. L. P3.14.05
Banna, G. P1.11.17, P3.18.55
Banovic, P. P2.08 .20
Bansal, D. EP.06.65, P2.06.71
Banwait, M. K. EP.06.53
Bao, H. P3.18.42
Bao, H. P3.18.32
Bao, L. EP.02.07, PT1.03.01
Bao, Y. P1.11.35
Bar, J. EP.09.01, OA06.04, P1.17.06, P2.15 .06, P3.18.28, P3.18.73, PT2.10.02
Bara, I. MA04.02, P3.18.13
Baramidze, A. MA10.09, P1.11.52
Barata, T. MA10.06
Barba, A. EP.08.07
Barba, A. OA05.03, P2.08 .37, P3.12.30, P3.18.12
Barba Joaquín, A. MA08.01
Barba Joaquin, A. P2.15 .12
Barban, S. EP.15.11
Barbé, F. EP.04.14
Barbie, D. P3.14.20, P3.14.22
Barbie, D. A. P1.07.43
Barbieri, P. P3.14.13
Barbieri, V. P1.07.51
Barbolosi, D. P1.04.39
Barbosa, G. EP.08.20, EP.09.03, EP.09.07, P1.17.72
Barco Sánchez, A. EP.06.71
Bareggi, C. P1.11.66
Barghout, S. P1.17.08, P1.17.09
Barioni, B. EP.01.05
Barjaktarevic, I. EP.07.14
Barkan, T. P3.09.03
Barker, C. OA16.02
Barlesi, F. EP.06.79, P1.17.21, P2.06.43, P3.14.15, P3.18.61
Barlo, N. P3.13.16, P3.18.16, PT2.11.02
Barmin, V. P3.14.19
Barned, S. P3.16.06
Barneto, I. EP.06.66
Barneto, MD, I. MA01.03
Barone, F. MA10.02
Barr, D. P3.01.28
Barr, M. P. EP.06.61, P2.06.82
Barradas, L. EP.07.25
Barrera-Garcimartín, A. PT2.15.04
Barreto, A. B. EP.15.01
Barrett, K. P3.12.62, P3.12.65, PL02.06
Barroso, A. EP.07.25
Barroso, D. P2.06.37
Barry, A. P3.16.23
Barry, A. M. P3.16.22
Barry, S. J. P2.06.82
Barsanti, P. A. P2.10.17
Barsheshet, Y. EP.03.08, P3.03.28
Barsouk, A. EP.14.17
Bart, A. EP.06.50
Bart, J. I. EP.08.25
Barta, J. EP.04.05
Barta, J. A. P3.01.01
Bartholmai, B. MA05.01
Bartholomew, K. EP.04.07, EP.04.10
Bartlett, G. P1.04.08
Bartlett, J. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Bartolessis, I. P3.03.49
Bartolomeo, V. MA06.07, P1.17.30
Bartolomeu, C. MA09.03, P1.04.33, P1.04.34, P3.01.23, P3.01.29
Barton, K. OA03.04
Barton, P. W. EP.15.16, EP.16.01
Barzilay, R. MA05.03
Basak Oven, B. OA13.02
Bascik, O. P2.08 .15
Baser, E. P1.17.58
Basílio, J. EP.13.20
Bassel, L. MA07.02
Bassig, B. J. EP.04.24
Bastardo, C. M. EP.07.25
Bastidas, J. PT1.08.03
Basu, S. P2.06.18
Basu Roy, U. MA06.09, P1.17.24, P1.17.71, P3.16.15
Basu-Roy, U. P3.01.51
Batah, H. P1.11.77
Bateman, N. EP.03.01
Bates, S. P1.11.14, P1.11.18
Batista, J. P. EP.17.30
Batista, P. d. EP.17.23
Batllori Casanovas, M. EP.06.78
Batra, U. EP.17.06
Batra, U. EP.06.16
Batra, V. EP.17.06
Battafarano, R. J. OA12.03
Battara, L. P3.12.20
Bauer, T. M. P3.12.21
Bauman, J. P2.15 .22
Bauman, J. R. PL02.15
Bauml, J. M. P3.12.46
Bayas, N. EP.01.08, EP.12.01
BAYKAN, A. EP.04.43
Bayle, S. P2.06.43
Baylin, S. B. P1.11.72
Bayman, N. OA16.02
Bayoglu, V. P2.10.02
Baz, D. V. OA10.01
Bazhenova, L. MA02.02, MA03.03, MA08.01, P3.12.12, PL02.12
Bazzano, C. P3.14.13
Bazzell, B. P2.10.01
Beal, H. MA09.05
Beal, J. R. EP.17.30
Beardsley, E. K. P1.11.85
Bearz, A. MA08.01, P3.12.30
Beasley, M. OA13.04, PL03.16
Beau, M. EP.06.39
Becerra, C. P3.12.71
Becharano, G. MA03.02
Becht, K. EP.01.16
Beck, K. S. P2.06.01
Becker-Commissaris, A. EP.04.32, EP.17.13, EP.18.01, P1.04.41, P2.15 .10
Beckham, T. MA10.05
Beckler, V. P1.04.32

Beckman, N. P2.08 .23
Béder, T. N. EP.06.09, P3.01.06, PT1.04.02
Beder, T. N. P1.17.11
Bednarczyk, M. PT2.15.03
Beghdad, F. EP.12.36
Behr, J. EP.06.45
Behr, J. EP.03.12, EP.11.23, EP.12.56, P3.12.67
Beks, H. P1.17.20
Belda Sanchis, J. EP.08.07
Belka, C. P3.16.19
Belka, C. P2.08 .14
Bell, J. L. OA15.03
Bellantuono, L. P1.04.47
Bellezza, G. OA07.03, PT1.08.02
Bellido Hernández, L. P2.15 .03
Bellido-Hernández, L. P2.02.41
Bello, I. EP.08.26, P2.15 .21
Bellosillo, B. EP.06.48, P2.06.74
Bellotti, R. P1.04.47
Belluomini, L. EP.11.20, MA02.05, P1.07.51, P3.12.08, P3.12.15, P3.18.85, PT2.15.01
Bellur, S. MA06.09
Bellver, M. PT1.08.04
Ben, X.-S. P1.07.55
Benavente, F. MA02.03
BENCHAKROUN, N. P2.10.07
Bendixen, M. PL03.13
Bénédic, A. EP.06.39
Benedict, J. OA04.04
Bengio, V. EP.06.24
Benharash, P. EP.07.14
Beninato, T. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P1.17.54, P2.06.65, P2.15 .34
Benini, A. EP.13.05
Benitez, J. P2.10.05
Benitez Montañez, J. P3.14.15
Benitez Montanez, J. P3.18.73
Benito Berlinches, A. EP.07.27
Benjak, T. OA15.01
Benjamin, L. EP.07.14
Bennati, C. P1.07.51, P3.12.15, PL02.15
Bennett, P. P2.06.08
Bennewith, K. P2.02.15
Ben-Shachar, R. MA03.05
Benso, F. P2.06.22
Bento, M. L. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.17.72, P2.08 .52
Bento, M. T. P1.04.28, P3.01.41
Benzekry, S. P1.04.39, P3.18.60
Beran, G. EP.17.21
Berardi, R. P1.11.24
Berchem, G. P1.17.29
Berezowska, S. MA07.01, OA09.01, PL03.16, PT1.07.01
Bergamini, M. EP.09.06
Berger, A. P2.02.37
Berger, W. EP.02.02, P2.02.18, P2.02.22
Berghmans, T. EP.05.06, MA02.08
Berghoff, A. P3.18.55
Bergin, R. P1.17.20
Berglund, A. EP.13.22, P1.17.14
Bergman, B. P3.18.56
Bergom, C. P2.08 .51
Berkman, N. P2.15 .06
Bernabé, R. MA06.03
Bernabe, R. P1.11.07, P1.11.37
Bernabé, R. P1.17.80, P3.18.12, PL03.10, PT2.17.05
Bernabé, MD, R. MA01.03
Bernabeu, M. OA01.02
Bernardi, M. P2.06.43
Bernatowicz, K. EP.17.21
Berretta, M. EP.11.01, EP.15.14
Berry, L. D. P1.07.37
Berry, M. F. P1.04.19
Bertaglia, V. P3.16.05
Berthet, J.-P. P2.06.87
Bertoglio, P. EP.08.03, EP.14.18, P2.06.81, P3.14.17
Bertolina, C. EP.14.08, P3.14.13
Bertolini, A. MA02.05
Bertolini, F. EP.11.20, EP.13.05, EP.15.11, P1.11.24, P3.14.06
Bertollo, G. P3.12.46
Bertolotti, M. EP.14.08, P3.14.13
Bertram, S. EP.07.22
Bertrán-Alamillo, J. EP.02.10
Bertrand, B. EP.06.39
Besse, B. EP.04.29, MA02.03, MA07.07, OA01.02, P1.04.39, P1.17.21, P3.12.21, P3.12.71, P3.14.15, P3.18.64, PL02.15, PT1.03.06
Best, J. P3.01.19
Bestvina, C. EP.13.47, MA10.02, P2.05.01, P3.01.48
Bestvina, C. M. OA17.03, P3.18.35
Betof-Warner, A. P3.18.87
Bettini, A. P3.18.82
Bettini, A. P1.07.51, P1.11.01, P3.12.15
Betts, K. OA18.03, P1.04.40
Bevers, K. P2.06.67
Bezerra, C. H. P3.01.06
Bezjak, A. EP.14.15
Bhalla, S. EP.04.06
Bhang, E. EP.08.17
Bhar, P. P1.11.78, P3.18.52, P3.18.53
Bharadwaj, T. P1.17.67
Bharat, A. P2.08 .01, PT1.09.02
Bhat, A. P3.01.07, PT1.01.01
Bhat, H. P3.01.22
Bhatia, S. MA04.05, OA02.03
Bhatnagar, P. EP.07.40, P2.06.85
Bhatt, K. MA11.04
Bhattacharyya, S. P2.06.84
Bhattacharyya, S. P1.07.26
Bhatti, S. EP.08.50, P1.11.27
Bhetariya, P. OA02.02
Bhise, R. P3.12.65
Bhosale, S. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Bhosle, J. EP.17.12
Bhowmick, N. P3.18.70
Bhoy, E. OA15.03
Bi, M. P3.12.07
Bi, N. MA11.09, P3.18.21, PL03.07
Bian, K. EP.04.17
Bian#, D. EP.08.36
Bianchi, F. P1.04.45, P2.06.54, PT1.03.04
Bianchi, F. P2.06.81
Biasion, S. EP.14.08, P3.14.13
Bibichadze, K. EP.17.26
Biello, F. EP.06.80, P1.11.66, P1.17.54
Bigay-Game, L. EP.17.39, OA05.02
Bignoli, F. EP.11.01
Bikkina, S. P2.08 .23
BILGIC, A. B. EP.13.43
Bilici, A. P2.10.02
Bilir, C. P2.10.02
Billard, A. P2.15 .29
Billè, A. P3.14.19
Billing, D. EP.08.51, EP.14.22, P2.08 .25
Billing, D. L. EP.13.08
Billingy, N. EP.04.32, EP.17.13, EP.18.01, P1.04.41, P2.15 .10
Bilski, M. P2.08 .21
Bimbrahw, K. P1.04.33
Bin, J. EP.12.39
Bindroo, S. P2.06.94

Binegdie, A. P1.17.31
Bing, J. P3.12.65
Bir, A. PT1.08.03
Bironzo, P. P1.17.29, P1.17.55, P2.06.22, P2.06.40, P3.03.17, P3.14.06, P3.16.05, PT2.12.04
Bischoff, H. P3.12.14
Bishop, H. P3.18.29
Bisson, K. P1.11.36
Biswas, B. PL02.06
Bitrus, M. EP.06.80
Bittoni, M. EP.01.31
Bivona, T. G. P3.03.02
Biyi-Olutunde, O. A. P1.17.76
Bizieux, A. EP12.64
Black, A. OA03.04
Black, M. P2.06.70
Blackhall, F. P3.13.04
Blais, N. P2.08 .54
Blakely, C. OA02.02, P1.07.40
Blakely, C. M. MA04.02
Blanchette, P. P1.17.70
Blanco, A. I. MA01.01
Blanco, M. MA01.01
Blanco, R. P1.11.37, P3.18.12
Blanco Clemente, M. P3.01.25
Blando, J. OA03.03
Blanton, R. P3.18.52, P3.18.53
Blasberg, J. EP.08.46
Blasberg, J. D. P3.18.84
Blasco, A. EP.06.77, OA05.03, P1.11.37, PL03.10
Blasco, I. P3.03.45
Blatt, R. P3.03.22
Blau, W. P3.12.14
Blechet, C. OA09.03
Blechter, B. P3.01.28
Bleeker, T. P1.17.28
Bleiberg, B. EP.14.17
B.Licht, P. P1.11.62
Bliss, J. EP.12.27
Bloch, G. EP.15.06
Block, M. PT1.04.01
Bloom, K. P2.06.68
Bloom, K. EP.06.50, P3.03.39
Bloudek, L. P3.12.19
Blum, R. EP.13.33, EP.17.02, P3.01.13
Blum, R. P1.17.18, PT2.17.02
Blum, S. I. MA04.05, OA02.03
Blumenfeld, P. P2.15 .06
Blumenschein, G. MA10.05, P2.02.36, PT1.01.03
Blumenschein, G. J. P1.11.70
Blumenschein, Jr., G. P2.06.102
Blumenschein Jr, G. OA07.01
Blume-Vulin, A. P1.11.48
Blyth, K. P3.14.08, P3.14.10
Boada, M. EP.08.26, MA01.01, P2.06.32, P2.06.56
Bobbili, P. P3.12.06
Bocchialini, G. P1.07.04
Boccuzzi, F. EP.14.10, P3.14.13
Bodei, L. P3.13.05
Bodell, K. P3.16.06
Bodor, J. N. OA08.02
Boeri, M. P2.06.97
Boettiger, K. MA11.06, P3.13.03
Boffa, D. EP.08.46
Boffa, D. J. P1.07.31, P2.08 .07
Bogdan, S. EP.12.27
Bogos, K. EP.16.05, MA11.06, P3.13.03
Boiarsky, D. P1.11.55
Boland, J. OA03.03
Boland-Froemming, J. OA09.03
Bolanos, A. P1.07.47
Bold, G. P2.10.08
Boldrini, L. EP.06.40, P1.07.22, P3.13.04
Boldt, G. EP.12.37
Bolt, M. MA01.04
Bolt, T. EP.12.56
Bolton, A. P1.17.12, P2.06.89
Boltong, A. P1.17.20
Bolufer, S. MA01.01, P2.08 .28
Bölükbas, S. EP.04.27, EP.07.22, P2.05.17
Bona, E. P3.14.13
Bonafè, M. P2.06.92
Bonalume, C. P1.04.51, P1.17.30, P2.15 .34
Bonanno, L. MA03.03, PT2.12.04
Bongard, C. P1.04.03, P1.04.15
Boni, V. P2.06.100, P3.18.29
Bonilauri, S. EP.15.11
Bonin, A. P3.12.72
Bonomi, L. EP.12.36
Bonù, M. L. P2.08 .26
Book, A. J. P2.08 .25
Bookstein, S. P2.06.68, P3.03.39
Boos, L. EP.06.83
Borba Reiriz, A. EP.06.01
Borchardt, I. EP.15.01, EP.15.09
Borczuk, A. OA09.01, PL03.16
Borda, K. EP.01.10
Borden, S. P1.04.33, P1.04.34, P3.01.29
Bordi, P. EP.11.05, EP.11.20, P1.07.04, P1.11.24
Borea, R. PT2.10.01
Borgeaud, M. P3.18.82
Borgetto, S. P1.11.54
Borghaei, H. EP.13.41, MA11.04, P1.17.78, PL03.06
Borghetti, P. P2.08 .26
Borgia, J. A. P2.06.64
Borkum, T. P3.03.22
Borodny-Kitts, A. P3.18.84
Boron, M. P3.01.19
Borra, G. EP.06.80, P1.07.51
Borraccino, M. P1.04.51, P1.17.30, P2.15 .34
Borràs, J. M. P1.04.35
Borregón, M. P3.18.12
Borrelli, C. P3.18.18
Borsati, A. P3.12.08, PT2.15.01
Bortnowski, W. EP.01.03
Bortolotto, C. P1.11.54
Bos, E. M. EP.12.49
Bosch-Barrera, J. MA06.03, MA08.01, P1.11.07, P1.11.37, P2.08 .49, P3.14.09, PL03.10
Bosch-Barrera , MD,, J. MA01.03
Bose, C. EP.06.34, EP.12.01
Bose, M. P2.06.84, P3.13.09
Bosquet, L. P3.12.29
Bossé, Y. MA07.04
Bossen, J. EP.03.06
Bossio, E. EP.12.25
Bostock, I. P1.07.37
Bota-Rabassedas, N. OA09.01
Bote, H. P2.08 .48
Bote de Cabo, H. EP.06.43
Botello, R. EP.16.06, EP.16.08
Botías, I. EP.08.26
Botling, J. EP.13.22
Bott, M. P1.04.17, P3.01.22, P3.18.11
Boualam, N. EP.17.33
Bouchaab, H. EP.09.17, P1.11.03, P3.18.82
Boudreau, D. K. MA07.04
Bou Farhat, E. P1.11.62, PT2.14.05
Bouhaddou, H. P3.13.16
Boukhaled, G. M. OA12.04
Boulanger, M. P2.15 .24
Boulate, D. EP.04.29, EP.17.11, P1.04.39
Boullier, C. P3.13.06

Boulouta, A. EP.01.19
Boumber, Y. P2.06.27
Boutros, J. P2.06.87
Bouwhuis, N. PT2.11.02
Bou Zerdan, M. P3.01.09
Bouzit, L. P2.06.45
Bowles, D. P3.12.71
Bowman, K. P3.12.04
Bowyer, S. P1.17.62
Boyapati, A. P2.06.102
Boyd, A. S. EP.17.08
Boyle, B. P1.04.54
Boyle, T. EP.13.25
Bozkurt, S. P3.01.09
Bozorgmehr, F. P3.12.46
Brabrand, J. EP.15.03
Bradbury, P. EP.06.75, OA12.02, OA12.04, P1.17.08, P1.17.09, P3.14.11
Bradbury, P. A. P2.06.99
Bradley, J. D. P2.08 .23
Braga, M. P1.17.29
Brahmer, J. P3.18.40, PL03.06
Brahmer, J. R. OA02.03, OA12.03, P1.11.72, P2.06.66, P3.01.19
Brain, K. EP.01.22
Brainson, C. EP.13.29
Brake, S. P1.07.05
Bramanti, E. P3.03.15
Brambilla, M. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Branco, M. OA14.04
Brandão, M. EP.05.06, MA02.08, P3.12.30
Brandao, M. P3.18.67
Brandolini, J. EP.14.18, P2.06.81
Brandt, W. P1.17.50
Brandt, W. S. MA07.05
Brant, B. P3.03.28
Brao, I. P2.06.37
Brao-Pérez, I. EP.16.04, P2.08 .60
Brase, J. P3.12.41
Brasoveanu, T. P2.06.70
Brauer, M. MA09.01, P3.01.29
Braune, E.-B. EP.12.26
Bravio, I. P3.14.19
Bravo Thompson, H. A. EP.12.34
Bray, V. OA03.04
Brcic, L. PT2.14.02
Breadner, D. EP.12.37, MA08.07, P1.17.70, P2.06.70, P3.18.52, P3.18.53
Breadner, D. A. P2.10.08
Breathnach, O. EP.08.34, P2.06.82
Brechot, D. EP.06.64
Brechtelsbauer, E. EP.17.33
Breen, D. P2.15 .06
Brenes, J. P2.06.37, P3.14.09, PT1.08.04
Brenman, E. P1.11.38
Brenner, D. R. P3.01.24
Brenner, H. P1.04.29
Bressers, A. P3.18.16
Brhane, Y. MA05.06
Bria, E. EP.11.20, MA02.05, OA08.03, P1.07.22, P1.07.51, P1.11.24, P1.17.54, P1.17.55, P2.10.05, P3.12.15, P3.13.04
Brice, K. P2.06.75
Brich, S. P1.17.44
Briere, T. MA10.05
Brietzke, M. P1.17.83
Briggs, L. EP.13.33, EP.17.02, P1.17.18, P2.06.89, P3.01.13, PT2.17.02
Briggs, P. EP.11.11
Briggs, S. EP.07.40
Brighenti, M. P1.11.01
Brighenti, M. P1.11.66
Brims, F. OA18.03, P1.04.08, P1.04.40, P1.17.12
Brinton, S. P3.18.14
Brioude, G. EP.04.29, P1.04.39
Brirken, S. P3.18.14
Briskin, C. P1.17.01
Brito, U. EP.07.25
Britschgi, C. EP.06.83, P2.08 .58
Brizola, L. EP.01.05
Brizzi, L. P1.11.54
Brocchi, S. P2.06.92
Broderick, S. R. OA02.03
Broeders, M. EP.17.13
Bronte, G. P3.12.20, P3.14.06
Brooke, M. P1.04.08
Brooks, D. G. OA12.04
Brosnan-Cashman, J. OA09.01
Broström, E. P3.18.56
Brouchet, L. EP.17.39, P2.05.15
Brouwer, A. F. P3.01.42
Brown, A. EP.04.38
Brown, A. P1.04.08
brown, a. EP.17.07
Brown, C. P1.17.08, P1.17.09
Brown, C. S. OA03.04, P2.06.61
Brown, D. W. EP.06.68
Brown, D. PT2.12.01
Brown, L. P2.15 .05
Brown, L. J. P1.17.62
Brown, L. M. P3.18.84
Brown, M. C. P1.04.29
Brown, M. P1.04.33, P1.04.34, P3.01.29
Brown, T. P1.07.40
Brown-Walker, P. OA12.02
Brück, P. MA01.07
Brule, S. EP.17.17
Bruna, J. OA05.03
Brunelli, V. P1.17.12, P1.17.47, P2.15 .13
Brunetti, L. EP.06.52, P1.11.17, P1.11.62, P1.17.54, P1.17.55, PT2.11.01
Brungs, D. MA08.01
Bruni, A. EP.13.05, P2.08 .26
Brunner, L. OA09.01
Bruns, R. P3.12.40
Brunson, K. P1.17.24
Brunswicker, A. EP.07.47
Brusselle, G. OA01.01
Brustugun, O. EP.12.26
Brutti, A. OA17.02
Bryan, D. S. P3.14.04
Bryant, A. P2.10.01
Bryant, D. OA09.03
Bryl, M. P2.15 .06
Bu, Q. P1.11.65, P3.18.69
Bubendorf, L. MA07.01, OA09.03, PL03.16
Bucheit, L. P2.06.76
Budathoki, P. P1.11.50
Budhani, I. A. P1.04.01
Budhathoki, P. P1.07.45, P1.17.10, P1.17.10, P3.13.28
Budolfsen, T. EP.15.03
Bueno, S. P3.14.02
Buglione di Monale e Bastia, M. P2.08 .26
Buglioni, S. EP.07.48
Bugueño, R. EP.17.27
Bujons, E. P2.08 .49
Bulliard, J.-L. P1.04.03, P1.04.15
Bulos, C. OA01.03
Bulotta, A. P1.07.51, P1.11.01, P1.11.24, P3.12.15
Bulpa, P. EP.15.19
Bunn, P. OA09.01, P1.07.37
Buradkar, A. EP.08.32
Buras, M. EP.13.10
Burcoveanu, D.-I. MA02.04
Burelle, S. P1.17.42

Burkard, T. MA01.07
Burke, A. P1.17.08, P1.17.09
Burley, C. OA17.04, P2.15 .18, PT2.16.05
Burn, K. P3.16.16
Burns, B. A. P1.11.70
Burns, T. F. OA08.02
Burotto, M. MA10.07, P1.11.85
Burrage-Burton, M. MA05.04
Burson, H. P2.15 .24, P3.16.16
Burt, B. EP.07.14
Burton, J. P1.17.28
Burwinkel, M. EP.08.32
Bushnell, D. OA13.03
Bussberg, C. P2.15 .05
Bussell, M. E. P1.17.77
Bustillos, A. MA10.06
Busund, L.-T.R. P1.11.62
Buth, J. P3.12.61
But Hadzic, J. EP.13.13
Buti, S. EP.11.05
Buton, C. EP.04.29, EP.17.11, P1.04.39
Butticè, S. P3.16.05
Büyükcelik, R. OA01.01
Buzacott, H. EP.17.09
Buzzacchino, F. P3.18.18
Bye, B. PT2.15.02
Byers, L. OA07.01, P2.02.36, P3.18.80, PT1.01.03, PT2.13.03
Byers, L. A. MA11.06, OA06.04, P2.06.84, P3.13.09, P3.13.11
Byers, S. P1.11.73
Bylicki, O. EP12.64, P2.06.43
Byun, T. E. P1.07.37

C

Cabalheiro, T. EP.13.28
Caballeria Lamelas, E. EP.05.01
Caballero, C. EP.06.77
Caballero Silva, U. EP.07.27
Cabanero, M. EP.06.75
Cabañero Sánchez, A. EP.07.27
Cabanillas-Paredes, L. R. EP.05.08
Cabanillas-Paredes, L. R. P2.05.06
Cabeza-Segura, M. P3.03.45
Cabitza, E. EP.15.11
Cabrera, C. P2.08 .37
Cabrera, M. O. P1.04.35
Cabrera San Millan, E. P3.03.15
Caccese, M. P3.12.15
Cacciotti, C. EP.12.37
Cackowski, M. MA11.05, P3.13.02
Cadou, A. P3.18.68
Cadranel, J. OA05.02, P2.15 .29
Caeser, R. P3.03.52
Cafarotti, S. P3.14.19, P3.18.82
Cagin, K. P2.06.64
Caglar, C. EP.01.19
Caglevic, C. P3.18.73
Caglio, A. P1.11.24
Cahal, S. EP.03.08, P3.03.22
Cahill, C. P3.03.08
Cai, C. P1.07.42, P1.07.56, P2.02.35, P2.06.29, P2.06.60, P2.08 .45, PT1.07.04
Cai, D.-X. EP.12.60, P3.01.04
Cai, D. OA03.01
Cai, G. PT1.03.02
Cai, H. P3.03.25
Cai, J. P3.03.23
Cai, J. EP.17.16, P1.17.37, P1.17.38
Cai, L. P2.08 .34
Cai, L. P3.09.07
Cai, L. P2.06.60
Cai, L. EP.09.05
Cai, M. PT1.09.03
Cai, M. P1.11.45
Cai, Q. EP.01.14
Cai, Q. P2.15 .33
Cai, S. P3.03.18
Cai, X.-T. OA03.04, P2.02.28, P2.06.36
Cai, X. P2.08 .59
Cai, X. P3.16.17
Cai, X. EP.17.16, P1.17.37, P2.10.16
Cain, E. P2.08 .42
Calabrese, F. PT2.14.02
Calabrich, A. EP.13.28
Calabrò, L. P3.12.20
Calabuig-Fariñas, S. EP.06.77
Calais, J. OA13.03
Calareso, G. P1.17.30
Calcagni, M. EP.06.40
Caldart Tregnago, A. EP.06.01
Caldecott, M. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Calderón, A. EP.08.26
Calderoni, M. P3.14.18
Calero-Nieto, F. P2.02.27
Cali Daylan, E. P3.18.19
Califano, R. P2.10.05, P3.12.30, P3.13.04, P3.18.80
Caliman, E. EP.11.20
Calip, G. S. EP.17.35
Call, S. EP.05.08, P1.07.24, P2.05.06, P2.08 .28
Callac, L. P2.06.79
Callegari, E. P3.12.20
Callegari, M. EP.01.05
Callegari, V. EP.11.20
Calleja Holgado, F. J. P2.08 .48
Callejo, A. P3.12.30
Calles, A. PL02.12, PL02.15
Calles Blanco, A. P3.18.61
Callister, M. EP.01.22, MA09.05
Callister, M. E. PL03.19
Calvayrac, O. P3.03.34, P3.18.60
Calvetti, L. P1.07.51, P3.12.15
Calvo, A. EP.13.27, PT1.08.05
Calvo, V. MA06.03, P1.11.37, P3.01.25, PL03.10
Calvo, MD, PhD, V. MA01.03
Camacho, L. P2.06.74
Camerini, A. EP.11.20, MA02.05, P1.11.24, P1.17.54
Cameron, E. EP.07.14
Cameron, R. P3.18.05
Camidge, D. EP.02.07
Camidge, D. R. P3.12.21
Camidge, D. MA02.03, PL02.15, PT2.10.02
Camidge, R. EP.12.23
Camilleri, P. P3.09.02
Camp, P. P2.15 .17
Campanella, A. EP.06.64, P1.07.22
Campbell, K. P2.15 .17
Campeau, M.-P. P2.08 .54
Campione, S. EP.11.03
Campo, G. EP.03.02
Campo-Cañaveral, J. L. MA01.01
Campos, B. P3.18.12, PL03.10
Campos, M. EP.17.16, P1.17.37
Campos, M. P1.17.38
Campos-Gomez, K. EP.12.18
Campos-Gomez, S. EP.12.18, P1.17.73
Campos Partera, M. P2.15 .06
Campos Vives, B. P2.08 .37
Camps, C. MA06.03
Camps, MD, PhD, C. MA01.03
Camus, J.-C. EP.15.06
CAN, G. EP.13.43
Canary, P. EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72
Canary MD MsC, P. P3.01.41

Canavan, M. P1.07.31, P2.08 .07
Cancellieri, A. EP.06.40, P1.07.22
Candeli, N. P2.02.04, PT1.02.04
Cang, S. P2.10.13, P3.12.07, P3.12.31, P3.12.48, P3.12.64
Cani, M. P3.03.17, P3.16.05
Cannary, P. EP.08.16, P2.08 .52
Cannings, J. P2.06.89
Cannon, M. EP.12.07
Cannone, M. EP.06.03
Cano Gil, D. EP.17.12
Canova, S. P1.11.01, P3.14.06
Canslan, K. P3.01.09
Cantale, O. P3.13.04
Cantero, A. OA05.03, P1.11.37
Cantini, L. P1.17.54, P1.17.55
Cantor, E. P2.15 .11
Cao, B.-S. EP.12.06
Cao, B. P3.18.41
Cao, G. OA06.02
Cao, J. PL03.07
Cao, J. P2.08 .50
Cao, L. P3.18.49
Cao, L. EP.12.08
Cao, P. EP.01.02, P1.04.07
Cao, T. P2.10.14
Cao, X. P3.18.42
Cao, X. P3.18.32
Cao, Y. P2.08 .32
Cao, Y. P2.06.74
Cao, Z.-Q. P3.03.14
Capaldo, S. EP13.48
Capdevielle, L. P2.15 .29
Capdevila, L. P2.06.37
Capelletto, E. P3.16.05
Capo, G. EP.13.39
Cappelli, A. EP.13.05
Cappia, S. P2.06.40
Cappuzzo, F. EP.03.02, EP.07.48, MA01.04, MA10.06, P1.07.07, P1.07.43, P1.11.17, P1.11.56, P3.14.17, P3.18.61, P3.18.74, P3.18.80, PT2.11.01
Cappuzzo, F. PL02.12
Caragliano, A. P2.08 .30
Caramaschi, A. P3.14.13
Caramella, C. EP.04.29, P1.04.39
Caramella, C. P3.12.30
Carballo, N. PT1.04.03
Carbone, D. EP.01.31, P2.08 .47
Carbone, D. P. P3.18.28, PL02.18, PT2.12.01
Carbone, D. OA11.02
Carbone, M. P3.14.07
Carbonell-Asins, J. P3.03.45
Carbonelli, C. P2.06.54
Carcedo, D. P1.17.80, PT2.17.05
Carcereny, E. EP.12.36, MA08.01, P1.11.07, P1.11.37, P3.03.44, PL03.10
Carcereny Costa, E. EP.06.78
Cardeña-Gutiérrez, A. EP.08.37, EP.12.63, P2.08 .37
Cardia, J. EP.13.20
Cardillo, G. EP.04.30, P2.05.10
Cardnell, R. P2.06.84
Cardnell, R. J. PT2.13.03
Cardona, A. EP.04.01, EP.15.18
Carlin, L. P3.14.08
Carlin, S. P3.13.05
Carlos, R. C. OA18.04
Carlos Benítez, J. P2.08 .37
Carlotti, D. EP.08.13
Carlson, K. P3.18.05
Carlson, N. P3.18.56
Carmona De Souza, G. OA18.02
Carnevale, A. P3.12.20
Carnio, S. P3.16.05
Caro, R. OA09.02
Caro-Consuegra, R. P3.12.30
Carolan, H. EP.08.17
Carolina da Cruz, A. P1.17.70
Carothers, A. EP.12.07
Carpo, B. EP.14.31
Carrasco, A. EP06.85
Carrasco, R. MA01.01
Carrasco Oliva, S. EP.07.27
Carrion-Estrada, D. P3.03.20
Carro, N. P3.18.18
Carroccio, P. EP.11.01
Carson, C. MA03.02
Carswell, O. EP.04.03, EP.04.08
Carta, A. P1.07.51, P3.12.15
Carta, A. EP.11.20, P1.11.24
Carter, B. MA10.05, P2.02.36, PT1.01.03
Carter-Bawa, L. PT2.16.03
Cartujano-Barrera, F. P3.16.08
Caruana, E. P1.04.54
Carus, J. P1.17.67
Caruso, C. M. P1.17.54, P1.17.55
Carvajal, C. EP.04.01
Carvalho, D. V. P3.01.06
Carvalho, L. PT2.14.02
Carvalho, R. PT1.03.03
Casadei, L. EP.15.11
Casale, M. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Casali, L. EP.06.09, P3.01.06, PT1.04.02
Casanova, A. P3.03.34
Casar, D. EP.13.13, P2.08 .16
Casas, F. EP.13.19
Casas-Mendez, F. P2.15 .06
Cascone, T. MA04.05, MA10.05, OA07.01, OA09.01, P1.11.70, P2.02.36, PT1.01.03
Casiraghi, M. P3.14.19
Castaldi, A. P2.08 .03
Castellana, R. EP.07.48
Castellano Carneiro, I. EP.12.63, P2.08 .37
Castellano-Carneiro, I. EP.08.37
Castellanos, E. P1.07.05, P3.13.10
Castillo, J. P3.03.45
Castillo, O. P3.01.46
Castillo-Barnes, D. EP.12.24
Castro, M. P2.06.18
Castro, M. PT2.17.04
Castro, S. EP.04.24
Castro Sanchez, A. MA10.06
Catania, C. P1.07.51, P1.11.66
Catasús, L. EP.06.48
Catino, A. OA17.01, P1.04.47
Catot, S. OA01.02, P3.12.30
Caturegli, G. P1.07.31, P2.08 .07
Caushi, J. X. P2.06.66
Cavalli, C. OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Cave, J. P3.14.05
Cawthon, R. P3.01.28
Cazes, A. P2.06.15
Ceccon, G. EP.09.06
Cecconi, L. EP.17.21
Cecere, F. L. EP.11.20, OA12.02, P1.11.24
Cecere, F. EP.07.48, P1.07.07, P3.14.17
Cedres, S. P3.12.30, P3.14.02
Celestino, G. F. P1.11.16
Celik, I. OA13.02
Celli, L. P3.03.15
Centeno, C. P3.03.44
Cerapio, J.-P. P3.03.34
Cerbone, L. EP.14.08, EP.14.10, P3.14.06, P3.14.13
Cerciello, F. P3.18.82, PT1.03.04
Cerea, G. P1.07.51, P1.11.24

AUTHOR INDEX AUTHOR INDEX AUTHOR INDEX

Ceresoli, G. L. OA12.02
Ceresoli, G. P3.14.06
Cerezal, L. J. P2.08 .28
Cerezo, S. P1.11.37
Cervantes, A. P2.06.100, P3.03.45
Cespedes, P. EP.04.24
Cetin, Ö. P3.03.54
Çetin Aktaş, E. P3.03.04
Cezare, T. EP.01.05
Chachoua, A. OA15.03, P3.18.87
Chae, Y. P1.17.26, P2.06.13, P2.06.21, P2.08 .01, PT1.09.02
Chaft, J. MA01.04, MA04.02, P1.07.43, P3.18.09
Chaft, J. E. EP.08.51, MA01.06, OA02.02, P1.07.37, P3.18.11, PL02.18
Chaft, J. E. P2.06.66
Chahine, R. P2.15 .19
Chainamnan, W. EP.04.37
Chaiton, M. EP.01.24, EP.01.25
Chaiwong, W. P3.01.30
Chakraborty, A. P2.06.17
Chakravarti, A. P2.08 .23
Chalabi, N. EP.06.79
Chalmers, A. PT2.14.01
Chalongviriyalert, P. EP.04.37
Chan, A. EP.08.17
Chan, A. EP.11.21
Chan, B. MA02.06, OA03.04
Chan, C. OA16.02, P3.13.04
CHAN, J. W. P1.17.60
CHAN, J. C. P1.17.60
Chan, L. W. P2.08 .45
Chan, S. MA08.05
Chandakas, V. P1.17.67
Chandana, S. OA06.04
Chander, P. P3.12.39
Chandra, J. P2.15 .22
Chandrashekaraiah, S. P2.06.17
Chang, A. T. P1.17.60
Chang, A. MA05.03, P1.04.12
Chang, A. P2.15 .15
Chang, A. PT1.03.01
Chang, C. P1.04.20
Chang, C. C. P1.04.19
Chang, G. C. MA08.02
Chang, G.-C. MA09.01, PL02.15
Chang, G. EP13.49
Chang, J.-H. P1.11.61
Chang, j. P3.12.48
Chang, J. OA07.01, PT1.01.03
Chang, J. W. EP.12.27
Chang, K. P1.04.20
Chang, T. EP.01.02
Chang, T.-Y. EP.03.10
Chang, W.-C. PL03.16
Chang, Y.-H. EP.06.55, P2.06.39
Chang, Y.-N. EP.15.02
Chang, Y.-C. EP.07.08
Chang, Y. P1.07.29
Chang, Y. OA18.04
Chang, Y.-C. MA05.02
Chang, Z. P2.08 .04, P2.08 .05
Changkhong, S. P3.03.07
Channick, C. EP.07.14
Chanock, S. OA14.05
Chapman, A. P1.17.20
Charalambous, A. OA18.01, P1.17.75
Charalambous, H. EP.08.18
Chargualaf, M. OA10.01
Chariou, P. OA03.03
Charkaoui, I. P1.17.57
CHARKAOUI, M. P2.10.07
Charoentong, P. MA04.06
Charpidou, A. P1.17.29
Charron, J. EP.06.06
Chaturvedi, P. K. P1.17.32
Chau, M. P1.17.24
Chaudhari, K. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Chaudhuri, A. P2.08 .51
Chaudhuri, A. A. MA03.05
Chauhan, A. EP.13.32
Chauhan, J. P2.06.17, P2.06.18
Chauhan, P. MA03.05
Chaunzwa, T. EP.13.08, OA07.02, P3.01.22
Chaunzwa, T. L. EP.08.51, EP.14.22
Chavarria Murillo, S. EP.08.07
Chavez Iniguez, A. P3.16.08
Chavez-Uceda, V. P3.16.08
Che, G. MA01.05
Chea, Y. EP.15.13
Chee, T. P2.06.51
Cheema, A. EP.11.22
Cheema, P. MA08.07, P1.11.36
Cheese, E. P1.17.67
Chella, A. EP.12.36
Chen, A. P3.03.20
Chen, A. MA04.09
Chen, B. P1.07.50
Chen, B. OA05.01
Chen, B. P2.02.21, P3.09.10
Chen, B. P1.11.83
Chen, C. MA04.03, OA11.04, OA14.01, P2.06.03, P3.18.08
Chen, C. EP.08.01, EP.08.01, EP.11.16, EP.18.05, P2.10.15
Chen, C.-J. P1.07.08
Chen, C. MA04.08, OA05.01, P3.03.25, P3.18.08
Chen, C.-M. EP.07.08
Chen, C.-Y. EP.09.15, P3.12.49
Chen, D. P2.08 .34
Chen, D. P1.07.06
Chen, D. P2.06.101
Chen, D. P2.08 .50
Chen, F. P2.02.29
Chen, G. P3.12.31
Chen, G.-Y. EP.12.21
Chen, H. MA04.01, MA04.08, P2.06.05
Chen, H. P1.17.38
Chen, H. EP.07.45
Chen, H. P1.11.70, P2.02.36, PT1.01.03, PT2.13.03
Chen, H. P2.02.02
Chen, H.-Y. EP.06.55, P2.06.39
Chen, H. PL03.07
Chen, H.-J. P1.11.05, P1.11.23, P2.06.91, P3.12.26, P3.18.39
Chen, H. P1.17.56
Chen, H.-H. EP.13.25
Chen, J. OA18.02
Chen, J. P3.01.37
Chen, J. EP.08.39
Chen, J. P2.08 .44
Chen, J.-W. EP.06.55, P2.06.39
Chen, J. EP.07.05
Chen, J. P1.11.83, P3.12.64
Chen, J. EP.06.67
Chen, J. P1.11.76
Chen, J. EP.12.58
Chen, J. OA06.01
Chen, J.-S. EP.06.20, EP.07.08, EP.07.16, OA07.04, P1.07.08
Chen, J. EP.07.49
Chen, J. MA10.01, P3.12.53, P3.13.25
Chen, J.-H. P3.03.40, P3.12.55
Chen, J. EP.12.57
Chen, J. P1.17.24

Chen, J. EP.08.06, EP.11.04, EP.12.51, EP.13.07, EP.13.26, EP.18.03, P1.07.57, P1.11.28, P1.11.33, P2.02.44, P3.03.35, P3.03.43
Chen, J. P1.11.65
Chen, K. EP.15.05
Chen, K. P1.07.01
Chen, K. EP.13.23
Chen, K.-N. OA02.03
Chen, K.-N. EP.08.30
Chen, K. P3.03.29
Chen, K. P2.08 .43
Chen, K. P3.18.28
Chen, K. MA09.07
Chen, K. MA06.04, MA09.09, OA16.04, P1.07.39, P2.02.02
Chen, K.-Y. EP.03.17, EP.09.15, EP.12.21
CHEN, L. P2.02.23
chen, L. MA10.01, P3.12.53
Chen, L.-W. EP.07.08
Chen, L. EP.06.58
Chen, L. P3.12.64
Chen, L. MA03.07, OA10.02, OA10.03, P3.13.25
Chen, L. P2.06.91
Chen, L. EP.14.22
Chen, L. EP.14.26
Chen, L. P3.18.06
Chen, M. EP.17.35, PL03.07
Chen, M. EP.13.30, P3.13.19
chen, m. P2.08 .27
Chen, N. P2.02.29
Chen, P.-C. P1.07.08
Chen, P.-H. EP.07.16, OA07.04
Chen, P. P1.11.12
Chen, P. MA02.07, OA06.01, OA06.01
Chen, P. P3.18.42
Chen, P. P3.18.32
Chen, P. P. PT1.06.02
Chen, Q. MA04.08, P2.08 .43
Chen, q. EP.18.10
Chen, R.-R. PT1.09.03
Chen, S. P2.08 .41, P3.03.23
Chen, S. P2.02.21
Chen, S. P1.04.16
Chen, S. MA07.01
Chen, S. EP.15.12
Chen, S. MA05.07
Chen, S. OA04.02
Chen, S. P1.04.48
Chen, T. P3.18.76
Chen, T. P1.04.42
Chen, T. P2.08 .32
Chen, T. P3.01.07, PT1.01.01
Chen, T.-H. MA05.02
Chen, V. MA01.07
Chen, W. EP.06.36, EP.08.35, P2.06.06
Chen, W. EP.04.11
Chen, W. P1.17.25
Chen, W. P3.12.12
Chen, W. P2.10.14
Chen, X. P1.07.50
Chen, X. MA03.09, P3.18.83
Chen, X. P2.10.14
Chen, X. P2.05.13
Chen, X. P2.10.13
Chen, X. P2.06.80
Chen, X. EP.01.15, EP.07.55
Chen, X. EP.06.14, P2.02.38
Chen, X. EP.11.15, P2.08 .46
Chen, X. P3.18.38
Chen, X. P2.06.80
Chen, X. P3.13.34
Chen, X. MA08.06
Chen, X. EP.07.30, P1.07.09
Chen, Y. EP.12.19
Chen, Y. P. P2.10.15
Chen, Y. P2.08 .32
Chen, Y. P3.14.21
Chen, Y. P1.11.25
Chen, Y. P3.13.15
Chen, Y. EP.15.05, P1.07.01
Chen, Y. OA01.04
Chen, Y. EP.01.02, MA09.01
Chen, Y. P2.02.19, P2.02.42, P3.03.50
Chen, Y. EP.18.08, P2.06.57, PT2.10.03
Chen, Y. P2.15 .21
Chen, Y.-T. EP.06.20
Chen, Y. MA11.03, P3.12.48, P3.12.55
Chen, Y. OA08.02, PL03.06
Chen, Y. P1.11.67
Chen, Y.-Y. MA05.02
Chen, Y. P1.07.38
Chen, Y.-M. P2.10.04, P3.12.49
Chen, Y. P3.18.08
Chen, Y. P3.18.79
Chen, Y.-F. PL02.09
Chen, Y. P2.10.12
Chen, Y. P1.11.20
Chen, Z.-X. P1.11.23
Chen, Z. P3.12.07, P3.12.31
Chen, Z. OA05.01
Chen, Z. H. PT1.06.02
Chen, Z.-G. EP.18.07
Chen, Z.-H. EP.12.60, P1.11.61, P3.01.04, P3.01.37
Chen, Z.-Y. P3.13.33
Chen, Z. P3.18.59
Chen, Z. MA05.07
Chen, Z. EP.07.02, P1.07.33
Chen, Z. OA01.04, P2.06.35
Chenard, M.-P. EP.06.39
Cheng, B. P1.11.12, P3.01.03, P3.01.05, P3.01.12
Cheng, C. P2.06.72, PT1.07.03
Cheng, G. EP.07.29
Cheng, H. EP.13.41, P3.18.19, P3.18.22
Cheng, J. EP.04.25
Cheng, K. P2.02.02
Cheng, L. EP.07.44, P2.06.86, P3.03.16
Cheng, L. P1.11.31
Cheng, M. L. P1.11.57
Cheng, Q. P1.11.41
Cheng, S. OA16.04
Cheng, S. EP.18.08
Cheng, T. EP.18.07
Cheng, W. OA06.02
CHENG, X. P3.12.74
Cheng, X. EP.17.16, P1.17.37, P2.08 .04, P2.08 .05, P3.18.08
Cheng, X. EP.02.07, PT1.03.01
Cheng, Y. MA04.08, MA08.06, OA06.01, OA06.03, P1.11.35, P1.11.46, P1.11.83, P2.10.12, P3.12.38, P3.12.48, P3.12.55, P3.12.64, P3.12.65, P3.18.74, P3.18.80, PT2.10.03
cheng, y. P2.15 .28
Cheng, Y. EP.07.51
Cheng, Z. EP.12.09
Chenli, Z. P2.02.12
Chen-Yoshikawa, T. EP.06.70, EP.14.05
Cheranda, P3.03.04
Cheranda, N. P2.06.10
Cherepanov, D. EP.12.35
Chernykh, M. V. EP.08.25
Cheung, B. P2.06.90
Cheung, K. P2.10.14
Cheung, W. P3.01.24
Chevalier, A. P2.06.44
Chewaskulyong, B. P3.01.30
Cheyne, L. P2.06.85

Chi, Y. EP.07.45
Chia, C. M. OA15.02
Chia , P. EP.15.13
Chian, K. P2.08 .47
Chiang, A. EP.13.03
Chiang, A. C. MA06.01, OA06.04
Chiang, C.-L. P2.10.04
Chiang, C. P2.06.02
Chiang, C.-J. P1.07.08
Chiang, I. P2.06.10
Chiang, N.-J. P3.12.27
Chiang, X.-H. P1.07.08
Chiappetta, M. EP.06.40, P1.07.22, P2.05.10, P3.14.19
Chiappori, A. MA11.01
Chiari, R. P1.07.51, P3.12.15, P3.12.21
Chiba, M. EP.05.07, EP.06.46, P3.09.05
Chiba, R. P1.07.21
Chidi, A. P2.08 .25
Chidi, A. P. P1.04.17, P3.01.22
Chiec, L. EP.17.03, P1.04.04, P2.15 .19
Chiffi, K. EP.04.16, EP.04.34, EP.07.09, EP.08.52, P2.08 .58
Chihara, Y. P1.11.40
Chih-Hsin Yang, J. P3.12.40
Chihuri, T. P1.17.71, P3.16.15
Chijioke, M. P1.17.76
Chijioke, O. OA09.03
Chikamori, K. P2.06.59
Chikvaidze, L. EP.04.23
Childress, M. EP.06.69, EP.06.76
Chilingirova, N. P1.11.82
Chillico, I. C. P1.11.54
Chin, C. D. OA08.01, P3.18.71
Chin, V. P1.17.62
Chitikela, S. D. MA09.08
Chiu, C.-H. MA08.02, MA09.01
Chiu, C. Y. P2.02.45
Chiu, G. OA05.04
Chiu, M.-L. P2.06.90
Chmielewska, I. EP.06.17, EP.13.17, MA10.04, P1.11.63
Cho, B. P3.14.11
Cho, B. J. OA12.04
Cho, B. C. OA13.02, P3.18.28
Cho, B. MA02.03, MA07.07, P2.06.102, P2.06.48, P2.10.10, P3.12.37, P3.12.46, P3.18.39, P3.18.57, PL02.15, PT1.03.06, PT2.12.02, PT2.12.03, PT2.12.04
Cho, C. EP.06.58
Cho, D. P1.07.29, P3.14.14
Cho, H. P2.15 .16
Cho, J.-H. P2.02.32, P3.13.08
Cho, J. B. EP.14.15
Cho, J. EP.07.46, EP.08.29, P1.07.15, P2.08 .31
Cho, S. OA13.01
Cho, S. P1.07.25, P1.07.52
Cho, Y. EP.12.12
Choe, J. P1.04.26, P1.07.32
Choi, A.-R. OA04.03
Choi, C. P1.04.26
Choi, C.-M. EP.01.18, EP.12.12, EP.13.21, MA02.02, MA05.08, PT1.09.05
Choi, E. P3.13.21
Choi, E. P3.01.01, P3.01.07, PT1.01.01
Choi, I. EP.08.15
Choi, M. MA09.06
Choi, M. EP.13.21, P3.01.38
Choi, N. P2.10.10
Choi, S. EP.14.11, P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Choi, S.-K. PT2.12.02
Choi, S. EP.06.21, P3.12.16
Choi, S. P3.01.36
Choi, S. EP.09.02
Choi, Y. EP.07.46, EP.08.29, P1.07.15, P2.08 .31
Choi, Y. C. EP.17.35
Choksi, MD, R. EP.12.32, EP06.86, EP12.65, P2.06.11, P3.12.24
Cholakova, M. P1.11.82
Choman, E. N. P1.04.36
Chong, I.-W. P3.12.27
Cho-Phan, C. EP.12.23, EP.13.44, P2.06.45
Choraria, A. P1.07.26
Chorev, L. EP.06.50
Chou, T. P2.06.02
Chou, T.-Y. OA09.01, PL03.16
Chouaid, C. PT1.04.03
Chouaid, C. P3.12.29, P3.18.74
Choudhary, S. EP.17.06
Choudhary, S. P1.04.20
Choudhury, N. EP.13.47, OA17.03
Choudhury, R. EP.17.06
Chougale, S. EP.01.07, P1.11.81
Chow, J. P2.02.15
Chowdhary, A. A. PL03.06
Chowdhury, D. EP.13.38
Chowdhury, F. EP.11.22
Chowdhury, M. MA10.07
Chowdhury, N. PT1.08.03
Chowell, D. P3.03.13
Choy, R. M. P2.10.17
Christensen, J. P2.08 .13
Christenson, E. P2.06.100
Christian, F. EP.15.06
Christiani, D. C. P1.04.29
Christofis, M. EP.09.17, P1.11.03
Christoph, D. EP.12.36
Christopherson, D. MA05.01
Christopoulos, P. P3.12.10, P3.12.14, P3.12.61
Christopoulou, A. P2.15 .26
Chrzanowska, K. MA11.05, P3.13.02
Chu, C.-Y. EP.12.21
Chu, H. OA12.04
Chu, L. P2.10.13
Chu, Q. EP.07.44, P1.11.65, P1.17.36, P3.12.59, P3.13.34, P3.18.62, PL02.09, PT2.17.04
Chu, Q. MA03.03, OA12.02
Chu, T. P3.18.63, PT2.11.03
Chu, W. P1.04.33
Chu, X. MA11.08
Chua, K. C. P1.11.18
Chua, K. C. P1.11.14
Chua, S. MA10.09
Chua, W. EP.04.20
Chugh, K. P1.11.21
Chukkalore, D. P2.06.10
Chul, K. P3.13.28
Chul Cho, B. OA06.04
Chun, E. P3.01.38
Chun Chen, C. OA09.03
Chung, C. MA10.05
Chung, C.-W. P2.10.10
Chung, J.-H. EP.07.26
Chung, J.-H. OA09.01, OA13.04, P1.07.25, P1.07.52
Chung, L.-Y. P2.08 .01, PT1.09.02
Chung, Y. P2.08 .13
Chunglo, Y.-T. MA05.02
Churg, A. PT1.06.03
Chwatko, J. EP.01.03
Ciampelli, N. EP.04.30
Ciancetta, A. P3.12.20
Ciappina, G. EP.11.01
Ciardiello, F. EP.06.79
Ciarrocchi, S. P3.12.20
Cicchetti, G. P1.07.22
Cicin, I. OA08.02, PT2.10.02

Cicin, I. P3.12.46
Cicognini, D. P2.08 .53
Ciepiałowska, P. MA11.05, P3.13.02
Cil, T. P3.18.74
Çil, T. OA13.02
Cilleruelo, Á. MA01.01
Cimorelli, A. P3.14.13
Cipi, A. P3.16.05
Cipriani, L. PT2.11.01
Cipriano, F. E. P1.17.74
Ciric, E. EP.13.13, P2.08 .16
Cisternas, L. EP.14.27, EP.17.27
Citarella, F. EP.11.20, P1.11.17, P1.11.62
Cittolin Santos, G. F. P1.17.50
Ciuleanu, T.-E. MA04.05, OA02.03, P3.18.37
Ciupek, A. EP.16.03, EP.17.08, P3.16.23, PT2.16.01
Civello, S. P3.16.14
Clark, C. D. EP.16.08
Clark, J. EP.17.02
Clark, M. L. P3.01.28
Clark, P. P2.06.12, PT2.13.04
Clarke, J. P1.11.75, P3.01.53
Clarke, M. A. P1.11.45
Clarke, R. EP.08.34, P2.06.82
Clarkson, N. S. P1.17.09
Clarkson, N. P1.17.08
Clavé, S. EP.06.48, P2.06.74
Clavell, C. EP.13.19
Clay, T. P2.06.89
Clayton, K. EP.16.02, P3.16.01
Clifford, S. P1.07.37
Climans, S. A. EP.12.37
Climent Marti, J. EP.06.78
Cloarec, N. OA05.02
Cluxton, C. P2.06.82
Cobbold, M. OA03.03
Cobo, M. MA06.03, P1.11.07, P1.11.37
Cobo , MD, M. MA01.03
Cobo Dols, M. MA04.09, OA08.03
Cobo Dols, M. MA08.01
Cobo-Dols, M. MA10.07, P1.11.85
Cobuccio, A. P1.04.15
Coburn, N. EP.09.04, EP.17.28
Codlin, A. P1.17.31
Codó, P. P3.18.64
Codony-Servat, J. EP.02.10, P2.02.34, P2.02.39, P2.02.46
Cody, B. OA09.03
Coelho, L. EP.01.05
Cognolato, G. EP.06.80
Cogo Destefani, V. P1.17.45
Cohen, E. P1.11.73
Cohen, E. P2.06.66
Cohen, M. P2.15 .22
Cohen, R. EP.14.17
Colantonio, I. P2.08 .26
Cole, R. P1.11.38
Colienne, M. P3.12.61
Colin, P. P3.18.61
Collado, R. P1.17.80, PT2.17.05
Collado-Rodríguez, L. EP.03.13
Collaud, S. P1.07.28
Collazo Lorduy, A. P3.01.25
Collignon, E. P2.06.61
Collotte, B. EP.17.39
Colombo, F. EP.09.06
Colonese, F. P1.11.01
Colón-Matos, F. OA14.05
Comacchio, G. EP.14.18
Compañ, A. P3.03.45
Compston, A. OA04.04
Cona, M. S. P1.11.66
Concannon, K. P1.11.56, PT2.11.01
Conde, E. EP.06.43, OA09.03
Conejo-Garcia, J. P3.03.20
Cong, Y. MA09.07
Conibear, J. P3.09.02
Conley, A. P2.06.74
Connolly, C. OA09.01, P1.17.24
Connor, T. OA03.03
Conrads, K. EP.03.01
Conrads, T. J. EP.03.01
Conron, M. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Conroy, M. P2.06.66
Consito, L. P3.16.05
Conte, M. P2.06.92
Conte, S. EP.06.42, EP.13.22
Conti, A. EP.04.38
Conway, M. P2.10.17
Cooke, S. P3.16.14
Cooper, A. MA01.04, OA06.04, P1.07.43, P1.11.55, PT2.13.04
Cooper, A. J. EP.13.08
Cooper, M. P3.12.39
Cooper, W. OA13.04, PT1.07.01
Cooper, W. A. MA07.01, OA09.01, P2.06.63, PL03.16
Coote, J. OA16.02
Copeland, H. EP.01.22
Corassa, M. EP.13.28
Cordente-Martínez, C. PT2.15.04
Cordero, D. P2.06.37
Coreas, N. P1.07.45, P1.17.10
Cornelissen, R. OA10.01
Cornelius, L. A. PL02.18
Coroiu, A. EP.01.24, EP.01.25
Coronado Erdmann, C. MA04.05
Corpa, E. MA01.01
Corr, P. G. P1.17.24
Corradini, S. P2.08 .14
Corradini, S. P3.16.19
Corrales, L. P1.17.77
Corral Jaime, J. MA08.01
Corrao, G. MA06.07, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Corre, R. EP12.64, P2.15 .29
Correa, B. EP.01.05
Correia, B. P1.17.52
Corso, F. MA06.07, P1.04.51, P1.17.30, P1.17.44, P2.15 .34
Cortellini, A. EP.06.52, P1.11.17, P1.11.24, P1.11.62, P1.17.54, P1.17.55, PT2.11.01
Cortinovis, D. P1.11.15, P3.12.15, P3.18.74
Cortinovis, D. L. MA02.05, P1.11.24, P1.17.54, P2.08 .53, P3.14.06
Cortinovis, D. EP.11.20
Cortot, A. P3.18.60, P3.18.66
Cortot, A. P3.12.40
Corvo-Félix, L. P2.15 .03
Cosenza, A. MA02.05, P1.07.04
Cosi, D. M. P3.12.20
Cossio, D. P1.17.12
Costa, B. EP.01.05
Costa, J. P3.12.15
Costa, M. P3.03.44
Costa, P. EP.17.04, P1.17.15
Costa, S. EP.13.20
Costa da Silva, B. P1.17.45
Costanzo, R. P3.18.18
Cotogni, P. P3.16.05
Cotton, A. EP.13.40
Cottrell, T. OA12.03, P2.06.99
Cottrell, T. R. P2.06.66
Coulter, J. P2.15 .05
Couraud, S. OA05.02
Court, S. P2.08 .19

Coves, J. P3.18.12
Cox, S. P2.10.05
Coyne, Z. MA03.01, P1.04.29
Cozen, W. P2.06.52
Craddock Lee, S. J. EP.04.06
Craig, M. P3.09.08
Crane, T. P3.01.52
Craver, A. EP.01.30, MA06.02
Crawford, A. P1.07.16, P1.17.01
Crawford, J. P1.11.73
Crawford, J. P1.11.75, P2.06.67, P2.08 .13
Crawford, S. EP.17.35
Crawford Williams, F. P1.17.20
Creelan, B. MA11.01
Creelan, B. P3.18.87
Crengle, S. EP.04.07, EP.04.10, PT2.17.04
Crestani, B. P2.06.15
Creswell, K. P1.11.73
Creusot, Q. EP.06.39
Crichton, L. EP.15.12
Cristofani, L. EP.06.52
Croci, S. P1.11.54
Crombag, M.-R.B. P3.18.54
Cronemberger, E. MA04.04
Crosbie, P. EP.01.22
Crosbie, P. A. P1.04.54, PL03.19
Crosbie, P. A. MA09.05
Crotta, R. P3.01.40
Crowley, S. MA01.01
Crowley Carrasco, S. P1.07.24
Cruse, T. EP.12.10
Cruz, P. OA01.02
Cruzalegui, F. P2.06.43
Cruz- Bermúdez , PhD, A. MA01.03
Cruz-Correa, M. MA07.07
Cruz-Rodríguez, M. EP.03.13
Csoszi, T. P1.11.82, P3.18.28
Cubukcu, E. MA11.04, P2.10.02
Cucurtull Salamero, M. C. EP02.12
Cucurull, M. P3.03.44, P3.03.49
Cucurull Salamero, M. EP.06.78
Cuellar, A. P2.06.37
Cuéllar, A. PT1.08.04
Cuenca, M. P2.02.04
Cuffe, S. EP.06.61, P2.06.82
cui, h. P2.15 .28
Cui, J. P1.11.43, P2.02.29, P2.06.80, P3.12.07
Cui, P. EP.17.16, EP.17.18, P1.17.37, P1.17.38, P1.17.40, P1.17.41
Cui, Q. P2.08 .35
Cui, Q. P2.06.53, P2.06.83
Cui, W. P3.18.86
Cui, X. EP.04.17
Cui, Y. MA11.10
Cui, Y. P2.08 .13
Cui, Y. P3.18.33
Cui, Z. MA02.07
Culligan, M. EP.15.08, OA04.01
Culver, K. P2.15 .05
Culver, K. W. EP.12.35
Cummings, A. EP.07.14, MA04.02, P2.02.16, P2.08 .22
Cummins, M. M. OA03.04, P2.06.61
Cundom, J. P3.12.62, P3.12.65
Cundom, J. P3.12.46
Cunha, G. L. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52, P3.01.41
Cunniffe, C. P1.17.07
Cupertino, A. P3.16.08
Cuppens, K. P1.07.41
Curado, M. P. P1.04.29
Curioni-Fontecedro, A. P3.18.65, P3.18.82
Curreri, K. P3.14.20
Currow, D. P2.15 .13
Curry, L. P2.15 .17
Curtin, J. C. PT1.03.06
Curtin, J. C. MA07.07
Curto, D. EP.06.43, OA09.03
Cuttano, R. P1.04.45, P2.06.54

D

D, Y. P2.08 .17
Daaboul, N. PT2.10.02
D'Abbiero, N. EP.09.06
D'Abundo, L. P3.12.20
Dacic, S. EP.06.58, EP.08.46, MA07.01, OA02.02, OA09.01, PL03.16, PT1.07.01
DAG, S. EP.13.43
Daga, H. P1.11.11, P3.18.04
Da Gama Duarte, J. EP.15.04, P1.11.49
D'Agnelli, S. MA02.05, P1.07.04
D'Agnelli, S. EP.11.05
Dagogo-Jack, I. EP.06.53
Dahbour, D. P1.17.39
Dai, C. EP.07.30
Dai, E. P3.03.11
Dai, I. OA13.02
Dai, W. P2.10.14
Dai, Z. P1.17.69
D'Aiello, A. P3.18.19, P3.18.22
Dakhil, S. P3.13.31
Dako, F. EP.01.04
Dakum, P. EP.17.22
Dale, R. EP.04.38
Dalle Fratte, C. MA01.07, OA13.02
Dal Maso, A. EP.13.15
D'Alonzo, G. OA17.01
Dalrymple, P. EP.16.01
Daly, R. MA01.06, P3.18.11, PT2.13.04
Dama, E. P1.04.45, P2.06.54
Damayanti, T. EP.04.22
D'Ambrosio, L. EP.03.02
D'Ambrósio, P. P1.17.05
D'Ambrosio, P. D. P1.17.74
D'ambrosio, P. EP.08.45
Damhuis, R. A. P3.13.16
D'Amiano, N. P2.06.66
D'Amico, T. P2.06.67
Damotte, D. P3.18.60
D'amours, M. F. EP.08.17
Dan, A. P3.13.17
Dancewicz, M. P2.15 .06
Dancey, J. P2.06.99
Dandekar, T. P1.04.45
Dane, F. P2.10.02
Danes, C. G. EP.12.35
Danforth, J. M. P3.01.24
Danhorn, T. P3.13.30
Daniele, G. P3.12.41
Daniels, J. PT2.11.02
Daniels, J. M. P2.08 .11
Daniels, M. MA11.04
Daniels, M. EP.16.02, P3.16.01
Dao, T. P1.17.31
Dao, V. P3.12.49
D'Arcangelo, M. MA08.01
D'Arcangelo, M. MA07.07
Darlison, L. P2.15 .14
Darnpornprasert, P. EP.04.37
Das, N. P2.08 .19
DAS, P. P1.07.26
Das, S. MA08.03, MA08.05
da Silva, F. G. P1.17.11
Da Silva, J. P1.11.18
da Silva Paiva, L. P1.17.82
Dauriat, G. EP.04.29

Dauriat, G. P1.04.39
Dave, R. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Dave, MHA, P. EP.12.32, EP06.86, P2.06.20, P3.12.24
D'Aveni, A. P3.12.15
Davey, Z. P2.15 .14
David, C. P3.03.28
David, E. P1.17.16
Davidson, M. EP.17.12
Davidson, P. P2.15 .13
Davies, M. P. MA05.06, P1.04.06, P1.04.11, P3.01.20
Davis, A. P2.06.89
Davis, A. P1.17.24
Davis, C. P2.10.05
Davis, C. EP.13.29, MA11.01
Davis, K. L. EP.08.22, P1.07.35
Dawar, R. EP.13.32
Dawe, D. EP.13.38, P1.17.42
Dawe, D. E. OA12.02
Dawkins, P. P1.17.12
Dawood, T. EP.12.61
Dayal, S. EP.06.51
Dayton, T. P2.02.04, PT1.02.04
De, B. MA10.05
Deac, O. P2.06.82
de Alcantara Sousa, L. P1.17.82
de Almeida, C. EP.13.28
De Almeida, C. E. EP.08.20, EP.09.03, EP.09.07, P1.17.72
Dean, M. L. P3.01.24
de Andrade, H. EP.13.28
De Angelis, A. EP.14.08
De Angelis, A. M. P3.14.13
Deasy, J. P2.08 .24
de Azevedo, C. EP.13.28
Debakker, S. P1.17.29
Debieuvre, D. P3.12.29
De Bock, G. H. OA01.01
De Braud, F. MA02.02
De Braud, F. M. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P2.15 .34
de Braud, F. P2.06.65
DeBraud, F. P1.17.44
de Bruijn, P. EP.12.49, EP.12.52, P3.18.66
De Cabo Lopez, L. EP.06.71
DeCamp, M. PT1.08.03
Decamps, C. P3.03.34
De Carvalho, D. V. P1.17.11
de Castro, J. MA06.03, P1.17.80, P3.18.12, PL03.10, PT2.17.05
De Castro , MD, PhD, J. MA01.03
de Castro Carpeño, J. MA08.01
de Castro Jr, G. OA05.04, PT2.12.04
de Cerqueira Mathias, C. P1.11.46
De Chellis, C. PT2.14.02
Decina, A. EP.06.64
Deckers, H. P3.03.46
Declich, M. P2.06.65
Dedhar, S. P2.02.15
Dee, E. C. OA18.02
De Florio, A. P1.17.30
De Gennaro, G. P1.04.47
Dégi, L. EP.16.05
De Giglio, A. P1.11.42, P2.06.92, PT2.11.01
de Gouveia, F. M. P1.17.11
de Gruijl, T. PT2.11.02
de Gruijl, T. D. P3.18.16
De Guia, C. P1.17.08, P1.17.09
Deis, N. P2.15 .08
De Jong, P. OA01.01
de Jong, W. K. P3.18.54
Dekeyser, B. P3.18.66
de Koning, H. EP.04.02, P1.04.09, P1.04.25
De Koning, H. J. P1.04.02, P1.04.06, P1.04.11
Delafontaine, B. P3.18.66
Delahaye, C. P3.03.34
Delalande, F. OA09.03
de Langen, A. J. P3.18.65
de Langen, A. MA02.03, P3.12.38, PL02.15
Delasos, L. P1.11.77
de la Torre, M. MA01.01
del Barco, E. P1.11.37, P3.01.25
del Barco Morillo, E. P1.11.07, P2.15 .03
Del Barco-Morillo, E. P2.02.41
Del Conte, A. MA02.05
Delcuratolo, M. D. P1.11.24
Delektorskaya, V. P3.13.29
De Leo, A. OA17.01
De Lepeleire, J. P3.18.03
Delfanti, S. EP.14.08, EP.14.10, OA12.02, P3.14.06, P3.14.13
Delfour, O. P2.06.43
Delgado, D. M. P2.10.17
Delgado, L. EP.13.19
Delgado, M. MA01.01
Delgado-Cano, D. OA01.02
del Giglio, A. P1.17.82
Del Giudice, T. P3.18.18
de Lima, V. C. EP.13.28
Della Corte, C. M. P1.07.51, P1.11.66, P3.14.06
Della Corte, C. EP13.48, P3.18.18
Dellaire, G. EP.01.21, P3.01.27, P3.01.31
Dell'Anna, C. EP.09.06
Delmonte, A. P1.07.51, P3.12.15
De Los Reyes, C. P3.16.08
Del Valle, D. M. P2.08 .23
de Marchi, P. P1.11.35
de Marinis, F. MA03.03, PT2.12.04
De Matteis, S. P2.06.92
Demedts, I. MA04.04
De Mello, B. P3.03.32
De Meo, M. EP.06.74
De Miguel, M. P3.18.68
de Miguel Perez, D. P3.13.13
Demir, T. P2.08 .01, PT1.09.02
DEMIRAL, A. N. EP.13.43
Demircan, T. EP.03.11
Demirkazik, F. EP.04.43
Demirkazık, A. EP.06.18
de Moraes, F. Y. OA18.02
Denault, M.-H. EP.08.17
Deng, C. P3.18.42
Deng, C. P3.18.32
Deng, C. P2.05.12, P3.13.20
Deng, H. MA03.08, P1.11.22, P2.02.12
Deng, H. EP.15.05
Deng, J. EP.07.14, P2.08 .22
Deng, P. EP.12.08, P3.12.64
Deng, W. P1.17.67
Deng, Y. EP.05.03
Deng, Y. EP.12.60, P1.11.61, P3.01.04, P3.01.37, PT1.06.02
Deng, Y. P2.02.38
De nicola, F. EP.03.02
Deniz, C. MA01.01
Deniz, G. P3.03.04
Denninger, V. P3.18.64
Dennison, J. PT1.04.03
de Oliveira Muniz Koch, L. MA04.05
Deora, N. K. EP.14.04
De Perrot, M. OA12.04, P3.14.11
De Petris, L. EP.12.26, P3.13.17
De Pinto, D. OA17.01
De Ponti, M. P2.06.65, P2.15 .34
Deppen, S. P2.06.43

Deraska, P. P1.11.80
De Rosa, C. EP13.48
DeRozas-Gutiérrez, J. EP.08.37
Desai, A. P2.06.27
Desai, H. D. P3.01.15, P3.01.16, P3.01.17
Desai, H. EP.17.37, P3.01.14
Desai, M. PT1.01.01
Desai, P. EP.13.24, MA07.02
Desai, P. A. P2.08 .56
de Santis, W. EP.06.58
Desar, I. P3.18.66
Descamps, T. P3.12.41
Deshayes, S. P1.17.21
Deshmukh, S. MA07.06
Deshmukh, S. P2.06.27
Desilets, A. P2.08 .54
Desitter, I. EP.06.64
Desmeules, P. EP.06.06, MA07.04, OA09.03
de Sousa, F. M. EP.07.25
DeStanchina, E. P3.03.32
Destro, C. P3.16.05
De Toma, A. P1.11.01
Detterbeck, F. OA11.02
Deutsch, J. S. OA12.03
Dev, D. MA07.05
Devaraj, A. P1.04.06, P1.04.11
Devarakonda, S. EP.13.40, MA08.05
Devde, P. EP.06.34, P3.12.05
Devgan, S. EP.06.27
Devienne, E. P3.03.34
Devkota, A. EP.11.22
De Vries, R. P1.07.41
DeVuono, I. EP.01.24
De Waele, P. EP.12.52
Dewan, A. EP.17.06
Dey, A. P2.06.18
D'Haese, P.-F. EP.04.42
Dhakal, A. P1.11.77
Dhaliwal, I. P2.06.70
Dhande, S. EP.12.01
Dhanju, S. P3.01.36
Dharmasena, V. P2.06.51
Dhingra, R. EP.02.08
Dhir, R. OA09.03
d'Hooghe, J. N. P3.01.10
Diacono, D. P1.04.47
Dialla, O. EP.12.36
Dianzani, I. P3.14.13
Diao, L. P3.13.09, P3.13.11
Diao, Y.-Z. EP.18.09
Diao, Y. P3.18.46, P3.18.48
Dias, F. EP.15.01, EP.15.09
Dias, F. C. P1.11.16
Dias, T. R. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52, P3.01.41
Diaz, A. P1.04.08
Díaz, A. P3.01.25
Diaz, C. A. P2.02.06, P3.03.49
Diaz, C. P3.03.44
Díaz, T. P2.06.32, P3.03.10
Diaz, Y. P1.17.71
Díaz Galindo, L. EP.08.47
Díaz-Gay, M. OA14.05
Diaz-Jimenez, D. P3.14.15
Dib, E. P3.12.42
Di Cesare, F. EP.04.30
Di Cillo, N. P1.04.45
Dick, A. P3.18.02
Dick, K. P1.17.28
Dicker, A. P. P2.06.93
Dickhoff, C. P3.13.16, P3.18.16
Dickinson, P. P3.09.02
Didier, A. EP.17.39
Didjurgeit, F. L. P3.01.06
Didjurgeit, F. M. EP.06.09
Diehn, M. MA03.01
Di Emidio, K. EP.15.11
Dienstmann, R. P3.14.02
Diergaarde, B. MA05.06
Di Federico, A. EP.08.03, MA01.04, P1.07.43, P1.11.42, P1.11.56, P1.17.54, P2.06.92, PT2.11.01
Di Fonzo, R. P2.05.10
Di Gilio, A. P1.04.47
Di Guglielmo, M. L. P3.12.20
Di Guida, G. P3.18.18
DIKSHA, D. EP.02.08
Di Liberti, G. P1.04.51, P1.11.66, P1.17.30, P2.15 .34
Di Liello, R. P3.14.06, P3.18.18
Dillon, R. P2.06.82
Dim, N. R. P1.17.76
Di Maio, M. P1.11.17
Di Mauro, R. P1.04.51, P1.11.66, P1.17.30, P1.17.44
Di Mauro, R. M. P2.15 .34
Dimeo, E. P3.13.13
Dimkpa, U. OA13.02
Di Modugno, F. EP.03.02
Dimou, A. P1.17.28, P1.17.51, P3.13.32
Din, A. P3.18.06
Ding, B. MA04.02
Ding, B.-S. EP.03.05, P2.02.09
Ding, H. P1.17.69, P2.10.16
Ding, J. P2.08 .09
Ding, K. P2.06.99
Ding, L. EP.14.01
Ding, P. OA03.04, P2.06.89
Ding, P. MA03.06
Ding, S. EP.17.32
Ding, V. Y. P3.01.07, PT1.01.01
Ding, Y. P3.03.25
Ding, Z. P3.03.06
Dingemans, A.-M. MA02.08
Dingemans, A.-M.C. EP.12.15, EP.12.49, P3.18.54
Dingemans, A.-M. EP.13.15
Di Noia, V. EP.07.48, MA08.01
Dinulescu, D. OA03.03
Di Pietropaolo, M. P3.14.06
Dirisu, N.-B. EP.17.22
Diriye, S. EP.01.31
Disselhorst, M. PT2.11.02
Dittberner, F. A. PL03.13
Divers, L. PT2.14.01
Divers, MD, S. EP.12.32, EP12.65, P2.06.11, P2.06.20, P3.12.24
Diwan, H. EP.06.16
Di-Xin Zhou, D. P2.06.61
Dixit, N. P1.17.17
Diz, P. OA05.03
Dizbay Sak, S. P3.18.01
Djordjevic, F. EP.11.09
D'Journo, X.-B. EP.04.29, EP.17.11, P1.04.39
Djunadi, T. P1.17.26
Do, A. EP.06.53, MA02.01
Do, J. P3.01.36
Do, K. P1.07.16
Dobbs, J. PT2.16.05
Dobbs, J. E. P2.15 .18
Dobnikar, N. EP.13.13, P2.08 .16
Dodd, C. J. P2.15 .14
Dodd, R. P3.16.10
Dodhia, A. P3.01.15
Dodi, A. EP.11.05, P1.07.51, P1.11.56, PT2.11.01
Dodlek, N. P1.17.75
Doebele, R. P3.12.71

Doemer, A. J. P2.08 .23
Doerr, F. EP.04.27, EP.07.22, P2.05.17
Doherty, D. P1.07.18
Doherty, G. P3.18.38
Dohr, M. EP.16.02, P3.16.01
Doig, J. P3.14.08, P3.14.10
D'Olimpio, J. T. OA13.02
Dollar, K. EP.04.20
Dols, M. C. OA10.01
Doman, T. EP.11.13, P1.11.19
Döme, B. EP.02.02
Dome, B. MA11.06
Döme, B. P2.02.18
Döme, B. P3.13.03
Domènech, M. P3.03.44
Doménech, M. P3.14.09
Domènech, M. P3.18.12
Domenech Viñolas, M. EP.06.78, EP02.12
Domik, A. P1.17.46
Domine, M. MA04.09
Dómine, M. OA05.03
Domine, M. P2.08 .37
Dómine, M. P3.01.25, P3.18.12, PL03.10
Domingo, G. P2.06.78
Domingo-Carreras, M. PT1.08.04
Dominici, M. EP.13.05, EP.15.11
Donahoe, L. MA03.01, OA12.04
Dong, F. EP.01.12
Dong, J. MA01.05
Dong, S. P1.07.55, P2.06.77, PT1.09.03
Dong, T. P1.11.44
Dong, X. EP.08.38
Dong, X. MA03.06, P2.10.12, P3.12.25, P3.12.41, P3.12.48, P3.12.57, P3.12.64, PT1.02.01
Dong, X. P1.11.28
Dong, Y. OA11.04
Dong, Y. P3.13.27
Dong, Z. EP.06.36, EP.08.35, P2.06.06
Dong, Z.-Y. OA03.04, P2.02.28, P2.06.36, P2.08 .59
Dong, Z. MA07.08, OA14.02, OA16.03, P3.03.19, PT2.11.05
Dongay, V. P3.03.34
Donnem, T. P1.11.62
Donoghue, M. P3.03.32
Donoghue, M. T. P3.03.01
Donsel, P. O. EP.15.10
Donthireddy, K. R. PL02.18
Donvito, S. OA17.01
Dooms, C. EP.13.16, PL02.15
Dorkham, N. EP.12.07, P1.17.33
Dorna, M. EP.01.05
Dor-On, E. P3.03.22
Doroshow, D. P3.12.39
Dortch, K. EP.07.20, P2.05.02, P2.15 .32
Dortch, BS, K. OA11.03
Doshi, J. P3.01.14
Doshi, J. D. EP.17.37
Dotsu, Y. EP.06.49
Doty, A. EP.16.07
Doucet, L. MA08.01
Dourado, P. EP.01.05
Doussine, A. P3.03.34
Dowlati, A. EP.17.03, OA06.04, P1.04.04, P2.15 .19, P3.13.12, P3.18.80
Dowling, G. P2.06.82
Downward, G. S. OA01.01
Dragnev, K. OA08.02
Dragnev, K. H. P3.18.28
Drago, F. PT2.10.01
Drazer, M. P3.01.48, P3.14.04
Drazer, M. W. OA12.01
Dresler, C. OA11.01
Drilon, A. P3.03.32
Drilon, A. MA02.03, MA02.04, P3.12.06, P3.12.58
Drilon, A. E. P2.06.102
Drilon, A. PL02.15
Drilon, A. D. P1.11.79
Driscoll, J. EP.03.01
Drosslerova, M. P1.04.54
Drusbosky, L. P3.18.52
D'Souza, D. P1.07.37
Du, H. P2.05.13
Du, J. P2.06.73
Du, M. EP.18.03
Du, W. P3.18.47
Du, X. P3.12.45
Du, Y. P2.10.16
Dua, D. EP.17.14
Duan, H. EP.08.38
Duan, J. P3.18.41, P3.18.81
Duan, j. P3.12.48, PT2.10.03
Duarte, A. P2.06.84, P3.13.09
Duarte D'Ambrosio, P. EP.17.04, P1.17.15
Dubashi, B. MA02.04
dubey, s. P2.06.94
DuBree, K. P2.15 .30
Dudhat, K. EP.01.13
Dudnik, E. EP.17.20
Duell, T. P3.12.14
Duell, T. P3.16.19
Dueñas-Hernandez, S. P2.15 .11
Duffin, R. P3.14.08, P3.14.10
Dugan, A. P2.06.13, P2.06.21
Duh, M. S. P3.12.06
Dulohery Scrodin, M. MA05.01
Dumais, K. EP.17.01, P2.06.75, P3.12.56
Dumitrascu, A. D. P1.17.30, P2.15 .34
Dumitrascu, A. P1.04.51, P1.11.66, P1.17.44
Dummer, T. J. P3.01.35
Dumoulin, D. W. OA01.01
Dumoulin, D. EP.13.15
Duncan, A. PT2.12.01
Dunn, S. EP.12.07
Dunne, J. P2.06.82
Dunphy, C. P3.01.36
Duplaquet, F. EP.11.18, EP.15.19
Duralı, D. EP.03.11
Duran, R. EP.09.17
durani, v. P3.03.52
Durbin, A. EP.06.57
Durhan, G. EP.04.43
Durney, C. H. MA05.03, MA05.05, MA09.01, MA09.03, P3.01.23, P3.01.29
Dursun, S. P3.18.01
Duruisseaux, M. P3.18.60
Dutau, H. EP.04.29
Dutau, H. P1.04.39
Duttargi, A. P3.13.13
Dworkin, S. EP.15.06
Dwyer, J. MA10.02
Dwyer, R. P2.08 .01, PT1.09.02
Dy, G. EP.08.32
DyBuncio, A. P1.04.36
Dyer, D. P1.04.32
Dyk, P. T. PL03.06
Dymshyts, D. P1.17.67
Dymun, A. P3.03.01
Dziadziuszko, R. MA02.03, P1.04.45, P3.18.74
Dziedzic, M. MA11.05, P3.13.02

E

E, M. PL03.07
Eapen, G. MA10.02
Eaton, C. OA17.04, P2.15 .18, PT2.16.05
Ebenstein, Y. EP.04.41

Eberhardt, W. E. P3.12.39
Eberth, J. P1.17.83
Eccher, S. P3.12.08
Eccles, L. J. P1.17.52
Echarri-González, M.-J. PT2.15.04
Economopoulou, P. EP.01.19, P2.15 .26
Edell, E. OA14.05
Edelman, M. EP.06.15
Edelman, M. J. P2.08 .23
Edun, M. P1.17.76
Edwards, A. EP.15.06, EP.17.15
Edwards, K. P3.14.01
Edwin Roger, P. C. P1.11.70
Eek, D. P1.17.14
Efuni, S. P3.18.39
Egaga, F. EP.17.22
Egenod, T. OA05.02
Eggleston, C. P3.18.17
Eggleton, S. P3.12.10
Eghbalizarch, M. P1.17.19, P1.17.81, P3.01.47
Eguchi, T. P2.06.47
Eguren Santamaria, I. P3.18.29
Egwuenu, C. PT2.16.04
Egyud, M. P3.18.17
Ehrhardt, B. MA09.04
Ehsan, S. P2.06.84
Ehya, H. EP.06.15
Eichhorn, F. MA04.06
Eichhorn, M. E. EP.01.20, EP.06.29
Eichhorn, M. MA04.06
Eid Mutlak, Y. EP.03.08
Eijkelboom, A. P3.01.10
Eiras, L. M. P2.10.08
Eisele, M. OA11.01
Eiseler, N. T. P2.06.76
Ekanem, V. J. P1.17.76
Ekblom, M. P3.12.72
Ekman, S. EP.12.26, P1.11.39, P3.13.17, P3.18.56
Eksamutchai, P. EP.04.37
Elamin, Y. MA10.05, OA07.01
Elamin, Y. Y. P1.11.70
Elashoff, D. P2.02.16
Elbl, U. EP.13.13
Eldib, H. PT1.08.03
Elepano, I. V. P1.17.31
Elgendy, M. P3.14.05
Elghawy, O. EP.14.17
Elguindi, S. P2.08 .24
El Helali, A. P2.06.90
El Kahtib, O. P1.17.53, P2.06.09
El-Khoueiry, A. B. P2.06.100
Elkins (In Memoriam), I. OA17.03
Elkrief, A. P1.11.55, P1.11.56, P2.06.12, P3.03.01, PT2.11.01
Ell, E. P3.01.51
Elliott, A. EP.13.41, P1.17.65, P3.12.03
Elliott, D. P2.10.01
Elliott, I. A. P1.04.19
Ellis-Caleo, T. J. P3.01.07, PT1.01.01
El-Omar, E. P2.06.63
Elon, Y. P2.06.93
Elran, R. P3.03.39
Eltaief, S. P3.12.29
Ely, S. P1.17.24, P2.08 .42
El Zarif, T. P1.17.54
Žemaitis, M. P2.15 .06
Emanuel, G. P1.17.52
Embún, R. P1.07.24
Emery, J. P1.04.08
Emidio, O. P3.12.34
Emig, M. P2.06.100
Eminizer, M. P2.06.66
Emmerick, I. P1.07.16, P1.17.01
Emri, K. S. EP.04.28, EP.04.33
Endo, H. EP.09.16
Endo, M. EP.07.01, EP.07.21, P1.07.49, P1.17.34
Endo, S. P2.06.33
Enerly, E. P1.17.67
Enfield, K. S. P3.01.49
Eng, J. MA01.06, P3.18.11
Eng, L. EP.01.24, EP.01.25, EP.06.75, OA11.01, P1.17.08, P1.17.09, P3.01.36, P3.14.11
Engelhardt, K. P1.07.37
Engelman, R. P3.03.22
Engin, A. P3.03.04
Engle, L. L. P2.06.66
Englmaier, V. EP.04.16
Engmann, E. OA13.02
Enoka, D. EP.04.07
Enön, S. P3.18.01
Enrico, B. MA01.08, OA07.03, PT1.08.02
Enriquez, A. P3.01.22
Enzinger, A. PT2.15.02
Epistolio, S. EP.06.35
Epstein, R. EP.08.28
Erasmus, J. PT1.04.03
Eraso, A. P2.08 .49
Ercolano, G. EP13.48
ERDIS, E. EP.13.43
Erhunmwunsee, L. P3.18.84
Eris, T. PT2.10.01
Erkan, M. EP.01.21
Erkmen, C. EP.04.05
Ermer, T. EP.08.46
Ernani, V. P3.13.32
Ernani, V. EP.13.10, P1.11.69
Erne, S. EP.04.16
Ernhofer, B. MA11.06
Ernhofer, B. P3.13.03
Ernst, S. M. EP.12.15
Ersen, E. EP.04.23
Esakov, Y. P1.04.44
Esakov, Y. EP.05.05
Escobedo-Sanchez, E. EP.12.18
Escribà5, J. P3.14.09
Escriu, C. EP.07.47, OA02.02, P3.18.74, PL02.06
Escudero, V. P1.17.80, PT2.17.05
Eshet, Y. P1.17.06
Espejo Zayas, M. P2.08 .37
Espinàs, J. A. P1.04.35
Espino, G. P3.01.40
Espinosa, N. A. P2.06.66
Espinosa-Olarte, P. EP.06.77
Espinoza, R. P2.06.39
Esposito, A. EP.13.47, OA09.02, OA17.03, P2.05.01, P2.06.65, P3.01.48
Esposito, G. P3.18.18
Esposito, L. P1.11.66
Essabbar, A. P2.06.43
Estaitia, Y. P3.03.31
Esteban-Tejero, L. EP.05.08
Esteve-Codina, A. P3.03.49
Esteve Gomez, A. EP.06.78
Esteves, H. P3.16.04
Estevinho, F. EP.07.25
Estrin-Lebovic, C. EP.16.06
Esumi, M. EP.06.81
Esumi, S. EP.06.81
Ethakota, J. P3.12.16
Etiuma, A. U. P1.17.76
Ettala, O. P1.17.67
Ettinger, D. P1.11.72
Euraree, P. EP.04.37
Evangelist, M. P3.12.71
Evangelista, J. EP.06.64

Evans, H. P3.01.01
Evans, M. P3.16.08
Evans, R. EP.17.07
Evans, W. K. EP.01.24, EP.01.25, OA11.01, P3.01.40
Evdokimova, E. P3.13.29
Everest, L. P1.17.08, P1.17.09
E Wilson, B. EP.17.38
Eze, C. P2.08 .14, P3.16.19
Ezeife, D. A. P3.01.24
Ezeife, D. PL02.06
Ezemba, N. P1.17.76
Ezhil, V. P3.09.02

F

Fabbri, A. P1.17.44
Fabozzi, T. P3.18.18
Fabre, C. P3.18.67, P3.18.68
Fabre, D. EP.04.29, P1.04.39
Faccioli, E. EP.08.03, EP.14.18, P3.14.06, PT2.14.02
Facheris, G. EP.08.03
Facktor, M. A. P1.04.31
Fadel, E. EP.04.29, P1.04.39
Fadul, C. E. P2.15 .15
Faehling, M. MA04.04, P3.12.14
Fahey, E. P1.04.01
Failor, M. P1.11.82
Faisal, W. EP.13.33, EP.17.02, P1.17.18, PT2.17.02
Faisal, W. P3.01.13
Faivre-Finn, C. MA02.08, OA16.02, P1.17.07, P3.13.04
Fakhari Tehrani, Y. EP.08.32
Fakih, O. EP.07.47
Fakorede, O. P3.01.18
Falchero, L. P2.06.43
Falchi, R. P2.08 .12
Falcon, C. P3.03.32
Falcoz, P.-E. P2.05.15
Falk, M. P3.18.64
Faller, B. A. PL03.06
Famianok, P. EP.08.08
Fan, A. PT1.04.03
Fan, H. P2.02.03
Fan, H. P3.12.69, P3.18.62
Fan, J. EP.08.39, P1.07.48
Fan, J. EP.18.03
Fan, J. MA05.09, OA11.04, P2.06.03, P2.08 .04, P2.08 .05, P2.08 .46
FAN, L. EP.07.29
Fan, M. EP.08.30
Fan, M. EP.12.58
Fan, M. MA01.05
Fan, P. MA05.07
Fan, S. P2.06.73
Fan, S. P3.12.48, P3.12.64
Fan, X. MA05.07
Fan, Y. P2.02.10, P2.06.55
Fan, Y. EP.11.10, EP.13.23, MA08.01, P1.11.25, P1.11.35, P1.11.46, P2.10.12, P3.12.31, P3.12.48, P3.12.55, P3.12.65
Fang, C. P2.15 .04
Fang, J. MA08.01, OA06.01, P2.15 .28, P3.12.07, P3.12.31, P3.12.48, P3.12.55, P3.12.64, P3.13.34, PT2.10.04
Fang, L. P3.18.74
Fang, Q. P2.02.21
Fang, S.-C. EP.12.06
Fang, S. P1.11.76
Fang, W.-T. MA04.03
fang, w. OA10.03, PL02.12
Fang, W. PT2.14.04
Fang, Y. EP.08.30
Fang, Y. EP.12.39
Fang, Y. EP.12.39
Fang, Y. P2.10.12, P3.12.41
Fang, Y. P3.03.37
Fanlo Ucar, H. P2.02.04
Fanuli, P. P3.16.05
Farahmand, P. P3.14.08, P3.14.10
Faretta, E. OA17.01
Farhikhteh, G. P1.17.44
Farias, A. J. P1.17.02, P1.17.16
Farias, G. EP.15.01
Farinaro, A. EP.11.03
Farinea, G. P2.06.22, P2.06.40, P3.16.05
Farjah, F. P3.16.16
Farmen, S. EP.12.35
Farnsworth, D. P2.02.15
Farnsworth, D. A. EP.02.03
Faroni, L. P2.08 .18
Faroni, L. D. EP.09.09
Farré, N. P1.07.22
Farris, M. P3.18.14
Farrugia, M. EP.08.32
Farzaliyeva, A. P2.08 .36
Fasnacht, N. OA08.02
Fathi, J. P3.16.13, P3.16.22, P3.16.23
Fathi, J. T. EP.17.08, OA11.01, P2.15 .30, P3.16.20
Fathi, S. P2.10.07
Fathima, A. EP.06.08
Fattoi, C. P2.15 .34
Faucher, M. P1.04.15
Favali, M. MA06.07, OA09.02, P1.04.51, P1.17.30, P1.17.44, P2.06.65
Favaretto, A. P1.07.51, P3.12.15
Favoretto Neto, J. P1.17.82
Favorito, V. P3.14.15, PT2.11.01
Favre, G. P2.06.43, P3.03.34
Fawole, A. P3.18.39
Febres-Aldana, C. P2.02.15
Federico, A. D. P1.11.55
Fehnel, C. EP.07.20, P2.05.02, P2.15 .32
Fehnel, BBA, CCRP, C. OA11.03
Fei, K.-L. P3.12.59
Fei, K. P3.18.81
Feilotter, H. EP.06.75
Feinberg, M. PT1.04.01
Feldman, J. OA17.03, P1.17.71, P2.15 .24, P3.01.51, P3.12.46, P3.16.15, P3.16.16, PT2.16.04
Feliciano, J. OA17.04, P2.15 .18, P3.18.40, PT2.16.05
Feliciano, S. P3.18.18
Felip, E. MA02.02, MA02.03, MA07.07, MA08.01, OA02.01, OA02.03, OA09.02, P1.04.51, P1.11.85, P2.06.65, P3.01.19, P3.12.13, P3.12.21, P3.12.30, P3.12.40, P3.12.46, P3.14.02, P3.18.58, P3.18.74, PL02.15
Felip Font, E. MA01.07
Fellah, H. P2.10.07
Felley-Bosco, E. P3.03.07
Fendrick, A. P2.10.01
Feng, A. P3.01.36
Feng, C. P1.11.45
Feng, D. EP.12.48
Feng, H. P3.18.05
Feng, H. P2.15 .25
Feng, J. EP.08.17, MA03.01
Feng, J. EP.07.29, EP.08.41
Feng, J. P2.08 .34
Feng, M. EP.04.35, EP.08.33
Feng, M. P1.11.67
Feng, P. EP.03.17
Feng, W. P3.03.11
Feng, W. MA10.01, OA10.02
Feng, W. P3.03.06
Feng, X. EP.04.04, OA01.03, PT1.04.04
Feng, X. EP.13.30, P3.13.19
Feng, Y. EP.15.05, P3.01.03, P3.01.05, P3.01.12
Feng, y. EP.18.10
Feng, Z. EP.09.05
Fenton, G. P3.13.12

Ferahta, N. EP.09.17, P1.11.03
Fere', E. P1.17.44
Ferencz, B. MA11.06
Ferlini, C. EP.17.35, OA06.04, P1.11.45
Fernamberg, K. PT2.12.03
Fernandes, M. G. PT1.03.03
Fernandes, P. P. EP.17.23
Fernandez, A. EP.12.34
Fernández, E. MA01.01
Fernandez, M. MA01.03, OA05.03, P1.11.07, P1.11.37, P3.01.25
Fernández, M. PL03.10
Fernández Banda, L. P2.08 .48
Fernandez-Cuesta, L. P3.18.60
Fernandez-Gomez, M. P2.06.78, PT1.04.01
Fernández Hinojal, G. MA08.02
Fernandez-Hinojal, G. MA08.01, MA08.01
Fernández-Ibarrondo, L. P2.06.74
Fernández Montes, P. P2.08 .37
Fernández Pedrero, C. P2.08 .48
Fernández-Pinto, M. OA09.02, P1.04.51, P2.06.65
Fernández-Varas, B. EP.16.04, P2.08 .60
Fernholm, E. P1.17.14
Ferracin, M. P2.06.81
Ferrante, S. P1.04.51
Ferrara, R. EP.08.03, P1.11.01, P1.11.17, P3.12.40
Ferrari, A. P2.08 .53
Ferrari, D. EP.01.05
Ferrari, G. P1.11.01
Ferrari, L. P1.04.51
Ferrari, M. P3.14.18
Ferrari, R. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52, P3.01.41
Ferrarin, A. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Ferraro, P. P2.08 .54
Ferrarotto, R. MA10.05
Ferraz de Carvalho, D. V. EP.06.09, PT1.04.02
Ferreira, A. P1.17.21
Ferreira, C. G. P1.11.16
Ferreira, C. EP.15.09
Ferreira, C. M. EP.15.01
Ferreira, D. OA13.03
Ferreira, D. P1.17.21
Ferriol, M. OA01.02
Ferriol-Galmés, M. P3.01.46
Ferris, A. OA02.01
Ferris, M. P3.18.17
Ferro, A. EP.08.03, P2.08 .26
Ferro, F. EP.07.25
Ferrone, M. P1.17.46
Ferté, C. P1.17.21
Fertmann, J. EP.06.45
Festari, M. P1.11.54
Fey, E. P1.17.67
Fiankevich, V. EP.08.08
Fibla, J. J. MA01.01
Ficken, C. P2.06.04
Fidelle, M. EP.04.29, P1.04.39
Fidler, A. P1.04.08
Fidler, M. J. PT2.15.03
Fidler, M. P2.06.64
Fidyk, E. P1.07.05
Field, J. MA05.06
Field, J. K. P1.04.06, P1.04.11, P1.04.29, P3.01.20
Figueiredo, J. EP.06.21, P3.12.16
Figueiredo, T. EP.13.20
Figueroa, P. MA01.04
Figueroa, S. MA01.01
Fijuth, J. P2.08 .21
Fila, M. EP.13.10
Filion, E. P2.08 .54
Filipava, T. EP.08.08
Filipello, F. EP.08.03
Filippi, A. R. P2.08 .53, P2.15 .34
Filippi, A. P1.04.51
Fillinger, J. MA11.06
Finazzi, T. P3.18.82
Fine, A. D. EP.06.68
Fine, L. P3.01.51
Fingerle-Rowson, G. P3.18.29
Fink, A. A. MA02.06, OA08.02
Finley, C. EP.17.15, P1.17.42, P1.17.46
Finley, D. J. P1.07.37
Finn, S. EP.06.61
Finocchiaro, G. P1.11.01
Fintelmann, F. MA05.03
Fiorani, C. EP.15.11
Fiorante, A. P2.06.66
Fiore, M. EP.08.13, P2.08 .30
Fiorenti, M. EP.06.52, P1.11.66
Fiorentino, M. P2.06.81
Firmbach Pasqualotto, F. EP.06.01
Fischer, F. EP.06.42
Fiske, Z. EP.12.07, P1.17.33
Fitzgerald, B. EP.08.32
Fitzmaurice, G. J. EP.06.61, P1.07.18
Fitzpatrick, O. M. EP.08.34
Flanagan, M. P1.17.50
Fleitmann, K. P1.17.47
Flickinger, J. PT1.08.03
Flieder, D. EP.06.15
Floch, N. P2.02.27
Flores, E. J. OA18.04
Flores Avile, C. EP.12.23
Florescu, M. OA12.02, P2.08 .54
Flores-Paco, P. EP.06.66
Florez, N. MA04.02, OA18.02, P1.07.45, P1.17.10, P2.06.44, P3.01.18, P3.01.19, P3.14.20, PT2.11.01, PT2.15.02, PT2.17.04
F. Nacer de Oliveira, D. P2.02.40
Foerster, R. P3.18.82
Follador, A. EP.11.20, P1.11.24
Fong, A. J. P3.18.84
Fong, K. EP.04.07
Fong, K. M. P2.06.51
Fonseca, H. V. EP.06.09, P3.01.06, P3.01.06, PT1.04.02
Fonseca Magalhães Filho, M. P1.17.45
Fonseca-Sánchez, E. P2.15 .03
Font, R. P1.04.35
Fontana Cassado, A. EP.05.01
Fonte, J. E. P3.01.06
Foo, A. P1.11.36
Forcella, D. P1.07.07, P3.14.17
Forde, P. MA01.07, P2.06.82
Forde, P. M. OA02.03, OA12.03, P1.11.72, P2.06.66, PL02.18
Forkheim, K. P1.17.42
Forns, N. EP.04.14
Forshaw, C. EP.17.32
Forster, M. P3.18.74
Forsting, M. EP.04.27
Forsythe, A. P1.17.78
Fortin, D. P2.06.70
Foschini, G. MA01.01
Foster, F. P1.17.46
Fotheringham, M. P2.06.66, P2.06.99
Fotopoulos, G. EP.08.18
Fotopoulos, G. P1.17.29
Fouad, T. M. MA04.09
Foulon, S. P3.14.15
Fountzila, E. OA09.02
Fountzilas, E. MA11.04, P2.15 .26

Fountzilas, G. P2.15 .26
Fournel, L. P2.05.10
Fox, J. EP.08.15
Fox, J. EP.16.02, P3.16.01
Fra, S. EP.07.27
Fraboulet, S. OA05.02
Fraga, G. EP.15.01, EP.15.09
Fragale, C. P3.12.20
Fraihat, M. P1.17.39
Fraile, C. A. MA01.01
Fraile-Barragan, S. PT2.15.04
Frain, L. EP.07.33
Frain, L. N. P1.17.27
Fraley, L. P2.10.01
Franceschini machado, G. EP.08.45
Francesco, B. MA02.05
Francesconi, M. P1.17.44
Francesconi, S. MA01.08
Franchina, T. EP.11.01, EP.15.14
Francis, E. P3.01.28
Franco, E. EP.01.05
Franco, L. EP.08.16
Franco, L. P1.04.28
Franco, L. P2.08 .52
Franco MsC, L. P3.01.41
Franco-Serrano, J. P3.03.45
Franks, K. P3.09.02
Franks, K. N. OA13.02, PT2.14.01
Fransen, M. F. P3.18.16, PT2.11.02
Frantzi, T. EP.01.19
Franz, M. P1.17.67
Franzoi, M. P1.17.21
Franzoni da Silva, P. P3.16.04
Frascino, M. P1.11.54
Fraser, A. EP.04.07
Frattini, M. EP.06.35
Frauenfelder, T. EP.04.16, EP.04.34
Freedman, H. EP.15.06
Freeman, J. P1.17.59
Frega, S. MA02.05
Freguia, S. EP.06.35, P3.18.82
Freire, G. P1.04.28
Freire, G. B. EP.08.16, P2.08 .52
Freire da Fonte, J. EP.06.09, PT1.04.02
Freire MD, G. B. P3.01.41
Freitas, C. EP.07.25
Freiwan, M. EP.06.45, P3.18.36
Frelaut, M. P3.14.15
French, D. EP.06.50
Frey, C. P2.10.17
Friboulet, L. P3.18.60
Friedberg, J. OA12.03
Friedberg, J. S. EP.15.08, OA04.01
Friedecky, D. P1.11.10
Friedrich, G. P3.01.19
Frisullo, G. EP.03.02
Froesch, P. EP.06.83
Frösch, P. EP.06.35, P3.18.82
Frost, N. MA04.05, P3.12.61
Frueh, M. OA02.01, P3.18.82
Früh, M. EP.06.83
Fry, S. PT1.03.01
Fu, C. EP.12.40
Fu, F. P2.06.05
Fu, H. EP.11.15
Fu, H. EP.08.30
Fu, P. P2.10.14, P2.15 .04
Fu, R. P1.04.21, P2.08 .35, P3.01.24, P3.13.33, PT1.09.03
Fu, W. P1.11.12
Fu, X. EP.12.20, P3.18.24
Fu, X. P3.03.06
Fu, Y. EP.07.18
Fuchs, F. P3.12.61
Fuchs, J. EP.12.30
Füereder, T. P3.18.55
Fuertes, B. EP.06.48
Fujii, R. P2.06.16
Fujikawa, R. P1.07.49
Fujimoto, H. EP.11.08
Fujimoto, K. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Fujinaga, K. EP.08.05
Fujino, K. P1.07.49
Fujioka, M. PT2.14.03
Fujioka, M. P2.06.95
Fujioka, N. P1.11.71
Fujisaka, Y. P3.12.33
Fujisaki, T. EP.14.21
Fujishima, S. EP.08.42, P3.12.54
Fujishima, S. EP.13.11
Fujita, K. P3.12.44
Fujiura, Y. EP.06.81
Fujiwara, A. EP.11.08
Fujiwara, R. P2.06.16
Fujiwara, Y. P1.11.17, PT2.10.01
Fujiwara-Kuroda, A. EP.04.36, EP.06.84, EP.14.16, P1.07.21
Fukami, T. P1.07.49, P3.09.05
Fuks, E. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52
Fuks MD, E. P3.01.41
Fukuda, A. EP.14.05
Fukuda, H. P3.18.04
Fukuda, K. P3.03.02
Fukuda, M. EP.06.49
Fukuda, S. EP.06.46, P1.07.49, P3.09.05
Fukuda, T. EP.06.49
Fukui, T. P1.11.40
Fukumoto, K. J. EP.08.09
Fukumoto, Y. P2.06.16
Fukunishi, Y. EP.13.12
Fukuyama, T. EP.06.12
Fulton, E. EP.07.33
Funahashi, J. P2.06.33
Funaki, S. EP.14.05, P2.06.41
Funaro, E. P1.07.17
Fung, L. P3.01.34
Fung, T. EP.11.21
Furak, J. P3.14.19
Furlanetto, J. P3.18.74
Furqan, M. OA06.04
Furrer, K. EP.09.10
Furumoto, H. EP.08.40, P2.08 .06
Furuse, H. PT1.05.01
Furuta, M. P3.09.09
Furuya, N. EP.12.29, P1.11.40, P3.12.09, P3.12.23
Fusco, F. EP.07.48, MA01.04, P1.07.43
Fusco, N. OA09.03
Futamura, S. EP.11.06
Futrell, M. MA06.09, P3.01.51

G

G, P. P2.06.18
Gabe, R. EP.01.22, MA09.05, PL03.19
Gabriele, D. P3.12.20
Gabrielli, F. P2.08 .18
Gadgeel, S. P3.12.21, P3.12.34, P3.12.38, P3.12.58, P3.12.71, P3.18.38, PL02.15
Gadi, V. MA05.04
Gafà, R. P3.12.20
Gage, D. P2.08 .22
Gagliano, A. P3.18.82
Gagné, A. EP.06.06, MA07.01, MA07.04, OA09.03, P3.13.06
Gaikwad, V. P2.02.43
Gainor, J. P3.12.71

Gainor, J. F. EP.06.53, EP.12.10, MA02.01, P1.07.43, P3.18.28, PT2.13.04
Gaire, S. P1.11.50
Gaisa, N. P3.12.61
Gaisl, T. EP.07.09
Gal, O. P3.09.08
Galán, G. MA01.01
Galant, N. EP.13.17, MA10.04, P1.11.63
Galateau-Salle, F. OA12.01
Galaverni, M. EP.09.06
Galery, E. OA03.03
Galetta, D. MA02.05, OA17.01, P1.04.47, P1.07.51, P3.12.06, P3.13.04, P3.16.05
Galffy, G. P2.15 .06, P3.13.03
Gallach, S. EP.06.77
Gallani, C. P1.07.04
Gallego-Llorente, M. P1.17.42, P2.15 .06
Gallerani, G. P2.06.81
Gallesio, I. EP.14.10
Galli, G. P1.11.01, P2.08 .53, P3.14.06
Gallina, F. EP.07.48, EP.08.03, MA01.04, P1.07.22, P2.05.10
Gallina, F. T. EP.03.02
Gallina, F. P1.07.07, P3.14.17
Galo, M. P2.06.78
Galot, R. P3.18.66
Galuppi, F. P2.06.92
Gálvez, C. MA01.01, P2.08 .28
Galwas-Kliber, K. P2.08 .21
Gambacorta, M. P1.07.22, P3.13.04
Gambardella, V. P3.03.45, P3.12.30
Gambini, G. P1.11.01
Gan, Z. P2.06.72
Ganci, M. L. EP.06.53
Gandara, D. R. EP.06.68, P2.06.93
Gandhi, M. M. P1.11.56
Gandhi, N. P1.17.65, P3.12.03
Gandhi, S. OA07.01, P1.11.60, P1.11.70, P2.08 .23, P2.15 .22
Gandler, H. EP.13.24, P2.08 .56
Ganesh, N. P2.06.18
Gangemi, A. EP.06.15
Ganiyu, A.-A. OA08.03
Gann, C.-N. OA13.02
Ganti, S. OA15.02
Gany, F. P1.04.17
Ganzinelli, M. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34, P3.14.18
Gao, A. P2.06.101
Gao, A. EP.04.06
Gao, B. P3.12.38
Gao, F. P3.12.07, P3.12.31
Gao, G. P1.11.67
Gao, G. EP.06.67, P1.11.31, P3.03.53
Gao, H.-B. P1.11.05
Gao, J. P1.07.50
Gao, J. P3.12.07
Gao, J. MA11.03
Gao, L. P1.17.20
Gao, N. EP.06.59, P2.06.72
Gao, R. PT2.17.03
GAO, S. P3.12.74
Gao, S. P3.03.51
Gao, T. P3.18.86
Gao, W. EP.14.20, P1.17.41, P2.02.07, P2.06.49
Gao, X. EP.12.38
Gao, X. EP.15.17
Gao, X. EP.13.30, P2.06.73, P2.08 .55, P3.13.19
Gao, X. P3.01.08
Gao, X. EP.07.45, P2.06.77
Gao, X. P3.14.21
Gao, Y. EP.11.19
Gao, Z. PT2.11.03, PT2.14.04
Garassino, M. C. MA06.07, P2.15 .34
Garassino, M. P3.01.48, P3.18.09
Garassino, M. C. OA09.02, OA17.03, P1.04.51, P1.11.42, P1.11.66, P1.17.30
Garassino, M. P1.17.44, P2.06.65
Garbo, E. MA01.04, P1.07.43, P1.11.56, P1.17.54, P1.17.55, P2.06.40, P3.03.17, P3.12.63, P3.16.05, PT2.11.01
García, A. MA01.03
Garcia, C. EP.12.27
García, J. OA05.03
García, J. P2.02.41
Garcia, M. V. P2.15 .11
Garcia, S. OA01.02
Garcia, V. EP.04.14
García-Bartolomé, M. P3.03.45
Garcia Campelo, M. R. MA08.02
Garcia Campelo, M. PT1.03.06
Garcia Campelo, M. P2.10.05
García Campelo, R. OA05.03, P1.11.07, P1.11.37, P3.18.12, PL03.10
García-Campelo, M. MA06.03
Garcia de Herreros, M. OA01.02
Garcia-Fontán, E. M. MA01.01
Garcia-Galea, E. P3.14.02
García Ledo, G. P2.08 .37
García Luque, F. EP.07.43, P2.08 .48
Garcia Manrique, T. EP.06.71
Garcia-Pardo, M. P3.14.11
Gardner, C. P3.16.08
Garfield, J. EP.06.15
Gargiulo, P. OA12.02
Gariazzo, E. P1.07.43, P1.11.56, P3.12.63, PT2.11.01
Garitaonaindia, Y. P3.01.25
Garnett-Benson, C. MA10.07
Garon, E. EP.07.14, P2.02.16, P2.08 .22
Garon, E. B. P3.18.87
Garrido, P. P3.01.19
Garrido-García, A. PT2.15.04
Gart, MBA, M. EP.12.32, EP06.86, EP12.65, P2.06.11, P2.06.20, P3.12.24
Gärtner, U. P2.06.100
Gasco, A. EP.06.68, EP.06.69, EP.06.76, P1.17.66
Gascón, N. EP.07.43
Gascón Costoso, N. P2.08 .48
Gashi, D. P3.03.04
Gas López, M. P1.17.67
Gaspar, B. EP.16.02, P3.16.01, P3.16.11
Gasparro, M. P3.14.15, P3.16.05
Gately, K. P1.07.18
Gatius, S. EP.04.14
Gaudreault, N. MA07.04
Gausa, P. P2.06.56
Gausachs, M. P2.06.37
Gauß, R. P2.08 .14
Gautrey, H. EP.06.51
Gautschi, O. EP.06.83, P3.12.06, P3.18.82
Gavrielatou, N. EP.01.19
Gay, C. PT1.01.03
Gay, C. M. MA11.06, OA07.01, P2.02.36, P2.06.84, P3.13.09, P3.13.11, PT2.13.03
Gaya, A. P3.09.02
Gazzah, A. P3.14.15
Gazzaniga, P. EP.06.74
Gazzoni, G. P1.11.69
Ge, C. P1.07.16
Ge, D. P2.02.01, P2.02.30, P2.08 .43, P3.18.08
Ge, H. PL03.07
Ge, H. P1.11.83, P1.17.69
Ge, J. P3.18.86
Ge, X. EP.11.19
Ge, Y. P1.11.76
Geater, S. L. P3.12.65
Gebitekin, C. EP.05.04

GEDIK, D. EP.13.43
Gedvilaite, V. P1.17.29
Gee, J. EP.01.04
Geguchadze, A. EP.17.24, EP.17.26
Gelblum, D. Y. EP.08.51, EP.13.08, EP.14.22, MA01.06
Geldart, T. P2.10.05
Gelibter, A. EP.06.52, EP.11.20, P1.07.51, P3.12.15
Gelibter, A. J. EP.06.74
Geller, MD, R. EP.12.32, EP06.86, EP12.65, P2.06.11, P2.06.20, P3.12.24
Gelsomino, F. EP.11.20, MA02.05, P1.11.24, P1.11.42, P1.11.54, P2.06.92
Gemma, C. P2.06.08
Gendarme, S. PT1.04.03
Genestroni, S. EP.06.80
Geng, D. EP.13.29, MA11.01
Geng, J. MA06.06, P1.17.61
Geng, J. EP.07.30, P1.07.09
Geng, J. P1.07.02
Gennarelli, R. P1.17.63
Gennari, A. EP.06.80
Gennissen, L. P2.15 .10
Genova, C. EP.11.20, MA08.05, P1.07.51, P1.11.24, P1.17.54, P3.12.15
Georgakis, G. P1.17.52
George, B. OA08.01, P3.09.02, P3.18.71
George, M. EP.01.24, EP.01.25, P3.01.40
George, S. P2.06.18
Georgiou, M. EP.08.18
Gerasimova, D. P3.03.22
Gerber, D. E. EP.04.06, EP.04.31, PL02.18
Geronutti, J. EP.01.05
Gerris, A. P3.18.03
Gesualdo, M. OA17.01, P1.04.47
Gewanter, R. MA01.06
Gewanter, R. M. EP.14.22
G. Gouveia, A. OA18.02
Ghandehari, S. EP.04.20
Ghandi, N. PT2.14.05
Ghasemi, O. EP.06.50
Ghazaleh, N. P1.17.67
Gheeya, J. P2.08 .47, PT2.12.01
Ghia, A. MA10.05
Ghidini, M. P1.17.54
Ghiringhelli, F. MA08.01
Gholian, E. EP.04.20
Ghosh, R. P1.17.58
Ghostine, S. EP.04.29, P1.04.39
Ghourchidian, N. EP.17.11
Ghuman, H. MA08.04
Giacobazzi, P. EP.13.05
Giangregorio, C. MA06.07, P1.04.51, P1.17.30, P1.17.44
Giani, C. P1.17.30, P2.15 .34
Giannakoulis, M. EP.06.64
Giannarelli, D. P3.12.08, P3.12.15, P3.18.85, PT2.15.01
Gianni, S. EP.09.06
Gianoncelli, L. P1.11.01
Gibbard, J. P1.17.71
Gibbons, D. P1.11.55
Gibbons, D. L. EP.04.31, OA07.01, P1.11.70, PT1.01.03
Gibson, A. A. P3.01.24
Gieske, M. P1.04.32
Gieske, M. R. P1.04.01
Gietema, H. OA01.01
Gil, H.-I. P3.01.45
Gil, J. MA11.06
Gil, M. EP.06.17, MA10.04, P1.11.63
Giladi, M. EP.03.08, P3.03.22, P3.03.28
Gilat, N. EP.04.41
Gill, J. EP.13.38
Gill, R. R. P1.17.27
Gilli, M. EP13.48, P3.18.18
Gillies, J. EP.17.02
Gilligan, A. M. EP.17.33
Gillis, K. P2.06.102
Gillis, R. EP.06.73
Gil Valdes, J. P3.13.03
Giménez-Capitán, A. EP.02.10
Gimeno-Valiente, F. P3.03.45
Ginsberg, M. MA01.04
Giordano, A. EP.06.40
Giorgadze, D. MA10.09
Giraldo, T. PT1.03.04
Girard, N. MA08.04, MA08.05, MA10.07, OA02.03, OA06.03, OA10.01, P1.11.15, P1.11.85, P3.12.10, P3.12.41, P3.12.46, P3.14.15, P3.18.38, P3.18.60, P3.18.80, PL02.12, PT2.12.03
Giridharan, T. P1.11.80
Girotti, P. N. P2.06.54
Girotti, R. P1.11.82
Giroux, D. J. OA12.01
Giroux-Leprieur, E. OA05.02
Gitlitz, B. OA02.01
Giudici, L. P3.18.82
Giuseppe Antonio, M. EP.14.10
Giusti, R. P1.17.54, P1.17.55
Giusti, R. EP.08.03
Gjaj-Levra, N. MA02.08
Gkaralea, L. EP.01.19
Glanemann, F. P3.12.61
Glass, C. OA09.01
Glassberg, M. P1.17.52
Globus, O. P1.17.06
Gluskin, R. P3.03.39
Glynn, K. P1.17.71, P3.16.15
Gnad-Vogt, U. P3.18.64
Gnetti, L. P1.07.04, P3.14.06
Gnjatic, S. P2.08 .23
Go, J. P3.13.05
Go, W. Y. P3.18.87
Gobbato, S. EP.06.80
Gobbini, E. P2.06.43
Godard, J. OA06.03
Godoy, I. EP.01.05
Godoy, M. P2.02.36, PT1.01.03, PT1.04.03
Godoy, M. C. EP.04.31
Goeman, F. EP.03.02
Goetsch, T. EP.06.39
Goffin, J. R. OA12.02
Gogishvili, M. P1.11.52
Gogishvilli, M. MA10.09
Goh, B. P3.12.41
Goh, N. EP.15.04, P1.11.49
Gohel, U. P3.01.15, P3.01.16
Goker, E. P2.10.02
Gokhale, P. P3.12.63
Göksel, T. P3.18.37
Goksu, S. S. P3.18.35
Golan, G. EP.06.50
Gold, I. P1.17.76
Gold, K. A. P3.18.87
Goldberg, J. D. OA15.03
Goldberg, S. EP.08.46
Goldman, J. PT1.04.01
Goldman, J. EP.07.14, OA13.03, P2.08 .22, PT2.10.02
Goldman, J. W. P3.18.87, PL02.12
Goldstein, J. EP.09.01
Goldsworthy, A. P2.06.51
Golledge, A. P2.06.89
Golozar, A. P1.17.67
Gomatou, G. EP.01.19
Gomes, M. P1.17.42

Gomez, A. P3.03.47
Gomez, D. P1.11.14, P1.11.64, P3.01.22
Gomez, D. R. EP.08.51, EP.13.08, EP.14.22, MA01.06, OA07.02
Gomez, L. P3.03.29
Gómez, M. T. P2.08 .28
Gomez, S. EP.16.01
Gomez, S. L. P3.01.07
Gómez de Antonio, D. P1.07.24
Gomez Giraldo, Z. P2.15 .11
Gómez-Hernández, T. P2.02.41
Gomez Marti, J. P2.02.15
Gomez-Randulfe, I. P3.12.30
Gómez-Randulfe Rodríguez, M. P2.10.05
Gómez-Serra, N. PT1.08.04
Gonçales, V. EP.01.05
Goncalves, I. B. P1.11.16
Gong, J. P1.04.04
Gong, L. EP.13.23
Gong, L. OA13.03
Gong, M. P3.18.35
Gong, S. EP.18.08
Gong, X. P3.03.25
Gong, X. P1.11.26, P2.02.14
Gong, Y. PT2.13.02
gong, y. P3.12.47
Gonnella, A. P3.16.20
Gonullu, G. P2.10.02
Gonzalez, I. OA18.04
González, J. EP.02.10, EP.04.13, EP.04.14, P2.02.34, P2.02.39, P2.02.46
González, J. D. EP.04.14
Gonzalez, L. EP.12.53
Gonzalez, L. OA01.02
González-Camblor, D. P3.03.45
González Cordero, M. P3.01.25
Gonzalez-Fernández, R. EP.06.66
Gonzalez-Kozlova, E. P2.08 .23
González Larriba, J. OA08.03
Gonzalez-Larriba, J. MA06.03
Gonzalez-Larriba, J. P1.11.37
González-Larriba, J. PL03.10
Gonzalez-Larriba ,MD, PhD, J. MA01.03
Gonzalez-Motta, A. OA18.02
Gonzalez-Santana, A. EP.12.18, P1.17.73
Gonzalez-Tablas, M. P2.02.41
González-Tampán, A. PT1.08.04
Gonzalez Valencia, A. EP.06.78
Gonzalez Velez, M. P3.13.13
González-Vidal, A. EP.06.48
Goo, L. PT1.03.01
Good, J. P3.09.02
Goodarzi, A. A. P3.01.24
Goodley, P. PL03.19
Goodwin, A. OA03.04
Gopalakrishnan, A. EP.06.08
Gopi, A. P3.01.15, P3.01.16
Gor, J. EP.13.04
Gorbatov, M. L. P1.17.16
Gorbunova, V. P3.13.29
Gordo, R. P1.17.80, PT2.17.05
Goren, E. OA12.01
Gori, S. P1.07.51, P3.12.15
Gorospe, K. A. OA14.03
Gorospe, L. EP.07.27
Gorria, T. OA01.02, P1.17.29, P1.17.54, P3.01.46
Gosi, G. EP.15.09
Gosling, A. P2.08 .19
Goss, G. P2.06.99
Goss, J. P2.15 .32
Gössling, G. EP.13.28
Gotkin, B. PT1.04.01
Goto, K. MA02.03, P2.06.59, P3.12.32, P3.12.41, P3.12.49, P3.18.58, PT1.05.02
Goto, Y. P1.11.11, P1.11.40
Goto, Y. P1.04.52, P3.03.36, P3.18.35, PT2.14.03
Götschke, J. EP.12.56
Gottfried, M. PT1.03.06
Gottlieb, M. EP.06.15
Goudsmit, A. EP.05.06, P3.12.30
Gough, D. EP.03.07
Gouin, S. P2.06.43
Gouldin, W. EP.13.25
Goumas, G. P2.15 .26
Gouvêa, F. M. EP.06.09, PT1.04.02
Govindan, R. EP.13.40, MA07.05, P1.17.50, P2.08 .51, PL02.18
Gower, A. EP.07.14, P2.02.16, P2.08 .22
Gowing, S. PT2.17.01
Goyal, K. P3.12.42
Goyard, N. EP12.64
Graber-Naidich, A. PT1.01.01
Gracia, E. EP.04.14
Grady, J. P. P2.06.61
Graf, R. P1.17.66, P3.12.42
Graf, R. P. MA06.01
Graham, B. EP.06.15
Grainger, A. PT1.04.03
Gramling, M. P3.13.18
Gramza, A. P3.18.73
Grand, A. EP.17.39
Grando, L. EP.08.07, EP.08.26
Granier, M. MA08.04
Grantham, S. P2.06.99
Granville, C. EP.17.01, P3.12.56, P3.16.21, P3.16.23
Granville, C. A. PT2.16.01
Grapatsas, K. EP.04.27, EP.07.22, P2.05.17
Grassi, P. P3.12.41
Grassi Bertozzi, L. EP.06.35
Gratama, J. C. EP.04.02, P1.04.02
Gratama, J.-W. P1.04.09, P1.04.25
Gratama, J.-W.C. P1.04.06, P1.04.11
Grau, E. P3.01.46
Grau Leal, F. EP.06.78
Graumann, J. P3.03.54
Grauslund, M. EP.12.42
Gray, J. P1.11.75, P3.18.09
Gray, J. E. EP.17.33, P2.06.102
Gray, K. P1.04.17, P3.01.22
Gray, S. G. EP.06.61
Greco, C. EP.08.03, EP.08.13, P2.08 .30
Greco, F. G. P1.17.30
Green, B. F. P2.06.66
Green, T. EP.15.12
Gregorio, C. EP.04.20
Gregory, D. EP.04.20
Greillier, L. EP.04.29, MA08.01, OA05.02, OA12.02, P1.04.39, P1.17.21, P2.06.43
Grenda, A. EP.13.17
Greystoke, A. P1.17.52, P2.06.85, P3.18.52
Greystoke, A. A. OA13.02
Gribaudo, R. P3.03.17
Gridelli, C. EP.11.03, OA12.02
Griesinger, F. P1.11.48, P3.12.13, P3.12.14, P3.12.39, P3.12.40, P3.18.61
Grieve, S. P1.17.78
Griffin, D. P3.01.24
Griffiths, K. EP.17.02
Grimalt, N. P3.03.45
Grimminger, F. P3.03.54
Grinberg, R. EP.06.73
Grindheim, J. MA04.02
Grisanti, S. P1.07.51, P1.11.01, P2.08 .26, P3.12.15
Grisold, A. P3.18.55
Gristina, V. P3.18.18

Groen, H. J. OA01.01
Grogan, E. P2.06.43
Grogan, L. EP.08.34
Grogan, M. OA04.04
Grogan, T. P2.02.16
Grohé, C. P1.07.47
Grønberg, B. P1.11.62
Grondelli, C. EP.09.06
Grono, L. EP.01.03
Gros, L. EP.06.13, P1.04.03, P1.07.14, P1.07.19, P1.11.03
Gröschel, A. P3.12.14
Gross, J. P1.17.05
Gross, J. L. P1.17.74
Grossi, F. P1.17.54, P2.08 .53, P3.12.15
Grossi, I. M. P3.12.04
Grosso, F. EP.14.08, EP.14.10, OA12.02, P3.14.06, P3.14.13
Grover, H. P2.06.17
Grubb, G. P3.18.56
Grujeski, A. P2.15 .06
Grullon, S. OA09.01
Grundberg, O. EP.12.26
Grusch, M. EP.02.02, P2.02.18, P2.02.22
Gryaznov, S. P1.11.82
Grzymski, J. P3.14.07
Gu, C. EP.13.23
Gu, H. P3.16.17
Gu, N. PT1.03.01
Gu, Y. EP.18.02
Gu, Z. PT2.14.04
Gu, Z. EP.13.10
Guaitoli, G. EP.13.05, EP.15.11
Guan, B. P1.04.16
Guan, H. P2.08 .55
Guan, J. P1.17.56
Guan, M. P3.18.44
Guan, W. P2.02.12
Guan, X. P2.06.58
Guan, X.-H. P1.11.23, P3.12.26
Guancione, G. P3.18.61
Guardia, G. EP.07.43
Guardia López, G. M. P2.08 .48
Guarino, T. P1.04.47
Guarneri, A. EP.06.40
Guarneri, V. EP.13.15
Guarrasi, V. P1.17.54, P1.17.55, P2.08 .30
Guart, J. P1.17.01
Gubens, M. P1.07.40
Guberina, N. EP.07.22, P2.05.17
Guddo, F. R. EP.06.03
Guenthart, B. A. P1.04.19
GUENZI, E. P2.06.15
Guerini, A. E. P2.08 .26
Guerini-Rocco, E. OA09.03
Guerrera, F. EP.08.03, EP.14.18, P2.05.10, P3.14.17, P3.14.19
Guevara, G. EP.06.66
Guevara Rodriguez, N. A. P1.07.45, P1.17.10
Guggino, G. EP.11.03
Guha-Thakurta, N. MA10.05
Guiab, B. P1.17.08, P1.17.09
Guibert, N. EP.17.39
Guida, A. EP.11.20, MA01.08, OA07.03, P1.11.24, PT1.08.02
Guida, M. EP.14.18
Guijarro, J. P3.03.45
Guijarro, R. MA01.01
Guillén-Navarro, M. EP.13.27
Guirado, M. P1.11.37
Guirado, M. P3.01.25
Guirao, Á. EP.08.26, MA01.01
Guirao, A. P2.06.32
Guirges, B. MA06.07, OA09.02, P1.11.66, P1.17.30, P2.06.65, P2.15 .34
Guisier, F. EP12.64, MA04.05
Gulati, A. PT2.10.02
Gulsen, E. P2.08 .36
Gümüs, M. P2.10.02
Güneş, S. G. P3.18.01
Gunn, K. P1.17.20
Günther, S. P3.03.54
Gunturkun, F. PT1.01.01
Gunturu, K. EP.14.31, EP.17.36
Guo, C. P3.14.21
Guo, G. P2.08 .46
Guo, H. EP.08.10, P2.08 .09
Guo, H. P3.14.23
Guo, H. P3.13.15
Guo, J. P2.10.16
Guo, J. P3.18.32, P3.18.42
Guo, J. P3.12.12
Guo, J. P2.06.101, P2.10.12
Guo, J. P3.12.70
Guo, M. PT2.16.05
Guo, M. Z. OA17.04, P2.15 .18
Guo, Q.-S. PL02.09
Guo, Q. P1.17.36, P3.12.48, P3.12.64
Guo, R.-H. P3.12.55
Guo, R. PT2.10.04
Guo, S. P3.12.07
Guo, W. P2.10.13, P3.18.41
Guo, W. EP.15.05, P1.07.01
Guo, X. P3.13.19
Guo, X. P3.12.64
Guo, X. EP.05.03, EP.07.29
Guo, Y. P3.18.81
Guo, Y. P3.12.07, P3.12.31
Guo, Y. P3.12.64
Guo, Z.-Q. P2.02.28
Guo, Z. P2.08 .59
Guo, Z. P3.12.01
Guo, Z. EP.12.60, P3.01.04, P3.01.37
Gupta, B. P3.13.13
Gupta, D. EP.12.30
Gupta, I. MA09.08
Gupta, K. EP.17.06
Gupta, M. EP.06.16
Gupta, N. P1.17.79
Gupta, P. EP.02.08
Gupta, P. S. EP.01.13, P3.01.17
Gupta, S. P1.07.26
Gurdikyan, S. EP.08.19
Gurrera, A. EP.06.03
Guru, A. P1.04.16
Guruceaga, E. EP.13.27, PT1.08.05
Guryeva, N. M. EP.08.25
Gusareva, M. A. EP.08.25
Gusmaroli, E. P1.11.01
Guthrie, K. P3.18.84
Gutierrez, A. N. EP.08.19
Gutierrez, C. P1.17.63
Gutiérrez, F. P1.17.80, PT2.17.05
Gutierrez, M. P1.11.73, P3.13.13, P3.18.74
Gutierrez, M. E. P3.18.73
Gutierrez Calderon, V. MA08.05
Gutiérrez García, B. EP.08.47
Gutiérrez-Gordo, M. EP.08.37
Gutta, R. P3.12.16
Guy, L. EP.13.39
Guyard, A. P2.06.15
Guzman, A. P2.15 .24
Guzmán, R. EP.08.26
Gwadry Sridhar, F. P1.11.36
Gwee, Y. P2.06.14
Gwin, M. E. EP.04.06

Gyori, D. P2.10.01
Gyotoku, H. EP.06.49
Gyuraszova, K. P3.14.08

H

Haas, J. S. OA18.04
Habashi, L. OA18.01
Haber, A. EP.03.08, P3.03.22, P3.03.28
Haberecker, M. P3.18.82, PT1.06.03
Habert, P. EP.04.29, P1.04.39
Habib-Ishaq, T. P1.17.58
Hache, O. EP.04.29, P1.04.39
Hacibekiroglu, I. OA13.02, P2.10.02
Haddad, S. P1.11.77
Haddox, C. L. OA08.01
Hadi, D. P2.06.82
Haefliger, S. OA13.01
Haeggblom, L. EP.06.50
Haggstrom, D. PL02.15
Hagiwara, M. EP.07.54, EP.08.40, P2.08 .06
Haigentz, M. PL03.06
Haja Mohideen, S. OA15.02
Hajiyeva, S. P2.05.07
Haj Khalil, T. P3.03.28
Hales, R. K. OA12.03
Halfdanarson, T. R. P3.13.32
Hall, H. P3.14.08
Halliday, A. P3.13.09
Halligan, M. EP.01.24, EP.01.25
Halloran, S. P1.07.05
Halmos, B. EP.13.25, EP.13.41, MA07.06, P1.17.65, P2.06.44, P2.06.52, P3.12.03, P3.13.31, P3.18.19, P3.18.22, P3.18.37
Halpin, R. A. OA03.03
Ham, S.-Y. EP.04.12, EP.04.12, P3.01.45
Hama, N. EP.01.29
Hamada, A. EP.05.07, EP.06.46, P1.07.49, P2.06.41, P3.09.05
Hamada, C. EP.13.12
Hamadneh, Y. P1.17.39, P1.17.53, P1.17.64, P2.06.09
Hamaji, M. EP.07.56
Hamamatsu, S. PT2.16.02
Hamamoto, R. P1.04.52, P3.03.36
Hamanaka, K. P2.06.47
Hamann, H. A. EP.04.06
Hamasaki, S. PT2.16.02
Hamatake, M. EP.07.50
Hambelton, G. M. P1.07.43
Hamidi, A. OA13.01, P3.13.34
Hamidou, Z. EP.04.29
Hamilton, P. P3.12.21
Hamm, J. P3.18.39
Hammond, S. OA03.03
Hammonds, M. P2.08 .22
Hamouda, I. EP.04.29
Han, A. P2.02.16
Han, B.-H. MA04.03
Han, B. EP.06.59, P1.11.74, P3.18.63, PT2.11.03
Han, C. B. P1.11.02
Han, D. EP.04.02, P1.04.02, P1.04.06, P1.04.09, P1.04.11, P1.04.13, P1.04.25
Han, D. EP.12.38, P2.06.46
Han, D. P3.12.55
Han, G. EP.12.06, MA04.08
Han, H. EP.12.47
Han, J. P3.18.57
Han, J.-Y. MA04.04, MA08.01, MA08.02, OA06.04, P1.11.32, P2.06.102
Han, L. OA06.02, P3.12.25, P3.12.48
Han, N. EP.13.23
Han, S. PT2.12.02
Han, S. S. P1.04.19, P3.01.07, PT1.01.01
Han, T. OA16.04
Han, X. OA07.01
Han, X. P1.11.33
Han, X. P1.11.02
Han, Y. EP.18.03
Han, Y. P2.10.14
HAN, Y. EP.12.31, P2.02.23
Han, Y. EP.06.59, MA07.01, OA13.04, P1.17.25, PL03.16
Han, Z. P1.11.28
Han, Z. P1.11.65
Han, Z. P3.12.07
Hanaoka, J. EP.02.11, EP.08.43
Hanash, S. PT1.04.03
Hanash, S. P3.13.09
Hancock, N. EP.01.22, MA09.05
Handa, M. EP.06.28
Hann, C. P3.18.40
Hann, C. L. OA06.03, P1.11.72
Hanna, M. OA09.03, OA13.04
Hanovich, E. P3.09.03
Hans, A. OA17.02
Hansen, J. L. EP.06.42
Hansen, J. EP.01.09
Hao, D. MA03.03, P1.17.42
Hao, J. P1.11.65
Hao, X. OA05.01
Hao, Y. OA05.01
Hao, Z. EP.13.29, MA07.06, MA11.01, OA13.03, P1.17.65, P3.12.03
Hara, K. P1.07.49, P2.02.26
Hara, N. EP.07.56
Hara, S. P2.06.59
Hara, S. P3.13.14
Harada, S. P2.06.27
Haratake, N. EP.07.35, P1.07.49, P2.06.41
Harden, S. EP.13.33, EP.17.02, MA06.06, P1.17.12, P1.17.18, P1.17.61, P3.01.13, PT2.17.02
Harel, M. P2.06.93
Haresh, K. P. MA02.04
Harkenrider, M. M. PL03.06
Harlow, L. P1.04.54
Haro, A. P3.03.05
Harpalani-Manghnani, M. EP.08.37
Harper, E. P2.15 .19
Harpole, D. MA04.09, P2.06.67, P3.18.05
Harputluoglu, H. P2.10.02
Harrell, K. PT1.03.04
Harris, A. P2.15 .32
Harris, C. OA16.02
Harris, E. P2.08 .13
Harris, E. EP.13.47, P2.05.01
Harris, R. EP.01.31
Harris, R. PL03.13
Harrison, N. P3.16.10
Harrison, V. P3.16.18
Harrison-Osagie, G. EP.17.22
Harrold, N. P2.08 .19
Hart, L. P3.18.14
Hart, N. H. P1.17.20
Hartmaier, R. MA03.03, OA02.02
Hartman, C. OA14.05
Haruki, T. EP.07.19, P3.01.44
Harvey, H. P3.12.10
Harvey, P. P3.03.29
Hasan, A. P1.11.14, P1.11.18
Hasegawa, K. P3.16.02, P3.16.12, PT2.16.02
Hasegawa, S. EP.14.05
Haselmann, V. P3.12.61
Hashemi, S. P1.11.62, PT2.11.02
Hashim, M. EP.02.02, P2.02.18, P2.02.22
Hashimoto, H. P1.11.11
Hashimoto, M. EP.14.05, P2.06.41
Hashinokuchi, A. EP.07.50, P1.07.49
Hashki, M. P2.05.05, P2.06.62,

	P2.10.09, P2.10.11, P3.03.31
Hashki, M. K.	P2.06.50
Hashmi, A.	MA03.05
Hashmi, M.	P3.13.31
Hasimoto, E.	EP.01.05
Haskins, M.	PT2.12.04
Hassan, A.	P1.11.77
Hassan, K.	P1.11.77
Hassing, M.	EP.04.32, EP.18.01, P1.04.41
Hastie, A.	EP.06.57
Hasumi, T.	EP.07.34
Hata, A. N.	EP.06.53
Hata, T.	P1.11.40
Hataji, O.	EP.06.81
Hatanaka, K.	EP.14.16
Hatanaka, Y.	P3.09.09
Hatanaka. C, K.	P3.09.09
Hattersley, G.	P3.12.04
Hatton, N.	EP.07.40
Hattori, A.	EP.07.01
Hattori, S.	EP.08.09
Hatz, R.	EP.06.45
Haulon, S.	EP.04.29
Haulon, S.	P1.04.39
Hauss, P.-A.	EP12.64
Hautzel, H.	EP.04.27
Hayakawa, D.	P2.06.95
Hayasaka, K.	EP.14.13, P1.07.13, P1.07.49
Hayashi, F.	EP.06.49
Hayashi, H.	MA08.04, OA06.03, OA10.01, P3.03.30, P3.03.42, P3.12.38, PL02.15, PT1.03.06
Hayashi, S.	EP.06.02
Hayashi, T.	MA07.01, P2.06.25, PL03.16, PT2.14.03
Hayes, J.	P1.07.04
Hayman, T.	P1.07.36, P3.13.26
Hazar Rethinam, M.	EP.06.79
Hazim, A.	P3.13.32
Hazim, A.	P3.18.87
He, C.	EP.12.38
He, C.	EP.03.14, EP.06.56, P2.06.46
He, C.	EP.17.18, P1.17.40
He, D.	P2.02.29
He, J.	P1.07.50
He, J.	MA02.07, MA08.06
He, J.	EP.08.04, EP.15.05, MA04.07, MA05.07, OA02.02, P1.07.01, P3.01.03, P3.01.05, P3.01.12, P3.01.39
He, J.	EP.05.03
He, J.	EP.14.20, P1.17.41
He, J.	P3.01.05
He, J.	P2.02.24
He, K.	P2.08 .47, P3.18.39, P3.18.52, PT2.12.01
He, L.	EP.08.21
He, Q.	EP.13.34
He, R.	EP.06.56, EP.12.38, P2.06.46
He, S. S.	P2.10.15
He, S.	EP.08.01
He, S.	P3.12.32
He, T.	P3.14.23
He, T.	EP.07.14
He, T.	P1.11.51
He, W.	P3.13.27
He, W.	PT2.10.01
He, X.	P1.07.50
He, X.	P1.11.67
He, X.	P3.03.09
He, X.	P3.13.22
He, Y.	P2.06.32, P3.03.10
He, Y.	P1.07.38
He, Y.	MA06.04, MA09.09
He, Y.	EP.14.01
He, Z.	EP.12.44, EP.17.19, P1.11.76, P1.17.38
He, Z.-Y.	EP.12.06
He, Z.	MA11.03, OA10.04, P1.17.36, P3.12.07
Heath, H.	EP.13.29
Hecht, J.	P3.18.87
Hecz, R.	P3.13.03
Hedoux, A.	EP12.64
Heeke, S.	EP.04.31, MA11.06, OA07.01, P2.02.36, P3.13.11, PT1.01.03
Heersche, N.	EP.12.15, EP.12.49
Hegarty, J.	P1.17.49
Hegi-Johnson, F.	EP.13.37
Hei, Y.	EP.12.19
Heidary, M.	EP.06.64
Heikkilä, E. K.	P3.12.72
Heineman, D. J.	P3.18.16
Heinen, K.	OA13.02
Heist, R. S.	EP.06.53
Helali, A.	EP.11.21
Helgeson, J.	P1.17.28
Helian, S.	P3.18.74
Helland, Å.	EP.01.09, P1.11.62, P1.17.67
Heller, L.	P3.12.04
Héluain, V.	EP.17.39
Hemead, H.	EP.07.47
Henchoz, Y.	P1.04.03
Hendriks, L.	MA02.08, P1.17.29, P3.18.80
Hendriks, L. E.	P3.18.54
Heng, C.	EP.15.13
Heng, W.	P1.17.69, P2.10.16
Henn, MHA, K.	P2.06.20
Hennah, L.	P2.06.85
Hennek, S.	OA09.01
Hennessy, B. T.	EP.08.34, P2.06.82
Hennink, M.	EP.16.02, P3.16.01
Henry, A. S.	PT1.01.01
Henry, J. T.	OA08.01, P3.18.71
Henry, S.	P3.01.07
Henschke, C.	OA15.01
Henschke, C. I.	EP.04.14, EP.06.13, P1.07.14, P1.07.19
Henschke, C.	EP.04.13
Henshall, C.	P2.15 .14
Heo, E.	EP.11.12
Herbst, R.	EP.08.46
Herbst, R. S.	MA11.04, P1.07.47
Hering, S.	P2.08 .14
Herman, J.	P1.11.72
Hermann, C.	MA01.07
Hermann, S.	EP.03.12, P3.18.02, P3.18.36
Hermansyah, E.	EP.13.02
Hermens, R.	EP.17.13
Hernández, A.	EP02.12, P3.03.44
Hernández, A.	P2.08 .49
Hernandez, A.	MA09.02
Hernández, E.	EP06.85
Hernandez, S.	PT2.13.03
Hernandez, S.	EP.06.43
Hernández Ferrandez, J.	EP.08.07
Hernández-Gallego, A.	EP.06.48
Hernández González, A.	EP.06.78
Hernández-Losa, J.	EP.06.48
Hernández Martínez-Esparza, E.	P2.15 .12
Hernando, F.	MA01.01
Hernando - Trancho, MD, F.	MA01.03
Hernan Trancho, F.	P3.14.19
Herold, S.	P3.03.54
Herraez-Baranda, L.	MA10.06
Herrera, M.	P3.14.11
Herrera, R.	EP.08.19
Herrera Gorrín, L.	EP.12.63
Herrera-Gorrín, L.	EP.08.37
Herrera Martinez, L.	EP.06.78

Herrero, R. P3.03.45
Herrero Márquez, A. EP.12.63
Herrero-Márquez, A. EP.08.37
Herrmann, K. EP.04.27
Herzberg, B. P2.06.12
Herzog, B. EP.13.40
Heukamp, L. OA09.03, P1.11.48
Heuvelmans, M. EP.04.02, OA01.01, P1.04.02, P1.04.09, P1.04.25
Heuvelmans, M. A. P1.04.06, P1.04.11
Heymach, J. OA07.01, OA09.01, P1.11.55
Heymach, J. V. EP.04.31, MA04.09, MA10.05, MA11.06, OA13.02, P1.11.53, P1.11.60, P1.11.70, P2.02.24, P2.02.36, P3.13.09, PT1.01.03, PT2.12.03, PT2.13.03
Hibino, M. P1.11.40
Hibino, Y. P3.12.35
Hicks, A. EP.17.01
Hicks, D. P3.13.26
Hicks, D. EP.16.06, PT2.16.01
Hicks, J. MA10.05
Higgins, K. EP.13.37, P2.08 .23
Hijazo-Pechero, S. EP.03.13, EP.14.03, PT1.08.04
Hila, M. A. EP.15.19
Hiley, C. P2.08 .19, P3.09.02
Hill, K. L. PT2.12.01
Hill, T. EP.13.04, MA05.03, P1.04.12, P1.17.13, P3.01.26
Hill, T. EP.17.32
Hillinger, S. EP.04.16, EP.04.34, EP.08.52, EP.09.10
Hiltermann, T. J. P3.18.35
Hiltermann, T. MA04.05
Hingorani, P. EP.17.35, OA06.04
Hiong, A. EP.13.33, PT2.17.02
Hiraiwa, N. EP.01.28
Hirama, R. PT1.05.02
Hirama, T. EP.07.38
Hirao, M. EP.01.29
Hiraoka, M. P3.12.32
Hirata, Y. EP.13.18
Hiremath, M. P3.18.65
Hiret, S. MA08.03, P3.18.68
Hironouchi, H. P3.18.65
Hiroshima, K. EP.14.02
Hirsch, F. OA13.04, OA18.01
Hirsch, F. R. OA11.02, P2.02.09
Hisamatsu, K. P2.06.16
Hishida, T. EP.07.01
Hjorthorn, O. P3.13.17
Ho, C.-C. EP.12.21, P3.12.13, P3.12.27
Ho, C. EP.01.02, EP.08.17, EP.13.38
Ho, E. P2.15 .30
Ho, I. P2.06.90
Ho, L. OA15.02
Ho, Y.-Z. MA05.02
Hoang, P. OA14.05
Hochmair, M. P1.07.35
Hochmair, M. J. OA02.02
Hochmair, M. P3.12.10
Hochman, T. OA15.03
Hock, K. OA04.04
Hocking, A. EP.17.09
Hod, K. EP.17.20
Hoda, M. A. EP.02.02
Hoda, M. R. P2.02.18
Hoda, M. P2.02.22
Hodges, R. EP.06.68
Hoehn, M. PT1.03.04
Hofer, B. P1.17.03
Hofer, T. P2.10.01
Hoffknecht, P. P3.12.14
Hoffman, R. EP.07.47
Hoffmann, K. P1.17.67
Hofmaier, J. P2.08 .14, P2.08 .14
Hofman, P. MA07.01, OA13.04, P2.06.87, P2.06.88, P3.18.60, PL03.16
Hofman, V. P2.06.87
Hofmann, K. P3.16.16
Hofmarcher, T. P1.17.29
Hofstetter, W. P2.02.36
Hofstetter, W. L. PT1.01.03
Hogea, C. EP.17.32
Högerman, M. P1.17.67
Hohlbauch, A. P1.17.63
Hojo, M. EP.14.21
Holjak, E. P2.06.70
Holley, R. OA16.02
Hollingsworth, S. OA03.03
Hollinshead, G. P3.16.10
Holouka, G. EP.01.05
Hölsä, O. EP.01.09
Holtz de Camargo Barros, L. P3.16.04
Homer, R. OA14.05
Hominal, S. P2.06.43
Honda, N. EP.06.49
Honda, Y. EP.06.28
Honeyball, F. P1.17.20
Hong, B.-K. P2.02.20, P2.06.38
Hong, C. EP.04.21, P1.04.22
Hong, C.-Y. EP.18.09
Hong, C. P3.18.46, P3.18.48
Hong, H.-Z. P1.04.21
Hong, H. OA03.01
Hong, L. EP.04.31, P1.11.55, P1.11.70
Hong, M. H. OA10.01
Hong, M. OA02.01, P2.06.48, P3.12.37
Hong, Q. MA08.01
Hong, T. P2.06.48
Hong, T. P1.07.20
Hong, W. P3.13.15
Hong, W. P3.09.07
Hong, X. P3.14.10
Hong, X. P2.10.16
Honigberg, B. P3.18.06
Hontsu, S. EP.07.56
Hood, B. EP.03.01
Hooper, J. EP.04.03, P1.17.35
Hope, A. EP.14.15
Hori, K. P3.12.35
Horiguchi, M. P3.01.18, PT2.15.02
Horinouchi, H. EP.04.08, P3.18.04, PT2.10.02
Horling, K. OA09.03
Horn, M. PT1.03.01
Horrigan, S. K. PT2.12.01
Horugsa, C. EP.17.29
Horvath, I. P1.04.54
Horvath, L. MA11.06, P3.13.03
Hoshi, F. EP.07.34
Hoshi, R. EP.02.09, P3.03.38
Hoshino, H. P1.07.49, P2.06.41
Hosomi, Y. EP.12.29, P3.12.09, P3.12.23, P3.18.04, P3.18.25
Hotta, K. MA07.03
Hou, L. EP.06.31, EP.06.36, EP.08.35, EP.08.49, P2.06.06
HOU, M. EP.13.42
Hou, N. PT1.02.04
Hou, R. EP.07.18
hou, x. P2.08 .50
Hou, X. PT2.10.03
Hou, X. EP.12.40
Hou, X. MA10.01, OA10.02, OA10.03, P3.18.69, P3.18.83
Hou, Z. P1.11.20
Houda, I. MA02.08, P1.11.62, P3.13.16, P3.18.16,

	PT2.11.02
Houghton, B.	OA03.04
Houssami, N.	P3.16.10
Houvras, Y.	P3.18.29
Hovey, C.	EP.15.15
Howard, S. E.	OA18.04
H.Owen, D.	EP.17.32
Hrabak Paar, M.	OA15.01
Hrubesz, G.	EP.06.54
Hruschka, G.	EP.01.05
Hsiao, C.-F.	P3.12.27
Hsiao, M.-P.	P2.15 .23
Hsieh, M.-S.	EP.06.20, EP.07.08, OA07.04
Hsieh, P.-C.	MA05.02
Hsing, S.	P2.06.89
Hsu, C.-C.	EP.03.04
Hsu, C.-L.	EP.12.21, P3.12.27
Hsu, C.-C.	P2.15 .23
Hsu, H.-H.	EP.06.20, EP.07.16, OA07.04
Hsu, J.	P3.12.38
Hsu, J.	OA02.01
Hsu, L.-I.	P1.17.63
Hsu, M.	P1.04.04, P2.15 .18, P2.15 .24, P3.13.12
Hsu, M. L.	EP.17.03, OA17.04, P2.15 .19, P3.01.19, PT2.16.05
Hsu, P.	PT1.03.01
Hsu, P.-K.	P2.06.02
Hsu, R.	MA07.06, P1.17.58, P1.17.65, P2.06.52
Hsu, W.-H.	EP.03.04, P3.12.27
Hsu, Y.-H.R.	EP.06.31
Hu, C.	EP.13.37, OA12.03, P1.11.72
Hu, C.	EP.12.08, P3.13.15
Hu, H.	EP.13.44, OA06.03
Hu, H.	P1.11.13
Hu, J.	P3.18.42
Hu, J.	EP.01.15, EP.04.25, EP.07.55, P3.18.08
Hu, J.	P3.18.32
Hu, J.	P2.02.09, P2.10.13, P3.12.55
Hu, M.	P3.18.79, PT2.13.01
Hu, M.	EP.07.41
Hu, N.	OA02.03
Hu, S.	EP.01.15
Hu, S.	EP.11.16
Hu, T.	P3.13.20, PT1.06.04
Hu, T.	P3.12.38
Hu, W.	P3.01.28
Hu, X.	PL03.07
HU, X.	P3.12.74
Hu, X.	P2.06.101
Hu, X.	P3.12.25
Hu, Y.	OA05.01
Hu, Y.-F.	P2.10.14
Hu, Y.	P3.03.18
Hu, Y.	MA08.01, P3.13.22
Hu, Y.	P2.06.98
Hu, Y.	EP.11.15
Hu, Z.	OA03.02
Hu, Z.	P3.12.04
Hu, Z.	PT1.06.04
Hu, Z.	EP.08.06, P3.03.43
Huag, J.	P2.10.14
Huang, B.-T.	P3.03.21
Huang, C.	EP.14.14
Huang, C.	P1.07.55, P2.06.77, P3.13.33
Huang, C.-L.	EP.06.33
Huang, C.-Y.	MA05.02
Huang, C.-K.	EP.12.21
Huang, D.	EP.13.35
Huang, D.-R.	EP.03.04
Huang, D.	MA08.01, MA11.03, P1.11.46, P1.11.83, P3.12.73, P3.18.86, PT2.10.04
Huang, D.	EP.08.21
HUANG, F.	P2.15 .07
Huang, F.	P3.18.42
Huang, F.	P3.18.32
Huang, G.	EP.12.39
Huang, G.	P3.18.05
Huang, G. H.	PT1.06.02
Huang, H.	EP.15.05, P1.07.01
Huang, H.	EP.06.70
Huang, H.-C.	P2.10.04
Huang, H.	P2.08 .55
Huang, J.	P3.12.38
Huang, J.	P1.04.17, P2.08 .25, P3.01.22, P3.18.11
Huang, J.	EP.06.38
Huang, J.-A.	P2.02.47
Huang, J.	P3.12.31, P3.12.48, PT1.09.04
Huang, J.	PT1.03.02
Huang, J.	P2.10.14
Huang, J.	P2.02.42
Huang, J.	P3.12.63, P3.14.22
Huang, K.-P.	MA05.02
Huang, L.	P1.11.02
Huang, L.	EP.15.05
Huang, L.	P2.08 .45
Huang, M.	P3.12.31, P3.12.47
Huang, M.	EP.06.59
Huang, M.	OA15.02
Huang, M.	EP.06.38
Huang, P.-C.	EP.12.23
Huang, P.-C.	EP.13.25
Huang, Q.	P2.02.24
Huang, Q.-L.	EP.12.60
Huang, Q.	P1.11.14, P1.11.18
Huang, Q.	EP.12.39
Huang, Q.	EP.11.24
Huang, R. S.	P1.07.37, P1.11.57, P1.17.66
Huang, S.	PT1.06.04
Huang, W.	P2.06.101
Huang, W.-Y.	P2.08 .35
Huang, W.-Z.	OA03.02
Huang, W.	PT1.03.02
Huang, W. T.	MA02.06
Huang, X.	P2.08 .34
Huang, X.	EP.12.09, P2.02.19, P2.02.42, P3.03.50
Huang, X.	MA06.05, P1.17.23
Huang, Y.	EP.06.36, EP.08.35, EP.08.49, OA10.03, P1.17.36, P2.06.06, P3.13.27
Huang, Y.	P1.04.42
Huang, Y.	P2.08 .43
Huang, Y.	P3.18.39
Huang, Y.	EP.15.05
Huang, Y.	P2.06.14
Huang, Y.	P1.07.06
Huang, Y.	OA05.01
Huang, Y.	OA06.01, P3.12.18
Huang, Y.	P1.04.24
Huang, Z.	P3.12.18, P3.12.73
Huang, Z.	PT2.10.02
Huang, Z.	EP.12.39
Huang, Z.	P1.07.42
Huang, Z.	EP.13.23
Huang, Z.	P2.02.42
Huang, Z. J.	P3.03.29
Huang, Z. J.	PT1.06.02
Huang, Z.-J.	P1.11.61, P3.01.37
Huang, Z.	EP.06.41, P2.06.24, P2.06.34
Hueniken, K.	EP.06.31, P1.04.29, P3.03.03
Hughes, A.	P2.02.27
Hughes, B.	P1.17.62, P2.06.99, P3.18.80
Hughes, B. G.	OA03.04, P3.12.65
Hughes, J. D.	EP.06.68
Hui, R.	EP.11.21
Hui, Y.	MA10.01, P3.13.25

Hui, Z. P3.18.47
Huidobro, G. P3.18.12
Hulbert, A. P2.06.69, P3.01.26
Hulenka, A. EP.08.08
Hung, J.-J. P3.12.60
Hung, R. P1.04.33, P1.04.34, PT1.04.04
Hung, R. J. MA05.06, P1.04.29
Hung, R. OA13.04
Hung, Y. P. EP.06.53
Hunt, A. S. EP.03.16, P3.03.46, P3.03.48
Hunt, A. J. EP.03.01
Hunting, J. P3.18.14
Hurtado, M. P2.06.43
Husain, A. P2.06.65
Husain, H. EP.06.69, EP.06.76
Huser, J. EP.06.83
Hussain, A. N. OA12.01
Hussain, S. EP.01.24, EP.01.25
Hussey, A. P1.17.46
Hwang, D. M. PL03.16
Hwang, J. EP.01.18
Hwang, S. P1.07.52, P2.06.48
Hwang, S.-H. P2.02.11
Hydbring, P. EP.12.26
Hyde, C. P3.16.18
Hyoung, S. P3.18.05
Hyun, K. P1.07.29, P3.14.14

I

Iachecen, F. EP.01.05
Iacobucci, A. P1.04.51
IASLC Pathology Committee members, I. MA07.01
Ibañez Esteve, C. EP.05.01
Ibarra, C. EP.14.27, EP.17.27
Ibekwe-Agunanna, L. N. EP.04.06
Ibrahim, A. H. P3.13.11
Ibrahim, M. N. EP.01.11
Ibrahim, O. MA10.02
Ichihara, E. P3.03.42, P3.12.33
Ichikawa, A. EP.17.05
Ichikawa, Y. EP.04.36
Ichinoe, M. EP.06.02, EP.06.12
Icht, O. EP.14.15, P3.09.03
Igbinoba, F. EP.17.22
Igbinomwanhia, V. EP.17.22, P1.17.76
Iglecia, N. P3.14.24
Iglesias, B. P3.03.45
Iguaran, A. P2.08 .49
Igwegbe, I. PT2.12.04
Iheagwara, U. K. PL03.06
Ihrke, E. P2.15 .01
Ikeda, N. EP.07.54, EP.08.40, P2.08 .06
Ikeda, S. P3.16.12
Ikeda, T. P3.12.49
Ikezawa, Y. P3.09.09
Ikoma, T. P1.11.40
Ikushima, H. PT1.03.05
Ikutegbe, K. P1.17.76
Ilfeld, L. EP.06.50
Ilie, M. P2.06.87
Illei, P. B. OA12.03
Illini, O. P1.17.29
Ilonen, I. P1.17.67
Ilves, P. P1.04.37
Imakita, T. P3.12.44
Imamura, Y. EP.06.70, P1.11.47
Imasa, M. B. P1.11.79
Imazu, R. EP.07.36
Imbimbo, M. EP.06.35, P3.18.82
Imbrescia, J. EP.13.05
Impalà, G. A. P2.06.22
Inampudi, K. K. EP.02.08
Incalcaterra, F. EP.13.05
Inculet, R. P2.06.70
Infurna, C. EP.11.01
Inge, L. J. OA09.03
Inoue, C. EP.04.18, EP.06.26
Inoue, H. P2.02.26
Inoue, H. P3.18.31
Inoue, M. EP.06.28
Inoue, R. EP.06.81
Inoue, T. EP.11.06
Inoue, Y. P3.03.03
Insa, A. MA06.03, P3.03.45, P3.12.30, P3.18.12
Insa , MD, A. MA01.03
Insolda, J. P3.12.08, PT2.15.01
Intagliata, S. P1.11.01
Invernizzi, L. MA06.07, OA09.02, P1.04.51
Invernizzi, L. M. P1.17.30, P1.17.44, P2.15 .34
Iovashvili, A. EP.17.26
Ippolito, E. EP.08.13, P2.08 .30
Iqbal, A. MA01.06, P3.18.11
Iranita Liza, F. EP.13.02
Iranzo, P. OA05.03, P3.12.30, P3.14.02
Ireland, L. P2.02.27
Irving, L. EP.13.33, P1.17.18, P3.01.13, PT2.17.02
Irving, L. EP.17.02, PT2.17.02
Isaac, J. PT2.16.04
Isaka, M. EP.07.01, EP.14.13, P1.07.13
Isaka, T. EP.07.01, EP.07.07, EP.07.24, EP.09.13, P2.08 .33
Isaksson, J. EP.13.22, OA05.04, P3.18.56
Isaksson, S. P2.02.40, P3.18.56
Isbell, J. P1.04.17, P3.01.22, P3.18.11
Ishchanov, D. G. EP.08.25
Ishihara, D. EP.02.11, EP.08.43
Ishii, G. P2.06.59
Ishii, M. P3.12.35
Ishii, S. EP.13.18
Ishimoto, L. EP.01.05
Ishimura, K. P2.06.16
Ishizawa, K. P1.17.68
Ishizawa, S. P1.17.19, P1.17.81, P3.01.47
Isla, D. MA10.06, P3.18.34
Islam, H. EP.01.30, MA06.02
Islam, M. EP.11.22
Islam, M. R. EP.01.30, MA06.02
Ismayilov, R. P2.08 .36
Iso, H. EP.08.42, EP.13.11, P3.12.54
Isobe, T. EP.11.08
Israeli, E. P1.04.36
Israel-Isah, S. EP.17.22
Israeli Weller, N. P3.09.03
Israel Moreno, T. EP.05.01
Issanov, A. P3.01.35
Issard, J. EP.04.29, P1.04.39
Isse, K. EP.06.50
Italiani, M. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Itchins, M. OA03.04, P1.17.62, P2.06.89
Itel, M. P1.04.08
Itelson, L. EP.04.41
Ito, D. EP.08.05, EP.14.25
Ito, H. EP.07.07, EP.07.21, EP.07.24, EP.07.54, EP.09.13, MA04.05, OA02.03, P2.08 .33, P3.18.04
Ito, K. EP.06.19
Ito, K. EP.06.81
Ito, M. EP.08.42, EP.13.11, P3.12.54
Ito, M. EP.05.07, EP.06.46, P1.07.49, P3.09.05
Ito, S. P3.09.09
Ito, T. P3.12.44
Itoh, S. P3.03.42
Itoh, T. P3.18.25
Iurato, A. EP.08.13, P2.08 .30
Ivancík, J. P1.17.29

Ivanova, E. P3.12.63
Ivey, S. EP.16.01
Iwama, E. P3.18.04
Iwamoto, N. EP.07.11
Iwanaka, S. P2.08 .08
Iwane, T. EP.13.14
Iwao, C. EP.13.14
Iwasaki, K. P3.13.01
Iwasawa, T. EP.07.04, EP.08.02
Iwawaki, N. P3.03.30
Iwaya, M. P2.06.47
Iwuji, C. P1.17.76
Iyengar, P. EP.08.51, EP.13.08, EP.14.22, OA07.02, OA18.02
Izergina, P. A. EP.08.25
Izquierdo, P. A. P2.06.75
Izumi, H. P2.06.59, P3.12.32, P3.12.49, PT1.05.02
Izumi, N. P2.02.26

J

Jabar, F. P1.11.62
Jabbour, S. K. PL03.06
Jacinto, A. P2.08 .18
Jackson, E. P1.04.54
Jacob, T. G. EP.02.08
Jacobovitch, S. EP.03.08
Jacobs, C. EP.18.01, OA01.01
Jacobs, F. P1.07.51
Jaeger, D. MA04.06
Jaén, Á. EP.05.08, P1.07.24
Jafarova, K. P3.12.51
Jaffee, E. P3.18.40
Jagiasi, S. EP.01.06, EP.12.01
Jahromi, M. S. PT1.03.01
Jaimes-Alpizar, E. P1.17.73
Jain, D. EP.06.22, EP.06.27, EP.13.46, EP.14.12, MA07.01, MA09.08, OA13.04, P3.18.72, PL03.16, PT1.06.03, PT2.17.04
Jain, P. EP.08.32
Jain, S. EP.14.12
Jain, S. EP.06.73, P2.06.89
Jaiswal, A. EP.06.58
Jakhetiya, A. EP.07.37, EP.14.04, EP.14.28
Jakhetiya, B. EP.14.28
Jaklitsch, M. T. EP.07.33, P1.17.27
Jakopović, M. OA15.01, P2.15 .06
Jakopovic, M. P1.17.29
Jalal, S. P2.10.01
James, H. P2.15 .31
James, J. OA09.03
James, T. EP.16.01
James, Y. P2.15 .32
Jamil, M. PT1.08.03
Jamnik, S. EP.17.31, PT1.01.02
Jamwal, A. P1.17.79
Janes, S. P2.08 .11
Jang, H. P3.12.68
Jang, S. MA05.08
Jani, C. P3.01.52, P3.14.01
Jani, C. T. EP.12.34
Jani, K. P1.07.36
Janjic, P. P2.08 .20
Jankowski, T. P1.11.82
Jankowski, T. EP.06.17, EP.13.17, MA10.04, P1.11.63
Janne, P. OA08.01, P3.12.62, P3.14.22, P3.18.58
Jänne, P. A. P2.06.44, P3.12.41
Janne, P. A. P3.12.63
Jänne, P. A. P3.18.61, P3.18.71, PL02.06
Jännie, P. MA08.01
Janning, M. P3.12.61
Janssens, A. P1.17.67
Janthur, W. EP.06.83
Jantus-Lewintre, E. EP.06.77
Janzen, I. P1.04.18
Janzic, U. P1.17.29
Jaques, L. EP.07.40
Jara-Acevedo, M. P2.02.41
JARABO, J. R. MA01.01
Jardin, C. F. P1.17.11
Jarry, U. P2.06.79
Jaruwattanakun, T. P3.01.30
Jasik, A. P1.17.28
Jasna But Hadzic, J. P2.08 .16
Jassim, R. P3.12.13
Jaus, M. o. EP.04.30
Jayakrishnan, R. P1.17.54
Jayram, D. MA06.09, P3.01.52
Jayram, D. K. EP.13.32
Jean, B. P3.18.67, P3.18.68
Jean-Baptiste Salomonsen, R. P1.17.58
Jefferies, J. PT1.03.01
Jeffery, D. P1.17.47
Jeji, T. EP.15.06
Jelercic, S. P2.08 .16
Jelercic, S. EP.13.13
Jemsi, M. P1.07.28
Jeng, M. Y. P3.03.01
Jensen, E. MA04.04
Jeon, H. EP.13.41
Jeon, J. P1.07.52
Jeon, J. P1.04.07, P3.01.42
Jeon, Y. EP.07.46, EP.08.29, P1.07.15, P2.08 .31
Jeong, D. EP.07.46, EP.08.29, P2.08 .31, PT2.11.04
Jesus, J. P1.17.52
Jetani, V. P3.01.15
Jetani, V. S. P3.01.16
Jha, S. P1.11.45
Jha, S. P2.06.94
Ji, H. P2.06.66
Ji, P. P2.06.99
Ji, W. EP.01.18, EP.12.12, EP.13.21, MA05.08, PT1.09.05
Ji, X. EP.14.01
Ji, Y. P3.13.31
Ji, Y. OA06.02, OA10.04, P1.11.76, P1.11.83
Ji, Y. OA06.02
Jia, B. EP.07.45
Jia, C. EP.06.67
Jia, C. EP.08.06
JIA, R. P3.12.74
Jia, S. EP.06.67
Jia, X. MA10.09, P1.11.52
Jia, Y. EP.11.19
Jia, Y. OA06.02
Jiang, A. EP.12.20
Jiang, B. P1.04.02, P1.04.06, P1.04.09, P1.04.11
Jiang, B.-Y. EP.08.31, OA03.01, P1.07.55, P2.08 .35, PT1.09.03
Jiang, B. P2.06.98
Jiang, B. OA10.04
Jiang, C. P1.11.44
Jiang, F. P3.18.08
Jiang, F. EP.13.35
Jiang, G. MA10.01, OA10.02
Jiang, H.-M. OA03.02
Jiang, H. PL02.06
Jiang, H. P2.02.24
Jiang, J.-Z. P3.12.59
Jiang, J. MA04.08
Jiang, J. EP.12.08
Jiang, J. P1.11.64
Jiang, J. PT2.10.04
Jiang, K. P3.12.18
Jiang, L. P2.06.98, P2.08 .44
Jiang, L. P3.12.66
Jiang, L. EP.08.27, P2.06.28

Jiang, L. P1.17.69, P2.10.16, PL02.06
Jiang, L. P1.11.34
Jiang, O. OA06.02, P3.12.64
Jiang, T. OA03.02, P3.03.53
Jiang, W. PL03.07
Jiang, W. MA10.05
Jiang, w. EP.18.10, P3.12.22
Jiang, X. P2.06.63
Jiang, Y. P3.12.38
Jiang, Y. EP.15.05
Jiang, Y. EP.13.06
Jiang, Z. P3.12.52
Jiang, Z. MA07.07
Jiao, W. P2.08 .29
Jie, G.-L. P2.08 .35, P3.03.14, P3.13.24
Jie, Y. P1.11.70
Jimenez, E. P3.01.25
Jiménez, F. PT1.08.04
Jiménez, M. OA01.02, P3.01.46
Jimenez, M. EP.08.22, P1.07.35
Jiménez, U. MA01.01, P2.08 .28
Jiménez Cabrera, S. P2.15 .03
Jiménez-Hernández, F. EP.03.13
Jimenez-Kurlander, L. P3.18.61
Jiménez-López, M. P2.02.41
Jimenez-Mendoza, E. P3.01.42
Jimenez Munarriz, B. E. P3.14.11
Jimenez-Sanchez, D. P2.06.66
jin, b. P2.15 .28, P3.12.48, P3.12.64, P3.18.62
Jin, R. EP.18.03
Jin, S. P1.11.14
Jin, W. EP.13.35
Jin, X. EP.12.27
Jin, Y. EP.13.35
Jin, Y. P1.04.31
Jinawath, A. P3.12.28
JING, D. P3.12.74
Jing, L. P3.18.77
Jinga, M.-R. P2.06.85
Jiyeon, K. P2.06.69
Jizawi, A. P2.06.56
J. Kwiatkowski, D. P1.11.62
Jo, A. P3.18.57, PT2.12.02
Jo, S. P3.12.37
Jobanputra, K. EP.01.06, EP.01.08, EP.06.34, EP.12.01
Jobanputra, K. N. P3.12.05
Johansson, M. EP.04.04, MA05.06, OA01.03, PT1.04.04
Johansson, M. EP.06.11, P3.18.56, PT1.04.04
John, A. P3.01.21
John, T. MA06.06, MA08.01, OA03.04, P2.06.61
John, T. EP.13.33, EP.17.02, P1.07.47, P1.17.18, P3.01.13, PT1.03.04, PT2.17.02
Johne, A. P3.12.10, P3.12.40
Johns, N. P2.08 .47
Johnson, B. PT2.15.02
Johnson, B. E. P1.07.37
Johnson, D. H. EP.04.06
Johnson, F. D. EP.02.03
Johnson, G. P3.13.32
Johnson, J. P3.18.84
Johnson, K. EP.06.68
Johnson, M. P3.12.13, P3.12.58, P3.18.65, P3.18.73, PL02.15
Johnson, M. L. MA02.06, OA06.03, OA08.01, P3.18.28, P3.18.38, P3.18.61
Johnson, M. P3.18.68
Johnson, S. P2.15 .32
Johnson, S. P1.17.42
Jones, A. C. P1.17.47
Jones, D. P3.01.22, P3.18.11
Jones, D. R. MA04.04, P1.04.17
Jones, J. MA08.02
Jones, K. P3.16.18
Jones, K. OA14.05
Jones, L. P3.18.84
Jones, T. P1.17.59, P3.13.07
Jongebloed, H. P1.17.20
Jongen, J. L. EP.12.49
Jonsson, B.-A. EP.06.11
Jönsson, M. P2.02.40, P3.18.56
Jopling, J. EP.04.38
Jordi-Ollero, O. EP.16.04, P2.08 .60
Jörger, M. P3.18.82
Joseph, B. P3.01.34
Joseph, R. OA10.01
Josephides, E. P1.17.55
Josephson, N. P3.03.29
Joshi, A. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Joshi, K. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Joshi, M.-B. P2.06.67
Joshi, R. P3.01.14
Josten, M. P3.12.61
Joubert, D. P2.06.87
Joubert, P. MA07.01, MA07.04, OA09.03, OA14.05, P1.11.36, PL03.16
Joubert, P. OA13.04
Jove, J. P2.08 .49
Jove, M. P2.06.37
Jové Teixidó, J. EP.08.47
J. Pinato, D. P1.11.62
Ju, Y. P3.13.23
Juan - Vidal, O. OA05.03, P3.01.25
Juan Vidal, O. P1.11.07, P3.18.74
Juan-Vidal, O. OA10.01, P3.12.38, P3.18.12, PL03.10
Juan-Vidal, O. J. MA08.02
Juergens, R. MA08.07, P2.10.06
Juergens, R. A. P3.18.35
Juhlin, A. EP.13.22, P1.17.14
Juneau, P. EP.13.25
Jung, C. P2.08 .01, PT1.09.02
Jung, E. P2.02.11
Jung, H. EP.07.46, EP.08.29, P1.11.32, P2.08 .31, PT2.11.04
Jung, J. EP.06.32
Jung, J. P2.06.01
Jung, S. P1.07.25
Jung, Y. EP.01.18
Jungblut, L. EP.04.16
Júnior Costa, Í. EP.01.05
JV, M. EP.09.03, EP.09.07
JV., M. EP.08.20, P1.17.72

K

Kaburaki, Y. EP.07.24, EP.09.13, P2.08 .33
Kachi, K. P3.16.12, PT2.16.02
Kaczorowska, M. MA01.07
Kadomatsu, Y. EP.06.70, P1.11.47
Kaesmann, L. MA02.08
Kagalwalla, S. P1.11.71
Kagamu, H. PL02.06
Kage, H. PT1.03.05
Kahala, D. EP.06.73
Kahn, A. PT1.01.01
Kahya, Y. P3.18.01
Kaifi, J. P1.07.37
Kailar, R. S. EP.17.03
Kaira, K. P1.11.40, PT2.14.03
Kaji, M. P1.07.21
Kajiwara, K. EP.13.12
Kakihana, M. EP.08.40, P2.08 .06
Kakinaha, M. EP.07.54
Kakked, S. EP.12.35
Kakuto, S. EP.03.03
Kalantri, S. P1.17.59, P3.13.07

Kalashnikova, E. MA03.02
Kalaskar, P. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Kalemkerian, G. P3.12.71, PT1.03.01
Kalfoutzou, A. EP.01.19
Kali, K. EP.01.23
Kalinka, E. MA10.04, MA10.09, P1.11.63
Kaltman, R. J. EP.04.24
Kalvapudi, S. P1.17.54, P1.17.55
Kam, J. P3.12.46
Kamada, K. EP.07.35
Kamali, C. EP.12.16, P3.13.17
Kaman, H. P1.07.28
Kamigaichi, A. P1.07.49
Kamio, T. P3.18.58
Kammer, M. P2.06.43
Kammer, M. N. EP.04.42
Kampschroeder, A. EP.16.06
Kamranpour, N. P2.02.16
Kamtam, D. N. P1.04.19
Kan, T. P3.03.28
Kanai, M. MA08.04
Kanai, O. P3.12.44
Kandar, B. P1.11.80
Kane, E. EP.06.58
Kane, R. P3.16.14
Kaneda, H. P3.12.33, P3.18.31
Kaneda, S. EP.08.05, EP.14.25
Kanemaru, R. P2.06.95
Kanematsu, T. EP.13.12
Kanemura, H. P3.03.30
Kang, C. H. P2.05.08
Kang, C. EP.07.31, P2.08 .02
Kang, C. PT1.09.05
Kang, D. EP.04.12
Kang, D.-Y. P3.01.45
Kang, E. C. EP.12.27
Kang, E. P1.11.32
Kang, H.-R. P1.07.25
Kang, j. EP.08.27, P2.08 .09, P2.08 .44
Kang, J.-H. P3.12.68
Kang, J. P3.18.79
Kang, J. J. P1.07.36
Kang, L. EP.14.14
Kang, L. EP.17.18, P1.17.40
Kang, M. P3.13.34
Kang, M.-S. P2.02.11
Kang, X. OA06.02
Kang, Y. EP.12.02
Kang, Y. EP.06.32
Kang, Y. EP.02.05
Kang-Fortner, Q. P3.18.74
Kanitthaniyom, C. EP.06.65
Kanno, C. EP.07.24, EP.09.13, P2.08 .10, P2.08 .33
Kanovsky, MHSA, D. P2.06.20
Kanters, D. EP.12.52
Kanu, C. T. P1.17.76
Kao, S. MA02.03, P1.17.62, P3.12.21, P3.18.74, PL02.15
Kao, S. C. P2.06.63
Kao, T.-N. EP.06.20, EP.07.26
Kapoor, R. P1.17.79
Kapoor, S. P2.06.17, P2.06.18
Kapula, N. P1.04.20
Kar, I. P2.08 .15, P3.01.09
Kara, H. V. EP.04.23
KARABULUT GUL, S. EP.13.43
Karacin, C. OA13.02
Karacosta, L. P3.13.09
Karacosta, L. G. P2.06.84
Karadurmus, N. P2.10.02, P3.12.46
Karam, D. P3.18.87
Karam Prasad, D. P1.17.51
Karapanagiotou, E. P1.17.54
Karas, T. P3.18.05
Karasoy, D. P3.18.01
Karatkevich, P. EP.06.63, P3.18.23
Kareff, S. OA18.01
Karger, A. P3.03.54
Karia, P. S. P3.12.39
Karikios, D. P1.17.20
Karim, N. P2.08 .23
Karipidis, S. P1.17.47
Karis, S. P2.08 .19
Karki, U. P1.11.50, P3.13.28
Karkouri, M. P2.10.07
Karlowatz, N. EP.06.11
Karlsson, A. P2.02.40, P3.18.56
Karout, L. OA18.04
Karu, H. P1.17.49
Karukonda, P. P2.08 .13
Kasajima, R. EP.07.07
Kasbekar, P. MA10.07, P1.11.85
Kase, K. P1.11.06
Kas-Elyas, K. P3.13.17
Käsmann, L. P3.16.19
Kassahun, S. P1.07.11
Kassam, S. P3.13.31
Kassin, M. MA07.02
Kastelijn, E. A. P3.13.16
Kasymjanova, G. EP.13.38
Katakami, N. P3.12.33
Katakura, S. EP.07.07, EP.12.29, P3.12.09, P3.12.23
Kataoka, Y. EP.02.11, EP.08.43
Kataria, N. P3.12.02
Kataria, P. P2.06.94
Katayama, H. PT2.16.02
Katayama, H. P3.18.04
Katayama, I. P2.06.95
Katayama, I. EP.13.12
Katayama, R. EP.03.03, P3.03.42
Katayama, Y. P3.03.12
Katcher, J. P3.01.01
Kathawate, V. PT1.03.01
Kather, J. N. P2.15 .34
Kato, T. EP.13.12, P3.12.33
Kato, T. EP.01.29
Kato, T. EP.06.70, EP.14.05, P1.11.47
Kato, T. EP.04.36, EP.06.84, EP.14.16, P1.07.21, P3.09.09
Kato, T. P3.18.38
Kato, Y. EP.11.07, EP.12.29, P3.12.09, P3.12.23
Katodritis, N. EP.08.18
Katona, Z. P1.17.29
Katsumata, S. EP.14.13, P1.07.13, P1.07.49, P2.06.41
Katsuno, M. P2.06.47
Katsurada, N. P3.12.33
Katzel, J. P2.15 .31
Kauffmann-Guerrero, D. EP.03.12, EP.06.45, EP.11.23, EP.12.56, P3.12.67, P3.16.19, P3.18.02
Kaufman, J. P2.08 .47, PT2.12.01
Kaufman, R. P3.01.18, PT2.15.02, PT2.17.04
Kauke, T. P3.18.02
Kauke, T. EP.03.12
Kauko, T. P1.17.67
Kaul, M. MA10.09
Kaul, M. MA11.04
Kauppi, P. P1.17.67
Kaushik, R. PT1.01.01
Kawachi, H. P1.11.40
Kawaguchi, K. EP.08.05, EP.14.25
Kawaguchi, T. EP.08.05, EP.14.25, EP.14.25
Kawaguchi, T. P3.12.33

Kawaguchi, T. EP.07.56
Kawaguchi, Y. EP.02.11, EP.08.43
Kawaguchi, Y. P2.08 .06
Kawai, D. EP.13.14
Kawai, K. EP.01.29
Kawaii, H. MA07.03
Kawakami, S. P3.16.12
Kawakita, N. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Kawamura, M. EP.07.34
Kawamura, T. EP.11.06
Kawano, Y. EP.13.18
Kawasumi, Y. EP.06.70, P1.11.47
Kawata, T. P1.07.13
Kayı Cangır, A. P3.18.01
Kaye, M. OA17.03
Kaynak, K. EP.04.23, EP.05.04
Kazerooni, E. P1.04.32
Kazerooni, E. A. P1.17.83, P3.16.16
K. Dhillon, I. EP.17.32
Ke, C. EP.08.38
Ke, E.-E. P1.11.05
Ke, J. EP.09.05
Ke, S. OA12.03
Keefe, D. P1.04.08
Keegan, T. P1.17.03
Kefeli, U. P2.10.02
Kehl, K. P3.14.22
Keijser, A. EP.18.01
Keister, C. P1.04.31
Keith, R. PT1.01.03
Keller, S. M. MA04.04
Keller-Evans, R. B. P1.11.57
Kelley, M. P2.10.01
Kelly, C. PT2.14.01
Kelly, G. P2.08 .23
Kelly, G. EP.12.10
Kelly, K. OA09.01, P1.17.24, PT2.17.04
Kelly, R. P1.11.72
Kelner, E. P1.04.37
Kelsey, C. P2.06.67, P2.08 .13
Kendell, C. EP.15.15
Kendre, P. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Kenmotsu, H. EP.13.14, EP.14.21, EP.17.32, P3.03.42
Kennedy, G. P1.17.67
Kennedy, O. P2.06.85
Kent, J. P2.02.27
Keogh, R. J. P3.18.40
Kerpel-Fronius, A. P1.17.24
Kerr, E. P2.10.01
Kerr, K. OA09.01, OA13.04
Kerr, K. M. PL03.16
Keshavjee, S. EP.14.15, MA03.01
Ketosugbo, K. P3.01.22
Kettner, N. PT1.04.03
Kezerle, Y. P2.06.65
Khagi, S. P3.09.08
Khajavi, L. P2.06.43
Khalil, M. EP.03.15
Khalil, M. P2.06.27, P3.18.61
Khallad, T. I. EP.01.11
Khan, A. H. P1.11.80
Khan, A. EP.12.61
Khan, A. P2.06.64
Khan, K. EP.13.38, P1.17.08, P1.17.09
Khan, S. EP.12.36
Khan, S. MA03.01
Khan, S. P2.06.70
Khan, S. R. EP.12.61, P2.10.08
Khandekar, A. OA14.05
Khandelwal, S. P2.06.18
Khanijo, S. EP.15.12
Khanna, S. P2.06.18
Khatavk, G. EP.09.08
Khatavkar, G. EP.08.14
Khatavkar, G. R. P3.09.01
Khater, A. P2.06.09
Khater, Y. P1.17.39
Khatkova, E. P3.01.11
Khatoon, W. EP.06.22
Khattra, S. P1.04.18
Khawari, M. EP.15.06
Khelifa, S. EP.06.51
Khodadad, T. P2.15 .15
Khodayari Moez, E. MA05.06
Khoo, T. P1.17.62
Khorasanchi, A. P2.08 .47
Khoruts, A. P1.11.71
Khosla, D. P1.17.79
Khullar, O. V. PL02.18
Khurana, S. MA09.08, P3.18.72
Kian, W. EP.06.73
Kidacki, M. EP.06.58
Kidane, B. PT2.17.01
Kiefl, R. EP.03.12, P3.18.02, P3.18.36
Kiel, L. P3.01.18, PT2.15.02, PT2.17.04
Kiesewetter, B. P3.18.55
Kieszko, R. EP.13.17, MA10.04, P1.11.63
Kievit, W. EP.18.01
Kijima, T. P1.11.40, P3.18.31
Kikuchi, S. EP.13.18
Kiladze, I. EP.17.24, EP.17.26
Kiland, K. P1.04.34, P3.01.29
Kilburn, B. EP.06.57
Kilic, B. EP.04.23
Kilic, D. P2.08 .36
Kilickap, S. MA11.04
Kim, A. W. OA02.01
Kim, B. PT2.12.02
Kim, B.-G. P3.01.45
Kim, B. EP.04.12
Kim, B. P3.13.21
Kim, C. P2.06.48
Kim, C. P1.17.32
Kim, C. P3.18.57, PT2.12.02
Kim, C. MA07.06, P1.11.50, P1.11.73, P2.06.102, P3.12.02, P3.13.13, PT2.12.03
Kim, D. P2.06.48
Kim, D. P1.07.20
Kim, D. EP.06.07
Kim, D. MA05.04
Kim, D. P1.17.32
Kim, D. EP.14.11, P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Kim, D.-W. MA07.07
Kim, D. P2.05.16
Kim, D. P2.10.10
Kim, E. MA10.09, P1.11.52, P2.06.102
Kim, E. EP.06.32, EP.13.21
Kim, G. P2.08 .13
Kim, H. P2.06.48
Kim, H. P1.07.20
Kim, H. P3.13.21
Kim, H.-Y. PT2.12.02
Kim, H. P1.04.26
Kim, H. EP.13.21
Kim, H. P3.01.38
Kim, H. EP.01.18, EP.07.46, EP.08.29, P1.07.15, P2.08 .31
Kim, H.-C. P2.05.11
Kim, H. P2.06.100, P2.06.48, P3.12.41
Kim, H. PT2.11.04
Kim, H. EP.01.18, EP.14.11, P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Kim, H. P1.07.52

Kim, H. P3.12.37
Kim, I. P1.11.32
Kim, I. EP.14.11
KIM, I. EP.08.48
Kim, J. Y. P1.17.32, P3.18.84
Kim, J. P1.04.20
Kim, J. P2.02.11
Kim, J. MA09.06
Kim, J. EP.14.11, P2.05.16
Kim, J.-W. P2.02.11
Kim, J. W. P2.06.100
Kim, J. P2.02.11
Kim, J. PT1.09.05
Kim, J. EP.07.46, EP.08.29, P2.08 .31
Kim, J. PT2.11.04
Kim, J. EP.04.40
Kim, J. P2.06.13, P2.06.21
Kim, J.-H. OA06.04
Kim, J. EP.06.32
Kim, J. P1.11.32
Kim, J. P1.17.26
Kim, K. EP.11.12
Kim, K.-J. P2.02.11
Kim, K. P1.07.52
Kim, K. P2.06.23
Kim, K. P3.12.37
Kim, M. R. P3.14.05
Kim, M. PT1.09.05
Kim, M.-H. P3.01.38
Kim, N. P3.01.32
Kim, P. P1.11.82
Kim, S. S. P3.18.84
Kim, S. MA08.02, P3.18.57
Kim, S.-A. P2.02.11
Kim, S.-H. MA09.06
Kim, S.-W. EP.08.22, MA02.03, P1.04.26, P1.07.35, P1.11.32, P2.06.102, PT2.12.04
Kim, S. P1.07.52, P2.02.11
kim, s. EP.06.07
Kim, S. P2.06.13, P2.06.21
Kim, S.-E. P1.04.26
Kim, S. P3.12.68
Kim, S. P2.15 .16
Kim, S. P1.07.10, PT1.05.03
Kim, S. Y. OA08.02, P1.17.54
Kim, S. P1.07.25
Kim, S. EP.08.46, MA06.01, P1.07.36, P2.15 .09
Kim, S. EP.06.32
Kim, S. P3.13.21
Kim, S. MA05.08
Kim, S. P3.18.37
Kim, T. P1.11.32, P3.12.41, P3.12.65, P3.18.73, PL02.06, PT2.12.04
Kim, T.-J. EP.14.30, MA07.01, PL03.16
Kim, W. PT1.09.05
Kim, Y. EP.13.21
Kim, Y. EP.04.08, OA04.03, P1.07.25, P1.07.52
Kim, Y. MA10.05
Kim, Y.-H. EP.14.11, P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Kim, Y. EP.08.22, P1.07.35
Kim, Y. P1.04.23
Kim, Y. T. P2.05.08
Kim, Y. P3.01.45
Kim, Y. EP.07.31, P2.08 .02
Kim, Y.-C. P3.13.08
Kim, Y.-S. P2.02.20
Kim, Y. P2.06.38
Kim, Y. J. P3.18.28
Kim, Y. MA08.01, MA08.04, OA05.04, OA06.03, P1.07.52, P1.11.32, P2.02.11, PT2.12.04
Kimball, K. P2.15 .24
Kim-Schulze, S. P2.08 .23
Kimura, T. P1.11.11, P3.12.35
Kimura, Y. EP.11.13, EP.11.17, P1.11.19
Kindler, H. OA12.01
Kindler, H. L. P3.14.04
King, J. OA16.02
King, J. C. P1.17.24, PT1.03.04
King, M. EP.15.16
King-kallimanis, B. P1.17.71, P3.16.15
Kinoshita, F. EP.07.11, EP.07.50
Kinoshita, H. P2.02.26
Kintz, K. OA09.03
Kinyua, D. P3.03.32
Kirita, K. PT1.05.02
Kiriyama, R. EP.07.19
Kirschner, M. B. EP.04.34
Kirschner, M. P2.15 .24
Kirtane, K. P3.18.87
Kirwan, L. P2.06.82
Kishikawa, S. PL03.16
Kishimoto, K. P2.02.26
Kisiel, M. P2.15 .24
Kiss, N. P1.17.20
Kitagawa, H. EP.13.14
Kitai, H. P3.09.09
Kitano, S. P3.12.58
Kitazono, S. P3.12.32, P3.12.38
Kittikundecha, T. EP.04.37
Kılıç, B. P3.03.04
Klebe, S. PT1.06.03
Kleemiss, M. P3.12.14
Klein-Goldberg, A. EP.03.08, P3.03.28
Klemm, F. P2.06.88
Klersy, C. P1.11.01, P2.08 .53
Klinedinst, N. J. EP.15.08, OA04.01
Kloecker, G. P1.17.59, P3.13.07
Kloeckner, M. EP.04.29, P1.04.39
Klotz, L. V. EP.01.20, EP.06.29
Klotz, L. MA04.06
K. Mhatre, S. EP.17.32
Knapp, B. P1.17.50
Knapp, B. J. EP.13.40
Knauss, B. OA04.04
Knesis, A. EP.06.50
Knetki-Wróblewska, M. EP.01.03, EP.13.17
Kneuertz, P. J. P3.18.84
Knight, S. EP.17.09
Knowles, S. P1.17.63
Knowlton, C. P3.13.26
Knox, E. P2.08 .42
Knuuttila , A. EP.01.09
Knuuttila, A. P1.17.67, P3.12.72
Ko, E.-L. P2.06.90
Ko, M. MA03.01
Ko, R. EP.14.21, P3.18.04, PT2.14.03
Koba, H. EP.06.25, EP.12.62, P1.11.06
Kobayashi, A. P3.01.19
Kobayashi, A. K. EP.08.09
Kobayashi, H. EP.14.21
Kobayashi, J. P1.07.23
Kobayashi, K. P1.04.52
Kobayashi, K. P3.12.65, PL02.06
Kobayashi, M. P3.18.04
Kobayashi, T. EP.12.29, P3.12.09, P3.12.23
Kobayashi, T. EP.11.08
Kobold, S. P3.18.36
Kocaman, G. P3.18.01
Koch, M. P1.17.67
Koch, S. D. P3.18.64
Koche, R. P3.03.32
Kochovska, S. P1.17.47
Kodama, Y. P3.12.35
Kodan, A. P2.15 .18

Kodani, M. P2.06.59
Koenig, D. P3.18.82
Koers, A. P2.02.27
Koga, T. P1.07.49
Kogure, Y. P1.11.11
Koh, J. EP.06.07
Koh, M. P3.13.21
Kohlhapp, F. J. OA06.04
Köhn, L. EP.06.11
Kohno, T. P3.03.36
Kohonen-Corish, M. R. P2.06.63
Koizumi, T. EP.06.26
Kojic, A. EP.11.09
Kojima, H. EP.14.13, P1.07.13
Kojima, M. P3.09.05
Kok, S. EP.15.13
Kokawa, S. P2.08 .08
Köksal, D. EP.04.28, EP.04.33
Koksal, D. EP.04.43
Köksoy, E. B. EP.06.18
Kokubo, K. P3.13.01
Kolb-Sielecki, J. MA10.06
Kollipara, R. K. MA03.02
Kolovic, D. EP.11.09
Koltun, B. P3.03.28
Komatsu, H. EP.14.09
Komuta, K. EP.11.06
Kondo, M. P1.11.11
Kondo, N. EP.14.05
Kondo, T. EP.07.07
Kondo, Y. EP.06.02, EP.06.12
Konduri, K. EP.06.23
Koneru, M. EP.13.29, MA11.01
Kong, B. P1.17.62
Kong, F.-M.S. P2.15 .04
Kong, F.-M. EP.06.47, P2.10.14
Kong, H. EP.03.05, P2.02.09
Kong, L. EP.14.01
Kong, L. P1.11.34
Kong, L. P2.08 .45
Kong, M. P1.17.59, P3.13.07
Kong, S. EP.12.19
Kong, S. P2.02.17, P3.14.16
Kongjia Luo, K. P2.05.04
Konno, H. EP.14.13, P1.07.13
Konno, S. P3.09.09
Kononets, P. P3.13.29
Koparde, V. MA07.02
Koppensteiner, L. P3.03.46, P3.03.48
KORASIDIS, S. P2.08 .03
Korbenfeld, E. MA10.06
Kordatou, Z. EP.08.18
Koren, L. P3.03.28
Korfiatis, N. P2.15 .26
Koride, S. OA13.02
KORKMAZ KIRAKLI, E. EP.13.43
Kornyeva, A. P2.15 .20
Kosai, K. EP.07.50, P1.07.49
Kose, O. EP.03.11
Koseoglu, S. OA13.02
Koshio, J. P3.13.14
Koshy, M. MA05.03
Kosmidis, P. P2.15 .26
Kosmidis, T. P2.15 .26
Koszik, L. EP.02.02, P2.02.18, P2.02.22
Kotani, H. P3.03.02
Kotecha, R. EP.08.19, P2.06.76, P3.09.08
Kotecki, N. EP.05.06
Kothari, M. P1.17.42, P2.15 .06
Kotlarski, M. P1.11.82
Kotnani, S. EP.01.13
Kotomale, A. P3.12.34
Kotsantis, I. EP.01.19
Kou, F. P3.18.76
Koubkova, L. P3.12.62, P3.12.65, PL02.06
Koufaki, M. I. P2.15 .26
Koujitani, Y. EP.07.56
Koulouris, A. P1.11.39
Kovacs, I. MA11.06, P3.13.03
Kovacs, J. EP.03.12, EP.06.45, P3.16.19
Kovitz, K. MA05.03, P1.04.12, P3.01.26
Kowal-Rosinska, M. P1.11.82
Kowalski, D. P3.18.28
Kowanetz, M. P3.12.38
Koyama, J. P3.12.35
Koyama, K. P3.18.04
Koyama, N. EP.13.18
Koyanagi, T. EP.10.01, P2.10.03
Koynov, K. D. P1.11.82
Kozina, J. V. EP.08.25
Kozono, D. EP.06.68
Kozono, D. E. P3.18.13, PL02.18
Kozuka, T. EP.13.14
Krainock, M. MA03.02, P3.18.04
Kramers, K. EP.12.15
Krasny, S. EP.08.08, P3.18.23
Kratz, J. P1.07.40, PT1.03.01
Kratzke, R. P1.11.71
Krause, E. P3.18.17
Krauss-Etschmann, S. EP.03.06, MA09.04
Krawczyk, P. EP.13.17
Krawczyk, P. EP.06.17, MA10.04, P1.11.63
Kreling Medeiros, A. P1.17.45
Kremeneuski, S. EP.08.08
Kremer, J. MA08.04
Kris, M. OA09.01
Kris, M. G. MA01.06, P1.07.37, P2.06.12, P3.03.01, P3.18.11
Krishna, M. P2.06.17
Krishna, V. EP.17.06
Krishnamurthy, A. P3.01.21
Kroemer, G. EP.04.29, P1.04.39
Kroeze, L. I. P3.01.10
Kropf-Sanchen, C. P3.12.61
Krpina, K. OA15.01
Kruczynski, A. P2.06.43
Krueger, S. P3.12.61
Krule, A. MA05.04
Krulewicz, S. P2.15 .05
Krupnick, A. P3.18.17
Krzakowski, M. EP.01.03, EP.13.17
Krzyżanowska, N. EP.06.17
Krzyzanowska, N. MA10.04, P1.11.63
Kshivets, O. EP.07.03
Ku, K. P3.09.08
Ku, M. EP.06.75
Ku, M. P3.01.36
Kuang, Y. EP.06.59, EP.07.44
Kubo, A. P3.12.33
Kubota, A. EP.11.06, EP.17.25
Kucerova, V. P1.11.10
Kudo, E. EP.07.35
Kudo, Y. EP.07.54, EP.08.40, P2.08 .06, P2.08 .06
Kuhlmann, A. P1.04.14
Kui, Y. PT1.02.01
Kukkurainen, S. P1.17.67
Kulasinghe, A. P2.06.68
Kulic, I. P3.13.05
Kulkarni, A. P1.11.71
Kulkarni, N. EP.13.41, P2.06.52
Kulkarni, S. P2.06.17, P2.06.18
Kulyk, L. P3.03.29
Kumar, A. P2.06.17, P2.06.18

Kumar, M. P2.08 .17
Kumar, P. P2.06.94
Kumar, R. MA07.02
Kumar, S. EP.08.24, EP.13.46
Kumarasamy, C. OA18.03, P1.04.40
Kumari, P. P2.06.17
KUMAR MISHRA, S. EP.12.33
Kumar Sharma, A. MA07.02
Kumata, S. EP.04.18, EP.06.26, EP.07.38, P2.06.33
Kumeda, H. P2.06.47
Kumjornkijakarn, P. EP.04.37
Kummar, S. MA02.04
Kuncman, L. P2.08 .21
Kunimasa, K. EP.11.06, P3.03.30
Kunst, P. PT2.11.02
Kunst, P. W. P3.01.10
Kunst, MS, L. P2.06.20
Kuo, C.-H. P3.12.49
Kuo, S.-W. EP.07.26
Kuon, J. P3.12.61
Kuramochi, E. EP.11.07
Kurata, T. EP.08.09, P3.12.33, P3.12.58, P3.13.01, P3.18.61
Kurian, A. W. P3.01.07, PT1.01.01
Kurihara, C. PT1.09.02
Kuriyama, A. P3.18.04
Kurkinen, L. EP.17.21
Kuroda, A. EP.14.05
Kurosaki, T. P3.03.42
Kurtz, D. M. MA03.01
Kuruvilla, M. P1.11.36, P1.17.70
Kuruvilla, S. EP.13.38
Kurz, C. P2.08 .14
Kus, T. P2.10.02
Kusiel, J. P1.17.65
Kusumoto, M. P1.04.52
Kutiel, T. S. P3.18.80
Kuwabara, Y. EP.13.18
Kuyama, S. EP.10.01, P2.10.03, P3.12.33
Kuznar-Kaminska, B. MA10.04, P1.11.63
Kwak, H. EP.01.18, EP.12.12, MA05.08
Kwak, K. OA04.03
Kwan Ho Chui, K. P2.15 .22
Kwiatkowski, D. J. P1.07.37, PT2.14.05
Kwisthout, J. P2.15 .10
Kwok, A. EP.11.11
Kwok, G. EP.11.21
Kwok, H. EP.11.21
Kwon, G. P2.06.48
Kwon, Y. P2.05.16
Kyoyama, H. EP.13.18
Kyriazoglou, A. EP.01.19

L

Laaksonen, S. P3.12.63
Labbé, C. P3.13.31
Labella, D. P2.08 .13
La Cava, G. EP.06.52, P1.17.54, P3.12.08, P3.12.15
Lacidogna, G. P3.12.15
Lacoux, C. P2.06.88
Ladak, Z. EP.15.06
Ladanyi, M. P2.02.15, PT1.06.01
Ladeirinha, A. F. PT2.14.02
Ladrera, G. R. P1.11.79
Lafayette, B. EP.13.28
Lafond, S. EP.17.15
Lagampan, C. EP.12.22
Lagisetty, K. PT1.03.01
Laguna, J. EP06.85, OA01.02, P3.01.46
Lahouegue, A. EP12.64
Lai, C.-L. P3.12.27
Lai, G. EP.04.08
Lai, G. G. OA15.02
Lai, Y.-H. P2.15 .23
Lai, Y. MA01.05
Lainakis, G. P2.06.65
Laird, B. PT2.14.01
Laird, J. P3.13.26
Laisaar, K.-T. P1.04.37
Laisaar, T. P1.04.37
Lakhani, N. P3.12.58
Lakhanpal, M. P3.18.35
Lakovski, D. P2.15 .06
Laktionov, K. MA10.09, P3.12.62
Laktionov, K. K. EP.08.25
Lala, D. A. P2.06.18
Lalla, M. EP.13.41
Lam, M. H. EP.12.52
Lam, S. MA09.02
Lam, S. MA05.05, MA05.06, MA09.01, MA09.03, P1.04.18, P1.04.33, P1.04.34, P1.04.36, P3.01.23, P3.01.29, P3.01.35, P3.01.49
Lam, V. P3.18.40
Lam, V. K. OA07.01
Lam, W. L. MA09.03, P3.01.23, P3.01.49
Lamaze, F. C. MA07.04, P3.13.06
Lamberg-Lundström, K. EP.13.22
Lammers, P. P2.15 .32
Lammers, P. P3.13.31
Lammers, P. E. PL03.06
Lamorgese, V. OA17.01
Lampaki, S. P2.15 .26
Lamprecht, B. P2.15 .06
Lamrani, L. EP.04.29, P1.04.39
Lan, F. P3.16.17
Lan, H. P3.18.86
Lan, Q. OA14.05, P3.01.28
Lancaster, H. L. P1.04.06, P1.04.11
Land, S. R. OA11.01
Landeras, L. P3.14.04
Landi, L. EP.03.02, EP.07.48, MA01.04, P1.11.56, PT2.11.01
Landi, M. T. OA14.05, P1.04.29
Landon, B. P1.11.72
Landry, G. P2.08 .14
Lane, L. PT1.03.04
Lang, C. P3.13.03
Langels, E. EP.12.26
Langer, C. EP.14.17
Langer, C. J. PL02.18
Langfort, R. EP.07.52
Langlais, A. OA05.02
Langleben, A. MA04.04
Langlotz, C. P3.01.07
Langlotz, C. P. PT1.01.01
Langton, D. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Lanser, D. A. EP.12.49, EP.12.52
Lantin, R. P1.04.08
Lantuejoul, S. MA07.01, OA12.02, OA13.04, P1.17.24
Lanuti, M. P1.07.37
Lanyado, A. P1.04.36
Lanzetta, C. P3.16.05
Lanzetta, I. P1.11.54
Lao, S. P2.06.35, P3.01.33
LaPlant, Q. EP.14.22
larkins, s. EP.17.07
Larvol, B. P3.13.18
Laskin, J. EP.08.17, P2.15 .17, PL02.12
Lattanzi, E. EP.09.06
Lattanzi, J. EP.15.01
Lau, A. P3.18.73
Lau, A. EP.02.09
Lau, A. P. P3.03.38
Lau, E. T. P2.06.63

Lau, J. P3.14.05
Lau, R. W. P1.17.60
Lau, S. C. OA13.01
Lauk, O. EP.07.09
Laurans, A. P3.18.67
Laurence, K. EP.11.11
Lauricella, L. EP.17.31, PT1.01.02
Lauricella, L. L. EP.17.23
Lauricella, L. L. P1.17.05, P1.17.74
Laurie, S. OA12.02, P2.06.99
Lavagnolo, P. PT2.15.01
Lavaud, P. P3.14.15
Lavecchia, M. P3.14.06
La Verde, N. P1.11.66
Law, H. EP.16.06, P3.16.21
Law, J. PL03.13
Law, J. EP.06.75
Lawrance, R. MA04.05
Lawrence, Y. R. EP.09.01
Lax, A. P3.12.06
Lazarev, S. EP.08.15
Lázaro, C. P2.06.37
Lazaro, M. MA01.03
Lázaro, M. MA06.03, P1.11.07, P1.11.37
Lazaro de Moraes, P. P2.08 .18
Lázaro-Quintela, M. PL03.10
Le, H. P2.15 .05, P3.12.19
Le, H. H. P3.12.29
Le, L. EP.06.75
Le, L. W. MA03.01
Le, U.-T. P2.15 .20
Le, X. EP.04.31, MA03.04, MA05.09, MA08.01, MA10.05, OA07.01, P1.11.55, P2.02.36, P3.12.38, P3.12.40, P3.12.41, PL02.12, PT1.01.03, PT2.13.03
Le, Y. Q. PT1.06.02
Leal, T. P3.12.41
Leal, T. A. PL02.18
Leamy, N. P01.01
Leaw, S. MA04.08
Leber, P. P2.15 .20
Le Bihan, C. P1.17.57
Leblanc, T. W. P2.15 .05
Lechtenberg, K. OA11.01, OA12.01
Lechtenberg, K. OA11.02
Leconte, I. MA07.07
Ledda, R. P1.04.53
Leddon, J. P3.18.39
Lederman, R. P3.01.18, PT2.15.02
Leduc, C. OA14.05
Lee, A. P1.17.52
Lee, A. EP.07.14, P2.08 .22
Lee, A.-M. P2.06.90
Lee, B. OA04.03
Lee, C. P2.06.48
Lee, C. P1.07.20
Lee, C.-M. P2.02.15
Lee, C. K. P2.06.61, P3.12.62, PL02.06
Lee, C. EP.13.37, OA03.04
Lee, C. MA09.06
Lee, C. PT1.09.05
Lee, C. EP.13.37
Lee, C.-T. OA04.03, P1.07.25, P1.07.52
Lee, C. EP.04.20, PT1.04.03
Lee, C. W. OA12.02
Lee, C. P2.06.23, P2.06.48
Lee, D. MA08.01, P1.04.26
Lee, D. P2.10.05
Lee, D. EP.04.20
Lee, E. P2.06.48
Lee, G. EP.04.40
Lee, G. EP.14.11, P2.05.16
Lee, G. P1.07.10, P1.07.30, P1.07.32, PT1.05.03
Lee, G. EP.06.32
Lee, G.-W. OA13.02, P1.11.32
Lee, H. EP.07.14
Lee, H.-S. P1.07.25
Lee, H. EP.04.40, EP.07.46, EP.08.29, P1.07.15, P2.08 .31, PT2.11.04
Lee, H.-S. P1.04.26
Lee, H.-T. P2.06.02
Lee, H. P3.13.21
Lee, H.-J. MA09.06
Lee, H. MA09.06
Lee, H. P2.08 .02
Lee, H. P3.01.45
Lee, I. EP.11.12
Lee, J. J. P2.02.36, PT1.01.03
Lee, J. EP.04.31, P1.11.55
Lee, J. OA07.01, OA09.01
Lee, J. L. P1.11.70
Lee, J. EP.12.12, EP.13.21, P1.04.26
Lee, J. P1.07.25, P1.07.52
Lee, J. P1.11.32
Lee, J. P1.17.32
Lee, J. EP.07.14
Lee, J. M. MA04.02, P1.07.37, P3.18.09
Lee, J. P2.15 .16
Lee, J. EP.13.21
Lee, J. EP.02.05
Lee, J.-O. P2.02.11
Lee, J. K. P1.17.66
Lee, J. P2.02.11
Lee, J.-Y. P3.01.32
Lee, J. EP.08.22, P1.07.35, P2.06.48
Lee, J. (. P3.12.37
Lee, J. P2.06.48
Lee, J. P3.01.32
Lee, J.-Y. EP.01.18
Lee, J. P1.07.20
Lee, J. P2.06.61
Lee, J. EP.12.27
Lee, J. MA09.06
Lee, J. P1.07.52, P2.02.11, PT2.12.04
Lee, J. P3.13.21
Lee, J. P3.12.13
Lee, J. P1.07.30
Lee, J. EP.01.18, EP.07.46, EP.08.29, P1.07.15, P2.08 .31
Lee, K.-Y. OA02.02
Lee, K.-W. P2.02.11
Lee, K. MA02.03, P1.11.32, P3.12.41, P3.18.57
Lee, K. MA09.06
Lee, K. P1.07.25
Lee, L. C. P1.17.22
Lee, M.-H. P3.12.27
Lee, M. P1.11.77
Lee, N. Y. EP.14.22
Lee, O. OA14.05
Lee, S. EP.06.32
Lee, S.-H. EP.07.46, EP.08.29, MA07.07, MA08.02, P1.11.32, P2.02.20, P2.08 .31, P3.18.09, PT1.03.06, PT2.11.04
Lee, S. P2.06.38
Lee, S.-H. P2.02.20
Lee, S. P2.06.48
Lee, S. EP.06.15
Lee, S. EP.09.02, EP.13.21
Lee, S. P1.11.32
Lee, S. P3.12.37
Lee, S. EP.13.21, OA02.02
Lee, S.-W. P2.02.32, P3.13.08
Lee, S. EP.02.05
Lee, T. P3.13.21
Lee, T. P3.01.07
Lee, T. PT1.01.01

Lee, T. T. P2.15 .04
Lee, V. P1.07.36, P2.06.14
Lee, V. H. MA08.02
Lee, V.-F. P2.06.90
Lee, W. L. P3.03.38
Lee, W.-C. P1.07.08
Lee, Y. OA04.03
Lee, Y. J. OA13.02
Lee, Y.-G. P1.11.32, P3.01.45
Lee, Y. EP.04.12
Legenza, M. PT1.08.03
Le Guen, Y. P3.12.29
Lehman, S. P1.17.28
Lehmann, F. P3.18.64
Lei, C. EP.12.31
Lei, Y. P2.02.35, P2.06.29, P2.08 .45
Leigh, L. P1.17.62
Leigh, L. P1.17.20
Leighl, N. OA12.02
Leighl, N. EP.06.75, P2.06.99, P2.10.06, P3.03.03, P3.12.38, P3.14.11, PL02.12
Leighl, N. B. MA03.01, P1.04.29, P1.17.08, P1.17.09
Leimbach, M. P2.15 .02
Leiner, M. P3.18.05
Leipzig, M. EP.04.38
Leite, C. P1.17.45
Le Marchand, L. P1.04.29
LeMense, G. P2.15 .30
Lemery, C. P3.16.22
Lemonnier, M. EP.17.11
Leng, X. EP.12.31, P2.02.23, PT1.07.03
Lensing, J. P1.17.28
Lenzini, A. P2.05.10
Leo, L. P1.07.04
León, S. EP.13.27, PT1.08.05
Leonard, B. P3.01.51
Leone, F. P3.12.15
Leone, G. P2.15 .34
Leonel, L. P. EP.17.23
Leonetti, A. EP.09.06, EP.11.05, EP.11.20, MA02.05, P1.11.24, P1.17.54
Leong, C. EP.17.09
Leong, J. P1.17.12
Leong, S. P1.04.36
Leong, T. EP.15.04, EP.17.09, P1.11.49, P1.17.12
Leon Mateos, L. MA04.09
Le Pavec, J. EP.04.29, P1.04.39
Leporati, R. EP.13.05, EP.15.11
Le Quesne, J. MA07.01, P2.06.04, P3.14.08, PL03.16
Lerma, L. MA06.07, OA09.02, P1.17.44, P2.06.65
Lermi, N. O. PT2.13.03
Lesage, J. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Lescouzères, M. EP.17.39
Letelier Farias, R. EP.14.27, EP.17.27
Leto di Priolo, S. P3.14.06
Lettieri, J. P1.17.83
Leung, A. P3.01.07, PT1.01.01
Leung, B. EP.08.17
Leung, D. OA10.01
Leung, D.-C. P2.06.90
Leung, E. P1.17.42
Leung, J. M. MA09.02
Leung, R. EP.11.21
Leung, W. P3.12.38
Leuzzi, G. P1.04.53, P3.14.18
Levantini, E. P3.03.15
Levchenko, E. MA04.04
Leventakos, K. MA03.03, OA08.01, P1.17.28, P1.17.51, P3.13.32, P3.18.71
Levine, B. P3.18.14
Levine, K. P2.02.37
Levitas, D. EP.06.73
Levy, B. MA03.03, P3.18.40
Levy, D. E. OA18.04
Levy, E. MA07.02
Levy, K. P3.16.22
Levy Faber, D. P1.04.46
Lewis, C. EP.04.07
Lewis, J. P1.11.55
Lewis-Hughes, A. OA04.04
Li, A. P3.18.20, P3.18.50
Li, A. P3.12.26
li, a. P2.06.98
Li, B. MA10.03
Li, B. OA05.01
Li, b. P1.11.84
Li, B. OA10.04
Li, B. P1.11.44, P2.06.101
Li, C. P3.18.76
Li, C. P3.12.12
Li, C. MA08.06
Li, C. P1.07.56, P2.08 .45
Li, D. MA11.03, P2.10.12
LI, D. P1.11.67
Li, D. P1.11.13
Li, F. EP.08.41
Li, F. PT1.09.03
Li, F. EP.18.09, P3.18.46, P3.18.48
Li, F. P1.07.27
Li, F. P3.01.33
Li, G. P1.11.65, PT1.07.03
Li, G. P1.17.66, P3.12.42
Li, H. OA16.04, P1.04.49
Li, H. EP.18.03
Li, H.-J. OA03.01, P1.04.21, P2.08 .35, PT1.09.03
Li, H. P1.07.55
Li, H. P2.06.19
Li, H. EP.04.31, EP.13.23, OA06.02, P1.04.42, P1.11.70
Li, H. EP.12.58
Li, H. EP.06.47
Li, J.-T. EP.12.60, P3.01.04, P3.01.37
Li, J.-X. P1.07.57, P3.03.35
Li, J. EP.06.56, EP.12.38, EP.13.35, P2.06.46
Li, J. P1.11.12
Li, J. PL02.12
li, j. P3.12.47
Li, J. MA06.05, P1.17.23
Li, J. P1.11.65, P3.13.22
Li, J.-L. EP.18.09
Li, J. P3.18.46, P3.18.48
Li, J. P1.11.34
Li, J. MA10.05, OA05.01, P3.12.25, PT1.06.02, PT2.10.03
Li, J. EP.08.21, MA08.06, P3.12.25
Li, J. P2.06.60
Li, J. EP.12.44
Li, J. OA13.03
Li, J. P3.12.48, P3.12.64, PT2.10.03
Li, J. EP.06.56, EP.12.13, EP.12.38, P2.06.46
li, j. EP.12.43
LI, K. EP.12.31, P2.02.23
Li, L. EP.06.56, EP.12.38, P2.06.46
Li, L. MA02.03
Li, L.-H. PL02.09
Li, L. EP.07.45
li, l. P2.15 .28, P3.12.41
Li, L. EP.07.51
Li, L. OA05.01
Li, M. P3.12.07
Li, M. MA03.07, OA10.02, P3.12.53, P3.13.25
Li, M.-J. EP.12.06
Li, M. P3.18.86
Li, M. EP.07.44

Li, M. P3.13.34
Li, M. EP.12.08
Li, M. EP.03.15, EP.04.35, EP.08.33
Li, M. EP.18.08
Li, M. PT2.12.01
Li, M. P1.17.54, P2.08 .47
Li, M. EP.14.23
Li, M. P1.07.42, P2.08 .45, PT1.07.04
Li, M. EP.11.19
Li, N. P1.11.13
Li, N. EP.04.25
Li, P. P3.13.09, P3.13.11
Li, Q. P2.06.101, PT1.06.04
Li, Q. MA05.07, P2.02.21
Li, Q. P2.06.29
Li, Q. P1.04.42, P2.05.09
Li, Q. EP.14.14
Li, Q. EP.06.31, P3.03.03, P3.12.51
Li, Q. EP.04.21, P1.04.22
Li, R. EP.12.28
Li, R. P3.18.21
Li, R. P. P2.10.15
Li, R. P2.10.14
Li, R. P1.07.01
Li, R. EP.07.05
Li, R. EP.07.30
Li, S. P2.02.15
Li, S. OA14.02
Li, S. P3.14.21
Li, S. EP.06.36, EP.08.35, EP.08.49, P2.06.06
Li, S. OA14.01, P2.06.49
Li, S. EP.13.30
Li, S. P1.17.25
Li, S. EP.06.45
Li, S. MA08.02
Li, S. PL02.09
Li, S. P1.04.49
Li, S. P2.02.16
Li, S. EP.04.35
Li, S. EP.12.40
Li, S. P3.18.47
Li, T. P1.04.16, P1.07.37, P3.18.39, PL02.18
Li, W. P2.05.13, P3.12.69
Li, W.-H. P3.12.59
Li, W. EP.06.30
Li, W. P3.12.46
Li, W. MA05.09, P3.12.25
Li, W. EP.06.69, EP.06.76
Li, W. P1.11.65, P1.11.83, PL02.12
Li, W. MA09.07
Li, W. P3.13.31
Li, W. OA15.03
Li, X. P3.13.22
Li, X. EP.07.51
Li, X. EP13.49, P1.07.46, P3.13.23
Li, X.-L. P1.07.48
LI, X. P1.17.69
Li, X. EP.04.21, P1.04.22
li, x. P2.15 .28
Li, X. EP.04.19
Li, x. P2.06.101
Li, X.-Y. P3.12.55
Li, X. EP.12.44, MA08.01, MA08.06, OA10.04, P1.11.83, P2.10.12, P3.12.25, P3.12.31, P3.12.38, P3.12.48, P3.12.64
Li, X. OA11.04
Li, X. P1.07.39
Li, X. P3.13.10
Li, X. P3.12.69
Li, X. P1.11.70
Li, X. P2.08 .57
Li, X. P1.11.31, P2.06.86, P3.03.16
Li, Y. MA01.05
Li, Y. MA01.05
Li, Y. P3.12.11
Li, Y.-S. P1.11.05
Li, Y. P3.13.34
Li, Y. P1.11.67, P3.12.47
Li, Y. P3.18.46, P3.18.48
Li, Y. P3.12.07
Li, Y. EP.15.05, P1.07.01
Li, Y. P2.02.01
Li, Y. MA11.03
Li, Y. P2.06.73
Li, Y. EP.06.41, P2.06.19, P2.06.24, P2.06.34
Li, Y. P2.10.06
Li, Y. P2.06.80
Li, Y. P2.02.02
Li, Y. MA10.09
Li, Y. PT2.10.04
Li, Y. EP.11.19
Li, Y. P3.01.02
Li, Z. EP.07.05
Li, Z. P3.18.86
Li, Z. MA01.05
Li, Z. MA06.04
Li, Z. EP.01.15, EP.04.25
Li, Z. EP.17.16, MA02.07, MA11.03, P1.17.37, P3.18.59
Li, Z. P2.05.13
Lian, F. EP.06.51
Lian, K.-H. EP.09.15
Lian, W. EP.14.20
liang, B. EP.01.14
Liang, C. P1.07.12, P2.06.30, P3.01.50
Liang, G. EP.17.18, P1.17.38, P1.17.40
Liang, H. EP.08.04, EP.15.05, MA05.07, P1.07.01
Liang, J. EP.04.17
Liang, J. EP.13.47, MA02.01, PT2.13.04
Liang, j. EP.18.10
liang, l. P2.15 .28
Liang, N. PT1.07.03
Liang, Q. P1.07.33
Liang, S. Y. P3.12.21
Liang, S.-K. EP.12.21
Liang, S. EP.09.12, P3.09.06
Liang, S. P3.18.74
Liang, S.-Y. P3.01.07, PT1.01.01
Liang, W. MA04.07, P1.11.12, P3.01.03, P3.01.05, P3.01.12, P3.01.33, P3.01.39
Liang, X. EP.12.20, P3.18.24
Liang, Y. OA03.02, P1.17.58, P2.15 .31
Liang, Y. P3.18.07
Liang, Y. EP.14.14
Liang, Y. EP.18.09, P1.11.28, P3.18.46, P3.18.48
Liang, Y. P3.01.36
Liao, B.-C. EP.03.04, P3.12.27
Liao, C. EP.12.02
Liao, D. P3.12.01
Liao, G. P1.07.42, P2.02.35, PT1.07.04
Liao, H.-C. EP.07.26
Liao, L. P3.12.63
Liao, R.-Q. P1.07.55, PT1.09.03
Liao, R. P2.08 .09
Liao, S. EP.12.39
Liao, W. EP.12.39
Liao, W. P1.17.76, P2.15 .32
Liao, W.-Y. EP.12.21, P2.15 .23, P3.12.27
Liao, Y.-T. P2.10.04
Liao, Y. EP.18.03
Liao, Y. EP.12.39
Liao, Y. PT2.17.03
Liao, Z. OA07.01, PT1.01.03
Libby, D. EP.04.13
Liberman, M. OA02.03, P2.08 .54, P3.14.19
Libreros Niño, A. EP.08.07

Licciardello, C. P2.15 .34
Licciardello, C. M. MA06.07, OA09.02, P1.11.66, P1.17.30
Licciardello, C. P1.04.51, P2.06.65
Licht, P. PL03.13
Licour, M. P1.17.57
Licskai, C. P1.17.46
Ligam, M. EP.15.06
Liguigli, W. P1.11.01
Lile, A. P2.15 .24
Lilla, S. P3.14.08
Lim, A. P3.03.32
Lim, D. W. OA15.02
Lim, E. P3.01.34
Lim, E. L. MA09.02
Lim, E. OA11.02, PL03.13
Lim, G. P1.07.29
Lim, J. P2.05.11
Lim, P. X. P2.10.17
Lim, S. MA08.05, P2.06.48, P3.12.37
Lim, S.-M. MA08.03, P3.18.57, PT2.12.02
Lima, E. P. EP.09.09
Lima, J. EP.13.20
Lima, L. P. P1.17.11, P3.01.06
Limaye, S. EP.04.08, P2.06.94
Lin, B. P3.18.09
Lin, C. P1.07.50
Lin, C.-C. P3.12.21, P3.18.67, PL02.15
Lin, C.-C. MA07.07, PL02.15
Lin, C.-C. P1.07.08
Lin, D. P2.06.96, P2.08 .38, PL03.16
Lin, E. P. P3.03.21
Lin, F. P2.06.61
Lin, G. P3.12.55, P3.13.22
Lin, G. P1.07.09
Lin, H. EP.08.15
Lin, H. P1.11.84
Lin, H. P2.02.02
Lin, J. MA02.03, P3.16.15
Lin, J. J. EP.06.53, MA02.01, MA02.04
Lin, J. PL02.15
Lin, J.-X. P1.11.05
Lin, J. P1.17.23
Lin, J. PL02.09
Lin, J. EP.06.36, EP.08.35, P2.06.06
Lin, J. MA04.02, P1.07.37
Lin, J.-T. P1.07.55, PT1.08.01
Lin, J. P1.07.33, P2.08 .09
Lin, L. PT2.11.05
LIN, L. P3.18.42
Lin, L.-J. MA05.02
Lin, L. P3.18.32, P3.18.69
Lin, L. EP.11.19
Lin, M. EP.15.05
Lin, M.-X. P2.02.44
Lin, M. EP.13.26
Lin, M.-W. EP.06.20, EP.07.08, P1.07.08
lin, s. PT1.09.01
Lin, S. EP.07.29, EP.08.41
Lin, S. P1.11.84
Lin, S. H. P1.07.35, P2.02.36, P2.08 .23, PT1.01.03
Lin, S. P3.18.67
Lin, V. T. OA08.02
Lin, W. MA10.01, P3.12.25
Lin, X. P2.08 .43
Lin, X.-C. P1.11.23
Lin, X. MA03.08, P1.11.22, P2.02.12
Lin, X. P2.15 .07
Lin, Y.-C. MA11.04
Lin, Y. MA07.08
Lin, Y.-T. P3.12.27
Lin, Y.-D. OA03.01, P1.04.21, P2.08 .35
Lin, Y. EP.12.41, PT1.06.04
Lin, Y. P3.12.07
Lin, Y. EP.14.14, P1.04.50
Lin, Y. P1.11.83
Lin, Y. EP.15.05
Lin, Z. P2.06.72
Lin, Z. P2.08 .04, P2.08 .05
Lin, Z. P3.18.69
Lin, Z. PT2.13.02
Lin, Z. EP.04.39, EP.06.72
Linardou, H. OA09.02, P1.04.51, P2.06.65, P2.15 .06, P2.15 .26
Lindner, V. EP.06.39
Lindop, J. MA09.05
Lindsay, C. R. P3.18.65
Ling, B. EP.18.05
Lingua, A. P1.11.85
Linkov, I. P3.03.32
Lin-Lin, Y. EP.07.42
Liou, D. Z. P1.04.19, P2.15 .30
Liptay, M. P2.06.64
Lirio, F. P2.08 .28
Lisberg, A. EP.07.14, OA10.01, P2.02.16, P2.08 .22
Lisberg, A. E. P3.18.74
Lisik-Habib, M. P2.08 .21
Lissenberg-Witte, B. I. P3.13.16, P3.18.16
Listì, A. P2.06.22
Litterman, N. EP.01.17
Liu, A. PT1.03.01
Liu, A. P3.12.48
Liu, B. MA08.05, OA06.01, P1.11.83, P3.12.48
Liu, B. P2.08 .57, P3.03.29
Liu, C. OA06.01
Liu, C. P3.18.86
Liu, C.-G. EP.13.26, P2.02.44
Liu, C. PT1.07.03
Liu, C. P3.12.48
Liu, C. P3.12.31, PT2.10.02, PT2.10.04
Liu, D. EP.07.41, EP.13.36, PT2.13.01
Liu, D. P1.04.16
Liu, D. EP.12.02
Liu, D. EP.12.46
Liu, F. EP.07.44
Liu, F. EP.17.03, P1.04.04
Liu, F. OA06.01, P3.12.74
Liu, G. EP.06.75, EP.13.38, EP.14.15, MA02.02, MA05.06, MA08.01, MA08.07, P1.04.29, P1.11.36, P1.17.08, P1.17.09, P3.03.03, P3.12.51, P3.13.31, P3.14.11, PL02.15
Liu, H. EP.04.02, P1.04.13
Liu, H. P2.02.02
Liu, H. EP.08.38
Liu, H. P2.05.03, P3.18.15
Liu, H. MA04.07, MA04.08, P1.07.38, P3.18.08, P3.18.20, P3.18.50
Liu, H. EP.08.06, P3.03.43
Liu, H. PT1.07.04
Liu, H. EP.07.41, EP.14.14, P3.13.27, P3.18.09, P3.18.79
Liu, H. EP.12.55
Liu, J. EP.01.15
Liu, J.-W. P3.12.26
Liu, J. EP.15.17
Liu, J. P2.02.02
Liu, J. P3.18.46, P3.18.48
Liu, J. EP.04.17
liu, j. EP.12.43
Liu, J. MA01.05
Liu, J. PT2.10.03
Liu, J. P2.08 .51
Liu, J. P1.07.38
Liu, J. P3.12.31, P3.12.64
Liu, J. P2.15 .04
Liu, K. P3.12.53, P3.18.69, P3.18.83

Liu, K. EP.12.57
Liu, K. P2.06.102
Liu, L. MA06.05, P1.17.23, P3.12.64
Liu, L. EP.06.67, EP.18.10, MA11.08, P1.04.12, P3.01.26, P3.18.27, P3.18.30, P3.18.43, P3.18.45
Liu, L. EP.12.46, P3.18.47
Liu, L. P1.17.02, P1.17.16
Liu, L. P3.18.41
Liu, L. EP.12.02
Liu, L. EP.08.21
Liu, L. P1.04.08
Liu, L. P3.18.07
Liu, L. MA04.08, P2.08 .43, PT1.07.03
Liu, M. P3.18.83
Liu, M. P3.01.46
Liu, M. EP.02.06
Liu, M. C. MA03.02, P3.18.04
Liu, M. EP.07.41, P2.02.12
Liu, M. EP.08.17
Liu, N. P3.01.24
Liu, N. P1.11.67
Liu, Q. P3.18.73
Liu, R. P1.04.05, P2.15 .31
Liu, R. P1.17.78
Liu, R. P1.07.42, PT1.07.04
Liu, S. P1.11.20
Liu, s. P1.11.84
Liu, S. PT1.07.03
Liu, S.-Y. P1.07.55
Liu, S.-Y.M. P1.07.55
Liu, S. P2.08 .04, P2.08 .05
Liu, S. EP.13.41, P2.02.37, P3.12.71, P3.13.13
Liu, S. V. MA11.04, P1.11.73, P2.06.44, PL02.15
Liu, T. P3.18.10
Liu, T. OA18.04
Liu, T. MA10.03
Liu, W. P1.17.60
Liu, W. EP.06.14
Liu, W. OA05.04
Liu, W. P2.06.85
Liu, X. EP.12.06
Liu, X. P2.06.80
Liu, X. P3.12.64
Liu, X. P2.15 .33
Liu, X. P1.11.34
Liu, X. EP.13.30, P3.13.19
Liu, X. P2.02.05, P3.12.50
Liu, X. PT2.13.03
Liu, X.-Y. PL02.09
Liu, X. MA11.10
Liu, X. EP.14.23, OA14.01, P2.02.07, P2.02.10, P2.06.49
Liu, X. P1.07.39
Liu, X. P3.12.55
Liu, Y.-H. P2.08 .43
Liu, Y. P1.17.38, P3.18.39
Liu, Y. EP.13.35
Liu, Y. MA01.05
Liu, Y. EP.06.64
Liu, Y. P1.04.50
Liu, Y. P3.03.10
Liu, Y. PL02.06
Liu, Y. P3.03.51
Liu, Y. P1.07.38
liu, y. P2.15 .28
Liu, Y. EP.18.08
Liu, Y. P3.01.07
Liu, Y. EP.15.17
Liu, Y. P3.03.18
Liu, Y. P3.18.76
Liu, Y. P1.11.28, P3.12.69
Liu, Y. P1.17.36, P2.08 .32
Liu, Z. EP.07.12, P1.07.54
Liu, Z. P2.02.47, PT1.09.04
Liu, Z. P3.12.31
Liu, Z.-Z. EP.18.09
Liu, Z. P3.03.23, P3.12.31
Liu, Z. EP.12.55, P3.13.15, P3.18.75
Liu, Z. P3.18.46, P3.18.48
Liu, Z.-G. P3.18.39
Liu, Z. P3.13.15
Liu, Z. EP.12.39
Liu, Z. P3.12.48, P3.18.75
Liu, Z. EP.04.25
Liu, Z. EP.08.04
Liurong Mao, L. P2.05.04
Livanou, M.-E. P1.11.39
Liva-Yonnet, S. EP.17.39
Livi, L. MA03.03, PT2.12.04
Ljujic, K. EP.11.09
Llenas, A. PT1.08.04
Lloyd, M. EP.17.02, P1.17.18, P3.01.13
Lloyd, S. P3.16.13
Lo, B. EP.06.54
Lo, T. P3.01.34
Lo, Y. EP.12.21
Lo, Y. P1.17.51
Lo Bianco, F. P1.11.42, P2.06.92
Löck, S. P1.07.22
Lockwood, W. EP.02.01, P2.02.15
Lockwood, W. W. EP.02.03, MA09.03, P3.01.23
Lococo, F. EP.06.40, EP.06.64, EP.14.18, P1.07.22, P2.05.10, P3.14.19
Lo Conte, L. OA07.03, PT1.08.02
Locquet, M. P3.12.63
Lodyga, M. EP.02.09
Lofters, A. EP.15.06
Loftus, L. P1.17.17
Logan, D. P1.17.70
Loges, S. P3.12.61
Loizides, S. EP.08.18
Lok, B. EP.13.38
Loliver, A. P3.14.15
Lomanto Navarro, L. EP.07.27
Lomibao, M. P3.03.32
Lomza-Laba, A. EP.06.17, EP.13.17
Lond, B. P2.15 .14
Londero, F. P3.14.19
Long, B. EP.13.34
Long, H. EP.06.62
Long, H. PL03.13
Long, J. B. EP.01.16
Long, J.-P. P3.01.37
Long, W. P3.18.39
Longarón, R. P2.06.74
Longo, F. P2.06.54
Longo, L. P3.12.08
Longo, V. OA17.01, P1.04.47, P3.13.04
Longshore, J. OA09.03
Loo, L. P2.06.52
Loong, H. EP.04.08
Loong, H. H. P3.12.41
Loparic, M. P2.06.56
Lopes, D. C. EP.17.30
Lopes, D. EP.13.28
Lopes, G. EP.12.34, EP.13.32, OA18.01, OA18.02, P1.11.15, P3.01.52, P3.12.71, P3.14.01
Lopes, G. M. P1.11.69
Lopes, Í. EP.01.05
López, A. EP.08.26
López, A. P3.01.25
Lopez, J. OA09.01
López, J. P2.08 .37
Lopez, J. S. P2.06.100
Lopez-Bailon, L. P3.03.20

López Castro, R. OA05.03, P1.11.07, P1.11.37, P3.18.12
Lopez-Castro, R. OA01.02
López - Castro , MD, R. MA01.03
López Gómez, C. P1.17.67
López-González, J. EP.06.66
López Gutiérrez, Á. P3.14.15
López-Herrero, M. EP.06.66
López Martín, A. PT2.15.04
Lopez-Rios, F. EP.06.43, MA07.01, OA09.03, PL03.16
López-Vilaró, L. EP.06.48
LoPiccolo, J. P3.12.63, PT2.11.01, PT2.15.02
Lorenzini, D. OA09.02, P1.17.44, P2.06.65
Lorenzo, M. MA01.01
Loreti, F. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Lo Russo, G. MA04.04, MA06.07, OA09.02, OA12.02, P1.04.51, P1.07.51, P1.11.01, P1.11.66, P1.17.30, P1.17.44, P1.17.55, P2.06.65, P2.15 .34, P3.12.10, P3.14.18, PL02.12
Lorusso, G. P3.14.06
Losada, B. P1.11.37
Lo Sasso, A. P1.04.47
Lou, F. P1.07.16, P1.17.01
Lou, G. EP.13.23
Lou, Y. P3.13.32, P3.18.87
Lou, Y. EP.06.59, PT2.11.03
Louie, A. EP.09.04, EP.17.28
Lovato, J. EP.04.29
Lovato, J.-B. P1.04.39
Love, N. EP.12.10
Love, S. EP.07.47
Lovely, B. P3.16.16
Love Stowell, S. MA03.01
Lovly, C. M. PL03.06
Low, J. P2.06.14
Lowery, C. P3.18.38
Lowy, I. MA01.07, MA10.09, P2.06.102
Loya, C. EP.06.15
Loza, M. P1.17.54
Lozano Ayala, J. EP.07.27
Lu, B. EP.08.01
Lu, C. EP.12.60, P3.01.04, P3.01.37
Lu, C.-W. EP.06.20
Lu, C. PT1.01.03
Lu, C. P2.02.01
Lu, D. EP.02.01
Lu, D. P2.02.47
Lu, H. P3.12.07
Lu, H. EP.13.23
Lu, H.-H. EP.07.16
Lu, J. EP.06.59, PT2.11.03
Lu, K. P3.12.48, P3.12.69
Lu, L. EP.07.51
Lu, S. MA06.04
Lu, S. EP.03.05, P2.02.09
Lu, S. P1.04.50
Lu, S. MA02.03, MA02.07, MA04.05, MA07.07, MA11.03, OA02.03, P2.02.08, P2.02.31, P2.10.13, P3.03.14, P3.12.41, P3.12.48, P3.12.64, P3.13.24, P3.18.35, P3.18.59, PT1.03.06, PT2.10.02
Lu, S. EP.12.31, P2.02.23
Lu, W. EP.13.01
Lu, W. PT2.13.03
Lu, X. OA06.01
Lu, Y. P1.07.42, P2.06.60, PT1.07.04
lu, y. P3.12.47, PT2.13.02
Lubawska, D. P3.14.10
Lucchi, M. EP.14.18, P2.05.10, P2.08 .03
Luce, A. P1.17.28, P1.17.51, P3.13.32
Lucena, C. EP06.85, P3.03.10
Lucena Pozo, C. EP.05.01
Lucherini, S. MA04.05, OA02.03
Lucía Gozálvez, C. P3.18.12
Luciani, A. P1.11.01
Luciano-Mateo, F. EP.03.13, PT1.08.04
Ludkovski, O. OA12.04
Lugini, A. EP.06.52
Lugon, M. P1.04.15
Lugowska, I. P2.06.100
Lugtu, K. P3.01.48
Luguera Sánchez, E. EP.08.47
Lui, N. P1.04.20
Lui, N. S. P1.04.19, P3.01.07, P3.18.84, PT1.01.01
Lui, Y. P1.11.13
Luizaga, L. EP.05.08, P2.05.06
Lujan, F. E. P2.06.84
Lukashova, E. P3.01.11
Lung Cancer Cohort Consortium, (. PT1.04.04
Luo, D. H. P2.10.15
Luo, D. P1.07.12
Luo, F. MA01.05, OA05.01
Luo, I. P3.01.07, PT1.01.01
Luo, J. P3.12.63, P3.14.22
Luo, J. P1.11.84
Luo, K. P1.04.50
Luo, L. MA11.10, P3.12.70
Luo, S. P3.03.41
Luo, S. P1.17.36, P3.12.74
Luo, T. P3.13.15
Luo, T. P2.08 .34
Luo, W. C. PT1.06.02
Luo, W.-C. P1.07.55
Luo, W. P1.11.61
Luo, W. EP.06.38
Luo, X. P3.18.32, P3.18.42
Luo, x. P3.12.48, P3.12.64
Luo, X. MA07.07
Luo, Y. P2.02.02
Luo, Y. OA12.02
Luo, Y. MA08.06, OA06.02, PL02.12
Luo, Y.-H. MA08.01, P2.10.04, P3.12.27
Luon, D. EP.13.03
Lupicka, M. P1.17.58, P2.15 .31
Luque Crespo, E. EP.06.71
Luta, G. P1.04.10
Luthra, G. EP.17.37, P3.01.14, P3.01.15, P3.01.16, P3.01.17
Luu, V.-P. P1.17.57
Lv, D.-Q. EP.12.06
Lv, D. MA08.01, MA11.03, OA10.04, P2.10.13, P3.12.48, P3.12.64
Lv, F. P2.08 .32
Lv, J. P3.13.22
LV, M. P2.02.25
Lv, W. EP.01.15, EP.04.25, EP.07.55
lyberis, P. EP.14.18
Lycan, T. P3.18.14
Lycan Jr., T. W. P3.18.14
Lyne, C. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Lyons, D. EP.12.10
Lyu, F. P2.08 .04, P2.08 .05
Lyu, J. P1.17.26
Lyu, Z. MA09.07, P3.01.08

M

Ma, C. P1.11.20, P1.11.34
Ma, G. EP.09.12, P3.09.06
Ma, H.-H. P2.08 .44
Ma, H. P3.18.76
Ma, J. EP.08.51, EP.13.08, EP.14.22
Ma, J. PT1.07.02
Ma, J. P1.11.02
Ma, K. EP.08.41
Ma, K. OA06.01
Ma, K. MA03.09, MA07.09, P2.06.58
Ma, L. P2.10.14
Ma, M. EP.07.45

Ma, N. EP.12.02
Ma, P. C. MA07.06, P2.06.52
Ma, R. P1.17.36, P2.10.12, P3.12.07, P3.12.48
Ma, S. P1.11.36, P1.17.70
Ma, S. P2.02.10
Ma, S. OA10.02, P1.11.76, P1.17.38, PT2.10.04
Ma, S. P2.06.72
MA, W. P3.12.74
Ma, W. EP.06.13, P1.07.14, P1.07.19
Ma, W. EP.02.09
Ma, Y. EP.01.15, EP.04.25, EP.07.55
Ma, Y. P2.02.02
Ma, Y. OA10.03
Ma, Z. P1.11.35, P1.11.46
Maassen, I. EP.17.13
Mabry, A. MA07.05
MacAulay, C. MA09.03, P1.04.18, P3.01.23, P3.01.49
Macchi, G. P3.16.05
MacDonald, I. E. P3.01.24
Macedo-Pérez, E. OA05.04
Macerelli, M. P1.17.54, P1.17.55
Macfarlane, M. P3.14.08
Machado, M. EP.01.05
Macheda, D. EP.15.14
Machiels, J.-P. P3.18.66
Machin, J. P2.15 .32
Macía, I. MA01.01
Mack, P. OA11.02
Mack, S. P3.14.04
MacKenzie, K. P2.15 .17
Mackler, N. J. PL03.06
Maclennan, M. EP.06.51
Maconi, A. EP.14.08
Madan, R. P1.17.79
Madden, S. P3.13.31
Maddox, R. P1.04.08
Madhi, H. EP.02.07, PT1.03.01
Madison, R. EP.06.69, EP.06.76
Madison, R. W. EP.06.68
Madre, C. P2.06.94
Maehara, V. EP.01.05
Maemondo, M. P3.13.14
Maenishi, O. P3.03.30
Maes, B. P1.07.41
Maff, R. P1.04.31
Maffezzoli, M. P3.14.05
Mafficini, A. P3.18.85
Magalhães Filho, M. P1.17.82
magdalena, M. EP.13.02
Magee, L. OA17.02
Mager, U. P3.18.56
Maggioni, G. PT2.14.02
Magiera, L. P2.02.27
Maglietta, G. EP.11.20, P1.11.24
Magnan, H. MA10.09, P2.06.102
Maguire, C. P2.08 .19
Maguire, F. B. P1.17.03
Maguire, R. EP.01.12
Mahadevan, N. P3.12.63
Mahadevia, P. J. P3.12.46
Mahajan, A. EP.04.24
Maher, K. OA18.01
Maheshwari, G. EP.08.14, EP.09.08, P3.09.01
Maheshwari, U. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Mahmoudpour, S. P3.12.10
Mahoney, J. MA08.03, MA08.05
Mai, J. EP.14.14
Maillard, M. P1.11.03
Mailleux, A. P2.06.15
Maiocco, G. P3.13.32
Maione, P. EP.11.03
MAITI, P. EP.12.33
Maitre, B. PT1.04.03
Majem, M. EP.08.07, MA10.06, P1.07.47, P1.17.80, P2.15 .12, PT2.17.05
Majem Tarruella, M. P3.18.38
Mak, M. P3.12.46
Makani, N. MA02.06
Mäkelä, T. P1.17.67
Makharadze, T. EP.17.26, MA10.09, P1.11.52
Maki, K. P1.17.83
Makihara, N. EP.08.09
Makino, H. EP.13.12
ma'koseh, M. P1.17.39, P1.17.53, P2.06.09
Maksym, G. P3.01.31
Malapelle, U. P1.07.51, P3.12.15
Malaret Verge, M. P2.15 .12
Maldonado, F. EP.04.42, MA10.02, P2.06.43
Malec, M. P3.14.04
Malhotra, A. P3.18.52, P3.18.53
Malhotra, K. OA03.03
Malhotra, M. MA03.02
Malhotra, R. K. EP.08.24
Malick, P. EP.13.46
Malik, N. EP.08.32
Malik, P. PT1.06.03
Malik, P. S. EP.02.08, EP.06.22, EP.06.27, EP.08.24, MA09.08, P3.18.72
Malik, S. PL02.18
Malkevich, V. P3.18.23
Mallick, J. OA09.03
Mallick, S. EP.08.24
Mallisetty, A. P2.06.69
Malone, S. T. EP.04.06
Maloney, D. G. P3.18.87
Malthaner, R. P2.06.70
Maltser, S. EP.15.12
Malucelli Favorito, F. EP.17.38
Maluf, F. C. EP.17.30
Malumbres, M. MA11.06
Mamede, I. P1.11.69
Mammana, M. EP.08.03
Man, H. J. OA12.04
Man, L. P1.11.28, P1.17.69
Mañas Mora, E. EP.12.11
Mañas-Mora, E. EP.12.24
Manby, F. P3.03.29
Mancini, B. OA13.03
Mancini, M. EP.06.03
Mandal, N. P3.16.09
Mandrekar, S. J. PL02.18
Mane, J. PL03.10
Mañes, A. P2.08 .49
Mañes García, A. EP.08.47
Mangan, Y. P3.14.05
Mani, H. EP.03.01
Maniar, V. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Manini, M. EP.11.05
Maniwa, T. EP.07.01, P3.18.04
Mankuzhy, N. EP.08.51
Manley, C. EP.06.15
Mann, H. MA04.09
Manna, M. P1.17.42
Manners, D. P1.17.12
Manning, B. P1.11.71
Manochakian, R. P1.17.51, P3.13.32
Manoj, P. P3.03.32, P3.03.52
Manos, D. P1.17.42
Mano-Sitton, R. P1.17.06
Mansfield, A. P1.17.51, P3.12.71
Mansfield, A. S. MA03.05, OA13.03, P1.17.28, P3.13.32
Mansharamani, A. P1.17.49

Mansoorian, S. P3.16.19
Mansouri, S. P3.03.54
Mantero, M. P1.07.17
Mantuano, F. P1.11.42
Mantz, C. P3.01.18, PT2.15.02
Manzanares-Martín, B. EP.06.66
Manzanera, A. MA10.02
Manzano, C. EP.04.14
Manzo, A. EP.11.20, P3.18.18
Mao, C. EP.17.16, P1.17.37, P1.17.38
Mao, L. P1.04.50
Mao, L. EP.06.41
Mao, R. P2.10.12
Mao, T. PT2.14.04
Mao, Y. OA05.01
Mao, Y. P3.18.86
Mao, Y. EP.11.19
Mao, Z.-J. P3.12.26
Mao, Z. P2.06.98
Mao, Z. P2.02.02
Mara, A. B. P1.11.70
Maramreddy, S. P1.17.26
Maranda-Robitaille, M. EP.06.06, MA07.04
Maranzano, E. OA07.03, PT1.08.02
Marar, R. I. P3.18.87
Maraver, A. P3.18.60
Marcelino, C. P. EP.17.23
Marchal, J. EP.11.02
Marchal Cabrera, J. EP.12.11
Marchant, T. OA16.02
Marchianò, A. P1.17.30
Marchianò, A. V. P1.04.53
Marco, A. PT1.02.04
Marco Gimenez, A. P2.02.04
Marcq, M. P2.06.43
Mardiros, A. P3.18.87
Marè, V. EP.08.13
Marech, I. OA17.01, P1.04.47
Marengo, F. P3.14.13
Margaritora, S. EP.06.40, EP.14.18, P1.07.22, P2.05.10, P3.14.19
Maric, S. P2.08 .20
Maridueña Moreno, M. P2.10.05
Marignol, L. EP.01.16
Marin, E. EP06.85, P2.06.56
Marinca, M. P2.15 .06
Marinelli, D. EP.07.48, EP.08.03, P1.11.17
Marinho, M. EP.15.09
Marín-Muñiz, A. EP.16.04, P2.08 .60
Marino, M. B. OA09.02, P1.17.30
Marino, S. P1.11.01
Mariño Siancas, C. EP.06.78
Mariotti, S. P1.07.51, P3.12.15
Mark, M. P3.18.82
Mark, M. EP.06.83
Markman, J. L. MA01.07
Markov, E. P1.17.52
Marko-Varga, G. MA11.06, P3.13.03
Markovets, A. MA03.03
Markovich, A. P3.13.29
Markovits, E. P2.06.68, P3.03.39
Markowitz, S. P1.04.40
Marks, J. P3.01.18
Marks, J. A. P1.17.22, P2.06.44, P3.14.20
Marks, S. P2.06.82
Markus, D. V. EP.17.30
Marlin, F. EP12.64
Marmarelis, M. EP.14.17
Marmarelis, M. E. P1.11.18
Maroney, R. P1.11.71
Maroni, G. P3.03.15
Marotta, C. OA18.04
Marques da Costa, F. P1.17.45
Marquette, C. P2.06.87
Márquez, D. EP.06.66
Marquina, M. PT2.15.04
Marrades, R. EP06.85
Marrades, R. M. P3.03.10
Marrades Sicart, R. P2.06.32
Marres, G. M. P3.01.10
Marrón, C. MA01.01
Marrone, K. A. P1.11.72, P3.18.40
Marsé, R. PL03.10
Marsh, L. PT2.14.02
Marshall, C. EP.01.22, MA09.05
Marshall, H. EP.04.07, P1.17.12
Marshall, H. M. P2.06.51
Marshall, H. P2.15 .32
Marshall, M. P1.11.38
Marshall, S. P1.17.20
Martin, A. P3.09.02
Martin, C. OA02.03, PT1.03.06
Martin, J. EP.06.54, EP.17.17
Martin, J. P2.08 .54
Martin, M. P2.02.27
Martin, T. MA10.05
Martín-Arana, J. P3.03.45
Martín de Bernardo Gisbert, L. P3.01.25
Martinelli, S. P2.06.04
Martinengo, G. P1.11.85
Martines, G. MA02.05, P1.07.04
Martinetti, L. P2.06.79
Martínez, D. EP06.85
Martinez, D. OA01.02
Martínez, D. P2.06.32
Martinez, J. G. P3.18.55
Martínez, M. P3.01.25
Martínez, M. P3.01.25
Martinez, S. P2.15 .31
Martínez, S. EP.08.07
Martinez, V. P3.01.27
Martinez, V. D. EP.01.21
Martínez Aguillo, M. PL03.10
Martinez-Avila, L. EP.07.42
Martínez-Barenys, C. MA01.01
Martinez-Caceres, E. EP.06.78
Martínez Hernández, D. EP.05.01
Martinez Jaramillo, S. EP.15.18
Martinez-Jaramillo, S. EP.04.01
Martínez-Martí, A. MA06.03
Martinez-Marti, A. OA02.01
Martìnez-Marti, A. P3.12.30
Martinez-Marti, A. P3.14.02
Martínez-Marti, A. P3.18.12, PL03.10
Martinez-Marti, MD, A. MA01.03
Martínez-Momblan, M. P2.15 .12
Martínez-Pallí, G. P2.15 .21
Martìnez Pèrez, À. P1.17.67
Martínez Recio, S. P2.15 .12
Martinez Tellez, E. EP.08.07
Martini, J.-F. P3.12.21
Martini, V. EP.06.80
Martin-Lopez, J. P3.01.25
Martín Martorell, P. OA08.03
Martìn Martorell, P. P3.12.30
Martín-Martorell, P. P3.03.45, PL03.10
Martino, A. P3.13.04
Martín-Ortega, J. EP.08.37
Martucci, F. P3.18.82
Maru, N. EP.08.09
Marušić, A. OA15.01
Marulli, G. P2.05.10
Mascaro, F. P1.11.54

Mascaux, C. EP.06.39, EP.12.36, OA05.02, OA10.01
Mascaux, C. P3.18.35
Mascaux, C. PT1.03.04
Masciale, V. P3.14.06
Masdi, M. EP.13.02
Maselli Schoueri, J. P1.17.82
Masfarré, L. P3.12.30
Maskey, R. P2.10.17
Massayavanich, I. EP.04.37
Masson, P. OA05.02
Massuti, B. MA06.03
Massutí, B. P1.11.07, P1.11.37
Massuti, B. P3.18.12, PL03.10
Massutí, MD, B. MA01.03
Masters, G. A. PL03.06
Mastromarino, M. P2.08 .03
Masucci, L. P2.08 .54
Masuda, K. P3.18.04
Masuda, T. P3.18.04
Masuda, T. EP.14.13, P1.07.13
Masuda, Y. EP.14.19
Mate, J. P3.03.44
Mate, J.-L. EP.06.48
Mateos, L. L. MA02.06
Mathavarjah, S. P3.01.27
Mathieson, L. EP.03.16, P3.03.46
Mathijssen, R. H. EP.12.15, EP.12.49, EP.12.52, P3.18.54
Matías-Guiu, X. P2.06.37
Matiello, J. P2.08 .18
Matilla, J.-M. OA11.02
Matitashvili, A. EP.17.26
Matsubara, D. MA07.01, MA07.03, OA13.04
Matsubara, T. EP.07.11, EP.07.50, P1.07.49
Matsubayashi, J. EP.08.40, P2.08 .06
Matsuda, H. P2.06.95
Matsuda, S. EP.14.21
Matsudo, K. EP.07.50
Matsui, A. P3.12.35
Matsui, H. EP.08.09
Matsui, S. EP.09.16, P1.17.68, PT1.05.04
Matsui, Y. EP.17.05
Matsui, Y. EP.01.29
Matsumoto, S. EP.14.05
Matsumoto, S. EP.05.02, P2.06.59, P3.12.49, PT1.05.02
Matsumoto, T. EP.06.12
Matsumoto, Y. PT1.05.01, PT1.05.02
Matsumoto-Ono, I. EP.13.18
Matsumura, M. EP.07.04, EP.08.02
Matsumura, Y. EP.07.10, P1.07.03
Matsuno, Y. EP.14.16
Matsuo, M. EP.06.49
Matsuo, S. P1.07.49
Matsuo, Y. EP.06.12
Matsuoka, A. P2.06.16
Matsuoka, S. P2.06.47
Matsushima, K. EP.14.13
Matsusima, K. P1.07.13
Matsuura, S. EP.06.81
Matsuyama, R. EP.09.13, P2.08 .33
Matsuyama, R. EP.07.24
Matt, U. P3.03.54
Matute, M. PT2.15.04
Maugeri-Sacca, M. PT2.11.01
Maurel, J.-M. P3.12.62, P3.12.65
Maus, M. P3.18.87
Mauti, L. EP.06.83, P3.18.82
M. Awad, M. P1.11.62
Maxfield, M. P1.07.16
Maxfield, M. W. P1.17.01
Maxwell, P. OA09.03
Mayans, J. EP.16.02, P3.16.01
Mayfield, W. R. MA05.03
Mazher, S. P3.01.24
MAZIERES, J. EP.12.54
Mazières, J. EP.17.39
Mazieres, J. MA08.01
Maziéres, J. OA05.04
Mazières, J. P2.06.43
Mazieres, J. P3.03.34, P3.12.06, P3.12.38, P3.12.40, P3.18.09, P3.18.60, P3.18.67, P3.18.68, P3.18.74
Mazor, Y. OA03.03
Mazzaschi, G. EP.09.06, EP.11.05, P1.11.24
Mazzei-Abba, A. OA08.01, P3.18.71
Mazzeo, L. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Mazzoni, F. MA02.05, P1.07.51, P1.11.24, P1.17.54
Mazzucco, R. EP.14.08
Mba, C. EP.17.22
McAdam, J. EP.15.16, EP.16.01
McAleer, M. MA10.05
McAllister, M. EP.07.33
McBride, S. M. EP.14.22
McCarrier, K. EP.12.35
McCauley, R. EP.08.32
McCulloch, J. P1.17.44
McDermott, S. P1.04.08
McDevitt, M. EP.06.68
McDonald, L. P1.11.85
McDonald, P. P2.02.15
McDonald, S. PT2.13.04, PT2.15.02
McEachin, O. PT1.04.01
McElderry, J. OA14.05
McFadden, K. P3.16.10
McFaline-Figueroa, J. PT1.02.04
McGovern, S. L. MA10.05
McGrath, A. P2.06.89
McGuire, A. OA09.03
McGuire, A. MA09.03, P3.01.23, P3.01.34
McGuire, A. L. EP.07.17, MA09.02
McHale, S. EP.16.07
Mcintosh, L. P1.07.16
McIntosh, S. P3.16.08
McIntyre, D. A. MA10.09
McKean, M. P3.18.67
McKenna Smith, C. P1.17.46
Mckheen, A. P3.12.16
McKinven, D. P3.14.08, P3.14.10
McKree Jansen, R. EP.04.07
MCLEAN, A. E. P2.06.63
McLeod, M. EP.04.10
McLouhghlin, J. EP.07.47
McMillan, M. T. OA07.02
McNeill, A. M. EP.17.35
McNevin, C. P2.06.82
McPhelim, J. EP.01.12, P2.15 .14
McQuilten, Z. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
McWilliam, A. OA16.02
McWilliams, A. P1.04.08, P1.17.12
Meador, C. EP.13.47
Meador, C. B. PT2.13.04
Meazza Prina, M. MA06.07, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Mederos, N. P1.11.03, P3.18.82
Mederos Alfonso, N. N. EP.09.17
Medhurst, E. OA18.01
Mediavilla-Medel, P. MA01.03
Medina, K. P1.11.37, P3.01.25, P3.18.12
Medina, S. OA01.02, P3.18.12
Medina Sánchez, K. EP.12.63
Medina Sanchez, K. P2.08 .37
Medina-Sánchez, K. EP.08.37
Medley, L. MA08.03

Medusa, P. P3.18.18
Medvedev, D. P2.06.66
Meerang, M. P3.03.07
Meeter, A. P2.08 .56
Meffe, G. EP.08.13
Megyesfalvi, Z. MA11.06, P3.13.03
Mehmet, A. P1.11.70
Mehr, S. OA13.03
Mehra, R. MA10.02, P3.13.12, P3.18.17
Mehran, R. PT1.01.03
Mehran, R. J. OA12.03, P2.02.36
Mehrotra, A. P2.05.02, P2.15 .32
Mehta, A. EP.06.16, EP.17.06
Mehta, M. P. EP.08.19, P2.06.76
Mehta, S. P1.17.22
Mehta, V. P2.15 .30
Mei, J. EP.07.12, P1.07.54
Mei, Q. P2.15 .25
Mei, S.-Q. P1.11.61
Meijboom, L. PT2.11.02
Meiman, D. OA06.04
Meir, J. E. EP.08.28
Mejia, R. P1.04.07
Mekha, M. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Melamed, O. EP.01.24, EP.01.25
Melear, J. P3.12.71
Melek, H. EP.05.04
Meletti Cavallari, C. P1.11.54
Melichar, B. P1.11.10
Melis, E. EP.04.30, EP.07.48
Melkadze, T. MA10.09, P1.11.52
Mella, M. P1.17.52
MELLOUKI, A. P2.10.07
Melo, A. C. EP.15.01, P1.11.16
Melo, J. P1.04.28
Melo, J. V. EP.08.16, P2.08 .52
Melo, J. V. P3.01.41
Melocchi, V. P2.06.54
Melosky, B. EP.07.17, EP.08.17
Melotti, B. P1.11.42, P2.06.92
Melsom, S. P1.04.08
Melvin, S. EP.03.01
Melvin, S. P1.04.10
Memmott, R. MA08.01, P2.08 .47, PT2.12.01
Mena-Guerrero, J. P3.01.46
Mencoboni, M. OA12.02
Mendel, W. P3.16.20
Mender, i. P1.11.82
Mendes, J. P2.15 .29
Mendes, S. V. EP.09.09
Mendivelso Botello, A. F. P2.15 .11
Mendogni, P. P3.14.17, P3.14.19
Mendonça, A. EP.01.05
Mendoza Montealegre, I. P3.01.31
Meneses, A. P3.01.52
Menezes, C. F. EP.06.09, P3.01.06, PT1.04.02
Meng, M. P2.10.15
Meng, P. P1.07.53
Meng, R. OA02.01
Meng, R. PT2.10.04
Meng, X. P1.11.34, P2.06.101, P2.06.57
Meng, X. OA06.01, OA06.02, P3.12.69
Menghesha, H. P3.14.19
MENG TENG, Y. EP.06.62
Menichetti, L. P3.03.15
Menis, J. P3.14.06, PT2.15.01
Menjak, I. MA08.07
Menju, T. P3.18.04
Mennecier, B. P2.15 .29
Menon, N. EP.08.14
Mensah, C. EP.17.22
Meoni, G. P3.12.15
Merajver, S. D. PT1.03.01
Merajver, S. EP.02.07
Mercadante, E. P1.07.07, P3.14.17
Mercatelli, R. P3.03.15
Merced, A. MA02.06
Mercer, R. EP.02.07
Mercier, O. EP.04.29, P1.04.39, P3.14.15
Meredith, R. A. EP.06.53
Merelli, I. P3.03.15
Merkhofer, C. M. P1.11.73
Merlini, A. P2.06.40
Merlotti, A. P2.08 .26
Meroueh, C. OA09.03
Merrick, D. T. P3.13.30
Merrill, N. PT1.03.01
Merrill, N. M. EP.02.07
Mersiades, A. J. OA03.04, P1.17.62, P2.06.61
Mertsch, P. EP.03.12, EP.11.23, EP.12.56, P3.12.67
Mesa-Frias, M. P3.12.13
Mesía, C. P2.06.37
Meskini, R. E. MA07.02
Mestiri, S. EP.12.61
Metaxas, Y. P3.18.82
Methot, J. P1.17.67
Metintas, M. P2.05.07
Metintas, S. P2.05.07
Metro, G. MA02.05, MA03.03, P1.17.54, P3.12.15, PT2.11.01
Mets, O. M. P3.18.16
Mettetal, J. P2.02.27
Mettias, A. OA13.03
Metzenmacher, M. EP.04.27, EP.07.22
Meyer, M.-L. EP.09.17, P1.04.03, P1.11.03
Meyer, M. G. PT1.04.05
Meyer, T. EP.07.23
Meyers, B. P1.07.37
Meza, K. P3.01.18, PT2.15.02
Meza, R. EP.01.02, EP.07.17, MA05.05, MA09.01, P1.04.07, P1.04.33, P1.17.19, P1.17.81, P3.01.35, P3.01.42, P3.01.47
Mezquita, L. EP06.85, OA01.02, P1.17.29, P3.01.46
M. Hopman, W. OA18.02
Mi, Y. P2.10.12
Miadzvedz, A. EP.06.63
Miao, L. EP.04.39, EP.06.72, P3.12.41, P3.18.51, PT2.10.03
Miao, Y.-R. P3.12.55
Michael, A. P1.04.54
Michaeli, Y. EP.04.41
Michaux, I. EP.15.19
Michavila, X. EP.08.26
Michel, P. L. P1.11.54
Michelini, A. P3.12.30
Michelon Menetrier, M. EP.06.01
Michels, S. MA07.07
Michenet, P. OA09.03
Miele, M. P2.08 .30
Mielgo, X. PL03.10
Migas, J. P3.13.31
Migliorino, M. P3.16.05
Mihashi, Y. EP.17.25, P3.12.36
Mikami, E. EP.11.07
Mikami, M. EP.04.36
Mišković, V. OA09.02, P2.06.65
Mikubo, M. EP.06.02, EP.06.12, P3.03.03
Milanese, G. P1.04.53, P1.07.04
Milani, C. P1.11.01
Milanowski, J. EP.06.17, EP.13.17, MA10.04, P1.11.63
Milch, V. P1.04.08
Milella, M. P3.12.08, P3.18.85, PT2.15.01

MILIA, J. EP.12.54, P3.03.34
Militsin, R. EP.03.08
Miliziano, D. P3.14.15
Miller, C. P3.14.08
Miller, K. P3.14.20, P3.14.22
Miller, K. EP.12.10
Miller, T. P3.03.29
Miller, Y. P3.13.30
Milne, D. EP.04.07
Milner-Watts, C. EP.17.12
Mimae, T. EP.07.01, EP.07.54
Mimori, T. PT2.14.03
Mimoun, N. P2.06.87
Min, H. J. P1.17.32
Min, j. EP.12.02
Min, R. P2.08 .01
Min, R. S. P1.17.26
Min, X. OA06.01, P3.12.48, P3.12.64, P3.13.15
Minami, S. EP.11.13, EP.11.17, P1.11.19
Minami, Y. MA07.01, PL03.16
Minari, R. EP.11.05, MA02.05, P1.07.04
Minchev, V. P1.11.82
Minchom, A. EP.17.12
Mindicini, N. P3.12.20
Mine, K. EP.06.49
Minegishi, K. P1.07.49
Minerva, E. P3.18.82
Minervini, F. P3.18.82
Mingo, E. P1.11.66
Mingo, E. C. EP.06.52
Minian, N. EP.01.25
Min Kim, T. P2.06.102
Minna, J. P1.07.37
Mino-Kenudson, M. EP.06.53, MA07.01, OA13.04, PL03.16
Mints, M. P3.03.39
Minuti, G. MA01.04, P1.07.51, P1.17.54, P1.17.55, P3.12.15
Minuti, G. P3.12.10
Miraftab, M. OA14.05
Mirallas, O. P3.12.30
Mirambeaux, R. EP.07.27
Miranda, B. EP.11.03
Miro, J.-M. EP.14.15
Mironova, O. A. EP.08.25
Mirosavljevic, A. P2.08 .20
Mirsky, M. EP.17.03
Misawa, K. EP.12.29, P3.12.09, P3.12.23
Mishima, S. P2.06.47
Mishina, Y. EP.07.04, EP.08.02, EP.14.24
Mishra, E. P1.04.54
Miskovic, V. MA06.07, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.15 .34
Missel, M. EP.15.10
Missy, P. P3.14.15
Mitchell, E. P1.04.31
Mitchell, M. P2.06.70
Mitchell, N. OA03.03
Mitchell, O. P3.14.04
Mitchinson, L. P3.16.14
Mithoowani, H. P1.17.70
Mitilian, D. EP.04.29, P1.04.39
Mitome, N. EP.07.01
Mitra, P. P3.18.65
Mitsudomi, T. MA04.09, OA02.03, P3.09.05
Mitsuhashi, S. EP.06.12
Mitsuishi, Y. P2.06.95
Mitsunaga, M. P1.11.82
Mittal, V. P3.01.51
Miura, K. EP.14.21
Miura, K. P2.06.47
Miura, N. P3.03.05
Miura, S. P1.11.11
Mix, M. D. P3.18.13
Miyagi, Y. EP.07.07
Miyahara, S. EP.14.19
Miyake, M. P1.04.52
Miyamatsu, S. P3.12.35
Miyamoto, E. EP.06.33
Miyamoto, K. EP.01.05
Miyamoto, N. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Miyamura, B. V. EP.17.30
Miyata, R. EP.07.56
Miyata, Y. EP.05.07
Miyauchi, E. EP.03.03, EP.06.26, P3.03.42, P3.12.58
Miyawaki, T. P2.06.95, P3.18.31
Miyazaki, A. EP.11.06
Miyazawa, A. P3.12.35
Miyoshi, T. EP.07.01, EP.07.10, P1.07.03
Mizen, J. P1.04.54
Mizuno, T. EP.06.70, P1.11.47
Mizunuma, M. EP.04.36
Mizutani, H. EP.12.29, P1.07.35, P3.12.09, P3.12.23
Mizutani, T. P3.18.04
Mizuuchi, H. EP.06.28
Mo, S.-L. OA03.02
Mo, Y. EP.17.19
Mochizuki, A. P3.03.36
Modi, D. MA10.09, P2.06.102
Moeller, J. P2.10.01
Moesgaard Eschen, A. P1.17.67
Mogavero, A. P3.12.15, P3.16.05
Mogenet, A. P2.15 .29
Moghaddam, S. J. P2.02.36
Moghanaki, D. EP.07.14, P2.08 .22, P3.01.51, P3.18.05
Mohamed, S. A. EP.11.22
Mohamed Hoesein, F. OA01.01
Mohammad, F. P2.06.88
Mohan, A. EP.06.27, P1.17.24
Mohan, S. MA11.04
Mohindra, N. EP.12.30
Mohindroo, C. MA07.02
Mohmaed Ali, M. EP.12.05
Mohon, R. P3.16.22, P3.16.23
Mohseni, Y. P3.18.87
Mojibian, A. P1.04.34
Mok, T. MA05.09
Molena, D. P1.04.17, P3.01.19, P3.01.22
Molero Savall, J. EP.08.47
Molfese, E. EP.08.13, P2.08 .30
Molina, A. M. P3.18.55
Molina, J. P1.17.28, P1.17.51, P3.13.32
Molina, J. R. P3.18.87
Molina Osorio, G. EP.08.47
Molinari, F. EP.06.35
Molina-Vila, M. EP.02.10
Moliner, L. P2.06.37, P3.14.09, PT1.08.04
Molinier, L. EP.17.39
Molinier, O. OA05.02
Molins, L. EP.08.26, P2.06.32
Moll, A. P3.01.46
Mollà, M. EP.13.19
Møller, L. B. EP.15.03
Mollica, M. P2.15 .24
Moloney, C. P2.06.82, P2.08 .01, PT1.09.02
Moloney, C. EP.08.34
Monaca, F. P2.10.05, P3.12.30, P3.13.04
Monaco, F. EP.11.01
Monestime, S. EP.17.01, P3.12.56, P3.16.21, PT2.16.01
Monge, A. EP.04.14
Monge, S. MA01.01

Mongil, R. MA01.01
Monkman, J. P2.06.68
Monnet, I. P1.17.54
Monroe, M. P1.17.83
Monsch, G.-M. EP.07.09, P3.18.82
Monsen, J. EP.12.59
Montagna, E. OA17.01, P1.04.47
Montague, D. OA17.02
Montague, T. P3.12.56
Montañés-Ferrer, C. P2.08 .49
Montanino, A. P3.18.18
Montano, J. P3.01.52
Montanya, E. PT1.08.04
Montella, L. P3.18.18
Montella, T. EP.15.01
Montella, T. C. P1.11.16
Montesinos, M. EP.04.14
Montironi, C. EP.06.48, EP06.85
Montrone, M. EP.11.20, OA17.01, P1.04.47, P1.11.24, P1.17.54, P3.12.15
Montuenga, L. EP.13.27, PT1.08.05
Montuenga, L. M. MA05.06
Montuenga, L. OA11.02
Monument, M. PT1.03.01
Monzani, D. P1.04.51
Moon, H. P1.04.26
Mooney-Doyle, K. EP.15.08, OA04.01
Moons-Pasic, A. PT2.11.02
Moore, D. A. P2.06.08
Moore, L. OA09.03
Moore, M. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Moore, M. OA13.02, P1.17.62
Moore, S. EP.13.38, EP.17.17, P2.10.06
Morabito, A. OA12.02, P1.11.24
Morabito, A. P3.01.18, PT2.15.02, PT2.17.04
Moraes, F. P2.08 .18
Morais, J. EP.01.05
Morales, G. P2.06.88
Morales-Espinosa, D. P2.06.100
Moran, L. P2.06.82
Moran, T. P1.11.37, P2.08 .49
Morán, T. P3.03.44
Moran, T. P3.12.30
Moran , MD, T. MA01.03
Moran-Bueno, T. EP.06.78
Morata, J. P3.03.49
Morcillo, E. I. EP.11.02
Morcillo Calero, E. I. EP.12.11
Moreau, L. OA05.02
Moreira, G. F. P1.11.16
Moremen, J. R. P3.18.84
Moreno, L. P3.01.46
Moreno, M. P3.18.12
Moreno, M. P1.11.37
Moreno, M. P3.01.25
Moreno, V. MA02.04
Moreno-Càceres, J. PT1.08.04
Moreno Conde, J. EP.06.71
Moreno-Manuel, A. EP.06.77
Moreno Mata, N. EP.07.27
Moreno-Olmedo, E. P3.09.02
Moretti, M. EP.07.42
Morgan, C. OA16.02
Morgand, C. P1.17.57
Morgan Stewart, H. P1.17.67
Morgenstern-Kaplan, D. EP.13.32
Morgensztern, D. EP.13.40, OA06.04, P1.11.78, P1.17.50, P2.08 .51, P3.18.52
Morgillo, F. P3.18.18
Morguelan, B. P1.17.59, P3.13.07
Mori, K. PT2.14.03
Mori, M. EP.17.25
Morilla, I. P1.11.37
Morillas, J. M. OA14.04, P2.02.06, P3.03.49
MORIN, C. EP.12.54
Morin, F. OA05.02
Morinaga, D. P3.09.09
Morise, M. P3.12.35
Morishita, A. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Morita, D. P2.08 .08
Moriya, Y. EP.14.02
Moriyama, G. EP.13.18
Morley, J. EP.16.01
Moro, M. OA17.01
Moroniti, J. P1.17.70
Morris, B. B. MA11.06
Morris, M. P3.13.05
Morris, P. G. EP.08.34
Mortarini, R. P1.17.44
Mortman, K. P2.08 .42
Mortman, M. F. P3.16.22
Morzaria, D. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Mosca, E. P3.03.15
Mosconi, C. P2.06.92
Moser, B. P3.14.19
Mosillo, L. P1.07.07
Mosimann, V. EP.09.17, P1.11.03
Moskovitz, M. MA08.05, OA13.01, P2.15 .06, P3.09.03
Mosleh, B. EP.02.02, P2.02.18
Mosqueda, M. EP.06.77
Mosquera , MD, PhD, J. MA01.03
Moss, N. EP.17.13, P1.04.41
Mosteiro, M. P3.12.30, PT1.08.04
Mosteiro, M.-A. P2.08 .49
Mosteiro Lamas, M. P2.06.37, P3.14.09
Mosteiro-Molina, S. EP.07.42
Motoi, N. OA13.04
Motta, G. P3.18.18
Motta, L. EP.06.35
Moudgalya, H. P2.06.64
Moultrie, R. P2.15 .05
Moumne, M. EP.13.39
Mountzios, G. P2.15 .26, P3.12.13, P3.18.80, PT2.15.02
Moura, F. P3.16.04
Moura, F. S. EP.17.30
Moura, J. F. P3.01.06
Moura, J. d. EP.06.09, P1.17.11, PT1.04.02
Moura de Gouvêa, F. P3.01.06
Mourão Dias, J. MA08.03, MA08.05, PT1.03.06
Mousavi Janbeh Sarayi, S. M. P1.17.19
Mousavi Janbeh Sarayi, S. P3.01.47
Moutafi, M. EP.01.19
Movahedi, P. P1.17.67
Moyle, J. EP.08.34, P2.06.82
Mruk, A. P1.11.82
Mu, C. P2.02.47, PT1.09.04
Mu, H. P3.18.74
Mu, J. MA08.06
Mu, S. P3.18.20
Mu, X. P3.18.76
Mu, X. EP.12.28
Mueller, B. MA01.06
Mueller, C. P3.18.34
Mugunthan, A. P2.08 .23
Mujica-Arencibia, F. EP.08.37
Mukae, H. EP.06.49
Mukherjee, S. P3.01.48
Mukherjee, T. P1.07.26
Muldoon, C. MA03.03
Mulherin, MD, B. EP.12.32, EP12.65, P2.06.11, P2.06.20, P3.12.24
Mulina, A. P1.11.45

Muller, D. PT1.04.04
Muller, V. P1.11.82
Mullin, A. EP.17.15
Mullins, M. A. EP.04.06
Mulquin, N. EP.11.18
Mulroy, J. MA06.09
Mulvey, C. OA13.03, P1.07.40
Mumblat, H. EP.03.08
Muminovic, M. P2.06.78
Munasinghe, W. OA06.04
Mundkur, Y. P2.06.17
Munera, E. EP.06.77
Munker, R. EP.13.29, MA11.01
Muñoz-Carrillo, J. OA01.02
Muñoz-Esquerre, M. EP.16.04, P2.08 .60
Muñoz-Lerma, A. EP.17.12
Muñoz-Mármol, A. EP.06.48
Muñoz Molina, G. EP.07.27
Muñoz-Pinedo, C. EP.03.13, EP.14.03, P3.14.12, PT1.08.04
Munoz-Schuffenegger, P. OA18.02
Munshi, N. MA01.07
Murakam, S. EP.07.07
Murakami, A. PT2.16.02
Murakami, H. EP.14.21
Murakami, H. EP.06.33
Murakami, K. EP.05.02
Murakami, K. EP.07.07, EP.08.40
Murakami, S. P2.06.59, P2.08 .33, P3.18.04
Murakawa, T. EP.08.09, P3.18.04
Murase, Y. EP.06.25, EP.12.62
Murata, D. P1.11.40
Murata, Y. P3.12.49
Murciano-Goroff, Y. R. MA02.06
Murgu, S. P2.05.01
Murgu, S. EP.13.47
Murison, K. MA05.06
Muro, S. EP.07.56
Murphy, A. EP.08.34
Murphy, D. P3.14.08
Murphy, D. J. P3.14.10
Murphy, E. P2.06.45
Murphy, S. P. P3.12.46
Murray, J. P3.18.40
Murray, R. MA09.05
Murray, R. L. EP.01.22
Murtagh, C. EP.06.61
Murugaesu, N. P2.06.85
MURUNGA, A. L. EP.17.10, P1.17.48
Mushtaq, A. P1.11.77
Musib, L. P3.12.38
Musilli, S. EP12.64
Mussi, C. MA02.04
Mussot, S. EP.04.29, P1.04.39
Mustafayev, F. N. MA06.09
Muthu, V. EP.06.79
Muthukumar, A. P3.12.06
Muthukumar, V. EP.06.08
Muthuramalingam, S. P3.14.05
Muto, M. P3.12.39
Muto, S. P1.07.49
Muto-Ishizuka, M. EP.06.53
Myers, R. MA09.02, MA09.03, P1.04.18, P1.04.36, P1.17.42, P3.01.23
Myers, R. L. P1.04.33, P1.04.34, P3.01.29
Myers, R. EP.04.05

N

Na, B. EP.07.31, P2.05.08, P2.08 .02
Na, F. P3.12.47
Na, H. P2.06.48
Na, J. PT2.12.01
Na, K. EP.07.31, P2.08 .02
Na, R. P2.06.32, P3.03.10
Naama, B. OA09.02
Naargund, R. S. P1.17.81
Nabe, Y. EP.06.28
Nabeta, G. EP.17.36
Nadal, E. EP.03.13, EP.14.03, MA06.03, OA05.03, P2.06.37, P3.14.09, P3.14.12, P3.18.09, P3.18.12, P3.18.28, PL03.10, PT1.08.04, PT2.12.03
Nadal, E. P2.08 .49
Nadal, MD, PhD, E. MA01.03
Nadal-Alforja, E. P2.08 .60
Naddeo, M. P2.06.92
Naeem, W. P2.06.64
Nafees, A. P1.17.08, P1.17.09
Naffakh, N. P1.17.13
Nafría, B. PT2.15.04
Nagano, T. EP.07.50
Nagao, T. EP.08.40
Nagarajan, V. P2.10.17
Nagasaka, M. MA02.02, MA02.03, P3.12.42, P3.18.57, PL02.15
nagase, w. EP.08.40
Nagasepam, M. D. EP.09.08
Nagashima, R. P1.07.21
Nagashima, T. P1.07.13
Nagashima, T. EP.07.07, EP.07.24, EP.07.54, EP.09.13, P2.08 .33
Nagrath, S. PT1.03.01
Nagrial, A. P1.17.62, P2.06.89
Nagy, A. EP.14.07
Nagy, T. P1.11.82
Nahar, K. P2.06.89
Naicker, K. MA04.08, P1.11.15, P1.11.35, P1.11.46
Naidoo, J. EP.08.34, MA10.07, P1.11.85, P1.17.29, P2.06.82, P3.01.19, P3.18.61, P3.18.65
Nair, P. P2.06.18
Nair, R. G. EP.04.06
Nair, V. S. P1.04.45
Naito, M. P2.08 .08
Naito, M. EP.06.02, EP.06.12
Naito, T. EP.14.21
Najmeh, S. P1.17.42
Nakagami, C. EP.06.26
Nakagawa, K. P3.03.30, P3.16.12
Nakagawa, K. EP.07.01, P3.18.04
Nakagawa, T. EP.06.33
Nakahara, H. EP.11.08
Nakajima, R. EP.07.01, P3.18.04
Nakamura, D. P2.06.47
Nakamura, M. EP.14.21
Nakamura, S. EP.07.04, EP.08.02, EP.14.24
Nakamura, S. EP.06.70, EP.14.05, P1.11.47
Nakamura, T. P2.08 .06
Nakamura, Y. P3.09.05
Nakamura, Y. EP.05.02, EP.13.12
Nakamura, Y. P2.06.95
Nakanishi, K. EP.06.70, P1.11.47
Nakanishi, K. EP.06.81
Nakao, A. P1.11.40
Nakashima, H. EP.14.19
Nakayama, T. P3.03.30
Nakazawa, S. P3.12.63, PT2.17.04
Nam, B.-H. P1.11.32
Nam, H. P3.01.45
Nam, S. H. P1.17.32
Namakydoust, A. P3.18.28
Nambirajan, A. EP.06.22, EP.06.27, EP.13.46, EP.14.12
Namjoshi, D. P3.13.05
Namoglu, E. C. P1.17.24, P2.08 .42
Namura, J. J. P1.17.82
Nancarrow, D. PT1.03.01
Nanjo, S. EP.12.62, P1.11.06, P3.03.02
Nannini, N. P2.06.81

Napier, C. E. P2.06.61
Napoli, F. P2.06.22, P2.06.40
Naqash, A. R. P1.07.43
Naquash, A. P1.11.17
Naqvi, H. EP.17.16, P1.17.37, P1.17.38, P2.15 .06
Naranbhai, V. EP.15.04, P1.11.49
Narbeburu, M. P1.17.57
Nardi-Agmon, I. EP.14.15
Nardone, V. P3.18.18
Narita, S. EP.04.36
Narra, V. MA05.04
Narula, A. P1.11.21
Narula, T. P1.11.21
Narumi, A. EP.11.13, EP.11.17, P1.11.19
Nash, J. P1.17.12
Nasirova, F. EP.08.22, P1.07.35
Naso, J. P3.01.23
Naso, J. MA09.03, P3.01.34
Nassar, A. P1.11.17, P1.17.54, P1.17.55
Nassar, A. H. PT2.14.05
Nassib William Jr, W. P1.17.45
Nassif, M. P2.08 .18
Nassour, N. EP.08.32
Natchimuthu, V. EP.04.06
Nathany, S. EP.17.06
Navab, R. OA14.03, PT1.02.02
Navajas-Chocarro, P. EP02.12, P2.02.06, P3.03.44, P3.03.47, P3.03.49
Navani, V. P3.01.24, PT1.03.01
Navarro, A. EP06.85, P3.18.74
Navarro, A. P3.03.10
Navarro, A. PT1.08.04
Navarro, R.-R. P2.15 .21
Navarro, V. OA05.03
Navarro-Martin, A. EP.07.42
Navarro-Martín, A. EP.16.04
Navarro-Martin, A. P2.08 .49
Navarro-Martín, A. P2.08 .60
Navarro Mendivil, A. P3.18.73
Navarro Ponz, A. P2.06.32
Naveh, N. P3.13.31
Naves, D. P3.13.16
Nawrocki, J. T. P1.11.73
Nayak, R. P2.06.70
Nazareth Aguiar Jr, P. P1.17.82
Nazari, S. EP.13.41
Naznin, F. EP.02.03
Ndibmun, C. P3.13.31
Neal, J. P3.18.09
Neal, J. W. P1.07.35, P3.01.07, P3.18.87, PL02.15, PL02.18, PT1.01.01
Neal, K. P2.06.56
Nechaeva, M. MA10.09
Neely, J. MA10.07, P1.11.85
Neff, T. P3.18.73
Negi, Y. P1.11.40
Negrao, M. OA07.01
Negrao, M. V. EP.04.31, MA04.02, OA08.02, P1.11.70, P2.02.36, P3.18.09, PT1.01.03
Negret, L. EP.13.32
Negrini, L. EP.06.80
Negrini, M. P3.12.20
Nei, L. PL02.09
Neil, J. M. OA18.04
Neilan, C. P2.10.17
Neilson, L. A. EP.03.16, P3.03.46, P3.03.48
Neish, D. P2.08 .13
Nelson, A. PT1.04.05
Nelson, D. P3.16.14
Nelson, G. P3.18.13
Nematian-Samani, M. P3.12.46
Nemoto, T. EP.08.42, P3.12.54
Nemrawi, L. P1.17.39
Nemsadze, G. MA10.09
Neron, Y. PL02.06
Nesbit, S. P2.08 .22
Neu, N. MA02.04
Neuhouser, M. L. P1.04.29
Neumann, M. EP.15.12
Newell, A. H. P1.17.22
Newsom-Davis, T. P3.18.38
Ng, C. S. P1.17.60
Ng, E.-C. P3.18.87
Ng, K. MA01.06
Ng, T. P2.05.02, P2.15 .32, P3.18.84
Ng, Z. OA15.02
Ngiam, C. MA04.02
Ngo, K. P3.12.63
Nguyen, A. MA10.07
Nguyen, A. P1.17.61
Nguyen, D. MA08.02, P3.12.46, PT1.03.06
Nguyen, L. EP.09.04, EP.17.28
Nguyen, P. P2.08 .19
Nguyen, Q. P2.08 .54
Nguyen, R. EP.13.04, P1.04.12, P1.17.13, P3.01.26
Nguyen, R. H. MA05.04, P2.06.69
Nguyen-Ngoc, T. EP.09.17
Nhung, N. OA02.02
Ni, H. EP.02.09
Ni, J. EP.13.36, P1.17.69, P2.10.16, PT2.13.01
Ni, Y. EP.03.05
Nibid, L. P1.11.62
Nibuya, K. EP.08.42, EP.13.11, P3.12.54
Nicholas, G. MA10.02
Nichols, B. P3.16.23
Nichols, B. N. EP.16.03, P3.16.21
Nichols, C. EP.01.17
Nichols, S. MA07.02
Nicholson, A. OA09.01, OA13.04
Nicholson, A. G. MA07.01, PL03.16
Nicholson, A. OA11.02
Nicholson, S. EP.06.61
Nick, D. EP.06.15
Nickel, B. P3.16.10
Nicoś, M. EP.06.17, MA10.04, P1.11.63
Nicolae, R. P2.08 .42
Nicolas, G. P3.12.29
Nicolazzo, C. EP.06.74
Nicq, C. P3.03.33
Nie, J. P2.06.28
Nie, K. P2.08 .23
Nie, L. OA05.01, P1.11.83
Nie, Q. P1.07.55
Nie, Y. EP.13.03
Nieda, G. M. PT1.01.01
Niedermaier, B. EP.01.20, EP.06.29, MA04.06
Niedzwiecki, D. P2.08 .13
Niekamp, M. P1.07.37
Nieminen, V. P1.17.67
Nieva, J. MA02.02, P1.17.02, P3.12.39, P3.12.46
Nieva, J. J. MA07.06, P1.11.72, P2.06.52
Nieves Arredondo Lasso, M. P3.18.02
Nightingale, C. P1.04.08
Nigita, G. PT2.10.01
Niho, S. EP.13.14
Nikhil, P. P2.02.43
Nikolaou, A. P2.15 .06
Nilsson, J. EP.06.11, P2.02.34
Nilsson, M. P2.02.24
Nilsson, M. B. PT2.13.03
Ning, F. OA06.02
Ning, Y. EP.12.38
Ninomiya, T. P3.18.04
Niño Mora, L. P2.15 .11

Nirula, M. MA07.02
Nishi, T. EP.10.01, P2.10.03
Nishii, Y. EP.06.81
Nishijima, R. EP.17.25
Nishimura, H. EP.13.18
Nishimura, K. K. OA11.01
Nishimura, K. OA11.02
Nishimura, T. EP.11.08, P2.08 .08, P3.13.14
Nishimura, T. P1.07.49
Nishino, K. EP.11.06, P2.06.59, P3.12.41, P3.12.58
Nishino, M. MA01.04, P3.14.22, PT2.11.01
Nishio, K. EP.06.46, P3.03.30
Nishio, M. EP.03.03, EP.08.42, EP.13.11, OA06.03, P3.12.54
Nishioka, N. P1.11.40
Nishiyama, A. P3.03.02
Nishiyama, K. EP.12.29, P3.12.09, P3.12.23
Nisi, M. P1.04.47
Nisticò, P. EP.03.02
Nistico', P. EP.07.48
Nitanai, K. EP.02.04
Niu, C. P2.02.29
Niu, H. P3.12.64
Niu, J. P3.18.28
Niu, S. EP.06.56, EP.12.38, P2.06.46
Niu, X.-M. P3.13.24
Niu, X. P3.18.59
Niu, Z. MA02.07
Nizzero, S. P2.06.56
Nocera, A. EP.06.40
Nogami, N. EP.05.02, EP.13.12
Noguchi, M. MA07.03
Noh, J. P3.13.21
Noinark, C. EP.04.37
Nokihara, H. EP.14.21
Nomata, Y. EP.06.70, P1.11.47
Nomura, K. EP.07.10
Nomura, K. P1.07.49
Nomura, S. P3.18.04
Nomura, S. P1.11.06
Nomura, S. P1.07.21
Nordgren, R. P3.14.04
Nordlund, J. EP.17.15
Nordman, I. P3.18.34
Norman, C. P2.06.99
Norman, R. OA18.03, P1.04.40
Noronha, V. EP.08.14, P3.09.01, P3.18.72
Norris, K. P3.01.51, P3.16.06
Notario, A. EP02.12, P3.03.44
Notario Rincón, A. EP.06.78
Notizia, L. P3.18.18
Notsuda, H. EP.04.18, EP.06.26, EP.07.38, P1.07.49, P2.06.33
Nousome,, D. MA07.02
Novakovic Lackovic, L. P2.08 .20
Novellis, P. P2.05.10
Novello, S. P1.07.51, P1.17.29, P2.06.22, P2.06.40, P3.03.17, P3.12.15, P3.12.41, P3.13.04, P3.16.05, P3.18.85, PT2.12.04
Novoa, N. P3.14.19
Nowak, M. OA14.05
Ntaskagiannis, D. EP.08.18
Nuccio, A. EP.08.03
Nuersulitan, R. EP.07.45
Numanami, H. EP.07.36
Nuñez, M. P2.08 .49
Núñez, M. PT1.08.04
Nuñez-Fernandez, M. EP.07.42
Nunzi, M. MA01.08, OA07.03, PT1.08.02
Nurkic, S. R. PL03.06
Nurmi, L. P3.12.72
Nurwidya, F. EP.04.22
Nute, A. P1.17.67
Nutzinger, J. P2.06.14
Nwaneri, M. O. PL02.18
Nwogu, C. EP.08.32

O

Oakland, T. P1.11.59
Oakman, C. P3.18.74
Oba, T. P1.11.40
Obernüfemann, C. P3.12.14
Oberoi, A. P2.06.100
Obiols, C. EP.05.08, P1.07.24, P2.05.06
Oblitas, G. EP.12.53
Oboh, O. E. P1.17.76
Obradovic, M. P1.04.31, P1.04.36
OBrate, A. P3.18.74
O'Brien, J. P3.01.53, P3.03.20
O'Brien, M. EP.17.12
O'byrne, K. P2.06.68
O'Byrne, K. P1.17.12
O'Byrne, K. J. EP.03.09
Ocak, S. EP.15.19
Occhipinti, M. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34, P3.12.15, P3.12.30, P3.14.06
Ochoa, C. D. P1.04.16
Ochoa-Alba, J. M. EP.05.08, P2.05.06
Ochsenreither, S. P3.18.29
Ock, C.-Y. P1.07.52, P1.11.32
O'Connor, M. L. EP.08.34
Octavio Gonzalez, L. P3.01.25
Oda, H. EP.06.33
Oda, K. PT1.03.05
Odia, Y. P2.06.76
Odintsov, I. P1.07.43
Odle, C. P3.18.05
O'Donnell, T. P3.18.13
Oduah, E. P1.11.75
Odunsi, K. P3.01.48
Odupitan, O. EP.01.04
Oertle, P. P2.06.56
Oettel, K. PL03.06
Oezkan, F. EP.04.27, EP.07.22
Officer-Jones, L. P2.06.04
Offin, M. EP.08.51, MA01.06, P2.06.12
Ogane, T. P1.07.03
Ogata, A. EP.01.05
Ogawa-Kobayashi, Y. EP.13.18
Ogbeide, O. P2.15 .32, PL03.06
Ogbudu, S. O. P1.17.76
Ogliari, F. P3.14.06
Ognissanti, D. PT2.11.01
Oguchi, Y. P2.06.47
Ogunyankin, O. EP.17.35, OA06.04
Ogurtsova, A. P2.06.66
Oguz, A. P2.08 .36
Oh, H. P2.10.10
Oh, H.-J. P3.13.08
Oh, I.-J. EP.13.21, P2.02.32, P3.13.08
Oh, J. P3.12.68
Oh, P. P1.07.36, P3.13.26
Oh, S. EP.07.14
Oh, T. MA05.08
Oh, W. EP.06.07
Oh, Y. EP.04.40
Oh, Y. PT2.11.04
O'Hagan, K. EP.16.02, P3.16.01
Ohara, S. EP.05.07, EP.06.46, P1.07.49, P3.09.05
Ohashi, K. MA08.04, P3.12.58
Ohashi, P. S. OA12.04
Ohde, Y. EP.14.13, P1.07.13, P1.07.49, P3.18.04
Ohira, T. EP.07.54, EP.08.40, P2.08 .06
Ohiwa, A. EP.11.08
Ohler, Z. W. MA07.02
Ohri, N. EP.08.15, P3.18.19, P3.18.22

Ohtaka, K. EP.04.36, EP.06.84, EP.14.16, P1.07.21
Ohtaki, Y. EP.07.10
Ohtani, S. EP.07.10, P1.07.03
Ohtsubo, K. P3.03.02
Oi, I. P3.12.44
Oiki, H. EP.06.46, P1.07.49, P3.09.05
Oishi, H. EP.06.26, EP.07.38
Öjlert, Å. P1.17.67
Ojo, O. O. P1.17.76
Okabe, K. EP.14.09
Okada, A. P1.11.40
Okada, K. EP.06.84
Okada, K. P2.06.16
Okada, M. EP.07.01, EP.07.54, P3.18.04
Okada, S. P1.07.49
Okada, S. EP.06.12
Okada, Y. EP.04.18, EP.06.26, EP.07.38, P2.06.33
Okada, Y. P3.12.44
Okado, S. P1.11.47
Okamoto, H. P3.18.25
Okamoto, I. MA03.03, OA10.01, P3.18.04, P3.18.31, PT2.12.04
Okamoto, K. EP.02.11
O'Kane, C. P1.17.20
Okano, T. EP.11.07, EP.12.29, P3.12.09, P3.12.23
Okazaki, S. EP.07.56
Okazaki, T. EP.07.21, P1.07.23
Oki, M. P3.03.42
Okishio, K. P1.07.35
Okonta, K. E. P1.17.76
Oko-Oboh, G. EP.17.22
Okoshi, M. EP.01.05
Okoye, I. J. P1.17.76
Okray, A. PT2.15.03
Oksen, D. P3.12.10
Okten, I. P2.10.02
Okubo, Y. P2.08 .33
Okudela, K. EP.07.04, EP.08.02
Okumura, M. EP.01.28
Okun, S. EP.02.01
Okunnuga, N. A. P1.17.76
Okura, E. EP.01.28
Olanrewaju, M. P2.06.99
Olazagasti, C. EP.13.32, P1.07.45, P1.17.10, P3.01.52, P3.14.01
Olchers, T. P2.06.65
O'Leary, C. P2.06.82
Olejnik, N. P1.11.48
Olesen, I. P1.17.18, P3.01.13, PT2.17.02
Olghi, N. P1.04.31
Oliva-Poch, E. P1.11.07, P2.08 .49
Olivares, A. P3.18.12
Olivares Hernández, A. P2.02.41, P2.15 .03
Olive, G. P2.06.51
Oliveira, I. P2.15 .06
Oliveira, L. EP.08.20, P1.17.72
Oliveira, L. EP.09.03, EP.09.07
Oliveira, N. EP.02.10
Oliveras, G. EP.06.48
Olivier, K. MA03.05
Olmo González, D. EP.02.10
Olmo-González, D. P2.02.34, P2.02.39, P2.02.46
Olsen, S. EP.06.73
Olson, P. P3.03.29
Olson, S. OA17.04, PT2.16.05
Olukomogbon, T. EP.17.22
Olumuyide, E. A. P3.03.13
Omero, F. EP.15.14
Omonijo, F. EP.17.22
Omonijo, O. P1.17.76
Omonisi, A. E. P1.17.76
on behalf of the Basic and Translational Science C, o. PT1.03.04
O'Neal, M. P3.12.10
Öner Dinçbaş, F. EP.05.04
ONER DINCBAS, H. F. EP.13.43
Ong, B. OA15.02
Ong, W. OA15.02
Onisile, O. EP.17.22
Onitilo, A. A. PL03.06
Ono, A. EP.14.21, MA08.05, P3.12.58
Ono, S. EP.06.49
Onodera, K. EP.04.18, EP.06.26, EP.07.38
Onorati, E. P2.08 .30
Onorini, P. MA02.05
Onyedum, C. C. P1.17.76
Ooi, G. S. OA15.02
Oomen- de Hoop, E. P3.18.54
Oomen-de Hoop, E. EP.12.52
Opitz, I. EP.04.16, EP.04.34, EP.07.09, EP.08.52, EP.09.10, EP.09.11, P3.14.19, P3.18.82
Opitz, M. EP.04.27
Oprea-Lager, D. PT2.11.02
Orain, M. EP.06.06, MA07.04, P3.13.06
Orakwe, O. I. P1.17.76
Oramas, J. P1.11.37
Ordu, C. A. P1.17.76
O Reilly, D. E. P2.06.82
O'Reilly, D. EP.08.34, P1.17.29, P1.17.54
Oresti, S. EP.11.20
Orfao, A. P2.02.41
Orfin, R. H. P3.16.08
Orlandi, F. EP.14.27, EP.17.27, P1.11.85, P3.18.34
Orlandi, R. P1.07.17
Orlowski, T. EP.07.52
Ormsby, R. P1.17.46
Oropesa Nuñez, R. P2.06.56
Orozco, J. P3.03.10
Ortega, A. MA08.04, OA05.03, P1.11.07, P1.11.37, PL03.10
Ortega, C. P1.07.51
Ortega-Franco, A. MA02.08
Ortega-Granados, A. L. P3.12.46
Ortiz, E. OA14.03
Ortiz, J. MA03.02
Ortiz-Cuaran, S. P3.03.33, P3.18.60
Ortiz Velez, C. P2.06.56
Osakabe, M. EP.06.19
Osarogiagbon, R. U. P1.17.77
Osarogiagbon, R. EP.01.04, MA05.03, P1.17.76, P2.05.02, P2.15 .32, PT2.17.04
Osarogiagbon, R. U. EP.07.20, OA11.01
Osarogiagbon, R. OA11.02
Osarogiagbon, MBBS, FACP, R. OA11.03
Osca, G. P2.08 .49
Oses, G. EP.13.19
Oshita, K. EP.13.12
Osoegawa, A. EP.07.35
Ospina, A. V. P3.01.25
Ostrin, E. P2.02.36, PT1.01.03, PT1.04.03
Ostrin, E. J. EP.04.31
Ostroff, J. P3.16.13
Ota, M. EP.07.56
Otegui, N. EP.13.27, PT1.08.05
Otene, S. A. P1.17.76
Otero, S. P2.06.37
Othman, A. P2.06.99
Othman, N. R. P2.05.05
O'Toole, K. EP.06.51
Otsuka, S. EP.04.36, EP.06.84, EP.14.16
Otsuka, Y. P2.06.95
Otterson, G. A. PT2.12.01
otty, z. EP.17.07
Ou, S.-H. P3.12.71

Ou, S. P1.11.70
Oudkerk, M. EP.04.02, P1.04.02, P1.04.06, P1.04.09, P1.04.11, P1.04.13, P1.04.25
Oughourlian, T. P2.08 .22
Ouyang, H. P1.04.12, P3.01.26
Öven, B. MA01.07
Oven, B. P2.10.02
Owczarczyk, K. P3.09.02
Owen, D. MA03.05
Owen, D. P2.08 .47
Owen, D. H. P1.17.55, PT2.12.01
Owen, S. PT1.03.06
Owonikoko, T. K. P3.13.12, P3.18.17
Oxnard, G. R. PL02.18
Oyeindielaye, A. P1.17.76
Ozaki, D. EP.14.02
Ozan, N. P1.17.57
Ozasa, M. EP.06.49
Ozcelik, M. P2.10.02
Ozdemir, F. P2.10.02
Özlem, O. P1.07.28
Oztekin Artuc, M. EP.04.33
Ozturk, A. P2.10.02
OZTURK, D. EP.13.43
Öztürk, E. P1.07.22
Ozyilkan, O. OA13.02

P

Paaske Johnson, S. P1.17.52
Paats, M. P3.18.66
Paats, M. S. EP.12.49, P3.18.54
Pabani, A. P3.18.40
Pabst, L. EP.06.39
Pacchiana, M. P3.16.05
Pachika, P. P3.13.07
Pacioles, T. PT1.08.03
Padda, S. EP.06.15
Padhi, P. EP.06.05
Padilla, A. P1.11.07, PL03.10
Padrones, S. P2.06.37, P3.14.09, PT1.08.04
Padrones-Sanchez, S. EP.07.42
Padrones-Sánchez, S. EP.16.04, P2.08 .60
Paek, Y.-J. MA09.06
Pagano, M. OA12.02, P1.07.51, P3.12.15, P3.14.06
Pages, P.-B. P2.05.15
Paglialunga, P. L. P3.14.24
Pagliarini, R. P3.18.68
Pai, L. P2.15 .22
Paik, P. MA01.06
Paik, P. K. P2.06.12, P3.18.11
Paik, P. P3.12.40
PAJIEP CHAPDA, M.-C. EP.12.54
Pal, D. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Pal, P. EP.06.75, OA12.04
Palau-Gallinat, D. EP.03.13, EP.14.03
Palenski, T. EP.17.35
Palermo, B. EP.03.02
Paley, D. EP.12.10
Palicio, N. V. OA08.03
Palladini, A. P1.11.54
Palleschi, A. P1.07.17
Palmer, D. OA03.03
Palmer, J. EP.13.39
Palmero, R. P2.06.37, PL03.10
Palmero, MD, R. MA01.03
Palmero-Sánchez, R. EP.16.04
Palmisani, J. P1.04.47
Palti, Y. EP.03.08, P3.03.22, P3.03.28
Pan, C. P2.08 .34
PAN, F. P1.17.69
Pan, F. PT2.14.04
Pan, H. P1.17.36, P3.12.64
Pan, J. EP.13.10
Pan, L. P3.18.07
Pan, M. P3.12.04
Pan, P. EP.12.57
Pan, P. P3.12.48, P3.12.64, P3.18.39
Pan, X. P2.10.13
Pan, Y. P1.11.05
Pan, Y. MA03.07, MA10.01, OA10.02, P3.12.53, P3.13.25
Pan, Y. EP.13.35, P1.17.36, P3.12.07, P3.12.31
Pan, Y. EP.08.21
Pan, Z. P3.12.52
Pan, Z. EP.06.38
Pancaldi, V. P2.06.43, P3.18.60
Panda, P. EP.04.08
Pandey, R. P2.02.43
Pandey, S. P3.12.02
Panditharatna, E. P2.02.27
Panetta, D. P3.03.15
Pang, F. P1.11.31
PANG, H. P3.12.74
Pang, K. H. EP.12.10
Paniagua, B. P2.08 .37
Pankongngam, C. P3.01.30
Pankovics, J. EP.06.35, EP.06.83, P3.18.82
Pannu, S. P1.07.43, P1.11.17
Panopoulos, C. P2.15 .26
Panov, N. P1.11.65, P1.11.83
Pantano, F. EP.06.52
Pantazopoulos, A. EP.01.19
Pantelas, J. P3.16.13
Panzardi, A. P1.11.66
Paoloni, F. EP.11.20, P1.11.56, P3.12.63, PT2.11.01
Papa, R. EP.06.03
Papadopoulos, K. P. OA08.01, P3.18.71
Papadopoulou, K. P2.15 .26
Papayanis, P. N. PT2.15.03
Papillon-Cavanagh, S. P1.11.59, P2.06.45
Papotti, M. OA13.04, PL03.16
Papotti, M. G. MA07.01
Parab, A. P2.06.94
Parakh, S. EP.13.33, EP.15.04, EP.17.02, OA03.04, OA05.04, P1.11.49, P1.17.18, P1.17.62, P2.06.89, P3.01.13, PT2.17.02
Paramonava, N. EP.08.08
Parasramka, S. EP.13.29
Pardina, M. EP.04.14
Pardo, M. P1.11.07
Pardo, N. P3.12.30, P3.14.02
Pardolesi, A. P3.14.18
Pardoll, D. M. P2.06.66
Paredes de la Fuente, R. PT2.10.01
Pareja, L. P3.14.09
PAreja Fernandez, L. EP.07.42
Parent, E. OA13.03
Parente, P. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Parikh, K. MA03.05, P1.17.28, P1.17.51, P3.13.32
Parikh-Patel, A. P1.17.03
Parisi, C. EP.17.23
Parisi, C. P1.17.21, P3.14.15
Parisi, S. EP.15.14
Park, B. P1.04.17, P3.01.22, P3.18.11
Park, B. P1.04.23
Park, B. P2.06.48
Park, B. P1.07.20
Park, C. P2.10.10
Park, C.-K. P3.13.08
Park, D. MA09.06
Park, E. OA18.04
Park, E. OA04.03
Park, H. P3.13.26
Park, H. S. EP.01.16, P1.07.36

Park, H. P3.13.08
Park, H. P1.07.30
Park, I. K. P2.05.08
Park, I. EP.07.31, P2.08 .02
Park, J. P3.03.29
Park, J. EP.12.12, P1.04.26
Park, J. P1.04.23
Park, J. EP.07.31, P2.05.08, P2.08 .02
Park, J. P1.11.32
Park, J. PT2.12.03
Park, J. P3.18.87
Park, J. P1.07.25
Park, J. EP.09.02
Park, J. P1.17.26
Park, J. P3.18.80
Park, M. EP.06.32
Park, N. P2.05.11
Park, S. L. P2.06.52
Park, S. P2.10.10
Park, S. EP.07.31, P2.05.08, P2.08 .02
Park, S.-G. P1.11.32
Park, S. E. P1.17.32
Park, S.-Y. P3.13.08
Park, S. S. MA03.05
Park, S. EP.07.46, EP.08.29, P2.08 .31, PT2.11.04
Park, S. P1.11.32
Park, S. P1.04.26
Park, S. EP.07.46, EP.08.29, P1.07.15
Park, S.-Y. P2.08 .31
Park, S. P2.02.16
Park, S. EP.14.11
Park, S.-I. P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Park, W. P2.02.11
Park, Y. EP.11.12, P2.15 .09
Park, Y. EP.06.32
Parker, K. EP.04.07, EP.04.10
Parker, S. P1.07.34
Parker, W. P1.04.34
Parkes, A. OA13.01
Parkin, M. EP.06.51
Parmar, A. EP.09.04, EP.17.28
Parmar, C. OA03.03
Paronetto, C. P2.08 .26
Parreira, A. P3.13.04
Parris, PhD, MPH, D. EP12.65, P2.06.11
Parsons, C. OA02.01
Partida, C. MA01.01
Partridge, A. PT2.15.02
Pasca-Fenesan, M. P2.15 .06
Pascoe, D. P1.04.08
Pasello, G. EP.11.20, EP.13.15, OA08.03, P1.07.51, P1.11.24, P3.12.15, P3.14.06, PT2.14.02
Pasello, G. MA04.09
Paskett, E. OA04.04
Pasmantier, M. EP.04.13
Pasqualin, L. P3.12.08
Pasquina, L. EP.06.69, EP.06.76
Pasquinelli, M. EP.13.04, MA05.03, P2.06.69, P3.01.26
Pasquinelli, M. M. P1.04.12, P1.17.13
Pasricha, S. EP.06.16
Pass, H. OA02.01
Passalacqua, I. EP.15.14
Passannante, R. P2.02.04, PT1.02.04
Passaro, A. MA08.02, P1.11.17, PL02.12
Passiglia, F. EP.11.20, MA02.05, P1.07.51, P2.06.22, P3.03.17, P3.16.05
Passlick, B. P2.15 .20
Pastor, E. MA01.01
Pastor, M. P2.15 .12
Pastorino, U. P1.04.53, P2.06.97
Pat, K. P1.07.41
Pataki, E. EP.16.05, OA17.02
Patel, A. P1.07.36
Patel, A. EP.17.06
Patel, A. P2.05.02, P2.15 .32
Patel, D. EP.13.38, P1.17.08, P1.17.09, P3.14.11
Patel, E. P3.09.08
PATEL, H. P3.12.04
Patel, J. P3.18.80
Patel, J. EP.12.30
Patel, J. D. P1.07.37
Patel, K. P3.01.17
Patel, K. M. P3.01.16
Patel, M. PL02.18
Patel, M. P1.11.71
Patel, M. P3.13.31
Patel, N. EP.12.30
Patel, P. P1.11.77
Patel, R. OA18.01
Patel, S. P3.01.14
Patel, S. P1.17.33, P1.17.58
Patel, S. P3.18.87
Patel, S. PT2.10.02
Patel, Y. N. EP.13.39
Patel, MD, T. EP.12.32, EP12.65, P2.06.11, P2.06.20, P3.12.24
Patella, M. P3.18.82
Paterlini, P. EP.06.64
Paterson, L. PT2.14.01
Pathan, A. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Pathy, S. EP.08.24
Patil, D. P2.06.94
Patil, M. P2.06.18
Patil, T. MA04.02, P1.07.40, P2.06.17, P2.06.18
Patil, T. EP.01.08, EP.06.34
Patil, V. P2.06.17
Patoliya (Desai), J. H. P3.01.14
Patrucco, E. P3.03.17
Patthey, C. EP.06.11
Paul, E. EP.11.11, EP.13.33, PT2.17.02
Paula, A. G. P2.02.24
Paula Navarro-Navarro, P. P2.02.41
Paulsen, E.-E. P1.11.62
Paulson, K. G. OA13.01
Paulucci, D. MA10.07
Pavan, A. P1.07.51, P3.12.15
Pavão, J. S. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52, P3.01.41
Pavlakis, N. OA03.04, OA13.02, P1.17.62, P2.06.61, P2.06.89
Pavlick, D. C. P1.11.57
Pavlisko, E. P2.06.67
Paweletz, C. P3.12.63
Pawlica, M. MA11.05, P3.13.02
Payen, L. P2.06.87
Payne, S. EP.13.25
Paz-Ares, L. EP.06.43, MA07.07, MA08.03, MA10.07, MA11.04, MA11.06, OA05.03, OA06.03, OA06.04, OA10.01, P3.18.74, P3.18.80, PT1.03.06
Paz-Ares, L. P1.11.85
Paz-Ares Rodriguez, L. MA08.01
Pearson, A. OA09.02, P2.06.65
Pearson, D. D. P3.01.24
Peay, H. L. P2.15 .05
Pecci, F. EP.11.05, MA01.04, P1.07.43, P1.11.42, P1.11.56, P1.11.62, P1.17.54, P3.12.63, PT2.11.01
Pedapathi, S. EP.08.14, EP.09.08
Pedapathi, S. R. P3.09.01
Pedeux, R. P2.06.79
Pedraza, S. EP.07.43
Pedraza Fernández, S. P2.08 .48
Pedrazzini, B. EP.06.35
Pedrazzoli, P. P1.11.01, P1.11.54, P2.08 .53
Pedrocchi, A. MA06.07, OA09.02, P1.17.30, P1.17.44, P2.15 .34

Pedrocchi, A. L. P1.04.51, P1.11.66
Pedrocchi, A. P2.06.65
Peeters, A. EP.13.16
Pegliasco, H. P1.17.21
Pêgo-Fernandes, P. M. EP.17.04, P1.17.15
Pei, G. P1.04.24
Pei, Y. EP.15.17
Peikert, T. MA05.01
Peiró, I. PT1.08.04
Peled, N. EP.06.73, OA08.03, OA09.02, P1.04.51, P2.06.65, P3.12.10, P3.18.28, P3.18.73
Pelegrina Sánchez, D. P2.08 .48
Pellerin, K.-A. MA07.04
Pellicanò, G. EP.11.01
Pellicioli, F. P1.11.01
Pellini, B. P3.18.61
Pellini Ferreira, B. MA08.01
Pelosi, G. EP.06.03
Pemberton, L. OA16.02
Pemmaraju, A. EP.15.12, P3.03.24
Penalva, M. MA01.04
Peñalver-Vera, A. PT2.15.04
Penault-Llorca, F. P2.06.43
Pencreach, E. EP.06.39
Penedo, F. P3.01.52
Peng, B. MA11.03
Peng, H.-C. EP.09.15
Peng, J. P3.12.07, P3.12.31
Peng, M. MA05.07
Peng, M. EP.07.30
Peng, X.-D. PL02.09
PENG, X. P3.12.74
Peng, Y. EP.13.10
Peng, Y. L. PT1.06.02
Peng, Y.-L. EP.12.60, P3.01.04, P3.01.37
Peng, Z. P3.18.08
Penkov, K. MA10.09, P1.11.52
Pennell, N. P1.11.77, PL03.06
Pennell, N. A. MA02.02, P3.12.12
Pennie, R. P2.06.04
Pennycuick, A. P2.08 .11
Penumadu, P. P1.07.26
Peppoloni, V. MA06.07, P2.15 .34
Perales, M. P1.17.17
Pereira, MA01.01
Pereira, D. R. EP.17.30
Pereira, E. MA06.03
Pereira, J. B. PT1.04.02
Pereira, K. P3.18.58
Pereira de Souza, V. P3.01.49
Perera, T. P. EP.12.52, P3.18.66
Peressini, M. EP.06.43
Perez, A. OA01.02
Perez, C. A. OA08.01
Perez, J. P2.15 .19
Perez, J. MA10.09, P2.06.102
Perez, L. P1.17.67
Pérez, R. PL03.10
Pérez-Bartivas, L. EP.06.66
Perez-Escuredo, J. P3.18.55
Perez Escutia, M. EP.07.43
Pérez Escutia, M. P2.08 .48
Pérez Fierro, J. P2.15 .12
Pérez-Granado, J. P3.13.18
Per Moreno, A. P3.03.20
Perni, S. MA10.05
Pernomian, L. S. EP.17.30
Pérol, M. MA02.02, OA10.01
Perol, M. P1.17.33, P3.12.12
Pérol, M. P3.12.29
Perol, M. P3.12.38
Peról, M. P3.12.62
Perona-Abellón, R. EP.16.04
Perona-Abellon, R. P2.08 .60
Peroni, M. EP.11.05, P1.11.24
Perrino, M. P3.14.06
Perrone, F. EP.11.05, EP.11.20, P1.11.24
Perrone, F. OA12.02
Perrone, G. P1.11.62
Pescott, C. P3.12.40
Pesola, F. MA09.05
Pesola, F. OA17.01, P1.04.47
Petelka, L. EP.12.10
Peternel, M. EP.13.13, P2.08 .16
Peters, S. EP.06.79, EP.09.17, MA02.06, MA11.04, OA05.04, OA08.02, P1.11.03, P1.11.15, P1.11.42, P3.01.19, P3.18.82
Petersen, R. H. EP.15.03
Petersen, R. EP.01.09
Peterson, J. MA02.01
Peterson, J. L. EP.06.53
Petersson, E. S. EP.12.42
Pethe, C. EP.01.06, EP.06.34, P3.12.05
Petrillo, L. P2.15 .24
Petrillo, P. OA17.01, P1.04.47
Petrini, I. P3.14.06
Petro, MD, D. P. EP.12.32, EP06.86, EP12.65, P3.12.24
Petro, MD, D. P. P2.06.11
Petroncini, M. EP.14.18
Petrone, A. M. P1.07.28
Petrovic, H. P1.17.04
Petruzelka, L. B. MA04.05
Petterson, S. P3.16.15
Pettersson, C. P1.17.58
Petty, W. J. P3.18.14
Pezeshk, A. P3.01.48
Pezeshkian, F. P1.17.27
Pezeshkian, F. EP.07.33
Pezzuto, F. PT2.14.02
Phadke, A. J. P1.04.19
Pham, N.-A. EP.03.15, EP.06.31, OA14.03, P3.03.03
Pham, R. EP.11.11
Pham, X. P3.12.65
Phelan, J. J. EP.06.61
Phellan Aro, R. MA05.06
Phelps, M. A. PT2.12.01
Philley, J. PT1.04.03
Phillips, B. P2.02.27
Phillips, E. P1.17.46
Phillips, I. P2.15 .27, PT2.14.01
Phillips, W. OA14.05
Phipps, N. EP.16.06
Piault, E. EP.17.21
Piccirillo, M. C. OA12.02
Pichon, E. OA05.02
Pickering, T. A. P1.17.02
Picone, A. EP.11.01
Piedra, A. P1.17.54
Pierre, A. MA03.01
Pierre, C. P2.06.79
Pierret, T. MA02.08
Pietzko, K. P2.06.100
Pignataro, D. P3.12.15
Pijuan, L. EP.06.48, OA01.02, P2.06.37
Pikelis, J. P2.08 .58
Pili, R. EP.06.05
Pilnik, N. EP.06.24
Pilotto, S. P1.11.24, P3.12.08, P3.16.05, P3.18.85, PT2.15.01
Pimentel, M. P1.17.05
Pimentel, R. OA08.03
Pinato, D. J. P1.17.54
Pincas, M. P1.04.46
Pine, S. R. EP.02.07

Pinel, P.-L. P2.06.79
Pinho, M. P3.18.74
Pinós, M. EP.02.02, P2.02.22
Pinós Ruiz, M. P2.02.18
Pinsolle, J. P2.06.43
Pinto Chengot, K. E. EP.08.28
Pintor dos Reis, P. PT1.03.03
Piotrowska, Z. EP.06.53, MA08.02
Pipopchaiyasit, N. P3.12.49
Pirard, L. EP.11.18, EP.15.19
Pirker, C. EP.02.02, P2.02.18, P2.02.22
Pisconti, S. P1.04.47
Pitroda, S. P. P1.11.55
Pittaro, A. EP.08.03
Pittell, H. P1.07.05
Pittman, P. OA09.03
Pivavarchyk, S. EP.06.63, P3.18.23
Piwkowski, C. EP.07.52
Piya, I. J. P1.11.69
Pizzillo, V. P1.04.47
Pizzutilo, E. MA02.05
Pizzutilo, E. G. P1.11.01, P1.11.66
Pizzutilo, P. OA17.01, P1.04.47
Plana, M. P2.06.37
Planas Canovas, G. EP.08.07
Planchard, D. EP.12.36, MA08.01, P1.17.21, P3.12.38, P3.12.62, P3.14.15, P3.18.54, PL02.06, PT2.12.03
Planck, M. P2.02.40, P3.18.56
Plans Marin, S. EP.14.03
Plans-Marin, S. EP.03.13, P3.14.12
Plappert, N. P3.03.20
Platta, M. P3.01.48
Plodinec, M. P2.06.56
Plomp, P. P3.18.16
Plonsky, M. EP.13.40
Pluchino, M. EP.11.05, MA02.05, P1.07.04
Plujà, A. P2.08 .49
Plummer, C. M. EP.04.31
Pluvy, J. EP.04.29, P1.04.39, P1.17.21
Pluzanski, A. P1.17.29
Podder, S. EP.13.47, P2.05.01
Poddubskaya, E. OA05.04
Podgaetz, E. MA03.02
Podobed, A. P3.14.19
Podsiad, M. P2.15 .30, P3.16.20, P3.16.22
Poghosyan, H. EP.04.15
Pogorzelski, M. OA13.01
Pogson, Z. P3.16.14
Pøhl, M. P1.11.62
Poi, M. P1.11.59
Pokharel, N. P1.07.45, P1.11.50, P1.17.10
Pokorny, A. P2.06.89
Polaczek, M. EP.07.52, P3.18.38
Poles, A. PT2.15.03
Poletto, S. P2.06.40, P3.16.05
Polinski, P. P2.02.04
Politi, K. EP.08.46
Pollizzi, K. OA03.03
Poltoratskiy, A. PL02.06
Pommerening, M. J. EP.07.33
Pompili, C. P3.01.19, PT2.17.04
Ponce, S. MA06.03
Ponce, MD, PhD, S. MA01.03
Pongor, L. MA07.02
Pons-Tostivint, E. EP.12.36, OA10.01, PL02.15
Pontual Lima, L. EP.06.09, PT1.04.02
Ponvilawan, B. EP.06.65, P2.06.71
Poola, A. P1.04.37
POON, W. P2.10.14
Popa, T. P2.06.66
Popat, S. EP.12.36, EP.17.12, MA02.03, P3.18.09, P3.18.65, PL02.12, PL02.15, PT1.03.06
Porciello, N. EP.03.02, EP.07.48
Porfilio, E. EP.17.15
Porfyridis, I. EP.08.18
Porkka, K. P1.17.67
Porneala, B. OA18.04
Porta, F. OA09.03
Porter, A. P2.15 .32
Portillo Funes, J. EP.11.01
Portu, M. EP.08.07
Portyanko, A. EP.06.63
Posadas, E. M. P3.18.70
Posadas, J. OA09.01
Posado-Domínguez, L. P2.02.41, P2.15 .03
Poskitt, B. P2.06.08
Post, R. OA09.03
Postnikova, O. V. EP.08.25
Pote, N. P2.06.15
Poteete, A. P2.02.24
Pothen, J. J. P2.06.69
Pothirat, C. P3.01.30
Potrony, M. P3.01.46
Potter, A. L. MA05.03, P1.04.12
Potter, S. P2.15 .05
Poulain, N. P2.06.04
Pouliot, J.-F. MA10.09
Poulos, C. P2.15 .05
Pourquier, P. P2.06.87
Powell, C. A. EP.03.05, P2.02.09
Powell, C. P2.02.13
Powery, H. W. P3.12.56
Powery II, H. W. EP.17.01
Powley, I. P2.06.04
Pozadzides, J. V. P1.11.70, P2.02.36, PT1.01.03
Pozo-Kaderman, C. P3.01.18, PT2.15.02
Pozonec, M. MA11.06
Pozonec, M. D. P3.13.03
Pozzessere, C. P1.04.03, P1.04.15
Pozzessere, D. P1.07.51, P3.12.15
Prabhash, K. EP.08.14, EP.09.08, P3.09.01, P3.18.72
Pradeep, B. P3.01.40
Pradère, P. EP.04.29, P1.04.39
Pradines, A. P2.06.43, P3.03.34
Pramanik, R. MA09.08
Pramesh, C. S. OA18.01
Prasad, S. P1.04.04
Prasad, T. EP.04.06
Pratomo, I. P. EP.04.22
Pratt, A. EP.15.06, P1.17.42, P3.16.07
Pravettoni, G. P1.04.51
Preeshagul, I. MA01.06, P3.18.11
Prelaj, A. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34, P3.12.41, P3.14.18
Prenen, H. P3.18.66
Presley, C. OA04.04, P2.08 .47, P2.15 .22, P2.15 .24
Presley, C. J. PT2.12.01
Press, R. H. EP.08.19, P2.06.76
Pretorius, L. EP.16.02, P3.16.01, PT2.16.04
Preusser, M. P3.18.55
Prevost, K. EP.06.64
Priano, I. P3.12.30, P3.14.02
Price, G. OA16.02, P1.17.07
Price, S. P3.18.14
Prieur, A. P2.06.87
Prince, S. EP.06.58
Privitera, E. P1.07.17
Prodam, F. P3.14.13
Proietti, V. P1.07.22
Pros, E. EP02.12, OA14.04, P3.03.44, P3.03.47, P3.03.49
Proto, C. MA06.07, OA09.02, P1.04.51, P1.11.01, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34, P3.14.18

Provencio, M. EP.12.24, MA01.01, MA06.03, OA02.03, OA05.03, OA09.01, P1.11.07, P1.11.37, P3.01.25, P3.18.12, PL03.10

Provencio , MD, PhD, M. MA01.03

Provencio Pulla, M. MA04.05

Provenzano, L. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34

Provenzano, N. EP.06.15

Prudente, R. EP.01.05

Pruitt, A. P1.17.65

Pruneri, G. P1.17.44, P2.06.65

Przybysz, D. EP.08.16, EP.08.20, EP.09.03, EP.09.07, P1.04.28, P1.17.72, P2.08 .52

Przybysz MD, D. P3.01.41

P. Simões, R. PT1.03.03

Psyrri, A. EP.01.19

Pu, D. MA01.05

Pu, Q. MA10.01, P3.13.15

Pu, X. PT2.10.04

Puentes, R. P2.06.44

Pugh, S. P2.08 .23

Pugh, T. J. OA12.04

Puig-Butillé, J. P3.01.46

Puig Sánchez, F. EP.07.27

Pujol, J.-L. P2.06.102

Pujol Besora, C. P2.15 .12

Puligheddu, C. P3.18.82

Punekar, S. P3.18.87

Pungartnik, P. EP.17.23

Punti, L. P1.11.37

Puntí, L. P3.03.44

Puntoni, M. EP.11.20, P1.11.24

Pupo, A. P2.06.12

Puranik, R. EP.01.08

Purcell, N. D. PT2.11.02

Puri, T. P1.17.49, P3.18.09

Puri, V. P1.17.50

Purohit, R. EP.07.37, EP.14.04

Purushottam, R. P2.06.18

Pushpam, D. MA09.08, P3.18.72

Puskulluoglu, M. P2.08 .21

Putnam, B. PT1.04.03

Puttagunta, N. P2.06.10

Pütter, C. OA13.02

Putti, G. P1.07.17

Pyo, H. P3.13.21

Q

Qadri, H. EP.13.32

Qasrawi, A. EP.13.29

Qayati, M. P1.11.70

Qi, C. MA02.04

Qi, Y.-F. P1.04.21, P2.08 .35

Qi, Y. MA04.03

Qiabi, M. P1.17.70, P2.06.70

Qian, D. PL03.07

Qian, F. EP.07.44

Qian, J. EP.07.44, PT2.11.03

Qian, L. P3.03.06

Qian, M. OA06.03

Qian, S. MA10.03

Qian, X. EP.13.35

qian, X. P1.11.84

Qian, Y. P2.08 .32

Qian, Z. P3.13.22

Qian, Z. P3.14.21

Qiang, G. PT1.07.02

Qiao, H. EP.12.40

Qiao, R. EP.07.44, OA06.01

Qin, A. A. P1.11.04, P1.11.53

Qin, A. EP.02.07, P3.12.42, PT1.03.01

Qin, B. EP.11.19

Qin, H. P2.02.07, P2.06.49

Qin, J. P3.12.07

Qin, J. EP.13.23

Qin, K. EP.04.31, P1.11.04, P1.11.53

Qin, Q. OA06.01

Qin, S. P3.03.51

Qin, T. P3.18.69

Qin, X. EP.14.23, P2.02.10, P2.06.49

Qin, X. P3.12.69

Qin, Z. PT1.03.01

Qing, G. PT2.17.01

Qiu, B. EP.07.05

Qiu, B. EP.14.14, P3.13.27

Qiu, F. P2.08 .46

Qiu, H. P1.04.49

Qiu, J. P3.03.32

Qiu, M. P2.08 .41, P3.03.23

Qiu, M. P2.08 .57

Qiu, S. MA03.09, MA07.09, P2.06.58

Qiu, T. MA11.10

Qiu, T. EP.12.55

Qiu, T. P2.08 .29

Qiu, W. EP.12.39

Qiu, X. OA06.02

Qiu, Y. P3.18.74

Qiu, Z.-B. P1.04.21, P2.08 .35

Qu, H.-T. P2.02.28, P2.06.36

Qu, X. P1.11.28, P1.11.58

Quaife, S. EP.01.22

Quaife, S. L. P3.16.14

Quaini, F. EP.11.05

Quantin, X. OA12.02, P3.12.62

Que, S. P3.03.11

Quek, R. G. P1.11.52

Quer, N. P2.08 .49

Querol, M. P2.06.56

Querol Vilà, M. EP06.85

Quesenberry, C. P. P2.15 .31

Quinn, C. EP.13.39

Quintana, B. MA06.09

Quintana Déniz, M. EP.08.47

Quintanal Villalonga, A. P3.03.01

Quintanal-Villalonga, A. P3.03.32, P3.03.52

Quintanilha, J. P3.12.42

Quintanilha, J. C. MA06.01

Quiroga, N. EP.08.26

Quist, M. EP.15.03, PT2.17.04

Quoix, E. OA05.02

Qureshi, A. P2.06.85

Qureshi, T. P2.15 .32

R

Ra, Y. P1.07.25

Rabara, V. P3.13.31

Rabea, A. PT2.17.04

Rabeau, A. EP.17.39

Rabey, M. EP.06.75

Rabey, M. R. MA03.01

Radhakrishnan, V. EP.06.08, P3.01.21

Radiyah, A. EP.13.02

Radonic, T. P3.13.16, P3.18.16, PT2.11.02

Radulovich, N. P3.12.51

Radwan, E. P2.06.99

Raez, L. EP.09.09, EP.13.32, P1.11.78, P3.12.56, PT2.17.04

Raez, L. E. EP.17.01, P2.06.75

Raez , L. E. P2.06.78, PT1.04.01

Raffo-Iraolagoitia, X. P3.14.08

Rafique, K. P1.17.08, P1.17.09

Rafizadeh, M. EP.12.27

Ragavan, M. P2.15 .31

Raghav, K. PT2.14.05

Raghuwanshi, Y. EP.17.03

Ragusa, M. OA07.03, PT1.08.02

Raikwar, S. EP.07.37

Raja M, K. P2.08 .17

Rajan, A. MA07.02
Rajaram, R. P2.02.36, PT1.01.03
Rajbhoj, A. EP.01.06, P3.12.05
Rajpal, S. P3.01.14
Rakaee, M. P1.11.62, PT2.11.01, PT2.14.05
Rakovic, K. P2.06.04
Ramachandran, P. P3.12.34
Ramaekers, K. P3.18.03
Ramaker, R. P3.01.53
Ramakrishnan, H. P3.12.16
Ramalingam, P. P2.02.43
Ramalingam, S. OA05.04
Ramalingam, S. S. PL02.18, PL03.06
Raman, S. EP.08.17
Raman, V. P2.06.67
Ramasamy, V. EP.15.06
Ramazanoglu, M. N. P2.08 .36
Ramella, S. EP.08.13, P2.08 .30
Ramesh, M. EP.08.32
Rami-Porta, R. EP.05.08
Rami-Porta, R. OA11.01
Rami-Porta, R. OA11.02, P1.07.24, P2.05.06
Ramirez, M. P3.18.84
Ramirez-Alejo, N. MA10.07
Ramírez Fallas, R. A. P3.18.37
Ramírez-Seco, N. EP.04.14
Ramkumar, K. P3.13.09, P3.13.11
Ramlau, R. P1.11.82, P2.06.100
Ramnath, N. P2.10.01
Ramon y Cajal, T. P3.01.46
Ramos, R. EP.08.26, MA01.01
Ramos-Santiago, J. W. P3.16.08
Ramoth, J. EP.06.50
Ramsey, S. P3.12.19
Ramshankar, V. P3.01.21
Ramshankar, V. EP.06.08
Ran, F. P3.12.12, P3.12.69, P3.18.62
Ran, F. P3.12.48, P3.18.86
Ran, J. PL03.07
Rana, Z. P3.18.17
Randive, M. EP.01.06, EP.01.08, EP.06.34, EP.12.01, P3.12.05
Rands, C. OA03.03
Randulfe, I. P3.13.04
Rangrongrajitpoom, P. P3.01.30
Rankin, N. EP.04.07, P1.04.08, P3.16.10
Rantala, H. P1.17.67
Rao, A. A. P2.10.17
Rao, B.-Y. P2.05.09
Rao, B. P1.04.42
Rao, C. P3.18.86
Rao, R. P1.04.04
Rao, S. MA10.02
Rapa, I. P2.06.40
Raphael, A. EP.04.41, MA06.08
Raphael, J. EP.12.37, P1.17.70, P2.10.08
Räppo, M. P1.04.37
Raptis, S. EP.13.38, P1.17.08
Raptis, S. R. P1.17.09
Rashed, L. P1.17.61
Raskin, J. P3.12.40
Rasmin, M. EP.04.22
Rastelli, F. EP.11.20, P1.11.24
RASTOGI, I. EP.12.33
Rastogi, T. PT1.03.01
Ratajczak, C. PT2.10.02
Ratiu, J. OA03.03
Rattigan-Brown, Y. P1.17.58
Rault, C. P1.17.52
Raut, A. P2.06.94
Raval, G. EP.13.39
Ravi, A. EP.08.24
Rawlinson, J. P2.15 .14
Ray, M. EP.07.20, P2.05.02
Ray, M. A. P2.15 .32
Ray, PhD, M. A. OA11.03
Raz, D. P3.18.84
Raza, A. EP.12.61
Rea, F. EP.14.18, PT2.14.02
Ready, N. P1.11.75
Ready, N. OA09.01
Reale, M. P1.07.51, P3.12.15, P3.16.05
Rebouças, I. P2.08 .18
Recalde, H. R. P1.11.54
Reck, M. MA04.09, MA08.05, MA11.04, OA09.02, P1.04.51, P1.11.85, P2.06.65
Reckamp, K. EP.06.21, P3.12.16, P3.18.70
Récoché, I. EP.17.39
Redder, E. OA04.04
Reddington, H. P1.07.16, P1.17.01
Redditt, V. EP.15.06
Reddy, A. OA03.03
Reddy, C. EP.07.39
Reddy, S. P1.11.78, P3.18.52, P3.18.53
REDDY, T. EP.15.07
Redin, E. P3.03.32, P3.03.52
Redman, M. OA09.01
Redondo-González, J. P2.15 .03
Redrado, M. EP.13.27, PT1.08.05
Reed, T. P3.18.74
Reed-Guy, L. EP.14.17
Reeves, J. EP.06.50, P2.06.68, P3.03.39
Refoyo, I. PT2.15.04
Regan, M. EP.15.08, OA04.01
Regany, C. EP.04.14
Rege, J. P1.17.78
Rego, M. d. EP.17.23
Reguart, N. EP.05.01
Reguart, N. EP06.85
Reguart, N. MA06.03
Reguart, N. P2.06.56
Reguart, N. P2.15 .21, P3.01.46
Reguart, N. P3.18.12
Reguart MD, PhD, N. MA01.03
Rehman, H. T. P2.15 .15
Rehman, N. P1.11.77
Reibel, J. EP.13.38
Reich, C. P1.17.67
Reid, F. EP.01.12
Reid, K. N. P1.17.83
Reid, M. P3.01.51, P3.16.20
Reilly, A. P2.06.82
Reinhorn, D. P3.09.03
Reinmuth, N. MA02.06, P3.12.40
Reis, R. M. P1.04.29
Reis de Jesus, G. P2.08 .18
Reisenauer, J. MA10.02
Reiss, M. EP.16.06
Reiss, M. EP.16.03, EP.16.08, P2.15 .05, P3.16.21, PT2.16.01
Reiss, S. EP.13.25, P1.07.05, P3.13.10
Rekhtman, N. OA13.04, P2.06.12
Remon, J. MA02.08, P1.07.43, P3.18.54
Remon Masip, J. P2.10.05, P3.14.15
Remon-Masip, J. P3.12.29
Ren, J. OA03.03
Ren, P.-R. PT1.09.01
Ren, S. EP.13.36, MA11.10, OA06.01, P1.11.31, P2.05.13, P2.06.86, P3.03.53, P3.09.10, P3.12.70, P3.18.62
Ren, X. P3.18.81
Ren, X. OA05.01, P3.18.47
Ren, Y. P3.12.69
Ren, Y. P3.12.64
Ren, Z. P3.18.76

Ren, Z.-R. EP.12.60, P3.01.04, P3.01.37
Rendina, E. MA01.04
Rendle, K. EP.04.05
Rengarajan, B. P3.13.31
Renyi-Vamos, F. MA11.06, P3.13.03
Repp, R. P3.12.14
Resio, B. J. P1.07.31, P2.08 .07
Resnick, A. P1.17.28
Restelli, M. OA09.02, P2.06.65
Restivo, D. EP.15.14
Resuli, B. EP.03.12, EP.11.23, EP.12.56, P3.12.67, P3.18.02, P3.18.36
Reungwetwattana, T. P3.12.28, P3.18.57
Reuss, J. OA12.03, P1.11.73, P2.06.66, P3.13.13
Reuss, J. E. P2.06.44
Revels, S. EP.07.14
Rezende, B. B. EP.17.31, PT1.01.02
Rhee, J. P1.17.20
Rhieu, B.-H. P3.18.19
Riaz, N. EP.14.22, OA07.02
Ribeiro Pinto Filho, D. EP.06.01
Ribera, A. P3.12.30
Ribes, J. P3.14.09
Ribes-Puig, J. EP.07.42
Riccardi, F. EP.11.03
Ricci, L. OA07.03, PT1.08.02
Ricciardi, S. EP.04.30, P2.05.10
Ricciardi, S. EP.06.52
Ricciotti, I. P2.06.92
Ricciuti, B. MA01.04, P1.07.43, P1.11.17, P1.11.42, P1.11.55, P1.11.56, P1.11.62, P1.17.54, P1.17.55, P2.10.09, P2.10.11, P3.03.31, P3.12.63, PT2.11.01, PT2.15.02
Rice, D. P2.02.36, PT1.01.03
Rice, J. PT2.14.01
Rice, J. OA11.03
Richard, D. J. EP.03.09
Richards, A. L. P3.03.01
Richards, D. P3.18.71
Richardsen, E. P1.11.62
Richardson, G. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Richardson, M. P1.11.36
Richey, M. EP.17.33
Richlitzki, C. P2.08 .14, P3.16.19
Richter, H. OA09.02
Richter, U. EP.08.52, P3.18.82
Ricketts, W. EP.06.57
Rico-Pastó, M. P2.06.56
Ricordel, C. P2.06.102, P2.06.79
Rider, A. B. EP.06.53
Rieke, D. T. MA02.04
Riely, G. P2.06.12, P2.08 .25, P3.12.13
Riely, G. J. P3.12.21
Ries, A. EP.02.02, P2.02.18
Ries, J. P1.04.01
Riess, J. P1.07.40, P1.17.03, P2.02.37, P3.12.38
Riess, J. W. MA03.03, P1.17.66
Rifaldi, F. P1.11.54
Rifi, N. P2.15 .05, P3.12.19, P3.12.29, P3.12.34
Rigamonti, A. P1.17.44
Righi, L. P2.06.22, P2.06.40, P3.14.06
Rigney, M. EP.16.02, EP.16.06, EP.16.07, P3.16.01
Rignol, G. P2.06.88
Rigotti, N. A. OA18.04
Rimm, D. P2.06.68
Rimner, A. MA01.06
Rinaldi, C. P1.07.05, P3.13.10
Rineer, J. M. OA13.03
Rink, C. EP.06.05
Rinsurongkawong, W. P1.11.55
Rintoul, R. C. P1.04.54
Rios, G. EP.01.05
Rios, P. EP.16.08, MA06.09
Ripellino, P. P3.18.82
Ripley, R. T. P1.07.37
Rishishwar, L. P2.06.74
Rittberg, R. EP.13.38
Ritter, T. P3.18.05
Rittmeyer, A. MA08.03, MA11.04, P3.12.14, P3.18.65
Riudor Guri, A. EP.05.01
Riva, F. P1.07.04
Riva, S. P1.17.20
Riva, S. T. P1.11.01
Rivas, C. P2.08 .49, P3.03.44
Rivas, F. MA01.01
Rivera, M. P3.16.08
Rivera Concepcion, J. P1.11.75
Rivera-Rodriguez, N. OA13.03
Riya, I. J. P1.11.69
Rizakos, T. P2.08 .23
Rizvi, N. OA09.01
Rizzi, S. P1.17.52
Robbins, H. OA01.03
Robbins, H. A. EP.04.04, MA05.06, PT1.04.04
Robbrecht, D. P3.18.66
Robert, A. EP.15.19
Roberti, C. P1.07.04
Roberti, M. MA04.06
Roberts-Thomson, R. OA03.04, P2.06.89
Robichaux, J. OA02.02
Robinson, C. P2.08 .51
Robinson, J. EP.13.33, PT2.17.02
Robinson, R. R. OA06.04
Roca, E. EP.11.20, P1.07.51, P1.11.24, P3.12.15, P3.14.06
Roca Carreras, I. P1.07.04
Rocco, G. P1.04.17, P3.01.22, P3.18.11
Rocha, P. OA06.03, P3.12.30, P3.14.02, P3.18.73
Roden, A. MA07.01, OA09.03, OA13.04
Roden, A. C. OA09.01, PL03.16, PT1.06.03
Rodi, H. P1.17.20
Rodig, S. J. P1.11.56
Rodón, J. OA08.01, P3.18.71
Rodrigo, A. EP.04.14
Rodrigu, C. MA01.01
Rodrigues, I. P1.17.05
Rodrigues, I. EP.13.20
Rodrigues, L. B. P1.17.74
Rodrigues-Abreu, D. PL02.12
Rodríguez, A. EP.08.07
Rodriguez, D. PL03.10
Rodriguez, E. EP.12.34, EP.13.32, P3.01.52, P3.14.01
Rodriguez, J. EP.04.06
Rodríguez-Abreu, D. EP.17.32, OA05.03, P1.11.07, P1.11.37
Rodríguez-Abreu, MD, D. MA01.03
Rodriguez Hernaez, P. EP.08.37
Rodríguez Hernáez, P. EP.12.63
Rodríguez Nogueira, L. P2.08 .48
Rodriguez-Rodriguez, I. EP.12.24
Roeder, T. EP.03.06, MA09.04
Roeper, J. P1.11.48
Rogers, C. PL03.13
Rogers, J. MA06.06, P1.17.61, P1.17.62, P2.06.89
Rogerson, S. EP.01.22, MA09.05
Roget, P. P2.15 .29
Rogowski, W. P2.06.100
Rohatgi, A. EP.13.40
Rohita, D. K. EP.11.22
Rohof, J. P1.04.25
Roisman, L. OA09.02, P2.06.65, PT1.03.04
Roisman, L. C. EP.06.73

Rojas, C. P3.12.62, P3.12.65, PL02.06
Rojas, C. P3.18.73
Rojas, F. R. P1.11.70
Rojkó, L. EP.16.05
Roland, Z. P2.10.17
Rolf, E. EP.01.20, EP.06.29
Rolfo, C. P3.13.13, PT2.10.01
Rolli, L. P1.04.53
Roma, J. P2.15 .32
Roman, A. P2.08 .21
Romano, F. EP.11.03
Romanò, R. MA06.07, P1.04.51, P1.11.66, P1.17.30
Romano, R. P1.17.44
Romanò, R. P2.06.65, P2.15 .34
Romanovschi, A. P1.17.46
Rombolá, C. A. EP.04.14
Romei, C. PT2.14.02
Romero, A. MA01.01
Romero, A. P3.01.25
Romero, L. MA01.01
Romero, O. A. OA14.04, P2.02.06, P3.03.49
Romero, T. P3.12.46
Romero , PhD, A. MA01.03
Romero-Sola, G. P3.12.30
Ronaghi, R. EP.07.14
Rong, Y. P1.04.50
Rong, Z.-X. OA03.04, P2.02.28, P2.06.36
Rong, z. OA16.03, P2.08 .59
Ronga, R. EP.11.03, P3.18.18
Ronner, M. EP.04.34, P3.03.07
Roof, L. P2.08 .47
Rosa, A. P2.08 .18
Rosado, M. EP.03.02
Rosado, P. P3.01.25
Rosas, D. EP.13.32, P2.06.78, P3.12.56
Ros Brasó, G. EP.08.07
Rose, S. P3.16.10
Rosell, R. EP.02.10, P2.02.34, P2.02.39, P2.02.46
Roselló, À. P2.08 .49
Rosenberg, B. EP.07.14
Rosenblum, R. P3.18.11
Rosengren, F. P2.02.40, P3.18.56
Rosenstock, R. EP.06.50
Rosenthal, L. P1.04.32, P1.17.83, P2.15 .24
Rosenthal, L. S. P3.16.16
Roskes, J. S. P2.06.66
Rosner, S. P3.13.12, P3.18.17
Ross, H. EP.13.25
Ross, H. J. P3.18.13, PL03.06
Ross, L. EP.07.23
Ross, P. EP.07.23
Rossi, M. R. P1.11.59
rossi, v. EP.04.30
Rossi, V. P1.07.17
Rossokha, E. I. EP.08.25
Rost, M. P1.17.54, P1.17.55
Rotem, O. P3.09.03
Rothenstein, J. MA08.07
Rothman, N. OA14.05, P3.01.28
Rothschild, S. P3.18.82
Rothschild, S. EP.06.83
Rotow, J. P1.07.40, P3.14.22, PT2.11.01
Rotow, J. K. P2.06.44, P3.12.63
Rottey, S. P3.18.66
Rotzinger, D. P1.04.15
Roubec, J. MA02.06
Roudko, V. OA03.03, P2.08 .23
Roumpoutsou, M. EP.01.19
Rounis, K. P3.13.17
Rousseau, A. P3.14.15
Rousseau, Z. EP.02.09
Roussos Torres, E. T. P2.06.52
Rout, M. MA01.07
Routy, B. P2.08 .54
Rowbotham, H. EP.01.17
Roy, A. P2.06.69
Roy, T. P3.13.13, P3.13.28
Roy, U. B. OA17.03, PT2.16.04
Roy, U. P2.15 .24
Roycroft, L. P1.11.78
Royo-Crespo, Í. P1.07.24
Rozhkova, I. MA10.09
Ruan, Y. OA16.03
Ruan, Z. P1.07.53
Ruan, Z. EP.12.20, P3.18.24
Ruano Raviña, A. P3.01.25
Ruano-Ravina, A. P1.04.29
Rubio, B. OA01.02
Rubio, C. EP.11.02
Rubio, G. OA01.02
Rubio, M. MA01.01
Rückert, A. P3.18.82
Rudich, A. P2.08 .47
Rudin, C. P3.03.01, P3.03.52
Rudin, C. M. EP.13.08, OA06.03, P3.13.05, PT2.13.04
Rudin, C. P3.03.32
Ruffinelli, J. P3.12.41
Ruffini, E. EP.14.18, P2.05.10, P3.14.19
Ruge, L. P3.18.29
Ruggirello, M. OA09.02, P1.04.53, P1.17.30
Rui, MPH, A. EP12.65, P2.06.11
Ruiter, G. MA08.02, P3.12.41, P3.18.67, P3.18.68, PT2.12.03
Ruiter, R. OA01.01
Ruiz, J. P3.18.14
Ruiz, S. EP.07.43
Ruiz-Dominguez, M. EP.07.42
Ruiz Gutierrez, I. P3.18.29
Ruíz-Martín, G. PT2.15.04
Rukazenkov, Y. OA02.02
Rulli, E. P1.17.44
Ruoff, C. P2.06.84
Rupérez, F. MA01.03
Rusch, V. OA11.01, OA11.02, P1.04.17, P3.01.22
Rusch, V. W. OA12.01
Russano, M. EP.06.52, P1.07.51, P2.15 .34
Russell, A. L. EP.03.16, P3.03.46, P3.03.48
Russo, A. EP.11.20, P1.07.51, P1.11.24, P3.12.15, P3.18.18, PT2.10.01
Ryan, J. P2.10.17
Ryan, R. EP.06.61, P1.07.18
Rybkin, A. EP.01.16, P1.07.36
Ryo, T. EP.06.70, P1.11.47
Ryu, J.-S. P2.05.11
Ryu, J. PT1.02.03
Ryu, R. PT1.04.03
Ryu, W. P2.05.11
Ryzhenkov, A. P1.17.67
Rzyman, W. P1.04.45

S

S, S. M. P3.09.01
Saad, M. P1.11.55, P1.11.70
Saad, S. EP.08.15
Saadatpour, A. P1.11.14, P1.11.18
Saalfeld, F. P1.17.29
Saavedra, M. EP.14.27, EP.17.27
Saavedra, O. P2.06.100
Saavedra Armero, V. MA07.04
Sabadash, S. EP.08.25
Sabatini, P. EP.06.75
Sabesan, s. EP.17.07
Sabia, F. P1.04.53, P2.06.97, P3.14.18
Sabo, E. P1.04.46

Sabogal, F. MA06.09
Saboury, B. P3.13.05
Sabrina, M. EP.06.52
Sacco, M. OA09.02, P1.17.30, P2.06.65, P3.01.48
Sachdev, J. P2.10.17
Sachdeva, K. P2.06.99
Sachdeva, M. P2.06.14
Sachdeva, R. EP.17.06
Sachdeva, R. P1.17.70
Sacher, A. EP.06.75, MA02.06, MA03.03, P1.17.08, P1.17.09, P3.14.11, PT2.12.04
Sachs Kindi, P. P3.16.04
Sadan, R. EP.06.50
Saddi, J. P2.08 .53
Sadig, N. P2.15 .24
Sadrolhefazi, B. PT2.12.03
Saenger, Y. P3.18.22
Saeteng, S. OA02.02, P3.01.30
Saez de Gordoa, K. OA01.02
Saffern, M. P3.03.13
Saffiedine, N. MA03.01
Safi, M. EP.06.75
Saghir, Z. EP.15.03
Saglam, O. F. EP.04.23
Saha, M. OA14.05
Sahin, U. MA01.07, P3.18.74
Sahraoui, S. P2.10.07
Sahu, S. EP.06.27
Saia, C. EP.04.05
Saichaemchan, S. P3.12.49
Saigi, M. P2.08 .49
Saigí, M. P3.01.25
Saigi, M. P3.03.47
Saigí, M. P3.03.49
Saigi Morgui, M. EP.06.78, EP02.12, P3.03.44
Saini, S. EP.01.17
Saintigny, P. P3.03.33
Sairaman, S. EP.06.08
Sais, E. P1.11.07
Sais, È. P2.08 .49
Sais, E. P3.12.30, P3.14.09
Saito, A. I. EP.08.23
Saito, A. EP.07.21, EP.08.02, EP.14.24
Saito, G. P3.18.25
Saito, H. EP.07.07, P2.08 .33
Saito, H. PT2.16.02
Saito, R. EP.12.29, P3.12.09, P3.12.23
Saito, S. PT2.13.04
Saito, T. EP.08.09
Saito, Y. EP.07.21
Saito-Koyama, R. P2.06.33
Saitta, A. P2.06.88
Saji, H. EP.07.01
Saka, A. K. EP.15.06
Saka, H. P1.11.11
Sakaguchi, H. P3.03.02
Sakaguchi, T. EP.06.81, EP.11.08, P3.13.14
Sakai, K. EP.06.46, P3.03.30
Sakai, K. EP.01.29
Sakai, K. EP.13.18
Sakai, M. P3.16.12
Sakai, T. OA06.03, P2.06.59, PT1.05.02
Sakai, Y. MA07.03
Sakakibara-Konishi, J. OA08.02, P3.09.09
Sakakura, N. P3.18.04
Sakakura, Y. P2.08 .08
Sakamoto, S. EP.14.29
SAKARIYA, D. P3.01.15
Sakashita, H. P3.13.14
Sakata, R. P3.01.44
SAKATA, Y. P3.09.05
Sakoda, L. P1.04.05
Sakoda, L. C. P2.15 .31
Sakowitz, S. EP.07.14
Sala, L. P2.08 .53
Sala, M. P3.18.12, PL03.10
Sala, M. P1.11.37, P3.01.25
Sala, S. P2.08 .18
Salahudeen, A. MA05.04
Sağlam, Ö. F. P3.03.04
Salaroli, F. EP.09.06
Salas, D. OA01.02
Salazar, A. P3.01.52
Saldaña, J. P2.06.37
Salehi-rad, R. EP.07.14
Salehjahromi, M. EP.04.31, P2.02.36
Salerno, F. EP.11.20
Salerno, J. P1.17.05
Salfi, G. P3.18.82
Salgado, M. P1.04.07
Salih, B. EP.04.28
Salmistraro, N. P1.11.66
Salmons, K. P3.01.28
Salomone, F. P3.18.18
Salomonsen, R. P2.15 .31
Salomonsson, A. P2.02.40
Salsman, J. EP.01.21, P3.01.27, P3.01.31
Saltos, A. MA04.02, P1.07.37
Salto-Tellez, M. OA09.03
Salva de Torres, C. P3.12.30
Salvadores Palacios, M. P2.08 .37
Salvarrey, A. MA03.01
Salvioli, S. P2.06.92
Samani, A. EP.17.34
Samant, K. EP.06.22
Samant, M. PL02.15
Samanta, S. P1.11.85
Samantas, E. P2.15 .26
Samarah, M. N. P2.05.05
Samarasinghe, K. PT1.03.04
Samaržija, M. OA15.01
Samejima, J. P1.07.03
Sami, H. P3.01.15
Sami, H. EP.17.37, P3.01.14, P3.01.16, P3.01.17
Samii, S. M. P3.18.16
Samkari, A. MA04.04
Samoedro, E. EP.04.22
Sampedro, C. A. EP.04.14
Samson, P. P2.08 .51
SAMSONIK, S. EP.05.05, P1.04.44
Samstein, R. P3.03.13
Samuel, E. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Samuel, J. EP.12.37
Samuel, S. EP.03.09
Sanatani, M. P1.17.70
Sanborn, R. E. MA07.07, P1.07.37
Sanborn, R. OA05.04
Sánchez, A. P1.11.07, P1.11.37
Sánchez, D. MA01.01
Sanchez, D. P2.06.56
Sánchez, L. P2.08 .28
Sánchez, L. MA01.01
Sanchez, L. EP.07.48
Sanchez, M. EP06.85
Sanchez, M. L. OA12.02
Sánchez, P. EP.06.66
Sánchez-Cespedes, M. EP02.12
Sanchez-Cespedes, M. OA14.04, P2.02.06
Sánchez-Céspedes, M. P3.03.44
Sanchez-Cespedes, M. P3.03.47, P3.03.49
Sánchez Cucó, A. EP.04.14

Sanchez -Espiridion, B. OA09.01
Sánchez-Güerri, I. EP.06.48
Sánchez-Lorente, D. P2.06.32
Sánchez Lorenzo, L. EP.06.79
Sánchez Martin, S. EP.06.78
Sánchez Naranjo, G. EP.07.43
Sandelin, M. P1.07.47, P1.17.58
Sanders, H. P2.15 .30, P3.16.20
Sanders, W. OA12.01
Sandiego, S. P2.08 .37, PL03.10
Sandiford, P. EP.04.07, EP.04.10
Sands, J. MA11.01, OA10.01, P3.14.20, P3.18.73, PT2.13.04
Sands, J. M. PL02.18
Sang, J. OA14.05
Sang, Y. P1.07.38
Sangaletti, S. P1.17.44
Sangraula, A. P1.04.10
Sangsawang, T. EP.04.37
Sankar, K. EP.06.21, P3.12.16, P3.18.70
Sankararaman, S. MA07.05
Sankhala, K. P3.18.74
Sansano, I. EP.06.48
Sansar, B. P3.18.34
Sanson, B. P2.08 .01, PT1.09.02
Santa Cruz, O. P2.08 .49
Santamaría-Velilla, D. P2.02.41
Santana, K. PT2.10.01
Santarpia, M. EP.15.14
Santiago, T. I. P1.11.70
Santillan, S. EP.13.19
Santiloni Cury, S. PT1.03.03
Santini, A. P3.12.20
Santini, D. EP.06.52
Santini, F. MA01.06, P3.18.11
Santisteve, S. EP.04.14
Santo, V. EP.06.52, MA01.04, P1.07.43, P1.11.17, P1.11.56, P1.11.62, P1.17.54, P1.17.55, P3.12.63, PT2.11.01
Santoni-Rugiu, E. EP.06.42, EP.12.42
Santoro, I. EP.17.31, PT1.01.02
Santos, E. P2.06.20
Santos, M. EP.01.05
Santos, R. P1.17.24
Santos, T. MA06.09
Santos, MD, E. S. P3.12.24
Santos Passos, F. EP.08.45
Santos-Pérez, S. EP.16.04, P2.08 .60
Sanz-Fraile, H. P2.06.56
Sanz-Santos, J. EP.05.08
Saowapa, S. EP.06.65
Saqi, A. MA04.02, OA09.01, OA13.04, PL03.16
Saracino, C. T. P1.11.66
Sarana, B. P1.04.37
Saremi, A. P1.07.16
Sarinc, S. EP.04.43
Sarioglu, M. EP.18.01
Sarkar, S. EP.04.15
Sarkisian, S. P1.17.78
Sarmento, F. A. P1.17.11
Sarmento, P. A. EP.06.09, P1.17.11, P3.01.06, PT1.04.02
Sarmento Neto, F. A. EP.06.09, P3.01.06, PT1.04.02
Sarris, E. P2.06.65
Sartor, E. EP.17.21
Sasagawa, Y. P1.07.03
Sasaki, A. EP.04.36, EP.06.84
Sasaki, R. EP.07.56
Sasaki-Toda, M. EP.13.18
Sassorossi, C. EP.06.40, P1.07.22, P2.05.10, P3.14.19
Sastre-Garzón, L. EP.16.04, P2.08 .60
Satapathy, S. EP.06.27
Satapathy, S. EP.13.46, PT1.06.03
Sato, K. PT1.05.01
Sato, M. P3.12.35
Sato, M. P3.12.35
Sato, S. P3.03.02
Sato, T. EP.07.35
Sato, T. EP.14.19
Sato, Y. P2.06.47
Sato, Y. P3.18.31
Satoh, Y. EP.06.02, EP.06.12
Satoskar, M. P2.08 .47
Satoyoshi, M. P3.01.07, PT1.01.01
Sauder, M. B. P3.12.46
Saulsberry, A. EP.07.20, P2.05.02
Saulsberry, DBA, A. OA11.03
Sauter, J. L. OA12.01
Savai, R. P3.03.54
Savai Pullamsetti, S. P3.03.54
Savaliya, P. P3.01.16
Savic-Prince, S. OA09.03
Savinelli, I. P3.03.17
Saw, S. P. OA15.02
Saw, S. P1.11.17
Sawa, K. P3.12.33
Sawabata, N. EP.07.21
Sawafta, R. A. P2.05.05
Sawasdisara, S. EP.17.29
Sawazumi, T. EP.07.04, EP.08.02
Saxena, A. EP.12.27, P3.12.71
SAXENA, S. EP.04.26
Sayani, A. EP.15.06, OA18.01
Saylors, G. S. OA02.03
Scaglione, I. P3.18.85
Scaglione, I. M. P3.12.08
Scagliotti, G. V. P2.06.40
Scagliotti, G. P2.06.22
Scalera, S. PT2.11.01
Scanlon, J. EP.15.12
Scaparone, P. P3.03.17
Scarabelli, L. EP.15.11
Scarpa, F. J. P2.06.44
Scattolin, D. EP.13.15
Schaapveld, T. EP.04.10
Schaapveld, T. EP.04.07
Schabath, M. B. P1.04.29, P2.15 .24
Schallenkamp, J. M. P2.08 .23
Schalper, K. EP.08.46
Schalper, K. A. OA09.01
Schär, S. EP.06.83
Scharpenseel, H. P3.18.29
Schelch, K. EP.02.02, MA11.06, P2.02.18, P2.02.22, P3.13.03
Schena, F. PT2.15.01
Schenker, M. OA05.04, P1.11.85
Scherpereel, A. OA12.02
Scherz, A. EP.06.83
Schiavone, G. EP.06.35, P3.18.82
Schimidt Camargo, V. L. PT1.03.03
Schlaepfer, F. P3.03.07
Schläpfer, F. EP.04.34
Schmid, S. EP.06.83, P3.14.11, P3.18.82
Schmid, S. P2.15 .20
Schmidt, S. P1.17.04
Schmidt-Hegemann, N. P3.16.19
Schmidt-Hegemann, N.-S. P2.08 .14
Schmitt, A. EP.06.57
Schmitt-Bormann, B. P3.18.64
Schmitt-Opitz, I. P2.08 .58, P3.03.07
Schneider, C. EP.03.12, EP.06.45, P3.12.67, P3.18.36
Schneider, C. P1.04.03, P1.04.15
Schneider, M. A. EP.01.20, EP.06.29
Schneider, M. MA04.06

Schneiders, F. L. P3.13.16, P3.18.16, PT2.11.02
Schneiter, D. EP.07.09, EP.08.52, EP.09.10
Schoenfeld, A. P1.11.55, P3.18.74, PT2.11.01
Schoenfeld, A. J. EP.08.51, MA11.01, OA07.02, P1.07.43, P1.11.56
Schönborn-Kellenberger, O. P3.18.64
Schoorlemmer, J. EP.18.01
Schott, I. P2.05.17
Schreiner, W. P1.07.11
Schrock, A. B. EP.06.68, P1.17.66
Schroeder, M. MA03.01
Schröer, V. P3.03.45
Schroeter, L. PT2.12.03
Schuchard, J. P3.12.46
Schuetz, S. R. P2.15 .15
Schuldink, I. P1.04.02
Schuler, A. EP.06.83
Schuler, M. EP.04.27, EP.07.22, OA05.04, P2.05.17
Schulze, K. MA04.02, P3.18.13
Schütz, D. P2.06.100
Schvartsman, G. EP.17.30
Schwartz, A. G. P1.04.29
Schwartz, G. MA03.02
Schwartz, J. P1.17.33
Schwarzenberger, P. EP.13.29, MA11.01
Schwecke, A. P1.17.28, P1.17.51
Schwecke, A. J. P3.13.32
Schwed, K. P1.07.05
Scicolone, S. EP.13.05
Scilla, K. P3.13.12, P3.18.17
Sciuto, L. MA07.02
Scognamiglio, C. EP.06.40, EP.14.18
Scott, S. P3.18.40
Scott, S. C. MA08.03, MA08.05, P2.06.44
Scott, MD, J. EP.12.32, EP12.65, P2.06.11, P2.06.20
Scott, MD, J. EP06.86, P3.12.24
Scotti, V. P2.08 .26, P3.12.15
Scruton, S. EP.15.15
Sculco, M. P3.14.06
Seah, E. P3.18.57, PT2.12.02
Searle, A. PT1.04.01
Sebahat, O. EP.11.18
Sebastian, L. P2.06.61
Sebastian, M. EP.17.32, P3.18.34
Sébastien, C. EP.12.36
Sebio-Garcia, R. P2.15 .21
Secundo, I. V. EP.06.09, P1.17.11, P3.01.06, PT1.04.02
Sedaghati-Khayat, B. OA01.01
Seder, C. W. P2.06.64
Sederias, J. OA12.02
See, K. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Seebach, F. MA01.07, MA10.09
Seeger, R. EP.12.25
Seeger, W. P3.03.54
Seely, A. J. EP.07.17
Seetharamu, N. EP.15.12, P2.06.10
Seetharamu, N. E. EP.08.28
Segal, B. P1.11.80
Segovia, J. P2.15 .11
Seguí, V. P3.03.45
Seguì, V. P3.12.30
Seibel, T. P3.18.64
Seijo-Maceiras, L. EP.04.01
Seike, M. EP.11.07
Seitz, E. P1.04.04
Sekar Lakshmisai, S. EP.17.37
Seki, Y. EP.17.05
Sekihara, K. EP.07.21, P1.07.49
Sekuła, M. EP.01.03
Selbie, L. MA06.06, P1.17.61
Selby, K. P1.04.03, P1.04.15
Selby, P. EP.01.24, EP.01.25, EP.15.06
Selep, J. P1.17.24
Selvarajah, S. EP.06.75
Semenkovich, N. P. MA03.05
Sempoux, C. P1.11.03
Sen, S. P3.18.29
Senan, S. EP.18.01, P3.13.16, P3.18.09, P3.18.16, PT2.11.02
Senatore, A. EP.06.40, P2.05.10
Sender, L. P1.11.78, P3.18.52, P3.18.53
Sendur, M. A. PT1.03.06
Sengupta, S. EP.13.39
Senior, M. OA09.03
Senosain, M. P2.06.43
Seo, J. PT1.09.05
Seo, J. P1.07.52, P2.02.11
Seo, S.-J. EP.02.05
Seo, Y. MA05.08
Seong, C.-H. P1.17.32
Sepesi, B. OA09.01, OA12.03
Sepulcri, M. EP.08.03, P2.08 .26
Sequeira, T. EP.07.25, P3.12.30
Sequero, S. EP.11.02
Sequero López, S. EP.12.11, EP.12.24
Sequist, L. MA05.03, OA15.03, P1.04.12, P3.01.18
Sequist, L. V. MA03.03, OA08.03, PT2.12.04
Serena, A. EP.09.17, P1.11.03
Sergeant, L. P1.17.20
Sergi, C. P1.07.51, P3.12.15, P3.18.18
Serhan, H. PT1.03.01
Serhan, H. EP.02.07
Serino, R. P1.04.51, P1.11.66, P1.17.30, P2.15 .34
Serizawa, M. P1.07.13
Serna, R. P3.01.25
Serna-Blasco MSc, R. MA01.03
Serra, E. P1.04.47
Serra Cassano, T. P1.04.51, P2.15 .34
Serra López, J. P2.15 .12
Serra Mitjans, M. P2.05.06
Serra-Mitjans, M. EP.05.08
Serrano, A. P3.13.09, PT2.13.03
Serrano, D. PT1.08.05
Serrano, V. OA01.02
Serry, J. P2.15 .06
Sertich, S. P1.17.65
Servetto, A. EP13.48, P1.11.66, P3.18.18
Servidio, L. OA08.03
Sese, M. EP.06.48
Sestito, A. MA06.06
Seth, A. EP.06.15
Sethi, A. P3.01.16
Sethi, H. MA03.02
Sethi, S. PT1.03.06
Sethjiwala, T. EP.06.34, EP.12.01
Setien, F. P2.02.06
Severcan, F. EP.04.33
Severson, D. T. P2.06.67
Sevitt, T. P3.09.02
Seymour, L. OA12.02
Sezer, A. OA13.02
Sforza, V. P1.17.54, P3.18.18
Sgambelluri, F. P1.17.44
Shabalin, I. P2.10.17
Shachar, E. MA06.08
Shackcloth, M. EP.07.47
Shadbolt, N. P1.17.47
Shagaya, U. PT2.16.04
Shah, A. P3.13.28
Shah, A. P1.17.22
shah, D. P2.06.94

Shah, H. P2.10.06
Shah, M. EP.08.14
Shah, N. P2.06.94
Shah, R. P2.10.05
Shah, R. P3.12.42
Shah, R. P3.01.15
Shah, S. P2.06.64
Shah, S. MA08.03
Shah, S. MA08.05, PT1.03.06
Shahriar, M. H. EP.01.30
Shai, M. P3.03.22
Shaikh, R. P3.13.16
Shameem, A. P3.13.07
Shammas, N. EP.08.50, P1.11.27
Shamseddine, A. EP.14.22
Shamsi, S. A. P3.01.24
Shan, G. P2.02.03
Shan, H. P1.11.51
Shan, J. P1.11.83
Shan, Y. EP.12.02
Shang, Y. P1.17.69, P2.10.16, P3.18.77
Shankarappa, V. OA03.03
Shanley, R. P1.11.71
Shanshal, M. P1.17.28, P1.17.51, P3.13.32
shao, f. EP.07.13, EP.07.28
Shao, L. EP.13.23
Shao, Q. P2.06.101
Shapiro, M. P1.11.77
Shariati, S. OA12.04
Sharma, A. P2.06.64
Sharma, A. MA09.08, P3.18.72, PT1.06.03
Sharma, E. EP.17.33
Sharma, K. P3.12.16
Sharma, M. EP.17.06
Sharma, S. OA14.05
Sharon, E. P1.17.67
Shaverdian, N. EP.08.15, EP.08.51, EP.13.08, EP.14.22, MA01.04, MA01.06, OA07.02, P2.08 .24
Shaw, A. MA01.04, P3.12.63, P3.14.22
Shaw, A. T. P3.12.21
Shaw, A. PT2.14.01
Shaw, R. P3.14.08
Sheena, R. P2.02.15
Sheffield, B. P1.11.36, P1.17.42
Sheffield, K. P1.17.49
Sheffield, K. M. EP.17.33
Sheikh, H. OA16.02
Sheikh, M. OA11.01
Shekhara, C. EP.06.22
Shen, B. P3.12.01
Shen, C.-I. P2.10.04, P3.12.27
Shen, C. P2.02.16
Shen, D. P1.07.38, P2.08 .34
Shen, H. P1.07.50
Shen, H. P2.08 .04, P2.08 .05
Shen, H. EP.02.10, MA02.07, P2.02.39
Shen, H. P1.04.29
Shen, J. PL02.15
Shen, K. MA02.04
Shen, L. P3.13.11
Shen, L. OA06.02
Shen, M. P3.18.47
Shen, M. MA11.03
Shen, W. P1.07.50
Shen, W. PL03.07
Shen, X. P2.08 .23
Shen, Y. PT2.14.04
Shen, Y. P3.03.06
Shen, Y. P2.15 .33
Shencheng, R. P2.02.30
Sheng, S. EP.11.19
Sheng, S. P3.12.46
Sheng, S. P3.13.22
Shenker, D. OA09.01
Shenolikar, R. P3.01.19
Shenouda, M. PT1.08.03
Shentzer Kutiel, T. P3.18.73
Shepard, D. A. P3.12.21
Shepherd, A. EP.08.15, MA01.06
Shepherd, F. EP.06.75, P1.17.08, P3.14.11
Shepherd, F. A. P1.04.29, P1.17.09, P3.12.62, P3.12.65
Sheppard, A. D. P3.12.06
Sheridan, S. PT2.14.01
Shersher, D. PT1.04.03
Sherwood, G. OA08.02
Sherwood, J. P3.12.16
Sheshadri, A. P1.11.60
Shete, S. S. P1.04.29
Sheth, S. EP.01.06, P3.12.05
Shetty, O. A. P3.18.72
Shi, C. EP.17.18, P1.17.40
Shi, C. PT2.11.03
Shi, H.-P. P3.12.55
Shi, H. EP.12.02
Shi, H. MA05.09
Shi, H. P3.12.07
Shi, H. P1.11.67
Shi, H. P3.12.17, P3.12.43
Shi, J.-X. MA04.03
Shi, J. EP.08.04
Shi, J. MA11.03, OA05.01, OA10.04, P2.10.12, P3.12.07, P3.12.31, P3.12.48, P3.12.64
Shi, J. OA14.05
Shi, J. P1.11.51
Shi, J. MA04.07
Shi, J. OA05.01
Shi, J. P1.04.20
Shi, L. P3.01.02
Shi, L. EP.03.06, MA09.04
Shi, L. PT2.12.04
Shi, M. P3.12.01
Shi, M. P3.12.48
Shi, M. M. P3.12.64
Shi, M. EP.12.39
Shi, Q. P1.11.83
Shi, Q. P3.18.44
Shi, Q. EP.12.31, P2.02.23
Shi, R. P2.02.15
Shi, R. P3.18.74
Shi, S. P2.06.34
Shi, W. P2.08 .43
Shi, X. EP.11.16
Shi, X. EP.13.34
Shi, Y. MA08.06, OA05.01, P3.12.07, P3.12.31
Shi, Y. P2.06.73
Shi, Y. EP.04.21, P1.04.22
Shiarli, A. EP.08.18
Shibata, K. EP.02.11
Shibata, Y. P2.02.24, P3.12.49
Shibayama, R. P2.06.95
Shieh, Y. P3.01.01
Shields, P. P2.08 .47
Shien, K. P1.07.49, P2.06.16
Shiga, K. P3.12.32
Shigefuku, S. EP.07.07
Shigematsu, H. P3.18.04
Shigeta, N. EP.07.07, EP.07.24
Shiggaon, S. P2.06.27
Shih, A. R. EP.06.53
Shih, D. P2.06.90
Shih, J.-Y. EP.12.21, OA02.02, P3.12.27, P3.12.46
Shiina, N. P1.07.21
Shiiya, H. EP.04.36, EP.06.84, EP.14.16, P1.07.21

Shiller, M. EP.06.23, P1.17.58, P3.18.61
Shim, B. Y. OA08.02, P2.06.100
Shim, B. P1.11.32, P3.18.57
Shim, B.-Y. MA08.01
Shim, H. MA07.01, OA13.04, P2.06.23, P2.06.48, PL03.16
Shim, S. PT2.11.04
Shima, T. EP.07.32
Shimada, K. P1.07.23
Shimada, Y. EP.07.54, EP.08.40, P1.07.49, P2.08 .06
Shimamura, T. P2.06.69
Shimizu, J. P3.18.04, PT2.12.04
Shimizu, K. P2.06.47
Shimizu, T. P1.11.06
Shimoji, M. EP.05.07, EP.06.46, P3.09.05
Shimokawa, M. P1.07.49, P3.18.31
Shin, D. S. P2.10.01
Shin, J. MA01.06
Shin, J. Y. EP.08.51, EP.13.08, EP.14.22
Shin, J. P2.06.48
Shin, S.-H. P1.11.32
Shin, S. P1.07.15
Shin, Y. EP.12.12, P1.04.26, P3.13.21
Shinada, K. EP.12.29, P3.12.09, P3.12.23
Shinbu, K. EP.11.07
Shinno, Y. P3.12.41, P3.12.58
Shinoda, M. EP.08.05, P2.08 .08
Shinomiya, Y. P3.09.09
Shinozaki-Ushiku, A. PT1.03.05
Shintani, A. P3.12.33
Shiomi, K. EP.06.02, EP.06.12, EP.07.21
Shiono, A. P3.03.42
Shiono, S. EP.07.01, EP.07.21, P1.07.49, P1.17.34
Shiotani, T. EP.07.06
Shiotsu, S. P1.11.40
Shiraha, N. EP.07.06
Shirai, Y. PT2.14.03
Shiraishi, K. EP.13.18
Shiraishi, K. P1.04.29, P3.03.36
Shiraishi, T. EP.14.19
Shiraishi, Y. P3.03.36
Shiratori, T. EP.02.11, EP.08.43
Shire, L. P3.01.20
Shirsi, N. EP.01.08
Shivakumar, S. EP.15.04, P1.11.49
Shivani, S. EP.02.08
Shivchhand, A. EP.01.06, P3.12.05
Shmueli, Y. EP.03.08
Shoji, T. P3.09.09
Shokri, E. P3.14.08
Sholl, L. MA01.04, MA04.02, OA09.01, OA13.04, OA14.05, P1.07.37, P3.12.63, P3.14.22
Sholl, L. M. P1.07.43, P1.11.56, PT2.11.01
Shong, L. P1.04.33
Short, C. P1.17.20
Shpyro, S. P3.18.39
Shrager, J. B. P1.04.19
Shrestha, A. B. EP.11.22
Shrestha, E. P1.17.10
Shrestha, S. P1.17.10
Shrivastava, B. Tech, A. EP12.65, P2.06.11
Shroeder, A. P3.01.48
Shroff, G. P1.11.60
Shu, C. OA09.01, P1.07.37
Shu, C. A. MA04.02, OA02.01
Shu, D. P3.18.17
Shu, Y. P2.10.12, P3.12.07, P3.12.31
Shu, Y. EP.12.57, P3.18.07
Shukair, A. P1.11.17
Shukuya, T. P2.06.95, PT2.14.03
Shula, L. P1.04.20
Shum, E. MA04.02, MA08.01, OA15.03, P1.07.37, P3.01.19
Shunyakov, L. P3.13.31
Shusted, C. EP.04.05, P3.01.01
Shweihat, Y. PT1.08.03
Shyamasundar, V. P. P2.06.17
Shyr, Y. P3.03.21
Si, G. P3.01.08
Si, H. OA11.04, P2.06.03
Siancas, G. R. EP.12.53
Siano, M. EP.06.83
Siddiqua, S. M. EP.01.30, MA06.02
Sidorenkov, G. A. OA01.01
Siegle, A. P2.15 .08
Siemienowicz, M. P1.04.08
Siena, S. P1.11.66
Sienel, W. P3.16.19
Signorelli, D. EP.12.36, MA08.03, P1.11.01, P1.11.66, P2.15 .34
Sihag, S. P1.04.17, P3.01.22
Sikarwar, M. P1.04.14
Sikkema, B. P3.18.66
Sikkink, K. EP.06.57
Silanus, C. EP.06.03
Silbermins, D. PT1.08.03
Silins, I. P2.15 .06
Silterra, J. MA05.03
Silva, C. A. P1.11.16
Silva, F. G. EP.06.09, P3.01.06, PT1.04.02
Silva, F. M. P1.17.74
Silva, F. EP.01.05
Silva, M. EP.04.02, P1.04.02, P1.04.06, P1.04.09, P1.04.11, P1.04.25
Silva Diaz, S. P2.10.05
Silverman, C. EP.01.24, EP.01.25
Silvestri, C. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Silvestri, G. P1.04.32
Silvestri, G. A. P3.16.16, PT2.17.04
Silvestrone, M. P1.07.37
Silvoniemi, M. P3.12.72
Simbirova, A. P1.07.22
Simes, J. P2.06.61
Simmonds, I. EP.01.22
Simó, M. OA05.03
Simoes, J. P3.12.46
Simões, S. EP.07.25
Simone, C. EP.08.15
Simone, II, C. B. MA01.06
Simone 2nd, C. B. EP.14.22
Simone II, C. B. EP.08.51, EP.13.08, P2.08 .23
Simonetti, J. P1.07.22
Simoni, N. EP.09.06
Simpson, M. EP.01.12
sinde, s. EP.15.07
Sindowski, T. P3.18.05
Singh, A. EP.14.17, P1.17.51
Singh, A. EP.07.33, P1.17.27
Singh, G. EP.01.13, P3.01.17
Singh, H. EP.11.22
Singh, J. OA15.03
Singh, J. OA06.03
Singh, M. P3.12.49
Singh, N. P1.17.79
Singh, P. K. EP.01.07, P1.11.21, P1.11.81
Singh, R. P2.15 .15
Singh, S. P2.06.94
Singh, S. EP.02.08
Singh, V. P1.04.54
Singhal, A. P2.06.10
Singhal, N. MA02.06
Singhal, S. P3.18.06
Singhal, S. P1.17.03
Singhi, E. P1.17.10

Singhi, E. K. EP.12.07, P3.12.03
Sinha, N. P3.01.14
Sini, C. P3.12.15, P3.16.05
Sinn, K. EP.02.02, P2.02.22
Sinohara, S. EP.08.05
Sio, T. EP.13.10
Siringo, M. EP.06.74, P1.11.24
Sisca, L. P1.11.17
Sisó, M. P2.15 .21
Sittig, M. P3.13.12
Situ, D. PL03.13
Situ, Y. P3.13.27
Siu Ching Li, M. P1.11.17
Sivakumar, K. EP.06.08
Sivertsen, K. P2.15 .30
Siyuan, L. P1.17.05
Skabla, P. EP.07.23
Skinner, D. P3.16.14
Skinner, V. P3.18.05
Skoulidis, F. MA10.05, P1.11.42, P1.11.70, P3.18.65
Skrable, B. EP.06.57
Skribek, M. P1.11.39
Slamon, D. P2.02.16
Slater, D. P3.13.31
Slebe, F. P3.18.55
Slotman, B. J. EP.01.16
Smaletz, O. EP.17.30
Smeltzer, M. EP.07.20, P2.05.02, P2.15 .32
Smeltzer, M. P. EP.06.53, P1.17.24, PT1.03.04
Smeltzer, PhD, M. P. OA11.03
Smelzer, M. P. MA07.01
Smesseim, I. P2.08 .11
Smirnou, S. EP.06.63
Smit, E. F. P3.18.54, P3.18.58, PT2.12.03
Smit, E. P3.12.40
Smith, A. PT1.03.01
Smith, C. EP.16.01
Smith, C. P2.15 .27
Smith, D. P1.07.35, P1.17.67
Smith, J. P2.15 .22
Smith, J. P3.12.46
Smith, J. P1.17.63
Smith, K. P1.17.51
Smith, K. E. P1.17.28, P3.13.32
Smith, K. N. OA12.03, P1.11.73, P2.06.66
Smith, M. I. EP.07.14
Smith, M. EP.07.47
Smith, R. P1.04.54
Smith, R. P1.04.32
Smith, R. A. P1.17.83, P3.16.16
Smółka, K. P2.08 .21
Snider, J. P2.06.45
Snodgrass, A. P3.18.05
Snoeckx, A. P3.18.03
Snow, S. EP.13.38
Soares, H. OA13.03
Soares, M. EP.07.25
Sobocki, B. EP.01.03
Socci, N. P3.03.32
Socinski, M. MA08.02
Socinski, M. A. P3.18.39
Soda, P. P1.17.54, P2.08 .30
Sodhi, S. P3.03.24
Sodré, B. EP.15.01
Soellner, M. EP.02.07
Soellner, M. PT1.03.01
Soffitto, R. EP.15.14
Sofis, A. EP.01.19
Soh, J. P1.07.49, P2.02.26, P3.09.05
Soh, M.-S. P1.04.23
Sohn, J. MA09.06
Sojar, M. EP.13.13
Solà, J. P1.04.35
Soland, M. P3.18.74
Solanes, A. P2.06.37
Solbes, M.-N. P3.12.10
Solé, X. P3.01.46
Soleda, M. P2.06.65
Solis soto, L. PT2.13.03
Solis Soto, L. M. P1.11.70
Solli, P. P1.04.51, P2.06.81, P2.15 .34, P3.14.18
Solomides, C. OA09.03
Solomon, B. P2.06.89
Solomon, B. MA02.03, MA06.06, P1.17.61, P1.17.62, P3.12.21
Solomon, B. J. OA03.04, P2.06.61, PL02.15
Soma, MPH, C. E. OA11.03
Somma, F. EP13.48
Somri-Gannam, L. P3.03.22
Somwar, R. P2.02.15
Son, J. EP.07.46, EP.08.29
Son, J. P2.08 .31
Sonet, J. OA09.01
Song, F. P3.01.08
Song, G. P3.18.37
Song, J.-U. P3.01.45
Song, J. P1.04.05
Song, J. EP.11.15
Song, J. MA10.05
Song, J. EP.13.41
Song, L. P2.08 .43
Song, P. MA04.07, P1.07.38
Song, Q.-B. PL02.09
Song, Q. P2.10.12, P2.10.13
Song, Q. P3.12.48
Song, S. EP.12.12, P3.12.37, P3.13.21
Song, W. P1.11.43
Song, X. P1.17.36, P3.12.48
Song, X. MA10.03
Song, Y. EP.12.02
Song, Y. EP.13.21, MA05.08
Song, Y. EP.03.05
Song, Y. P3.12.55
Song, Y. EP.03.05, P2.02.09, P2.02.13, P2.15 .33
Song, Y. P3.03.18
Song, Z. EP.18.06, MA02.07, OA06.01, P3.12.74
Song, Z. P2.10.12, P3.12.48
Sonoda, D. EP.06.12
Soo, R. P1.17.24
Soo, R. A. MA08.02, P3.12.21, PT2.12.03
Soo, R. P2.06.14, PL02.15
Sooi, K. P2.06.14
Soon, Y. EP.13.37
Soon-Shiong, P. P3.18.52, P3.18.53
Soon-Shiong, P. B. P1.11.78
Sørensen, J. B. EP.12.42
Sostero, E. EP.04.16
Soter, S. P1.11.82
Soto, F. P1.11.60
Soto, L. M. P3.13.09
Soto-Diaz, S. P2.06.66
Soto Parra, H. MA08.01
Soto Parra, H. P3.12.15
Sottotetti, E. P1.17.44, P2.15 .34
SOUDORN, C. EP.04.37
Soulos, P. EP.01.16
Sound Tsao, M. OA11.02
Souri, A. OA17.02
Soussan-Gutman, L. EP.06.73
soutif, c. EP.11.18
Souto, L. d. PT1.04.02
Souza, J. PT1.03.03
Sovacool, K. L. MA07.02

Sowunmi, A. EP.01.04
Sozzi, G. P2.06.97
Spackman, E. P3.01.24
Spagnoletti, A. OA09.02, P1.04.51, P1.11.66, P1.17.30, P1.17.44, P2.06.65, P2.15 .34
Spasic, J. EP.11.09
Spathas, N. OA09.02
Spector, M. OA09.02
Spees, C. P2.15 .22
Spelman, T. MA06.06, P1.17.61, P1.17.62
Sperandi, F. P1.11.42, P2.06.92
Sperduti, I. EP.07.48, P3.14.19
Spicer, J. P3.18.29
Spicer, J. EP.07.17
Spicer, J. D. MA04.05, OA02.03
Spiegelman, L. MA06.09
Spigel, D. OA05.04
Spilman, P. R. P1.11.78, P3.18.52, P3.18.53
Spinelli, G. EP.06.52
Spinelli, N. P3.03.24
Spinnato, F. P3.18.18
Spira, A. P3.18.74
Spira, A. P3.12.13, P3.12.38, P3.18.29
Spira, A. I. MA02.06, OA08.01, P1.07.37, P3.12.46
Spisarova, M. P1.11.10
Spitaleri, G. PL02.15
Sposito, M. P3.12.08, PT2.15.01
Spreafico, G. P1.07.17
Springfeld, C. MA02.03
Spurr, L. P1.11.55
Spyratos, D. MA02.06
Sreeram, I. EP.14.03, P3.14.12
Sridhar, A. P1.17.51
Sridhar, H. P3.03.52
Srirattanakarn, P. EP.04.37
Sriuranpong, V. P3.12.49
Srivastava, G. P2.06.56
Srkalovic, G. PL03.06
S. Santos, MD, E. EP.12.32, EP12.65, P2.06.11
Staaf, J. P2.02.40, P3.18.56
Stacey, D. EP.12.25
Stadhouders, R. OA01.01
Staeble, S. P2.06.100
Staley, C. P1.11.71
Stamatiou, A. EP.09.17, P1.11.03
Stancu, A. OA05.02
Stando, R. P2.08 .21
Stanic, K. EP.13.13, P2.08 .16
Stanic, N. EP.11.09
Stansfield, L. P3.12.34
Stanzi, A. P3.14.06, P3.14.18
Stanzione, B. P1.07.51, P3.12.15
Starich, B. OA03.03
Starodub, A. P3.18.29
Staten, N. P3.18.06
Stati, V. EP.07.48
Staunton, L. P1.07.18
Stavroulaki, K. P2.08 .51
Stecca, C. P1.11.69
Steenland, K. P3.01.28
Stefaniak, K. P3.18.38
Steimer, D. P1.17.27
Steinack, C. EP.07.09
Stein Deutsch, J. P2.06.66
Steiner, R. OA09.02
Steinmann, N. EP.09.11
Stella, G. M. P2.08 .53, P3.14.06
Stelling, S. P2.15 .17
Stelmach, M. J. EP.06.42
Stencel, K. EP.07.52, P2.15 .06
Stenehjem, D. PT2.12.01
Stenzinger, A. P3.12.61
Stephans, K. EP.07.39, P1.07.34
Stephen, M. M. P3.01.24
Stephen, S. G. P1.11.70
Stephens, E. P2.06.51
Sterman, D. MA10.02, PT1.01.03
Sternberg, D. P3.18.28
Steurer, S. P2.06.65
Stevens, W. I. P1.17.24
Stevenson, J. P1.11.77
Stevenson, S. EP.04.10
Stewart, A. P3.13.09
Stewart, A. C. PT2.13.03
Stewart, C. P3.13.11
Stewart, C. P2.06.84
Stewart, D. J. EP.03.10
Stewart, G. L. P3.01.49
Stewart, S. J. P3.18.17
Stigma and Nihilism Task Group, N. PT2.16.03
Stikker, B. S. OA01.01
Stiles, B. P3.18.19, P3.18.22
Stinchcombe, T. PL02.18
Stinchcombe, T. E. P2.15 .05
Stinchcombe, T. P1.11.75, P3.18.13
Stirling, R. EP.13.33, EP.17.02, P1.17.12, P1.17.18, P3.01.13, PT2.17.02
St-Laurent, G. P3.03.38
Stockler, M. OA03.04, P2.06.99
Stockley, L. EP.06.75
Stoen, E. P3.18.14
Stojanovic, G. P2.15 .06
Stokes, M. P1.17.58
Stoleriu, M. P3.16.19
Stone, E. P1.17.12
Stone, T. P1.17.67
Stork, T. P1.07.28
Strandman, V. P1.11.39
Straus, C. M. P3.14.04
Streich, G. MA08.01
Strohbehn, G. W. P2.10.01
Strumfa, I. PT2.14.02
Studentova, H. P1.11.10
Studts, J. P2.15 .24, P3.16.13
Studts, J. L. PT2.16.03
Stumpo, S. P1.11.42
Stuschke, M. EP.04.27, EP.07.22, P2.05.17
Styles, L. PL02.12
Stynchula, S. OA04.04
Su, B. EP.07.41
Su, C. P3.18.62
Su, C. C. P3.01.07, PT1.01.01
Su, C. EP.02.06, EP.06.67, EP.18.02, MA11.08, P2.02.05, P3.03.37, P3.12.50, P3.18.27, P3.18.30, P3.18.43, P3.18.45
Su, E. P3.18.65
Su, H. EP.12.02, P2.10.13, P3.12.48, P3.13.15
Su, H. P2.06.03
Su, H. P3.18.42
Su, H. P3.18.32
Su, I.-H. EP.12.23
Su, J. P2.08 .35
Su, J. P1.11.12
Su, K. P2.06.30
Su, M. MA11.03
Su, M.-T. P2.06.33
Su, w. P3.12.48, P3.12.64
Su, W. EP.12.09, P2.02.19, P2.02.42, P3.03.50
Su, W. OA06.01, P3.13.15
Su, X. P2.10.14
Su, Y. P1.11.12
Suardi, P. EP.13.02
Suárez, F. EP.04.01
Suarez, M. EP.04.14

Suarez, M. P2.15 .21
Suárez-Cuartin, G. EP.16.04, P2.08 .60
Suarez-Farinas, M. P2.08 .23
Suay, G. P1.11.37
Subach, H. EP.06.63
Subbiah, V. P3.12.58, P3.12.71
Subedi, A. EP.11.22
Subramani, P. P1.07.26
Subramaniam, A. EP.02.03
Subramanian, M. EP.03.01, EP.04.24
Subramanian, S. EP.06.65, P2.06.71
Succony, L. P1.04.54
Suda, K. EP.05.07, EP.06.46, OA11.02, P1.07.49, P3.09.05
Sudhakar, Y. P3.01.14
Sudhaman, S. MA03.02
Suga, J. M. P2.15 .31
Sugai, M. EP.08.42, EP.13.11, P3.12.54
Sugawara, S. EP.11.13, EP.11.17, MA02.02, OA10.01, P1.11.19, P3.13.14, PT2.14.03
Sugimoto, R. EP.06.19
Sugio, K. EP.07.35
Sugiura, H. EP.03.03
Sugiyama, E. P2.06.59, PT1.05.02
Suh, H.-W. MA09.06
Suh, K. P2.02.11
Sui, D. OA07.01
Sui, J. P2.06.12
Sui, J. P3.03.18
Sujenthiran, A. EP.17.34
Sukalinskaya, A. EP.08.08
Sukla, A. EP.14.12
Sullivan, I. EP.11.11
Sullivan, I. PL03.10
Sullivan, K. EP.15.12
Sumitomo, H. EP.14.29
Sumiyoshi, S. EP.06.33
Summers, Y. P3.13.04
Sumpton, D. P3.14.08
Sun, A. P1.17.42
Sun, B. P3.18.41
Sun, C. MA03.09, MA07.09, P2.06.58
Sun, D. P1.11.65, P3.18.08
Sun, D. P3.18.77
Sun, D. PT2.13.02
Sun, F. EP.08.33
Sun, F. EP.11.21
Sun, H. P3.12.52
Sun, H. P1.11.23
Sun, H. EP.12.39
Sun, J. P3.18.46, P3.18.48
Sun, J.-M. EP.07.46, EP.08.29, P1.11.32, P2.08 .31, P3.18.57, P3.18.73, PT2.11.04
Sun, J. P1.04.23
Sun, K. P3.18.17
Sun, L. P1.11.02
Sun, L. MA04.07, MA08.06, OA06.01, OA10.04, P1.17.36, P3.12.64, PT2.10.04
Sun, L. EP.14.17
Sun, L. EP.12.60
Sun, M. EP.11.04, EP.12.51
Sun, M. MA08.01, OA06.02, P3.12.07, P3.12.31
Sun, M. EP.03.05, P2.02.09, P2.02.13
sun, M. P2.02.25
Sun, P. P1.17.67
Sun, Q.-G. EP.13.07
Sun, R. P3.12.17, P3.12.43
Sun, S. P3.12.07, P3.12.31
Sun, S. PT1.06.04
Sun, S. EP.08.17
Sun, V. P3.18.84
Sun, W. P2.08 .38
Sun, X. P2.08 .29
Sun, X. MA03.04
Sun, Y. P2.02.25
Sun, Y. EP.13.35
Sun, Y.-L. EP.12.04, P1.11.05
Sun, Y. P1.11.65
sun, y. EP.07.13, EP.07.28
Sun, Y. MA02.07, OA06.02, P3.12.74
Sun, Z. P1.07.46
Sun, Z. EP.04.19
Sunaguchi, N. EP.02.05
Sundar, S. P1.17.47
Sundersingh, S. P3.01.21
Sundh, J. P3.18.56
Sundsvold, E. P1.17.28
Sung, Y. P2.06.01
Sunshine, J. C. P2.06.66
Suppli, M. H. EP.12.42
Surapaneni, S. P1.11.36, P1.17.70
Surapaneni, V. P1.11.81
Suraweera, A. EP.03.09
Suriyaphan, N. P3.12.28
Sürmeli, H. EP.14.06
Surmont, V. F. P3.18.54
Suryawanshi, S. P1.11.85
Sushmitha, S. EP.13.46
Susilparat, P. P1.04.38
Sutarto, R. EP.04.22
Suzawa, K. P1.07.49, P2.06.16
Suzuki, J. P1.07.49, P1.17.34
Suzuki, K. P2.06.95
Suzuki, K. EP.03.01, EP.04.24
Suzuki, K. EP.07.01, P2.06.25, P3.18.04
Suzuki, K. EP.07.21
Suzuki, S. EP.14.09, P2.02.26
Suzuki, S. P3.03.30, P3.03.42
Suzuki, S. P1.11.80
Suzuki, T. EP.06.26, EP.07.38
Suzuki, T. P3.03.42, P3.18.25, PT2.14.03
Suzuki, Y. EP.06.81
Suzuki, Y. EP.04.18, EP.07.34, P2.06.33
Sverzellati, N. EP.11.05, P1.04.53
Swalduz, A. P3.03.33, P3.18.60, P3.18.66
Swaminathan, B. OA02.02
Swanson, N. P3.13.13
Swanson, S. J. OA02.03, P1.07.37
Swift, S. MA07.02
Swisher, S. OA07.01
Syahruddin, E. EP.04.22
Syahrudin, E. EP.13.02
Syeda Ashna, F. P1.07.45
Symeonidou, C. EP.08.18
Symon, Z. EP.09.01
Syrigos, K. P1.11.39
Syrigos, K. N. P1.17.77
Szalai, Z. P3.18.28
Szalay, A. S. P2.06.66
Szapary, P. P1.11.14
Szczesna, A. MA11.04
Szczyrek, M. EP.13.17
Szczyrek, M. MA10.04, P1.11.63
Szegedi, R. P3.13.03
Szeitz, B. MA11.06
Szeitz, B. P3.13.03
Szewczyk, M. OA09.02

T

Taşaltın, C. EP.04.28, EP.04.33
Tabbo', F. P3.12.15
tacconi, c. P2.08 .30
Tachihara, M. P3.18.31, PT2.14.03, PT2.17.04
Tadesse, F. P1.17.61
Tadic Latinovic, L. P2.08 .20
Tafavvoghi, M. P1.11.62
Tagawa, T. P3.03.05

Taguchi, H. P3.09.09
Taguchi, O. EP.06.81
Taguchi, Y. EP.05.02, EP.13.12
Taihei, T. P1.17.68
Tajanen-Doumbouya, P. P1.17.67
Tajè, R. P1.07.07
Taje, R. P2.05.10
TAJE', R. EP.03.02, P3.14.17
Tajima, K. P2.06.95, P3.18.04
Tak, P. MA10.02
Takabe, Y. PT2.14.05
Takada, I. EP.07.24, EP.07.53, EP.09.13, P2.08 .33
Takada, K. EP.07.11, P1.07.49, P1.11.17, P1.17.54
Takagi, R. EP.06.84
Takahama, T. P3.16.12, P3.18.80
Takahashi, K. P2.06.95, P3.03.36, PT2.14.03
Takahashi, K. P3.18.25
Takahashi, M. PT1.05.02
Takahashi, N. EP.07.21
Takahashi, N. MA07.02
Takahashi, S. EP.08.40
Takahashi, S. P2.06.31
Takahashi, T. EP.13.18
Takahashi, T. EP.14.21
Takahashi, Y. EP.01.29
Takai, T. P2.06.33
Takakuwa, Y. EP.04.36
Takami, K. EP.01.29
Takamochi, K. P2.06.25
Takamori, S. P1.17.34
Takamori, S. P1.07.49
Takanami, K. EP.04.18
Takashima, Y. P3.09.09
Takayama, K. P1.11.40, P3.03.12, PT2.14.03
Takeda, M. EP.07.56
Takegahara, K. EP.14.05, P2.06.41
Takehara, E. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Takehara, T. P3.03.30
Takemoto, S. EP.06.49
Takemoto, T. EP.05.07, P3.09.05
Takemura, C. P1.04.52
Takenaka, H. EP.06.70, P1.11.47
Takenaka, T. EP.07.11, EP.07.50, P3.03.05, P3.18.04
Takeno, A. EP.01.29
Takeno, N. P1.07.21
Takenoyama, M. EP.07.50
Takeuchi, S. MA02.06, P3.03.02
Takeuchi, T. EP.09.16, EP.14.29, PT1.05.04
Takeuchi, Y. EP.01.28
Takeyasu, Y. EP.08.09, P3.18.04
Takhar, H. P2.06.89
Taki, T. P2.06.59
Takigami, A. P3.13.14
Takizawa, H. EP.09.16, EP.14.29, P1.17.68, PT1.05.04
Takumi, Y. EP.07.35
Talab, Y. P1.17.39, P1.17.53, P2.06.09
Talbot, S. P2.02.27
Tallafigo, L. P2.08 .37
Talocco, C. EP.08.13
Talsania, A. PL02.18
Tam, A. P2.02.36, PT1.01.03
Tamagawa, S. EP.06.02, EP.06.12
Tamam Shenholz, N. EP.17.20
Tamarozzi, P. EP.11.05, P3.14.05
Tambo, Y. EP.12.62, P1.11.06
Tamima, S. P2.15 .31
Tamimi, F. P2.06.09
Tamiya, M. EP.11.06, P3.18.04
Tamkhane, K. EP.01.08, EP.12.01
Tammemagi, C. M. P3.01.29
Tammemagi, C. M. P1.17.19, P1.17.81, P3.01.47
Tammemägi, M. EP.04.07
Tammemägi, M. C. P3.01.35
Tamura, T. EP.07.06, EP.10.01, P2.10.03
Tan, A. C. P1.11.79
Tan, A. P1.11.38
Tan, D. S. MA02.04, MA08.02, OA15.02, P3.12.41
Tan, D. PL02.15
Tan, F. P3.18.21
Tan, H. C. P1.11.79
Tan, J.-L. MA08.03, P3.12.46
Tan, K. P1.04.17
Tan, K. P2.06.14
Tan, K. EP.13.10
Tan, L. P1.17.61
Tan, L. PT2.17.01
Tan, L. EP.04.35, EP.08.33
Tan, N. P1.17.83
Tan, Q.-Q. P3.12.26
tan, s. P2.15 .28
Tan, W. OA15.02
Tanaka, F. MA04.05, OA02.03
Tanaka, H. P3.03.42, PT2.14.03
Tanaka, H. P3.03.42, P3.12.33
Tanaka, I. P3.12.35, P3.18.31
Tanaka, R. P2.06.33, P3.18.04
Tanaka, T. EP.11.06
Tanaka, Y. P2.06.59, PT1.05.02
Tanariyakul, M. P2.06.71
Tane, K. EP.07.10, P1.07.03
Tane, S. P1.07.49
Tang, C. MA10.05
tang, c. P2.15 .28
Tang, D. P2.02.07, P2.06.49
Tang, H. EP.03.14, EP.06.56, EP.12.38, P2.06.46
Tang, H. EP.06.67
Tang, J. P1.11.13
Tang, J. P3.12.64
Tang, J. EP.12.48
Tang, K. EP.17.09
Tang, K.-J. EP.12.06, MA08.03
Tang, K. P3.12.73
Tang, L.-B. EP.12.60, P3.01.04, P3.01.37
Tang, L.-B.B. P1.11.05
Tang, M. OA06.03
Tang, M. EP.03.09
Tang, S. EP.12.03, P1.04.30
Tang, W. P1.11.84
Tang, W.-F. OA03.02, PT1.09.03
Tang, X. P2.06.101, P3.18.86
Tang, Y. P3.18.76
Tang, Z. P1.11.68
Taniguchi, H. P3.03.02
Taniguchi, H. EP.06.49, P1.11.40
Taniguchi, Y. EP.08.09
Tanimoto, A. P3.13.09
Tanimura, K. P1.11.40
Tanimura, T. P2.02.26
Tanizaki, J. P3.18.04, PT2.14.03, PT2.17.04
Tanizawa, K. P3.12.44
Tanni, S. EP.01.05
Tansawet, A. EP.04.37
Tan Shao Weng, D. EP.04.08
Tantraworasin, A. P3.01.30
Tao, S. P1.04.22
Tao, W. P2.06.102
Tapan, U. P1.07.37
Taralli, S. EP.06.40
Taranchon-Clermont, E. P3.03.34
Tarantini, F. P1.04.51

Taranto, P. EP.17.30
Tarasevych, S. PT2.11.02
Tarazona, N. P3.03.45
Tardon, A. P1.04.29
Tareen, A. EP.12.61
Tarenchon-Clermont, E. P2.06.43
Tartarone, A. P1.11.66
Tartour, E. P3.18.60
Tassi, V. OA07.03, P2.08 .12, PT1.08.02
Tatrai, E. MA11.06
Tatsuoka, C. P3.13.12
Taube, C. EP.04.27, EP.07.22, P2.05.17
Taube, J. MA04.09
Taube, J. M. P2.06.66
Taur, M. P1.04.37
Taus, A. EP.08.07
Taus, Á. P2.06.74
Tavalire, H. P2.10.01
Tavares de Morais, M. PT1.04.02
Taveira, F. T. P1.11.16
Taverna, C. P3.18.82
Tavora, F. PL03.16
Tavora, F. R. MA07.01
Tay, R. P2.06.89
Taylor, F. P1.04.29
Taylor, K. L. P1.04.10
Taylor, R. P1.07.47
Taylor, S. P1.11.69
Tayyab, A. P1.17.26
Tazbirkova, A. P2.06.89
Tech, S. P3.12.39
Teerenstra, S. EP.18.01
Teglas, V. MA11.06, P3.13.03
Tehfe, M. P2.08 .54
Teixeira, C. EP.13.28
Teixidó, C. EP.06.48
Teixido, C. EP06.85, OA01.02, P3.01.46
Teixidó Febrero, C. EP.05.01
Teixidor, E. P3.14.09
Teixidor-Vilà, E. P2.08 .49
Teles Costa Grillo, I. EP.08.45
Telles, F. EP.15.01, EP.15.09
Temes, M. EP.07.43, P2.08 .48
Tempel Brami, C. P3.03.22
Tempel-Brami, C. EP.03.08
Temurtaş, F. EP.04.33
Tena, I. OA05.03
Tendler, S. P3.13.17
Teng, J. EP.07.44, PT2.11.03
Teng, X. EP.12.38
ten Haaf, K. P1.04.35
Tenório Cerezoli, M. P1.17.45
Teo, M. EP.08.34
Terada, N. P1.11.06
Terada, Y. P2.06.47
Teramoto, K. EP.02.11
Teramura, T. P3.03.30
Teriete, P. P2.10.17
Terra, R. EP.17.31, PT1.01.02
Terra, R. M. EP.17.04, EP.17.23, P1.17.05, P1.17.15, P1.17.74
Terra, R. OA11.02
Terrando, F. EP.14.18
Terukina, H. P2.06.25
Tessitore, A. P3.18.82
Teulé, A. P2.06.37
Thakur, M. OA13.03
Thakur, N. P2.08 .17
Thakur, P. P2.08 .17
Thakur, R. EP.08.32
Tham, W. OA15.02
Thamarai Selvan, P. P3.01.21
Thamaraiselvan, P. EP.06.08
Thamlikitkul, L. EP.17.29
Thamrongjirapat, T. P3.12.28
Thavaneswaran, S. P2.06.61
Thavendiranathan, P. EP.14.15
Theegarten, D. EP.04.27, EP.07.22, P2.05.17
The Lung Cancer Cohort Consortium, f. OA01.03
Theodore, R. MA06.09
Theophanous, S. P1.17.67
Theou-anton, N. P2.06.15
Theriau, C. P2.10.06
Thet, Z. EP.11.22
Theuns, C. P3.18.03
Thiagarajan, M. P3.12.49
Thieme, P. O. PL03.06
Thirunavukkarasu, B. EP.14.12
Thiruvalluvan, M. P3.18.70
Thiry, C. MA06.09
Thoele, K. EP.17.33, P1.17.49
Thomas, A. A. P2.15 .15
Thomas, A. MA07.02
Thomas, D. M. P2.06.61
Thomas, E. R. P1.04.16
Thomas, J. S. P2.06.100
Thomas, K. P2.02.15
Thomas, M. MA04.06, OA05.04, P2.15 .02, P2.15 .08, P3.12.10, P3.12.40, P3.12.61, P3.18.80
Thomas, M. P3.18.09
Thomas, P.-A. EP.04.29, P1.04.39, P2.05.15
Thomas de Montpreville, V. P3.14.15
Thomassen, A. P3.12.06, P3.12.71
Thompson, B. PL02.12
Thompson, C. G. OA13.01
Thompson, J. P3.13.13
Thompson, J. E. P1.11.73
Thompson, R. C. P2.08 .23
Thomson, C. C. P1.04.32
Thor, M. EP.13.08, P2.08 .24
Thorell, A. P1.11.39
Thorley, R. EP.01.22, MA09.05
Thu, K. L. EP.02.09, OA14.03, P3.01.49, P3.03.38
Thunnissen, E. OA13.04
Tian, B. MA05.07
Tian, H. P3.18.08
Tian, J. EP.09.12, P3.09.06
Tian, L. P3.12.17, P3.12.43
Tian, P. MA01.05, P3.12.46
Tian, T. EP.08.01, EP.12.20, P3.18.24
Tian, T. EP.06.56, EP.12.38, P2.06.46
Tian, W. P3.12.74
Tian, X. P1.17.56
Tian, Y. PT2.13.03
Tibdewal, A. EP.08.14, EP.09.08
Tibdewal, A. R. P3.09.01
Tibes, R. P3.18.74
Tie, H. P1.07.06
Tiemann, K. OA09.03
Tiemann, M. P1.11.48
Tiemessen, M. PT2.11.02
Tighiouart, M. P3.18.70
Tillery, K. P2.15 .24
Timmerman, R. P3.18.05
Timricht, R. EP.17.11
Tinelli, G. P3.12.20
Tippornwong, M. EP.04.37
Tischfield, S. P3.03.32
Tiseo, M. EP.09.06, EP.11.05, EP.11.20, MA02.05, MA03.03, MA08.01, P1.07.04, P1.11.24, P1.11.56, P1.17.55, P3.12.15, P3.14.05, P3.14.06, PT2.11.01
Tissera, S. EP.13.33, EP.17.02, P1.17.18, P3.01.13
Tissot, C. P1.17.21
Tjota, M. Y. OA12.01
Toba, H. EP.09.16, EP.14.29, P1.17.68

Toba, H. PT1.05.04
Tod, A. EP.15.08, OA04.01
Toda, M. P1.07.49
Todd, J. P2.06.89
Toderis, L. EP.17.20
Todesco, A. EP.04.29, P1.04.39
Todori, M. EP.06.19
Toffalorio, F. P3.12.21
Toffart, A.-C. OA05.02
Togka, K. P1.04.25
Tognetto, M. MA02.05
Togo, T. EP.06.26
Tohmasi, S. P1.17.50
Toi, Y. EP.11.13, EP.11.17, P1.11.19, P3.03.42, P3.12.33
Tokaz, M. P2.10.01
Tokunaga, T. P3.03.05
Tokuyama, S. EP.01.29
Tolmacheva, E. A. EP.08.25
Toloza, E. M. P3.18.84
Tomar, V. PT2.16.04
Tomasik, B. EP.01.03, P1.17.54
Tomasini, P. MA07.07, P3.12.46, P3.18.68
Tomida, S. P2.06.16, P3.03.30
Tominaga, J. EP.04.18
Tominaga, S. P3.13.14
Tomita, H. P2.06.25
Tommasi, R. P1.04.47
Tomono, H. EP.06.49
Ton, T. G. P1.04.31
Tonda, R. P3.03.49
Tondon, C. EP.06.39
Tondulli, L. P1.07.51, P3.12.15
Tong, B. C. P3.18.84
Tong, C. EP.09.05
Tong, F. MA03.06
Tong, K. EP.16.02, P3.16.01
Tong, L. P3.01.18
Tong, L. EP.08.38
Tong, R. PT2.13.02
Tong, S. P1.07.50
Tonini, G. EP.06.52
Tonkin, K. P2.15 .32
Too, C. OA15.02
Toomey, S. P2.06.82
TOPAL, H. K. EP.13.43
Topper, M. P1.11.72
Toppi, L. P2.08 .30
Torasawa, M. P2.06.95, P3.03.36
Torchia, A. EP.07.48
Torelli, T. P1.17.44
Torigoe, H. P2.06.16
Tornese, A. P2.05.10
Torok, S. MA11.06
Torres, J. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Torres, T. P3.03.22
Torres Alvarez, R. P3.01.42
Torresan, S. P3.12.30
Torres-Martinez, S. EP.06.77
Torri, V. P1.17.44
Tortora, G. P3.13.04
Tortorella, A. P1.11.54
Toschi, L. EP.11.20, MA02.05, P1.07.51, P1.11.01, P1.11.24
Toshiyama, R. EP.01.29
Toste, P. EP.07.14
Totaro, G. P3.18.18
Toumazis, I. P1.17.19, P1.17.81, P3.01.47
Toumbacaris, N. MA01.06
Touri, F. EP.06.79
Toyama, S. P3.12.44
Toyoda, M. EP.07.04, EP.08.02, EP.14.24
Toyoda, T. P1.07.49
Toyooka, S. P2.06.16
Toyozawa, R. P3.18.04
Trachu, N. P3.12.28
Tran, C. OA02.01
Tran, E. EP.06.40
Tran, H. OA07.01, PT1.01.03
Tran, H. T. P1.11.60, P2.02.36
Tran, T.-V. OA14.05
Tran, V. EP.01.17
Trani, L. MA07.07
Trap, L. OA01.01
Trape Pujol, J. EP.06.71
Trasatti Romao, V. EP.08.45
Travis, W. OA09.01, OA13.04, OA14.05, P3.18.11
Travis, W. D. OA12.01, PT1.07.01
Travis, W. OA11.02
Treeyapong, P. P3.01.30
Treggiari, S. EP.04.30
Tregnago, D. P3.12.08, P3.18.85, PT2.15.01
Trego, K. P2.10.17
Trejo, D. PT1.03.01
Trejo, E. P1.17.17
Trejo-Martín, P. PT2.15.04
Trestini, I. P3.12.08, P3.18.85, PT2.15.01
Trevino, S. PT2.13.03
Triana, C. P2.15 .11
Triebel, F. P3.18.34
Triggiani, L. P2.08 .26
Trinchieri, G. P1.17.44
Tripathi, N. P1.17.24
Tripathi, R. EP.06.16
Triphuridet, N. P1.04.43
Trippa, F. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Trisolini, R. P1.07.22
Triulzi, T. P1.17.44
Trodella, L. P2.08 .30
Trofarello, L. P2.06.92
Trokic, D. P2.08 .20
Tronchetti, J. EP.04.29, P1.04.39
Troost, E. G. P1.07.22
Trosman, J. R. P2.15 .31
Trouillot, V. MA06.09
Trousse, D. EP.04.29, P1.04.39
Troutman, S. OA02.01
Trovò, F. MA06.07, OA09.02, P1.04.51, P1.11.66, P1.17.30, P2.06.65, P2.15 .34
Trovo', F. P1.17.44
Trudu, L. EP.13.05, EP.15.11, MA02.05
Trujillo Reyes, J. EP.08.07
Truong, A. P1.17.61
Tsai, C. OA07.02
Tsai, H.-L. P1.11.72
Tsai, J. P2.06.75
Tsai, J.-H. EP.12.35
Tsai, T.-H. EP.12.21
Tsakonas, G. P1.11.39
Tsang, E. P1.17.08, P1.17.09
Tsao, A. S. OA12.03, P2.08 .23
Tsao, M. EP.03.15, OA09.01, OA12.01
Tsao, M. S. P1.04.29, P3.12.51, PT1.03.04
Tsao, M.-S. EP.06.31, OA12.02, OA12.04, OA14.03, P2.06.99, P3.03.03, PL03.16
Tsarkouskaya, Y. EP.08.08
Tsegaye, D. P2.15 .13
Tseng, C. EP.12.45
Tseng, Y.-H. P2.10.04
Tseng, Y.-T. P3.03.21
Tsereteli, A. EP.17.26
Tsereteli, A. EP.17.24
Tsitsi, T. P1.17.75
Tsoukalas, N. P2.15 .26
Tsuboi, M. EP.07.01, EP.07.10, OA02.02, P1.07.03,

P1.07.47, P3.18.09
tsuchida, s. EP.06.04
Tsuchida, T. PT1.05.01
Tsuchiya, H. P3.12.32
Tsuda, T. P3.03.42
Tsugitomi, R. EP.08.42, EP.13.11, P3.12.54
Tsuji, A. EP.09.16
Tsuji, K. P3.09.09
Tsukada, H. P1.07.37
Tsukazan, T. R. P1.17.74
Tsukioka, T. P2.02.26
Tsutani, Y. EP.05.07, EP.06.46, EP.07.01, P1.07.49, P3.09.05, P3.18.04
Tsyhankova, I. MA01.07
Tu, D. OA12.02
Tu, H.-Y. P1.07.55, P1.11.05, P1.11.61
Tu, J. OA07.01, P1.11.70
Tu, L. MA01.05
Tu, W. OA12.02
Tuccillo, C. EP13.48
Tuck, A. C. P2.06.88
Tucker, J. PT1.04.03
Tudos, O. P1.11.82
Tufman, A. EP.03.12, EP.06.45, EP.11.23, EP.12.56, OA08.03, P3.12.67, P3.18.02, P3.18.36
Tukachinsky, H. EP.06.68
Tupper, H. EP.07.14
Türeci, Ö. MA01.07, OA13.02, P3.18.74
Turgeman, I. OA18.01
Turki, E. EP.06.80
Turkowski, K. P3.03.54
Turlington, D. EP.13.40
Turna, A. EP.03.11, EP.04.23, EP.05.04, P3.03.04
Turna, H. EP.05.04
Turnbull, O. M. P2.06.61
Tuta Quintero, E. EP.04.01
Tworek, D. P2.08 .21
Tyan, P. P3.18.64
Tymoshyk, I. P3.01.36
Tzchori, I. EP.03.08, P3.03.22
Tzukazan, M. T. P1.17.74

U

Ubonviroj, P. EP.04.37
Uchibori, K. EP.03.03, EP.08.42, EP.13.11, P3.03.42, P3.12.54
Uchida, J. EP.17.25, P3.18.31
Uchiyama, S. EP.17.05
Udagawa, H. MA08.04, P2.02.24, P2.06.59, PT1.05.02
Udager, A. PT1.03.01
Ueda, K. EP.02.11, EP.08.43
Ueda, S. EP.13.12
Ueda, T. EP.06.25, EP.12.62, P1.11.06
Ueda, Y. EP.14.19
Uehara, T. P2.06.47
Uema, D. PT2.10.02
Uematsu, K. EP.13.18
Uematsu, S. EP.13.14
Uenishi, T. P3.13.01
Ueno, H. EP.06.70, P1.11.47
Ueno, T. EP.07.21
Ufoaroh, C. U. P1.17.76
Ufondu, A. P1.07.34
Ufuk, F. P3.14.04
Ugalde, A. P1.17.20
Ugalde, P. F. P1.17.27
Ugel, S. P3.18.85
Uitterlinden, A. G. OA01.01
Ujiie, H. EP.05.07, EP.06.84
Ulaner, G. P3.13.05
Ulas, E. B. P3.13.16, PT2.11.02
Ulintz, P. PT1.03.01
Ulloa, S. EP.17.08, P3.16.13, P3.16.20
Ullrich, P. P2.15 .02
Ulrich, S. EP.07.09
Umar, A. P1.17.76
Umemura, S. P2.06.59, P3.12.49, PT1.05.02
Umeno, T. EP.10.01, P2.10.03
Umeyama, Y. EP.06.49
Umiker, B. P3.18.35
Uncu, D. P2.10.02
Underhill, C. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Ungaro, A. P3.18.18
Ünsal-Kaçmaz, K. MA01.07
Unsöld, L. P2.15 .02, P2.15 .08
Upadhyay, D. P3.01.16, P3.01.17
Upadhyay, V. A. PL02.15
Uprety, D. P1.17.49
Urakami, K. P1.07.13
Urban, D. MA08.03, P1.17.06
Urban, L. P1.11.82
Urbanic, J. J. P3.18.13
Urbanska, E. EP.01.09
Urbanska, E. M. EP.06.42, EP.12.42, PT2.17.04
Urbizu, A. EP.06.48
Ureña, A. MA01.01
Ureña, A. EP.08.26
Uriarte, A. P2.06.99
Urikura, A. P1.04.52
Urquhart, R. EP.15.15
Ursino, G. P2.15 .31
Ursol, G. MA04.04
Urtasun, A. P3.16.11
Urtecho, B. P3.14.11
Urtecho Suarez, S. EP.06.75
Ürün, Y. P3.18.34
Usama, A. EP.11.22
Uslenghi, C. U. P3.14.18
Usman, F. EP.08.17
Uson Junior, P. L. EP.17.30
Utsumi, T. EP.08.09
Uttam, S. P2.06.66
Uy, K. P1.07.16, P1.17.01
Uyeki, J. V. OA08.02
Uzenabor, S. MA09.04

V

Vachani, A. EP.04.05, P3.01.01
Vagge, S. P2.08 .26
Vaghani, D. EP.17.37
Vagionas, A. P2.15 .26
Vahora, S. EP.13.29, MA11.01
Vaia, A. EP.11.03
Vaidya, R. EP.13.44
Vaidya, S. P3.18.73
Vail, E. EP.06.21, P3.12.16
Vailati Negrao, M. MA10.05
Vaíllo, X. P2.08 .28
Vakhomchyk, T. EP.06.63
Valdes, M. MA08.07
Valdivia, A. P3.12.30, P3.14.02
Valdiviezo, N. P3.12.62, P3.12.65, PL02.06
Valencia-Clua, K. EP.02.10
València-Clua, K. P2.02.34, P2.02.39, P2.02.46
Valencia-Uribe, J. P2.06.78
Valera, A. EP.06.35
Valin Barajas, J. P2.08 .48
Valipour, A. P2.15 .06
Valladeau-Guilemond, J. P2.06.43
Valle, Ó. EP.11.02
Valle Carcel, O. EP.12.11
Valle-Carcel, O. EP.12.24
Vallois, L. EP.06.39
Vallone, S. P3.16.05
Valsecchi, C. P1.04.53
Valsecchi, M. PT1.08.03

AUTHOR INDEX AUTHOR INDEX AUTHOR INDEX

Valter, A. P1.17.29
van Boerdonk, R. A. P2.08 .11
van Bömmel-Wegmann, S. EP.17.34
van den Bos, M. P3.18.54
Vandenburg, B. PT1.03.01
van den Heuvel, M. EP.04.32, EP.18.01, P1.04.41
van den Heuvel, M. M. P3.01.10
van den Hurk, C. EP.04.32, P1.04.41, P2.15 .10
van de Poll, L. EP.04.32, P1.04.41
van der Aalst, C. EP.04.02, P1.04.02, P1.04.09, P1.04.25
van der Aalst, C. M. P1.04.06, P1.04.11
Vander Borght, T. EP.11.18
van der Drift, M. A. P3.18.54
van der Geest, D. MA10.08
Vanderpuye, V. PT2.17.04
van der Sangen, M. P3.01.10
van der Schee, M. P1.04.54
van der Sijs, I. H. P3.18.54
Vanderwalde, A. EP.13.41, MA07.06, P1.17.65, P2.06.52, P3.12.03
van der Wekken, A. PL02.15
van der Wekken, A. J. P3.18.54
van der Zeeuw, S. L. P3.18.54
van de Ven, P. PT2.11.02
Van de Walle, V. EP.12.52
van Dorp, M. P3.18.16
van Genugten, J. P3.14.03
van Haarst, J. PT2.11.02
Van Hal, G. P3.18.03
Van Heemst, J. OA01.01
van Herk, M. OA16.02
van Herpen, C. P3.18.66
Vanhove, K. EP.13.16
van Laren, M. PT2.11.02
Van Loo, P. MA11.06
van Maldegem, F. P3.18.16
Van Meerbeeck, J. P3.18.03
Van Rooij, J. G. OA01.01
van Schaik, R. H. EP.12.15
Van Schil, P. P3.14.19
Van Schoor, Z. P1.17.67
Vansteenkiste, J. EP.13.16
van Tilburg, P. PT2.11.02
Vaporciyan, A. OA07.01, P1.11.55, P2.02.36, PT1.01.03
Vardi, I. P1.17.06
Varela, M. EP.06.48, P2.06.37
Varena, M. MA06.09
Varesano, N. P1.04.47
Vargas, H. P2.15 .11
Vargas-Aliaga, A. EP.06.66
Vargas Parada, I. EP.08.47
Varlotto, J. PT1.08.03
Varlotto, J. M. PL03.06
Varlow, M. P1.17.20
Varughese, PharmD, MBA, P. EP.12.32, EP06.86, EP12.65, P2.06.11, P2.06.20, P3.12.24
Vasconcelos, I. P3.18.29
Vaseghi, G. EP.07.17, MA09.02
Vasileiou, K. EP.06.64
Vásquez, C. EP.06.48
Vass, C. P2.15 .05
Vathiotis, I. P1.11.39
Vavalà, T. P1.07.51, P3.12.15
Vaz de Melo Sette, C. P1.17.82
Vaz-Luis, I. P1.17.21
Vazquez, S. OA01.02
Vázquez, S. P1.11.07, P1.11.37
Vazquez Armendariz, I. P3.03.54
Vedovelli, L. PT2.14.02
Veeraraghavan, H. P1.11.64
Veerla, S. P2.02.40
Veerman, G. D. P3.18.54
Veerman, G. EP.12.15
Veerman, G. D. EP.12.49
Vega, C. EP.07.33, P1.17.27
Vega Legorburu, N. EP.05.01
Veillon, R. P3.12.40
Velasco, R. N. P1.11.79
Velazquez Manana, A. I. P1.17.17
Velcheti, V. MA02.03, MA08.02, MA10.07, OA05.04, P1.11.85, P3.12.58, P3.18.28, PT1.01.03
Velchetti, V. P3.18.87
Veldhuizen, S. EP.01.24, EP.01.25
Velez, M. EP.07.14, P2.08 .22
Velez, M. A. P2.02.16
Velichko, S. MA03.02
Vellequette, G. EP.13.40
Velotta, J. P2.15 .31
Velotta, J. B. P3.16.16
Velthuis, E. P3.12.40
Veltman, J. D. PT2.11.02
Vendittelli, A. EP.06.52
Venkataraman, P. EP.17.06
Vennapusa, B. EP.06.51
Venuta, F. P3.14.19
Vera, J. P2.08 .42
Vera, K. P3.18.34
Vera-Badillo, F. P2.06.99
Vera-Dumpiérrez, M. EP.08.37
Veras, I. P2.08 .18
Verberkt, C. EP.04.32, P1.04.41, P2.15 .10
Verberkt, C. EP.18.01
Verbiest, A. P1.17.67
Verfaillie, S. P1.07.41
Vergé, R. P2.05.15
Verma, J. P3.01.15, P3.01.17
Verma, M. PT2.10.02
Verma, S. EP.12.37, P2.06.70
Vermeulen, R. C. OA01.01
Veronesi, G. P1.04.45, P2.05.10
Verweij, J. EP.12.52, P3.18.66
Verzè, M. EP.11.05, MA02.05, P1.07.04
Vézian, A. P3.18.60
Vezzoli, F. EP.06.80
Viana, A. C. P1.17.82
Viani, G. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Vibhakar, P. P2.15 .22
Vicente, R. MA01.01
Vicente Baz, D. MA01.07
Victorian, A. P2.06.84
Vidal, A. P3.14.24
Vidal, A. P2.06.37
Videtic, G. EP.07.39, P1.07.34
Videtic, G. M. PL03.06
Vidiri, A. EP.07.48
Vieillot, S. P2.06.43
Vienne, M. P3.03.34
Viggiano, A. P3.18.18
Vignaud, E. P3.03.33
Vignault, C. P2.06.87
Vigorito, R. P1.17.30
Vikman, H. EP.13.22, P1.17.14
Vikström, A. P3.18.56
Viktorsson, K. P3.13.17
Vilà, L. P3.18.12, PL03.10
Vila-Fornells, A. EP.04.14
Vilaia, A. PT2.14.02
Vilariño, N. OA05.03, P3.12.30
Vílchez Pernias, E. EP.07.27
Villalobos, J. L. MA01.01
Villalobos, M. P2.15 .02, P2.15 .08
Villalón, D. OA17.02
Villano, J. EP.13.29, P1.17.65

Villaruz, L. P2.06.102
Villatoro, S. P2.06.37
Vincent, M. MA08.07, P1.17.70, P3.18.52, P3.18.53
Vincenzi, B. EP.06.52
Vingiani, A. P1.11.66
Vinod, S. P1.17.12
Viñolas, N. P2.06.32
Viola, L. EP.04.01
Virani, A. PT2.10.02
Vire, B. P2.06.87
Visca, P. EP.03.02
Viscardi, G. EP.08.03, EP.11.03, EP13.48, P1.07.51, P2.15 .34, P3.14.06, P3.18.18
Visser, I. P1.04.13
Visseren-Grul, C. MA02.06, OA08.02
Viswanathan, S. EP.17.32
Vita, E. P3.13.04
Viteri, S. MA06.03, P3.01.25, P3.12.40, P3.16.11
Vitiello, F. EP.11.03, EP13.48, P3.18.18
Vitoc, V. P1.11.82
Vitti, M. EP.14.10
Vlacich, G. R. P2.08 .51
Vlahos, H. P1.17.08, P1.17.09
Vlassak, S. OA13.02
Vliegenthart, R. OA01.01
Vocaturo, F. EP.06.40
Vogazianos, P. EP.08.18
Voinovich, M. OA04.04
Voitko, O. MA04.04
Vojjala, N. P3.12.42
Vokes, E. P3.01.48
Vokes, E. E. OA02.03, OA17.03, PL02.18
Vokes, N. EP.04.31, P1.11.55, P1.11.56, P1.11.60, P1.11.70, P2.02.36, PT1.01.03, PT2.11.01, PT2.13.03
Voland, R. PT1.08.03
Volante, M. P2.06.22, P2.06.40
Volders, P.-J. P1.07.41
Volk, R. P1.17.83
Volodin, A. EP.03.08
Voloshin, T. P3.03.28
Voltolini, L. P3.14.19
Vomvas, D. EP.08.18
von Briel, T. EP.06.83
von der Thüsen, J. MA07.01, OA13.04
von der Thüsen, J. H. PL03.16
Von Garnier, C. P1.04.03, P1.04.15
von Moos, R. P3.18.82
Voon, P. J. P1.11.15
Voon, P. MA08.05, P3.12.46, P3.18.34
Vorobeva, M. P3.13.29
Vorontsov, A. P3.03.28
Voß, H. P2.15 .02
Voulaz, E. P2.05.10, P3.14.19
Vozikis, A. P2.15 .26
Vozy, A. P3.18.74
Vrankar, M. EP.13.13, P2.08 .16
Vu, T. P2.08 .54
Vucic, E. A. P3.01.49
Vukelic, N. EP.15.04, P1.11.49
Vyas, R. K. EP.14.04
Vykoukal, J. P3.13.09

W

Waddell, T. K. MA03.01
Wadhwa, M. EP.17.06
Wagenius, G. EP.13.22, P3.13.17
Wagh, A. P2.15 .30
Wagner, J. OA03.03
Wahid, U. EP.04.06
Waibel, C. EP.06.83
Wainwright, J. EP.04.05
Waissengrin, B. EP.06.21, P3.12.16, P3.18.70
Wakabayashi, M. EP.07.01, PL03.16
Wakahara, J.-I. EP.14.19
Wakasu, S. EP.07.50, P1.07.49
Wakelee, H. MA04.04, P3.01.19, P3.12.58
Wakelee, H. A. P1.17.54, P3.01.07, PT1.01.01
Wakuda, K. EP.14.21
Waliany, S. MA02.01
Walker, A. OA16.02, P1.04.36
Walker, A. OA09.01
Wall, M. OA03.04
Wallace, A. EP.01.21, EP.07.17, P3.01.27
Wallace, T. EP.12.10
Walls, G. P1.17.07, P3.13.04
Walraven, I. EP.04.32, EP.17.13, EP.18.01, P1.04.41, P2.15 .10
Walsh, G. L. P2.02.36, PT1.01.03
Walsh, L. P3.13.06
Walston, A. P1.17.28
Walstra, A. P1.04.09, P1.04.25
Walstra, A. N. P1.04.02
Wals Zurita, A. EP.06.71
Walter, D. P1.17.01
Walter, J. EP.11.23
Wampfler, J. A. EP.13.10
Wan, C. P2.06.28
Wan, J. EP.06.14
Wan, L. EP.12.55
Wan, L. OA06.02
Wan, Q. EP.04.19, P1.04.27
Wan, R. P3.18.81, PT2.10.03
Wan, X. P3.18.32
Wan, Y. P3.12.32
Wang, B. X. OA12.04
Wang, B.-C. P1.07.55, P1.11.05
Wang, B. EP.11.15
Wang, B. PT1.03.06
Wang, B. EP.12.58
Wang, B. EP.12.57, P2.10.12, P3.12.48, P3.18.07
Wang, C. P3.13.15
Wang, C. MA04.08, OA02.03, P3.12.48
Wang, C. PT2.14.04
Wang, C. MA10.05
Wang, C.-C. P3.12.49
Wang, C. EP.13.29, MA11.01
Wang, C. P3.12.01
Wang, c. EP.18.10
Wang, D. P2.06.91
Wang, D. P2.06.66
Wang, D. P3.13.27
Wang, D. EP.07.30, P1.04.24
Wang, D. P3.12.31
Wang, D. EP.18.09, P3.18.46, P3.18.48
Wang, F. MA03.08, P1.11.22, P2.02.12
Wang, F. EP.12.60, P1.11.61
Wang, F. P3.09.07
WANG, F. EP.06.56, EP.14.20, P2.06.46
Wang, G. P3.13.05
Wang, H. P2.06.98
Wang, H. P3.12.18
Wang, H. P2.06.98
Wang, H. OA10.04
Wang, H. P2.06.96
Wang, H. EP.03.14, EP.06.56, EP.12.38, P2.06.46
Wang, H. P1.11.68, P3.03.16
Wang, H. EP.06.38
Wang, H. MA05.07
Wang, H. P1.07.38
Wang, H. P1.11.43
Wang, H. EP.06.20
Wang, H. P3.03.11
Wang, H. EP.12.41, PT1.06.04
Wang, H. EP.17.18, EP.18.06, P1.17.40, P3.12.45
Wang, H. P1.04.49

Wang, J. P2.02.02
Wang, J. MA11.10, P3.12.70
Wang, J. EP.12.41, MA08.03, PL02.06, PT1.06.04
Wang, J. PT1.02.01
Wang, J. MA01.05
Wang, J. P2.10.14
Wang, J. P3.12.38, P3.12.64, P3.18.41, PL02.09, PT2.10.03, PT2.17.03, PT2.17.04
Wang, J. P1.17.36
Wang, J. P3.03.11, P3.13.20
Wang, J. EP.04.17, P2.02.07, P3.13.09, P3.13.11
Wang, J.-F. MA05.02
Wang, J.-Z. P3.03.14
Wang, J. EP.07.45, P1.11.29
Wang, J. P1.04.20
Wang, J. PT1.07.03
wang, j. P2.02.08
Wang, J. EP.11.19, P1.11.83, P1.17.36
Wang, J. P1.17.69, P2.10.16
Wang, J. P2.02.02
Wang, J. PT1.03.02
Wang, J. MA05.07
Wang, K. EP.06.10
Wang, K. MA01.05, P3.12.07, P3.12.31
Wang, K. P1.17.22
Wang, L. P1.07.50
Wang, L. EP.12.06, EP.18.08, P1.07.38, P1.11.51, P1.11.65, P3.03.53
Wang, L. MA01.05, P3.12.01, P3.18.45
Wang, L. P2.08 .34
Wang, L. P1.17.38
Wang, L. MA03.08, P1.11.22
Wang, L. P3.12.07, P3.12.31, P3.12.64
Wang, L. OA02.03
Wang, L. P3.12.48
Wang, L. OA05.01
Wang, L. EP.18.08
Wang, L. P3.12.48
Wang, L. OA06.01, P1.11.44, P2.06.101, P3.18.62, PT2.10.03, PT2.10.04
Wang, L. P2.06.34
Wang, L. P3.18.77
Wang, L. MA11.09, PL03.07
Wang, L. EP.01.15, EP.04.25, EP.07.55
Wang, M. P2.10.13
Wang, M. P1.07.38
Wang, M.-M. P2.06.53
Wang, M. P3.13.27
Wang, M. EP.13.30, MA08.01, P2.06.73, P2.08 .55, P3.12.48, P3.12.66, P3.13.19
Wang, M. MA08.03, MA08.05
Wang, M. MA10.03, PT2.10.03
Wang, M. P2.08 .32
Wang, M. P3.12.51
Wang, N. EP.12.40
Wang, P. MA09.03, P3.01.23
Wang, P. P1.11.76
Wang, P. P3.12.48, P3.12.74
Wang, Q. P2.02.05, P3.12.50, P3.13.09, P3.18.43
Wang, Q.-M. EP.12.06, P3.12.55
Wang, Q. EP.06.10, EP.17.03, P1.04.04, P2.15 .19
Wang, Q. P3.03.48
Wang, Q. P2.10.14
Wang, Q. P1.11.76, P3.18.76
Wang, Q. OA06.01, OA08.03, OA10.02, OA10.04, P1.11.76, P1.17.38, P2.10.13, PT2.10.04
Wang, Q. P1.07.02
Wang, Q. OA05.01, P3.12.25, PT2.10.03
Wang, Q. P3.18.39
Wang, Q. EP.15.05
Wang, Q. EP.04.35, EP.08.33, P1.07.55
Wang, R. EP.14.23
Wang, R. EP.08.04, EP.15.05, MA05.07, P1.07.01
Wang, R. P2.06.84, P3.13.09, P3.13.11
Wang, S. MA04.04
Wang, S. P2.06.34
Wang, S. MA04.08
Wang, S. EP.12.58, P2.06.34
Wang, S. P3.12.38
Wang, S. P3.13.22
Wang, S. P1.07.39
Wang, S. MA02.07
Wang, S. EP.07.44
Wang, S. P2.15 .04
Wang, S. P2.06.72
Wang, S. EP.06.14
Wang, S. P3.12.71
Wang, T. EP.04.39, EP.06.72
Wang, T. EP.18.04, MA01.05, MA01.05
Wang, T. P3.12.07, P3.12.31
Wang, V. EP.07.33
Wang, W. EP.12.17, MA02.02, OA14.02, P2.06.42, P2.08 .32, P3.01.33, P3.12.12
Wang, W. MA10.03
Wang, W. MA11.03
Wang, W. EP.06.59
Wang, W. EP.13.23
Wang, W. MA04.07, MA04.08, MA06.04, MA09.09, P3.18.08
Wang, X. OA05.01
Wang, X. Q. P2.10.15
Wang, X. OA06.02
Wang, X. EP.03.05, P2.02.09, P2.02.13, P3.12.64
Wang, X. EP.08.12, EP.13.03, MA06.01
Wang, X. P3.18.13
Wang, X. EP.11.16, EP.18.05
Wang, X. EP.12.57, P3.18.07
Wang, X. P1.11.13
Wang, X. P3.12.01
Wang, X. MA11.04
Wang, X. OA06.01
Wang, X. MA01.04, P1.07.43, P1.11.42
Wang, X. PT2.10.03
Wang, X. EP.12.44
Wang, X. MA03.09, MA07.09, P2.06.58
Wang, X. P2.05.13
wang, x. EP.13.09
Wang, Y. MA10.03
Wang, Y. EP.14.20, MA10.05, OA05.01, P1.11.35, P2.15 .28, P3.12.17
Wang, Y. P3.12.17, P3.12.43
Wang, Y. OA14.01, P2.06.49, P3.18.47
Wang, Y. P3.18.76
Wang, Y. PL02.18
Wang, Y. P3.12.48
Wang, Y. P2.02.35
Wang, Y. P1.11.13
Wang, Y.-R. MA05.02
Wang, Y. P2.10.13
Wang, Y. MA08.07, P1.04.29, P2.02.08, P2.15 .17, P3.03.14, P3.03.18
Wang, Y. PL03.07
Wang, Y. EP.07.55
Wang, Y. OA06.01
Wang, Y. EP.13.35
Wang, Y. J. P2.10.15
Wang, Y. S. EP.18.04
Wang, Y.-S. EP.12.06
Wang, Y. EP.04.39, EP.06.72, MA07.07, OA10.03, P1.11.67, P3.12.47, P3.12.69, P3.18.51
Wang, Y. EP.06.38
Wang, Y. EP.02.10, MA02.07, P2.02.39, P3.18.21
Wang, Y. P2.02.13, P2.06.98, P2.15 .33
Wang, Y. EP.12.39
Wang, Y. P3.18.77
Wang, Y. P2.06.24
Wang, Y. P3.18.67
Wang, Y. EP.12.57

Wang, Y. OA17.04
Wang, Y. P2.15 .18, PT2.16.05
Wang, Y. EP.14.01, P1.11.29
Wang, Y. P2.06.72
Wang, z. EP.18.10
Wang, Z.-H. EP.12.06, P3.12.55
Wang, Z. P3.12.25
WANG, Z. P3.12.74
Wang, Z. EP.12.13
Wang, Z. MA03.06
Wang, Z.-J. PL02.09
Wang, Z. MA11.09, P3.12.59, P3.18.81
Wang, Z. P3.18.77
Wang, Z. M. MA10.03
Wang, Z. P3.03.11
Wang, Z. P2.06.30
Wang, Z. P3.12.64, P3.12.69
Wang , Y. P3.12.43
Wang, MBA, B. EP.12.32, EP06.86, EP12.65, P2.06.11, P2.06.20, P3.12.24
Wannaphut, C. P2.06.71
Wannasai, K. EP.06.53
Waqar, S. EP.13.40, P2.08 .51, PL02.15
Waqar, S. N. P1.07.37, PL02.18
Warburton, L. P1.17.62
Ward, J. P1.17.50
Ward, J. P. EP.13.40, P3.18.87
Warittikoon, S. P1.04.43
Warkentin, M. T. MA05.06, P3.01.24
Warner, E. P3.01.18
Warner, E. T. MA05.03
Warren, G. W. OA11.01
Warsinske, H. MA03.01
Washimi, K. EP.07.07, P2.08 .33
Wassell, E. EP.15.16
Wastelin, F. EP.12.52, P3.18.66
Watanabe, F. EP.08.05, P2.08 .08
Watanabe, H. P1.07.49, P1.17.34
Watanabe, H. EP.07.19, P1.04.52
Watanabe, H. EP.06.70, P1.11.47
Watanabe, K. EP.12.29, P3.12.09, P3.12.23
Watanabe, K. PT1.03.05
Watanabe, M. EP.07.06
Watanabe, N. MA08.04
Watanabe, S. P3.16.12
Watanabe, S. P3.03.30
Watanabe, S. P1.11.06, P1.11.40
Watanabe, S.-I. EP.07.01, EP.07.19, P1.04.52, P3.01.44, P3.03.36, P3.18.04, PL03.16
Watanabe, T. P1.07.49
Watanabe, T. EP.06.26, EP.07.38
Watanabe, Y. P3.03.42
Watanabe, Y. EP.06.26, EP.07.38
Wategaonkar, R. EP.01.06, P3.12.05
Watermann, I. OA09.02
Watson, D. C. EP.13.32
Watson, D. P2.06.18
Wauters, E. EP.13.16, P3.18.29
Wauters, I. EP.13.16
Weber, J. MA07.05
Weber, M. P3.16.10
Wedeken, K. P1.11.48
Weder, W. OA02.02
Wedge, D. OA14.05
Wefel, J. S. MA10.05
Wei, B. MA04.07
Wei, C.-F. P1.07.08
Wei, C. P3.12.45
Wei, F. P3.12.17, P3.12.43
Wei, G. P2.02.25
Wei, L. P2.08 .47, PT2.12.01
Wei, Q. P2.06.101
Wei, S.-L. MA05.02
Wei, S. P3.13.27
Wei, S. PT2.10.03
Wei, S. EP.06.56, EP.12.38, P2.06.46
Wei, W. OA16.03
Wei, X.-W. EP.12.60
Wei, Y. OA06.01, P1.11.13
Wei, Y.-F. EP.12.21, MA11.04, P3.12.49
Wei, Y. P1.07.39
Wei, Z. P1.11.34
Wei, Z. PT2.17.04
Wein, A. N. MA07.05
Weinberg, F. EP.13.04, MA05.03, P1.04.12, P1.17.13, P2.06.69, P3.01.26
Weinberg, J. MA10.05
Weinberg, U. EP.03.08, P3.03.22, P3.03.28
Weinmann, D. P1.17.28
Weintraub, L. PT2.10.01
Weiss, M. P3.13.31
Weissferdt, A. OA09.01, OA13.04, PT1.07.01
Weitz, M. P2.06.13, P2.06.21
Weitz, T. P3.18.52, P3.18.53
Weksberg, D. C. PL03.06
Welch, J. P3.18.87
Weldon, C. B. P2.15 .31
Wells, J. P3.16.21
Wells, N. EP.01.16
Wells-Di Grigorio, S. OA04.04
Welsh, J. MA10.05
Wen, C. P1.04.04
Wen, G. P3.12.25
Wen, J. OA06.01
Wen, J. EP.12.58
Wen, J. P2.06.57
Wen, M. P3.12.07
Wen, Q. OA06.02
Wen, Y.-F. EP.12.21
Wen, Y. EP.06.38
Wender, R. EP.04.05
Weng, C.-D. P3.12.26
Weng, M. P1.07.42, P1.07.56, P2.06.60, P2.08 .45, PT1.07.04
Weng, T.-I. EP.12.21
Weng, Y. P1.04.19
Wenger, M. MA01.07, P3.18.74
Wenzel, C. P3.12.61
Wermke, M. OA13.01, P1.17.29, P3.12.61
Werner, R. EP.04.16, EP.09.11
Werner, R. S. EP.08.52, EP.09.10
Werner-Wasik, M. P2.08 .23
Wesseler, C. P3.12.14
Westeel, V. OA05.02, OA12.02, P3.18.60
Weston, S. P3.16.20
Weyant, M. J. EP.03.01, EP.04.24
Whang, B. B. P1.07.37
Wheatley-Price, P. EP.03.10, EP.06.54, EP.12.25, EP.13.38, EP.17.17, MA08.07, P1.11.36, P2.10.06
Wheeler, E. EP.04.03, EP.04.08, OA18.01, P1.17.35
Whelan, K. EP.01.21, P3.01.27
Whipple Neibauer, M. OA05.04
White, M. A. P2.10.17
Whittaker, K. P1.17.20
Whop, L. P1.04.08
Widlak, P. P1.04.45
Widyastuti, K. EP.13.02
Wiest, I. C. P2.15 .34
Wiesweg, M. EP.04.27, EP.07.22, P2.05.17, P3.12.61
Wijaya, S. P2.06.14
Wijeratne, S. OA09.01
Wilbur, D. PT1.04.05
Wilcox, H. EP.04.03, EP.04.08, P1.17.04, P1.17.35
Wilder, F. P3.01.18
Wildgust, M. P3.12.46

Wilhelm, C. P3.03.01
Wilking, N. P1.17.14
Willard, M. D. MA02.06, OA08.02
Willborn, K. C. P1.11.48
Willén, L. EP.13.22
Willett, F. EP.06.51
William Jr., W. N. P3.18.58
Williams, C. MA06.06, P1.17.61
Williams, L. P2.06.08
Williams, R. M. P1.04.10
Williams, T. M. P3.18.13
Williams, T. P3.12.19
Williamson, I. R. P2.15 .14
Willig, A. P2.06.88
Willis, A. MA06.09
Willmann, J. OA18.02
Wills, B. P2.15 .11
Wilson, D. O. MA05.06
Wilson, K. R. EP.06.51
Wimbush, S. P3.18.17
Winckels, S. P3.18.34
Winder, T. MA04.09
Wingler, M. P2.15 .29
Wingrove, J. P2.06.17, P2.06.18
Winiarczyk, K. EP.13.17
Winquist, E. EP.12.37
Wins, R. MA01.01
Wint, A. J. OA18.04
Winter, H. EP.01.20, EP.06.29, MA04.06, P3.03.54
Wirth, C. OA14.05
Wislez, M. OA05.02, P3.18.60
Wistuba, I. OA09.01, P2.02.36, PT1.01.03
Wistuba, I. I. PT1.07.01
Wo, Y. P2.08 .29
Wojas-Krawczyk, K. EP.06.17
Woldmann, L. P3.01.19
Wolf, F. P2.15 .34
Wolf, J. P3.18.29
Wolf, J. MA02.03, PL02.15
Wolf, T. EP.06.39
Wong, A. P1.11.38
Wong, C.-K. P3.12.49
Wong, C. EP.15.13
Wong, J. P2.06.90
Wong, K. K. P2.06.63
Wong, K.-K. OA15.03
Wong, M. EP.17.02
Wong, W. MA06.01
Wong, Y. P3.12.49
Wong Shee, A. P1.17.20
Woo, A. EP.06.32
Woo, M. S. P1.17.22
Woo, W. P2.06.13, P2.06.21, P2.08 .01, PT1.09.02
Wood, J. OA16.02
Wood, T. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Woodard, G. EP.06.58, EP.08.46
Woodard, G. A. P1.17.24
Woolf, D. OA16.02, P3.09.02
Woolfe, D. P2.08 .19
Woolley, S. EP.07.47
Woolschot, T. P1.04.41
Worst, M. A. EP.12.07, P1.17.33
Worthy, G. MA04.05
Wozniak, A. EP.07.52
Wozniak, A. OA08.01, P3.18.71
Wozniak, A. OA17.03, P1.07.37
Wrangle, J. MA08.02, P1.11.78, P3.18.52
Wray, A. MA03.02
Wright, C. P1.17.20
Wright, G. EP.17.02, P1.17.12, P1.17.18, P3.01.13, PT2.17.02
Wright, M. P3.01.26
Wright, V. EP.15.06
Wroe, A. EP.08.19
Wu, A. MA01.06
Wu, A. J. EP.08.51, EP.13.08, EP.14.22
Wu, B. Z. P3.01.49
Wu, B. P3.12.32
Wu, C. C. EP.04.31, P2.02.36
Wu, C.-C. MA05.02
Wu, C. EP.04.20
Wu, C. P3.13.22
Wu, C. P2.02.20, P2.06.38
Wu, C. OA06.01
Wu, C. EP.06.36, EP.08.35, EP.08.49, MA11.10, P2.06.06
Wu, D.-H. P2.02.33
Wu, E. P3.01.51
Wu, F. P1.11.31
Wu, F. P2.05.13, P3.03.53
Wu, G. OA06.02
Wu, G. MA10.01, OA10.02, PT2.10.03
Wu, H. PT2.10.04
Wu, H.-C. EP.12.06
Wu, H.-G. P3.13.21
Wu, H. P3.18.76
Wu, H. PT1.06.05
Wu, H. EP.07.41
Wu, J. EP.04.31, OA07.01, P1.11.55, P1.11.70, P2.02.36, PT1.01.03
Wu, J. EP.12.39
Wu, J. EP.12.39
Wu, J. P1.07.55
Wu, J. P3.18.45
Wu, J. EP.13.34
Wu, J. P3.12.69, PT2.10.03
Wu, J. P1.11.46
Wu, J. P3.03.25
Wu, J. OA11.04
Wu, L. EP.09.12, P2.08 .34, P3.09.06
Wu, L. OA12.04
Wu, l. EP.12.43
Wu, L. EP.12.06, MA02.07, MA08.06, MA11.03, OA06.01, P1.11.65, P2.10.12, P3.12.07, P3.12.25, P3.12.41, P3.12.48, P3.12.55, P3.12.64, P3.13.15, PL02.09, PT2.10.03
Wu, L. MA08.06
Wu, L. EP.12.60, P3.01.04, P3.01.37, PT1.06.02
Wu, M. PT1.07.03
Wu, N. MA04.07
Wu, N. EP.13.40
Wu, Q. MA01.05
Wu, Q. EP.12.38
Wu, Q. EP.07.41
Wu, S.-G. EP.12.21, P3.12.27
Wu, S. EP.09.05, P1.07.42, P1.07.56, P2.08 .45, PT1.07.04
Wu, S. MA07.06, P2.06.52
Wu, S. P3.12.31
Wu, S. P2.08 .51
Wu, S. P1.07.50
Wu, S. P3.01.48
Wu, T. P3.18.80
Wu, W. EP.06.36, EP.08.49
Wu, W. P1.11.58
Wu, X. EP.12.41, PT1.06.04
Wu, X. P3.18.81
Wu, X. P3.18.81
Wu, Y. P3.18.43
Wu, Y. P1.11.76
Wu, Y.-L. P1.07.47
Wu, Y.-L. EP.08.31, OA03.01, P1.04.21, P1.07.55, P1.11.05, P1.11.61, P2.06.53, P2.06.77, P2.08 .35, P2.08 .43, P3.12.55, P3.13.33, P3.18.09, PT1.09.03, PT2.12.03
Wu, Y. P3.12.25, P3.18.39
Wu, Y. P1.17.38

AUTHOR INDEX AUTHOR INDEX AUTHOR INDEX

Wu, Y.-C. P2.06.02
Wu, Y. P2.08 .55
Wu, Y. P3.09.04
Wu, Y. EP.12.28
Wu, Y. MA11.09
Wu, Y. MA08.06
Wu, Z.-N. P2.02.28, P2.06.36
Wu, Z. P2.08 .29
Wu, Z. EP.12.41, PT1.06.04
Wu, z. EP.18.10
WU, Z. P3.12.74
Wu, Z. EP.12.39
Wynes, M. W. MA07.01, OA09.01, OA11.01, P1.17.24, PT1.03.04, PT1.07.01
Wynes, M. OA11.02

X

Xavier, F. EP.01.05
Xavier, V. P2.08 .18
Xenophontos, E. EP.08.18
Xi, W. EP.12.28
Xi, Y. P1.07.50
Xi, Y. P3.13.09, P3.13.11
Xia, F. P3.03.18
Xia, L.-L. P3.03.14, P3.13.24
Xia, M. MA10.03, P1.11.65, P1.11.83
Xia, P. EP.04.25, EP.07.55
Xia, R. EP.13.10
Xia, Y. EP.11.15, MA03.04, MA05.09, P2.08 .04, P2.08 .05, P2.08 .46
Xia, Y. P3.12.46
Xia, Y. EP.12.13
Xiang, B. P1.17.13
Xiang, J. EP.18.03
xiang, l. P3.12.47
Xiang, M. EP.03.05, P2.02.09
Xiang, Y. P1.07.50
Xiao, F.-M. P1.11.05
Xiao, F. P1.07.12, P2.06.30
Xiao, H. EP.07.29, EP.08.41
Xiao, J. P2.08 .57
Xiao, K. P1.17.36
Xiao, m. EP.18.10
Xiao, S. OA10.03, OA10.04
Xiao, W. P2.02.38
Xie, B. P1.17.69
Xie, D. OA03.02
Xie, F. EP.13.23
Xie, H. P1.11.13
Xie, H. P1.04.04
Xie, H. OA11.04, P2.06.03
Xie, J. P1.04.50
Xie, J.-B. MA04.03
Xie, J. P2.08 .57
Xie, J. EP.04.17
Xie, J. P2.06.19
Xie, L. EP.03.05, P2.02.09
Xie, M. MA11.08, P3.18.27, P3.18.30
Xie, R. P2.06.60
Xie, S. PT1.07.02
Xie, S. P1.07.01
Xie, W. P3.18.49
Xie, X. P2.06.03
Xie, X. P2.02.12
Xie, Y. P3.18.69
Xie, Y. EP.04.20
Xie, Y. PL03.06
Xie, Z. P2.08 .35
Xin, H. P2.02.09
Xin, L. EP.13.29, MA11.01
xin, t. P2.15 .28
Xin, Y. P1.17.43
Xin, Y. EP.13.07, P3.03.35
Xing, F. P2.06.19
Xing, L. MA08.06, P3.12.73
Xing, M. MA09.07
Xing, M. EP.08.38
xing, p. EP.12.43
Xing, S. P2.08 .24
Xing, W. P2.08 .43
Xing, X. P2.06.88
xing, y. PT1.09.04
Xionag, A. P3.12.73
Xiong, A. P1.11.83, P3.12.69
Xiong, D. P3.01.39
Xiong, J. MA07.08
Xiong, L. PT2.11.03
Xiong, Y. P3.18.47
Xiong, Y. EP.06.05, EP.18.10
Xiong, Y.-Y. PT1.09.03
Xiu, J. MA07.06, P2.06.52
xiu, w. P3.12.47
Xu, B. P1.17.56
Xu, B. EP.11.15
Xu, C. EP.06.68
Xu, C.-R. P3.12.55
Xu, C. R. PT1.06.02
Xu, C.-R. EP.12.60, P1.11.05, P1.11.61, P3.01.04, P3.01.37
Xu, C. EP.09.05
Xu, D. MA11.01
Xu, f. P2.15 .28
Xu, F. MA01.05
Xu, H.-Y. P3.12.17, P3.12.43
Xu, H. P3.12.64, PT2.10.04
Xu, H. P3.12.66
Xu, H. P3.03.11
Xu, J. P1.07.53
Xu, J. P3.18.81
Xu, J. EP.07.44
Xu, J. MA11.03
Xu, J. MA06.04, MA09.09
Xu, J. P1.11.84
Xu, K. EP.03.14, EP.06.56, EP.07.17, EP.12.38, MA09.01, P2.06.46
Xu, L. EP.12.38
Xu, L. EP.12.38
Xu, L. EP.03.14, EP.06.56, EP.12.38, P2.06.46
Xu, L. OA11.04, P2.06.03
Xu, N. P2.06.03, PT2.14.04
Xu, N. MA10.03
Xu, R. P2.08 .29
Xu, S. P1.11.15
Xu, S.-L. PT1.09.01
Xu, S. P2.06.95
Xu, W. MA03.03, PT2.12.04
Xu, W. P1.04.29
Xu, W. EP.01.15
Xu, X. P2.08 .34
Xu, X. MA10.03
Xu, X. EP.13.23
Xu, X. EP.12.58
Xu, Y. EP.13.30, P2.06.73, P2.08 .55, P3.12.66, P3.13.19
Xu, Y. EP.13.23
Xu, Y. P1.11.51
Xu, Y. EP.07.41, EP.13.36, P3.18.79, PT2.13.01
Xu, Y. EP.03.14, EP.06.56, EP.12.38, P2.06.46
Xu, Y. MA03.09, MA07.09, P2.06.58
Xu, Y. P3.13.34
Xu, Y. P2.05.03, P3.18.15
Xu, Y. MA02.03
Xu, Z. P2.06.88
Xu, Z. C. MA08.02
Xu, Z.-P. OA03.04, P2.02.28, P2.06.36
Xu, Z.-Y. P3.13.33
Xue, F. EP.08.21

Xue, J. P3.09.04, P3.12.47
Xue, L. EP.06.62
Xue, Q. P1.07.53

Y

Yadav, A. EP.07.37
Yadav, A. k. EP.14.04, EP.14.28
Yadav, H. N. EP.02.08
Yadav, K. EP.06.22
Yadav, K. EP.06.27
Yadav, S. C. EP.02.08
Yaghi, O. P2.08 .42
Yagi, K. P1.17.68
YAKAR, M. EP.13.43
Yakoub, D. EP.13.39
Yalamanchili, S. EP.04.24
YALMAN, D. EP.13.43
Yamada, T. MA02.06, P1.11.11, P1.11.40, P3.03.12, P3.12.33
Yamaguchi, D. EP.08.05
Yamaguchi, H. EP.06.44
Yamaguchi, H. EP.04.36
Yamaguchi, K. P1.07.13
Yamaguchi, M. EP.07.50, MA08.04, OA08.02, P3.03.42, P3.18.04
Yamaguchi, O. EP.05.02, EP.13.12
Yamaguchi, R. EP.11.07
Yamaji, M. EP.07.36
Yamamoto, K. P3.12.33
Yamamoto, K. EP.07.07
Yamamoto, M. EP.01.29
Yamamoto, N. PT2.12.03
Yamamoto, N. P1.11.11, P3.18.31
Yamamoto, R. P3.13.14
Yamamoto, S. EP.05.02, EP.13.12
Yamanaka, Y. P3.13.01
Yamanashi, K. EP.07.56
Yamanda, S. EP.11.17
Yamasaki, H. EP.04.36
Yamashita, K. MA07.03
Yamashita, M. EP.10.01, P2.10.03
Yamashita, N. EP.13.12
Yamato, H. EP.01.28
Yamazaki, K. P3.03.05
Yamazaki, K. EP.07.50
Yamazaki, Y. EP.11.13, P1.11.19
Yammani, D. EP.17.03
yan, d. P2.15 .28
Yan, E. P1.11.52
Yan, H.-H. P1.07.55, P1.11.05, P3.01.04
Yan, H. P3.12.64
Yan, J.-J. P3.12.26
Yan, J. P1.17.69, P2.10.16
Yan, J. EP13.49
Yan, L.-X. EP.08.31, OA03.01, P1.07.55
Yan, M. EP.09.04, EP.17.28
Yan, N. n. EP.12.44
Yan, S. EP.07.45
Yan, W. EP.07.45, EP.08.30, P2.08 .43
Yan, W. EP.12.55
Yan, X. EP13.49
Yan, X. EP.08.38, EP.18.03, MA04.04, P1.07.38
Yan, Y.-J. MA05.02
Yanagawa, J. EP.07.14
Yanagawa, N. EP.06.19
Yanagisawa, A. P3.16.12
Yanagitani, N. EP.08.42, EP.13.11, MA02.02, MA08.03, P3.12.54, PL02.06
Yang, A. OA15.03
Yang, A.-X. P3.01.37
Yang, B. P3.18.39
Yang, C.-T. MA03.03, P3.12.46
Yang, C. P3.03.51
Yang, C.-F.J. P1.04.12, P3.18.84
Yang, C.-F. MA05.03, P3.01.18
Yang, C.-H. P3.18.74
Yang, C.-J. P3.12.27
Yang, C.-Y. EP.12.21
Yang, C. OA03.03
Yang, D. EP.03.05, OA11.02, P2.02.09, P2.02.13, P2.15 .33
YANG, D. P3.12.74
Yang, D. EP.12.28
Yang, E. P3.13.21
Yang, F. EP.18.03, MA04.08, OA16.04, P2.08 .41, P2.08 .43, P2.08 .50
Yang, F. MA10.03
Yang, F. P2.02.39
Yang, F. P3.12.25
Yang, F. P2.02.07
Yang, G. P2.10.14
Yang, H. P3.09.07
Yang, H. OA06.02
Yang, H. P3.14.07
Yang, H. MA02.03
Yang, h. EP.18.10
Yang, H. P2.06.30
Yang, H. P3.01.01
Yang, H. P1.11.65
Yang, H. EP.12.08
Yang, H. P1.11.44
Yang, I. A. P2.06.51
Yang, J. C. MA03.03, MA08.02, P3.12.65, PL02.06
Yang, J.-H. EP.03.04, MA07.07, MA08.01, P3.12.27, P3.18.80, PT1.03.06, PT2.12.04
Yang, J. P3.03.18
Yang, J.-J. P1.07.55, P1.11.05, P1.11.23, P1.11.61, P2.06.91, P3.12.26, P3.12.55, PT1.03.02
Yang, J. T. OA07.02
Yang, K. P3.13.21
Yang, L. EP.13.36, PT2.13.01
Yang, L. P2.05.14
Yang, L. P3.12.64
Yang, L. MA10.03
yang, L. EP.13.09
Yang, L. OA14.05
Yang, L. OA06.01
Yang, M. P1.11.31
Yang, M. P3.03.27
Yang, M. Z. P2.15 .31
Yang, M. OA11.04, P3.12.48
Yang, n. EP.18.10, MA02.03, P3.12.64
Yang, P. MA05.02
Yang, P.-C. MA09.01
Yang, P. P1.11.78
Yang, P. EP.13.10, P1.04.29
Yang, R. EP.07.05
Yang, R. EP.12.19
Yang, R. OA06.01, OA06.02, PL02.12
Yang, S. P1.17.38
Yang, S. P3.12.07, P3.12.31
Yang, S. MA05.07
Yang, S. EP.07.41, P3.18.79
Yang, S. P2.02.21, P3.09.10
Yang, S. P3.03.01
Yang, S.-R. OA11.02, OA12.01, OA14.05
Yang, T.-Y. MA08.01, P3.12.41, P3.12.65
Yang, W. PT2.12.01
Yang, W. P2.02.29, P2.06.80
Yang, W. MA08.06, P3.12.64
Yang, W. P2.06.72
Yang, X. P1.11.51
Yang, X. P3.18.69
Yang, X. EP.08.30
Yang, X. EP.07.45
Yang, X.-N. EP.08.31, P1.07.55, P2.06.77, P2.08 .35, P3.13.33, PT1.09.03
Yang, X. EP.08.10, P2.08 .09

Yang, Y. P3.13.09
Yang, Y. OA14.05
Yang, Y. EP.08.21
Yang, Y. EP.06.38
Yang, Y. MA03.08, OA04.02, P3.18.59
Yang, Y. EP.12.19
Yang, Y. MA03.08, P1.11.22, P2.02.12
Yang, Y. MA11.09
Yang, Y. P1.04.24
Yang, Y. EP.09.12
Yang, Y. P2.06.48
Yang, Y. P1.07.20
Yang, Y. MA04.08
Yang, Y. EP.01.15
Yang, Y. OA10.03, PT2.10.04
Yang, Z. P1.17.43, P3.03.25
Yang, Z. P2.06.30
Yang, Z. PT2.13.02
Yang, Z. MA08.02
Yang, Z. P2.02.42, P3.03.50, P3.12.31
Yankelevitz, D. OA15.01
Yankelevitz, D. F. EP.04.14, EP.06.13, P1.07.14, P1.07.19
Yankelevitz, D. EP.04.13
Yano, S. EP.06.25, EP.12.62, P1.11.06, P2.06.59, P3.03.02, P3.03.12
Yano, Y. EP.17.25
Yao, B. MA04.08, P1.11.82
Yao, F. MA04.03
Yao, J. P1.11.65
Yao, J. P1.11.65
Yao, L. EP.09.05, P1.04.49, P1.07.42, P1.07.56, P2.02.35, P2.06.60, PT1.07.04
Yao, M. EP.17.09
Yao, W. P1.11.13
Yao, W. MA02.07, P1.17.36, P3.12.07
Yao, Y.-H. P1.11.23
Yao, Y. EP.12.06, EP.12.20, P2.10.12, P3.12.55, P3.18.24, PT2.10.04
Yao, Z. EP.12.39
Yao, Z. PT2.13.02
Yaringaño, J. P3.14.02
Yasavoli-Shahari, H. OA12.04
Yaseen, A. P1.17.53, P2.06.09
Yaser, S. P1.17.39, P1.17.53, P2.06.09
Yashiro, M. P2.02.26
Yasin, A. P1.17.64
Yasuda, D. EP.06.28
Yasufuku, K. MA03.01
Yasui, H. P1.11.11
Yasukawa, T. EP.14.02
Yatabe, Y. EP.07.19, MA07.03, OA02.02, OA11.02, OA13.04, P1.04.52, P1.17.24, PL03.16
Yatomi, M. EP.14.02
Yau, E. EP.08.32, P1.11.80
Yawei Liu, Y. P2.05.04
Yazici, O. OA13.02, PT2.10.02
Yazigi, A. P1.17.21
Yden, M. EP.08.43
Ye, C. EP.11.14
Ye, F. P3.12.07, P3.12.64
Ye, H. P3.03.50
Ye, J.-D. EP.09.15
Ye, J. EP.01.15, EP.04.25, EP.07.55
Ye, K. EP.17.18, P1.17.40
Ye, L. P3.03.53
Ye, M. PT2.10.04
Ye, W. P3.01.39
Ye, X. P3.03.25
Ye, Z. EP.04.17
Ye, Z. P2.15 .04
Ye, Z. EP.15.05
Yea, S. P3.12.38
Yeates, E. P1.11.85
Yeboa, D. MA10.05
Yeh, C.-L. P3.03.21
Yeh, C.-Y. P2.10.04
Yeh, P.-W. MA05.02
Yeh, Y. P2.06.02
Yeo, N. P1.17.62
Yeramaneni, S. P1.17.22
Yeskov, I. EP.08.08
Yeskov, S. EP.08.08
Yeung, V. P3.13.13
Yewle, S. EP.08.14, EP.09.08
Yewle, S. B. P3.09.01
Yi, E. EP.02.05
Yi, J. P1.04.06
Yi, S. P3.12.07
Yi, T. P3.12.07, P3.12.64
Yi, X. P2.06.77
Yidagur Gangadharaiah Lokesh, K. EP.12.33
Yilmazel, B. EP.06.68
Yim, H. C. P2.06.63
Yin, B. EP.17.16, P1.17.37
Yin, C. P2.15 .17
Yin, H. EP.04.35
Yin, H. PT1.09.03
Yin, J. C. EP.06.56, P2.06.46
Yin, J. P3.09.10
Yin, J. EP.03.05, P2.02.09
Yin, K. P1.11.05
Yin, M. P2.02.19, P3.03.50
Yin, N. P3.09.04
Yin, W. MA05.09
Yin, X. P2.08 .55
Yin, X. P2.06.57
Yin, Y. P1.04.36
Yin, Z. EP.09.14
Ying, Y. P2.06.42
Yip, C. MA04.05
Yip, R. EP.04.13, EP.06.13, OA15.01, P1.07.14, P1.07.19
Yip, S. OA03.04
Yip, S. P1.11.59
Yılmaz, S. P3.18.01
Yılmaz, Ü. EP.04.33
Ynoe de Moraes, F. EP.17.38
Yoden, M. EP.02.11
Yoesaka, K. P3.03.30
Yoh, K. P2.06.59, P3.12.58, PT1.05.02, PT2.12.03
Yokomakura, N. EP.14.13, P1.07.13
Yokose, T. EP.07.07, P2.08 .33
Yokosuka, S. EP.13.18
Yokota, I. P2.06.33
Yokouchi, H. OA06.04
Yokoyama, K. EP.04.36
Yokoyama, T. P3.03.42, P3.12.33, P3.18.04
Yokoyama, T. P3.12.35
Yonar, D. EP.04.28, EP.04.33
Yonemori, Y. EP.14.02
Yong, S.-H. EP.06.32
Yong Shim, B. P2.06.102
Yoo, I. P2.06.01
Yoo, S.-S. EP.09.02
Yoo, S. S. P2.02.20, P2.06.38
Yoon, D. P1.07.15
Yoon, H. MA09.06
Yoon, H. P3.12.37
Yoon, H.-I. P2.08 .13
Yoon, S. EP.13.21
Yoon, S. P1.04.26, P3.12.37
Yoon, S. P1.17.26
Yoong, S. P1.17.20
Yoshichika, R. P2.06.16
Yoshida, H. P3.18.04

Yoshida, J. EP.06.28
Yoshida, M. P3.16.12
Yoshida, N. P3.12.35
Yoshida, T. P3.12.13, PL02.15
Yoshida, Y. EP.07.19, P3.01.44, P3.18.04
Yoshii, Y. EP.07.56
Yoshikawa, M. P1.07.49, P2.06.16
Yoshikawa, T. P1.11.47
Yoshimoto, J. EP.06.46
Yoshimura, A. P1.11.40
Yoshioka, H. EP.07.01
Yoshioka, T. P1.17.68
Yoshizawa, A. EP.06.33, MA07.03, PL03.16
Yotsukura, M. EP.07.01, EP.07.19, P3.01.44
You, G. P1.11.09
You, M. EP.12.43
You, P. EP.09.05
You, S. P1.04.23
Young, A. P1.17.24
Young, F. MA10.06
Young, L. P1.17.54
Young, L. C. P1.11.36
Young, T.-H. EP.07.16, OA07.04
Young, T. EP.07.14
Young, V. EP.06.61
Younis, O. P1.17.39, P1.17.53, P1.17.64, P2.06.09, P2.06.62, P2.10.09, P2.10.11
Younis, O. M. P2.05.05, P2.06.50, P3.03.31
Younus, J. P1.17.70
Yousef, S. P1.17.39
Yu, A. EP.04.21, P1.04.22
Yu, A. MA10.07, P1.11.85
Yu, A. P3.18.50
Yu, B. MA04.07, MA04.08
Yu, C. P3.18.76
Yu, C. P3.16.15
Yu, C.-J. MA09.01
Yu, C. MA04.08
Yu, F. EP.18.08
Yu, G. P2.02.02
Yu, G. OA05.01, P3.12.48, P3.12.64
Yu, H. P1.07.50, P3.18.10
Yu, H. EP.13.35
Yu, H. P1.11.80
Yu, H. OA05.01, P3.12.25, PT2.10.03
Yu, H. MA01.06, P1.11.64
Yu, H. A. MA08.02, P3.03.01
Yu, H. EP.12.41, EP.12.58, P3.12.53, P3.13.30, PT1.06.04
Yu, H. P3.12.07, P3.12.31
Yu, J. P1.11.31, P2.02.21, P2.06.86
Yu, J. P3.12.48, P3.12.64
Yu, J. P3.18.20, P3.18.50
Yu, J. P2.02.09
Yu, J. P1.11.34, P1.11.44, P2.06.101
Yu, J. OA11.04
Yu, K. P3.12.70
Yu, L. EP.11.15
Yu, L. OA09.01
yu, m. P3.12.47
Yu, M. MA03.07, MA10.01, P3.12.53, P3.13.25
Yu, N. EP.13.10
Yu, Q. P2.06.30
Yu, Q. MA02.07, OA10.04, P1.17.36, P3.12.69
Yu, S. EP.13.30, P2.08 .55
Yu, S. EP.13.23
Yu, W. MA04.07
Yu, W. PT2.12.02
Yu, X. EP.11.10
Yu, X. EP.07.29, EP.08.41
Yu, X. EP.13.23, EP.13.34, OA06.02, P1.11.65, P2.10.13, P3.18.39
Yu, Y. MA08.06, MA11.03, OA06.02, OA10.04, P3.12.38, P3.13.15, P3.13.34, PL02.09
Yu, Y. EP.14.22
Yu, Y. MA11.03, P2.10.13, P3.12.48, P3.12.64, P3.18.59
Yu, Y. EP.18.08
Yu, Z. P2.02.09
Yu, Z. EP.06.45
Yu, Z. EP.05.03, EP.07.29, EP.08.41
Yu, Z. P3.12.07, P3.12.48
Yuan, B. P1.11.51
Yuan, D. P3.12.57, P3.18.63
Yuan, J. PT2.14.04
Yuan, J.-M. MA05.06
Yuan, K. P2.06.04
Yuan, R. P1.04.18, P1.17.42
Yuan, Y. OA13.03
Yuan, Y. EP.12.23
Yuda, H. EP.11.08
Yue, D.-S. MA04.03
Yue, D. EP.04.17, MA04.08, PT1.07.03
Yue, S. EP.17.35
yun, C. EP.07.41
Yun, J. EP.14.11, P1.04.26, P1.07.10, P1.07.30, P1.07.32, P2.05.16, PT1.05.03
Yun, J. P3.13.25
Yun, J. P2.02.32
Yun, M. P2.10.10
Yun, S. EP.07.31
Yun, T. EP.07.31, P2.05.08, P2.08 .02
Yun, Z. OA12.04
Yusa, T. EP.14.02
Yusof, H. M. P3.14.05

Z

Zaara, S. P1.17.22
Zabaleta, J. P2.08 .28
Zabor, E. P1.11.77
Zadravec, K. P2.15 .17
Zaeimi, F. M. OA12.04
Zaemes, J. P3.13.13
Zahed, H. OA01.03, PT1.04.04
Zahra, C. J. P2.06.51
Zahurak, M. OA12.03
Zaidi, M. EP.04.15
Zaidi, N. P3.18.40
Zaini, J. EP.04.22
Zaki, K. P3.14.05
Zakkar, A. MA05.04
Zalcberg, J. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Zalcman, G. MA08.01, OA12.02, P2.06.15
Zalcman, G. P3.18.60, P3.18.65
Zambelli, V. P2.06.22, P2.06.40
Zammit, F. P3.18.66
Zamora-Chavez, G. MA03.01
Zanconati, F. EP.06.03
Zanella, S. PT2.14.02
Zanfardino, S. P1.04.16
Zang, A. OA05.01, P3.12.25
Zang, D. EP.11.04, EP.12.51, EP.13.07, EP.13.26, P1.07.57, P2.02.44, P3.03.35
Zang, X. EP.13.41
Zang, Z. EP.06.05
Zanghi', A. P2.06.97
Zang Zang, Z. P3.03.48
Zanitti, M. OA09.02
Zanivan, S. P3.14.08
Zannori, C. MA01.08, OA07.03, P2.08 .12, PT1.08.02
Zapata, S. EP.17.27
Zaporojan, V. P1.11.82
Zaragoza Bueno, M. P2.10.05
Zarroug, M. P3.14.05
Zawertailo, L. EP.01.24, EP.01.25
Zayed, A. P1.17.53, P2.06.09
Zayed, A. M. P1.17.39, P1.17.64

zayed, M. P1.17.39, P1.17.64
Zazas, E. EP.01.19
Zec, A. MA06.07, OA09.02, P1.04.51, P1.17.30, P1.17.44, P2.06.65
Zeck, J. P1.11.73
Zegarra Cárdemas, J. A. EP.06.37
Zemankova, A. P1.11.10
Zemer-Tov, E. P3.03.28
Zeng, A. P3.12.64
Zeng, D. EP.12.39
Zeng, J. EP.13.33, EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Zeng, J. P2.08 .34, P3.18.08
Zeng, l. EP.18.10, P3.12.22
Zeng, L. P1.11.05
Zeng, S. PT2.10.03
zeng, s. P3.12.47
Zeng, W. P2.02.16
Zeng, Y. P1.11.84
Zeng, Y. P3.03.19
Zenke, Y. P2.06.59, PT1.05.02, PT2.14.03
Zeps, N. EP.17.02, P1.17.18, P3.01.13, PT2.17.02
Zer, A. PT2.10.02
Zernova, J. S. EP.08.25
Zhai, J. EP.11.19
Zhai, K. P1.11.34
Zhai, S. P3.03.11
Zhai, X.-W. OA03.02
Zhai, X. MA01.05
Zhai, X. EP.07.45
Zhan, C. P2.02.03, P2.02.30
Zhan, L. P1.11.15
Zhan, L. EP.13.38
Zhan, L. J. P1.17.09
Zhan, L. P1.17.08
Zhan, P. EP.13.01, EP.13.06, EP.14.26, P1.11.41, P3.18.33
Zhan, Q. P1.17.69
Zhan, W. P1.07.56, P2.02.35, P2.06.29
Zhan, Z.-X. PL02.09
Zhang, A. L. P3.13.12
Zhang, B. EP.05.03
Zhang, B. P3.13.25
Zhang, B. P1.11.67
Zhang, B. P3.18.74
Zhang, b. EP.18.10
Zhang, B. EP.04.31, P2.02.36, P3.13.09, P3.13.11, PT1.01.03, PT2.13.03
Zhang, B. P2.06.24, P2.06.34
Zhang, B. EP.07.44, MA04.03
Zhang, B. P2.06.66
Zhang, C. EP.08.31, OA03.01, OA03.02, P2.08 .35
Zhang, C. P3.03.06
Zhang, C. P3.01.49
Zhang, C. EP.07.51
zhang, c. P1.17.69
Zhang, D. EP.06.59
Zhang, D. P3.12.07, P3.12.31
Zhang, D. P3.13.19
Zhang, F. P2.10.14
Zhang, F. P2.15 .22
Zhang, G. OA10.04
Zhang, G. P3.18.21
Zhang, G. P1.07.38
Zhang, G. MA10.03
Zhang, G. EP.07.05, P3.12.45
Zhang, H. MA10.01
Zhang, H. P1.07.53
Zhang, H. P1.17.61
Zhang, H. OA03.02, P1.07.38
Zhang, H. P3.13.19
Zhang, h. Q. P1.11.51
Zhang, H. EP.12.19, P1.17.36, P3.13.27
Zhang, H. MA11.10, P1.07.38, P3.12.07
Zhang, H. P3.03.18
Zhang, H. EP.17.16, P1.11.78, P1.17.37, P2.06.72, P3.03.29, P3.13.22, P3.18.52, P3.18.53
Zhang, J.-T. OA03.01, P2.06.77, P3.13.33
Zhang, J. EP.06.13, P1.07.14, P1.07.19
Zhang, J. P2.06.66
Zhang, J. P3.18.47
Zhang, J. EP.08.30, OA06.01, P3.12.74
Zhang, J. EP.12.03, P1.04.30
Zhang, J. EP.04.31, MA11.06, OA07.01, P1.11.55, P1.11.60, P1.11.70, PT1.03.04, PT2.13.03
Zhang, J. J. P2.02.36, PT1.01.03
Zhang, J. PT1.03.06
Zhang, J. EP.08.10, P2.06.83, P2.08 .09
Zhang, J. MA08.03, MA08.05, P1.04.29
Zhang, J. P3.18.39
Zhang, J. P2.06.30
Zhang, J. P2.06.26, P3.13.34
Zhang, J. P2.10.14
Zhang, J. P3.13.23
Zhang, J. EP.02.10, P2.02.39
Zhang, J. P2.10.14
Zhang, J. PL03.07, PT2.10.04
Zhang, J. P1.17.69
Zhang, J. P3.12.38, P3.18.49
Zhang, K. EP.08.38
Zhang, L. EP.14.20
Zhang, L. EP.07.44
Zhang, L. EP.12.08, PT2.10.04
Zhang, L. OA10.03, P1.17.36, P2.15 .28, P3.18.83, PL02.12, PL03.07, PT2.10.04
Zhang, L. P3.12.07, P3.12.31
Zhang, L. P1.11.28, P1.11.58
Zhang, L. P3.09.10
Zhang, L. P3.12.01
Zhang, L. EP.18.07
Zhang, L. P3.03.18
Zhang, M. P2.06.34
Zhang, M. PT1.01.01
Zhang, M. EP.12.08
Zhang, M. P1.07.44, P2.08 .39
Zhang, M. P3.12.45
Zhang, M. EP.15.17
Zhang, M. P1.11.51
Zhang, M. MA11.03, P2.10.12
Zhang, N. P3.18.08
Zhang, P.-L. P3.12.55
Zhang, P. MA04.07, MA04.08, MA08.06
Zhang, P. P3.13.27
Zhang, P. EP.18.07
Zhang, P. P2.06.101
Zhang, Q. P2.06.29
Zhang, Q. P3.18.08
Zhang, q. EP.06.40
Zhang, Q. EP.17.34
Zhang, Q. P2.08 .43, P3.03.26
Zhang, Q. EP.15.05
Zhang, Q. P2.06.83, PT1.06.05
Zhang, Q.-Y. P1.11.61
Zhang, Q. P3.13.22
Zhang, R. P2.08 .23
Zhang, R. P3.09.04
Zhang, S. MA05.09
Zhang, S. EP.17.16, P1.17.37
Zhang, S. PT2.13.02
Zhang, S. P3.18.43
Zhang, S. EP.06.30
Zhang, S. P3.18.37
Zhang, S. P3.03.06
Zhang, S. P1.11.02
Zhang, S. EP.04.06
Zhang, T. EP.12.03, P1.04.30, PL03.07
Zhang, T. EP.01.14

Zhang, T. EP.09.14
Zhang, T. PL03.07
Zhang, T. EP.06.75
Zhang, T. P3.12.48, P3.12.64
Zhang, T. OA14.05
Zhang, V. P2.10.12
Zhang, W. EP.06.36, EP.07.44, MA04.03, MA11.03, P3.12.55, PT2.11.03
Zhang, W. P3.01.39
Zhang, W. EP.04.17
Zhang, X. PT1.07.02
Zhang, X.-L. PT1.09.01
Zhang, X. MA02.02
Zhang, X. EP.06.30
Zhang, X. P3.12.48
Zhang, X. EP.17.18, P1.17.40, P3.12.45
Zhang, X. EP.06.56, P2.06.46
Zhang, X. P3.03.53
Zhang, X. PT1.06.04
Zhang, X. P3.12.01
Zhang, X. EP.07.15
Zhang, X. EP.06.67, EP.18.02, P3.18.45
Zhang, X.-H. P2.06.91
Zhang, X.-C. P1.11.05, P2.08 .35
zhang, x. P3.12.47
Zhang, X. P1.11.74, PT2.11.03
Zhang, X. P1.07.55
Zhang, Y. MA01.05, MA10.07, MA11.03, OA06.01, OA06.01, P2.06.101, P2.10.14, P3.12.04, P3.12.55
Zhang, Y.-P. OA03.04, P2.02.28, P2.02.33, P2.06.36, P2.08 .59
Zhang, Y. MA04.01, P2.06.05
Zhang, Y. OA16.03, P3.03.19, PT2.11.05
Zhang, Y. EP.07.44
Zhang, Y. EP.12.41, PT1.06.04
Zhang, Y. EP.14.20
Zhang, Y. P3.18.08
Zhang, Y. P3.18.09
Zhang, Y. P3.03.32
Zhang, Y. EP.08.38, OA10.01, P2.02.09
Zhang, Y. EP.18.10, P2.10.13, P3.12.22, P3.12.48, P3.12.57, P3.12.74
Zhang, Y. EP.01.01, PT2.13.02
Zhang, Y. P2.06.29
zhang, y. P2.15 .28
Zhang, Y. P3.13.27
Zhang, Y. P2.06.03
Zhang, Y. EP.14.20
Zhang, Z. P3.18.10
Zhang, Z. P2.08 .04, P2.08 .05
Zhang, Z. OA06.02
Zhang, Z. EP.04.31
Zhang, Z. PT1.03.02
Zhang, Z. MA01.06
Zhang, Z. EP.03.14, EP.06.56, EP.12.38, EP.13.35, MA08.06, OA06.02, P2.06.46, P3.12.48
Zhang, Z. EP.12.39
Zhang, Z. MA08.06, MA10.03, OA06.02, P1.11.76, PT2.10.03
Zhang, Z. EP.12.44
Zhang, Z. P3.13.34
Zhang, Z. P2.08 .50
Zhang, Z. EP.12.08
Zhang, Z.-F. P1.04.29
Zhang#, P. EP.08.36
Zhao, B. P3.18.10
Zhao, B. P3.18.28
Zhao, C. P2.06.101, P3.18.27, PT2.14.04
Zhao, C. P1.07.46
Zhao, C. P1.11.31, P2.06.86, P3.03.16
Zhao, C. P3.03.29
Zhao, D. EP.07.49
Zhao, D. P2.06.03
Zhao, D. EP.12.28
Zhao, D. P1.17.38
Zhao, F. P3.03.51
Zhao, G. MA04.08, P3.12.31, PT1.07.03
Zhao, H. EP.07.30, P1.07.09
Zhao, H. OA10.03
Zhao, H. P2.02.25
Zhao, H. OA16.04
Zhao, J. P2.05.02, P2.15 .32
Zhao, J. P1.07.38
Zhao, J. EP.06.67, EP.13.30, MA03.04, P2.15 .28, P3.13.19, P3.18.45
Zhao, J. MA11.09
Zhao, J. EP.12.06, EP.13.23, OA08.03, P1.17.36, P3.12.40, P3.12.41, P3.12.55, P3.18.62, PL02.09, PT1.07.03, PT2.10.03
Zhao, L. P3.18.10
Zhao, L. EP.18.08
Zhao, L. PL03.07
Zhao, M.-F. EP.12.06
Zhao, M. MA11.03, OA06.01, P2.10.13
Zhao, Q. P3.18.51
Zhao, R. EP.07.41
Zhao, R. EP.06.59
Zhao, S. EP.06.67
Zhao, S. P2.06.43
Zhao, S. P2.08 .47
Zhao, W. OA14.05
Zhao, W. PT2.13.02
Zhao, W.-H. PL02.09
Zhao, W. P3.12.07
Zhao, X. P3.18.09
Zhao, X. EP.12.38
Zhao, X. MA11.09
Zhao, X. P3.03.51
zhao, x. P1.17.69, PT1.06.04
Zhao, Y. OA06.02, P1.11.83, P1.17.36, P3.12.07, P3.12.31, P3.12.38, P3.12.48, P3.12.69
Zhao, Y. MA04.07
Zhao, Y. EP.08.04, P2.06.35
Zhao, Y. P1.17.69, P2.10.16
Zhao, Y. OA10.03
Zhao, Y. EP.12.58, P3.18.77
Zhao, Y. P3.18.62
Zhao, Z. P3.18.86
Zhao, Z. MA11.10
Zhao, Z. P2.02.35
Zheng, C. MA02.07
Zheng, D.-Y. P2.02.33
Zheng, D. P3.16.17
Zheng, D. P1.17.69, P2.10.16
zheng, g. EP.08.01
Zheng, H. MA02.04
Zheng, H. P3.13.22
Zheng, J. EP.18.09, P3.18.46, P3.18.48
Zheng, J. EP.15.05
Zheng, J. P2.02.38
Zheng, J. EP.11.14
Zheng, L. MA08.01, OA06.01
Zheng, L. P1.11.09
Zheng, M.-M. P1.11.05
Zheng, P. P3.18.39
Zheng, R. P3.12.31
Zheng, S. EP.04.17
Zheng, W. P3.18.86
Zheng, W. MA04.07, MA04.08, P1.11.35
Zheng, X. MA01.05
Zheng, X. P3.01.03
Zheng, X. P1.11.12
Zheng, X. EP.06.14
Zheng, Y. P2.02.09, P2.02.13
Zheng, Y. MA10.03
Zhi, X. P3.12.70
Zhi, X. EP.01.26
Zhong, D.-S. PL02.09

Zhong, D. P3.12.48, P3.13.34
Zhong, G. P3.03.11
Zhong, H. P3.03.32
Zhong, H. EP.07.44, EP.13.45, P1.11.74, P1.11.83, P3.12.73, PT2.10.03, PT2.11.03
Zhong, J. PL02.09, PT2.17.03
Zhong, J.-X. P3.13.24
Zhong, J. P1.11.08, P1.11.30
Zhong, Q. P3.01.12
Zhong, Q. EP.15.05
Zhong, R. MA05.07
Zhong, R. PT2.11.03
Zhong, S. K. P1.04.05
Zhong, S. P2.15 .19, P3.13.12
Zhong, W. EP.13.30, P3.12.73
Zhong, W. P1.07.33
Zhong, W.-Z. EP.07.02, EP.08.31, OA03.01, OA03.02, P1.04.21, P1.07.55, P1.11.05, P2.06.53, P2.06.77, P2.08 .35, P2.08 .43, P2.08 .44, P3.13.33, PT1.08.01, PT1.09.03
Zhong, w. EP.08.27, EP.18.03, P2.06.28, P2.06.83, P2.08 .27
Zhong, X. OA14.05
Zhou, A. P3.12.07, P3.12.31
Zhou, B. EP.08.44
Zhou, C.-C. EP.12.06, P3.18.58
Zhou, C. EP.18.06, MA02.02, OA06.02, OA10.04, P1.11.20, P1.11.35, P1.11.46, P1.11.65, P1.11.68, P1.11.83, P3.12.12, P3.12.69, P3.12.73, P3.14.23, P3.18.61, P3.18.62, P3.18.68, P3.18.78
Zhou, C. EP.12.58
Zhou, C.-Z. EP.12.06
Zhou, C. EP.12.48, EP.18.10, MA03.08, P1.11.22, P1.11.65, P2.02.12
Zhou, c. EP.18.10
Zhou, D. D. OA03.04
Zhou, F. EP.12.06, EP.18.06, OA10.04, P3.14.23, P3.18.78
Zhou, F. EP.02.10, P2.02.39
Zhou, G. EP.11.16
Zhou, H. EP.09.05, EP.11.24, P1.04.49, P1.07.42, P1.07.56, P2.02.35, P2.06.29, P2.06.60, P2.08 .45, PT1.07.04
Zhou, H. P2.15 .04
Zhou, H. P3.18.28
Zhou, H. EP.11.19
Zhou, H. EP.11.04, PT2.10.03
Zhou, H. EP.06.56, EP.12.38, EP.13.35, P2.06.46, P3.01.39
Zhou, J. EP.03.05, P1.04.48, P2.02.09, P2.02.13
Zhou, J. EP.12.55
Zhou, J. EP.11.14
Zhou, J. EP.11.14, P3.12.31, P3.12.48, P3.18.75
Zhou, J. P1.11.13, PL02.09
Zhou, J. EP.12.47
Zhou, K. EP.04.39, EP.06.72
Zhou, L. P3.18.47
zhou, l. P3.12.47
Zhou, M. EP.02.10, P2.02.34, P2.02.39, P2.02.46
Zhou, M. P1.11.65
Zhou, M. EP.11.15, MA03.04
Zhou, N. P3.13.34
Zhou, Q. P3.03.18
Zhou, Q. EP.08.31, EP.12.60, P1.07.55, P1.11.05, P1.11.61, P3.01.04, P3.01.37, P3.18.35, P3.18.58, PT1.06.02
Zhou, Q. h. EP.18.04
Zhou, R. OA06.01
Zhou, R. P3.12.07
Zhou, T. P2.08 .50
Zhou, W. PT2.13.02
Zhou, W. P2.02.25
Zhou, X. K. EP.12.27
Zhou, X. P3.03.11
Zhou, X. P2.02.16
Zhou, X. A. P2.02.02
Zhou, X. P3.14.21
Zhou, X. P2.02.29
Zhou, X. EP.18.08
Zhou, Y. MA02.06, OA08.02
Zhou, Y. EP.08.36
Zhou, Y. EP.18.08
Zhou, Y. P2.02.16
Zhou, Y. P1.11.84
Zhou, Y. P2.08 .04, P2.08 .05
Zhou, Y. P1.04.42
Zhou, Y. P3.12.01
Zhou, Z. P3.18.59
Zhou, Z. MA06.05, P1.17.23
Zhou, Z. EP.07.49
Zhou, Z. P1.17.63
Zhou, Z. P2.08 .09
Zhu, B. OA14.05
Zhu, B. P1.11.70, P2.02.36, P3.12.07, P3.12.31, P3.13.34, PT2.13.03
Zhu, C. P2.06.101, P3.13.20, PT1.06.04
Zhu, C. P2.02.25
Zhu, D.-X. PL02.09
Zhu, H. OA10.03, OA10.04
Zhu, H. OA09.01
Zhu, H. MA02.07
Zhu, H. P3.13.15
Zhu, J. EP.06.13, P1.07.14, P1.07.19
Zhu, J. P2.08 .04, P2.08 .05
Zhu, J. P2.06.48
Zhu, J. EP.06.67, OA05.01, P3.12.25, PT2.10.03
Zhu, K. P2.15 .15
Zhu, L. PT2.14.04
Zhu, L. EP.08.21
Zhu, L. P1.11.09
Zhu, L. P3.12.01
Zhu, O. P2.06.102
Zhu, Q. MA04.02
Zhu, Q. P3.18.08
Zhu, S. OA04.01
Zhu, S. P1.04.05
Zhu, S. P2.02.31
Zhu, W. P1.07.12, P3.01.50
Zhu, W. P2.08 .50
Zhu, W. P1.11.34
Zhu, X. PL03.07
Zhu, Y. P1.11.13
Zhu, Y. PT2.10.02
Zhu, Y. EP.04.19, P1.04.27
Zhu, Y. EP.12.31, OA10.03, OA10.04
Zhu, Y. MA05.09
Zhu, Y. P1.04.42, P2.05.09
Zhu, Y. P3.12.01
Zhu, Y. P3.12.57, P3.18.63
Zhu, Z. P2.15 .31
Zhu, Z.-Y. MA04.03
Zhuang, K.-M. P2.02.28, P2.06.36
Zhuang, K. P2.08 .59
Zhuang, W. MA08.06, OA05.01, P3.12.18, P3.12.69
Zhuang, X. P3.12.64
Zhuang, Z. P3.12.31
Zhulikov, Y. P3.13.29
Zhuo, M. EP.07.45, EP.08.30
Zia, A. OA12.04
Ziaks, T. P3.13.26
Ziel, K. A. EP.12.10
Zimmerman Savill, K. M. P2.06.45
Zinner, R. P1.17.65
Zins, M. EP.04.29, P1.04.39
Zinzala, H. P3.01.15, P3.01.17
Zirkin, s. EP.04.41
Zisis, C. P3.14.19
Zisman-Rozen, S. P3.03.28
Zito, E. P1.11.66, P1.17.30, P2.15 .34

Zitvogel, L.	EP.04.29, P1.04.39
Zius, K.	OA11.01
Zlatanova, T.	P1.17.29
Zocco, A.	P2.05.10
Zoernig, I.	MA04.06
Zollinger, B.	EP.03.01, EP.04.24
Zoratto, F.	EP.11.20, P1.11.24
Zosel, R.	P1.04.08
Zou, B.	P2.06.101
zou, b.	P3.12.47
Zou, C.	P1.11.31
Zou, J.	P1.11.13
Zou, L.-L.	PT1.09.01
Zou, Q.	P1.04.27
Zou, Q.	EP.14.14
Zou, Q.	EP.06.30
Zou, S.	P2.06.74
Zou, W.	P3.12.18
Zou, X.	P2.06.76
Zou, Y.	P2.06.43
Zoumplis, D.	EP.17.21
Zu, K.	EP.13.44
Zucali, P.	P3.14.06
Zucali, P. A.	OA12.02
Zugazagoitia, J.	P2.08 .48
Zugazagoitia, J.	EP.06.43, PT2.12.03
Zuil, M.	EP.04.14
Zukin, M.	EP.13.28
Zullo, L.	P1.07.43, P2.10.05, P3.14.15
Zuluaga León, J. A.	EP.06.60
Zulueta, J.	EP.04.13
Zuniga, N. M.	EP.13.32
Zuniga, R.	OA08.01, P3.18.71
Zurawski, B.	MA04.04
Zureigat, H.	P1.11.77
Zurera, C.	EP.06.78
Zurera, M.	EP.06.43, P2.08 .48
Zvirbule, Z.	MA10.06
Zwezerijnen, G.	P3.18.16
Zwicky Eide, I.	EP.12.26