Randomized phase III study of nivolumab after surgery and adjuvant chemotherapy in NSCLC (ECOG-ACRIN EA5142, ALCHEMIST).

Jamie E. Chaft, Zhuoxin Sun, Charles M. Rudin, Charles B. Simone II, Kurt R. Oettel, David E. Kozono, Ramaswamy Govindan, Jacob Sands, John V. Heymach, Luis E. Raez, Shakun M. Malik, Tom Stinchcombe, Sumithra J. Mandrekar, David E. Gerber, Jeffrey D. Bradley, Everett E. Vokes, David R. Gandara, Charles A. Staley, Suresh S. Ramalingam, Onkar Khullar; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute/Mass General Brigham and ECOG-ACRIN, Boston, MA; Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY; New York Proton Center and Memorial Sloan Kettering Cancer Center, New York City, NY; Gundersen Lutheran Hospital/Clinic, La Crosse, WI; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Alvin J Siteman Cancer Center at Washington University School of Medicine in St. Louis, St. Louis, MO; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Cancer Institute/Florida International University, Miami, FL; Clinical Investigations Branch, CTEP/DCTD, National Cancer Institute, National Institutes of Health, Rockville, MD; Duke Cancer Institute, Durham, NC; Alliance Statistics and Data Management Center, Mayo Clinic Rochester, Rochester, MN; Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Hospital of the University of Pennsylvania Radiation Oncology, Philadelphia, PA; Department of Medicine, The University of Chicago, Chicago, IL; University of California Davis Comprehensive Cancer Center, Sacramento, CA; Winship Cancer Institute, Emory University, Atlanta, GA

Background: The NCI's ALCHEMIST program has screened thousands of patients with resected lung adenocarcinoma for mutations in *EGFR* and *ALK*. EA5142 studied the efficacy of adjuvant nivolumab after standard of care adjuvant therapy in patients with resected lung adenocarcinoma without sensitizing *EGFR* and *ALK* alterations and squamous cell carcinoma. **Methods:** Patients enrolled in the ALCHEMIST screening trial (A151216) with resected NSCLC tumors at least 4 cm and/or lymph node positive (N1/2) (for lung adenocarcinoma, without sensitizing *EGFR* and *ALK* alterations), were centrally tested for tumor cell PD-L1 expression using the DAKO 28-8 clone. After completion of all planned adjuvant therapy (chemotherapy and/or post-operative radiation) patients were randomized 1:1 to adjuvant nivolumab 480 mg IV every 4 weeks for up to 1 year or best supportive care. Patients were stratified by tumor histology, stage (AJCC 7^{th} edition IB/IIA vs IIB/IIIA), prior adjuvant treatment, and PD-L1 status ($<$1% vs $\geq$1%). The primary study endpoints were disease free survival (DFS) in all patients and in patients with high tumor PD-L1 expression ($\geq$50%). Overall survival was powered to be tested hierarchically, if DFS was positive. **Results:** Between July 2016 and October 2019, 935 patients were randomized across 378 sites. The treatment arms were balanced for age (median 66 years), sex (52% male), smoking status (10% never smoked), histology (29% squamous), stage and PD-L1 expression (29% PD-L1 high). With a median follow-up of 72.6 months, nivolumab did not improve DFS in the intention to treat population (median DFS 71.3 months vs. 68.8 months in observation arm), hazard ratio (HR) 0.97 (95% CI 0.81-1.17, p=0.78) or the PD-L1 $\geq$50% subset (median DFS 89.8 months vs. 78.5 months in observation arm), HR 0.86 (95% CI 0.59-1.25, p=0.43). In multivariate analysis, adjusting for age, gender, and smoking history, the DFS HR was 0.99 (95% CI 0.82-1.19, p=0.89) in all randomized patients and 0.82 (95% CI 0.56-1.2, p=0.31) in the PD-L1 $\geq$50% subset. As the primary recurrence endpoint included any lung cancer, including new primaries, a sensitivity analysis was performed excluding new primary lung cancers, DFS HR 0.97 (95% CI 0.80-1.18, p=0.76) in all patients and HR 0.88 (95% CI 0.60-1.30, p=0.52 in the $\geq$50% subset. The median duration of treatment with adjuvant nivolumab was 9.4 months (range 0-12.7 months). The most common reasons for nivolumab discontinuation were adverse event (29%), patient withdrawal (11%), and disease progression while on treatment (10%). Treatment related grade 3-5 toxicities were reported in 25% of patients: Grade 3: 23%, Grade 4: 2%, Grade 5: $<$1%. **Conclusions:** In patients with resected NSCLC ($\geq$4cm or LN+, *EGFR/ALK*-) adjuvant nivolumab did not improve DFS, irrespective of tumor PD-L1 expression. Clinical trial information: NCT02595944. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, U10CA180821, U10CA180888, U10CA180868, UG1CA189863, UG1CA189956, UG1CA189971, UG1CA233180, UG1CA233247, UG1CA233253, UG1CA233290, UG1CA233329, UG1CA233337; National Cancer Institute; UG1CA189830, UG1CA189858, UG1CA189821, UG1CA233302, UG1CA233327, UG1CA233340 and P30CA008748.

8001 Oral Abstract Session

Adjuvant erlotinib versus observation after complete resection of *EGFR*-mutant NSCLC: Final overall survival results of Alliance A081105.

Ramaswamy Govindan, Sumithra J. Mandrekar, David E. Kozono, Jamie E. Chaft, David E. Gerber, Jacob Sands, Sharmila Giri, Gregory A. Masters, Joel W. Neal, Michael Constantine, Lyudmila Bazhenova, Angelina D. Tan, Jeffrey D. Bradley, David R. Gandara, Karen Kelly, Suresh S. Ramalingam, Geoff Oxnard, Shakun M. Malik, Everett E. Vokes, Tom Stinchcombe; Alvin J Siteman Cancer Center at Washington University School of Medicine in St. Louis, St. Louis, MO; Alliance Statistics and Data Management Center, Mayo Clinic Rochester, Rochester, MN; Alliance Protocol Operations Office, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Alliance Statistical and Data Management Center, Mayo Clinic Rochester, Rochester, MN; Helen F. Graham Cancer Center and Research Institute, Newark, DE; Stanford Cancer Institute, Stanford, CA; Dana-Farber Cancer Institute, Milford, MA; UC San Diego Moores Cancer Center, San Diego, CA; Hospital of the University of Pennsylvania Radiation Oncology, Philadelphia, PA; University of California Davis Comprehensive Cancer Center, Sacramento, CA; International Association for the Study of Lung Cancer, Denver, CO; Emory University, Winship Cancer Institute, Atlanta, GA; BlossomHill Therapeutics, Inc., San Diego, CA; Clinical Investigations Branch, CTEP/DCTD, National Cancer Institute, National Institutes of Health, Rockville, MD; Department of Medicine, The University of Chicago, Chicago, IL; Duke Cancer Institute, Durham, NC

Background: The ALCHEMIST clinical trial platform, launched by the National Clinical Trials Network (NCTN) in 2014, screened patients with resected non-small cell lung cancer (NSCLC) for molecular markers and tailored post-operative adjuvant therapy trials. A081105 evaluated whether adjuvant erlotinib improved overall survival (OS) following complete resection in patients with early stage *EGFR* mutated lung adenocarcinoma. **Methods:** A081105 was a randomized phase III trial enrolling patients with completely resected stage IB (≥4 cm), II, or IIIA non-squamous NSCLC (per the 7th TNM staging classification) harboring *EGFR* exon 19 deletion or L858R mutations. Patients were randomized 1:1 to erlotinib 150 mg daily for up to 2 years or placebo/observation, stratified by stage, prior chemotherapy, *EGFR* mutation subtype, and ECOG performance status. The primary endpoint was OS in the per-protocol (PP) population with centrally confirmed *EGFR* mutations, designed to detect a hazard ratio (HR) of 0.67 in favor of erlotinib with a power of 86% and one sided type I error rate of 5%. Secondary endpoints included OS and disease free survival (DFS) in a modified intent-to-treat (mITT) population with local or centrally confirmed EGFR mutations, and safety. A prespecified backstop analysis was conducted after a minimum of 5 years of follow-up on all patients. **Results:** Trial enrollment was discontinued when 390 of the intended 450 patients had been enrolled due to the proven benefit of adjuvant osimertinib. Among 390 enrolled patients, the arms were balanced for age (median: 67.0 years), sex (70% female), race (70% white), stage (II: 51%, IIIA: 37%), prior chemotherapy (82%), ECOG PS 0 (60%), and exon 19 deletion (57%). Adjuvant erlotinib did not significantly improve OS compared with placebo/observation in the overall PP population (364 patients, 108 events, HR 0.89; 95% CI, 0.59–1.34; 1-sided P = 0.29) or within exon 19 deletion (HR: 0.94) or L858R mutation (HR: 0.82) subgroups. Five-year OS rates were 78.6% versus 77.9%, respectively. Results were consistent in the mITT analysis (379 patients, 113 events, HR 0.86; 95% CI, 0.58–1.28). Erlotinib improved DFS (mITT: 181 events, median: 68 vs 50 months, HR 0.74; 95% CI, 0.55–1.01). Across both arms, 11% of patients started non-protocol treatment (Osimertinib: 9%) prior to disease progression, and 9% withdrew consent for all follow-up prior to recurrence. In the erlotinib arm, 3 deaths on study were reported; grade 3 or higher adverse events were reported on 39% of patients. Median duration of treatment on Erlotinib arm was 16 months; only 37% of patients completed the planned treatment. **Conclusions:** In resected *EGFR*-mutant NSCLC, adjuvant erlotinib did not improve overall survival but improved DFS. Additional studies are exploring efficacy in selected subsets of patients using genomics and proteomic analyses. Clinical trial information: NCT02193282. Research Sponsor: NCI, USA; U10CA180821, U10CA180882.

Neoadjuvant lorlatinib in stage III NSCLC harboring ALK fusion: A phase 2 multi-center study (LORIN).

Chao Zhang, Yan Hu, Ben-Yuan Jiang, Lixu Yan, Si-Ying Ren, Jing-Hua Chen, Qing Zhou, Dan-Qing Li, Wenliang Liu, Yi-Long Wu, Wen-Zhao Zhong, Meng-Min Wang, Ze-Li Li; Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China; The Second Xiangya Hospital of Central South University, Changsha, China; Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Department of Pathology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; Guangzhou Twelfth People's Hospital, Guangzhou, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Peking Union Medical College Hospital, Beijin, China; The Second Xiangya Hospital, Central South University, Changsha, China; Lung Cancer Research Institute Department of Pulmonary Medicine II, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital, Guangzhou, China; Guangdong Provincial People's Hospital, Guangzhou, China

Background: While adjuvant alectinib has established itself as the new standard for resected anaplastic lymphoma kinase (ALK) fusion non-small cell lung cancer (NSCLC), there is limited data on neoadjuvant treatment for locally advanced ALK fusion NSCLC. Given the groundbreaking efficacy of lorlatinib in advanced NSCLC, it is worth exploring its clinical feasibility as neoadjuvant treatment for stage III ALK+ NSCLC. **Methods:** This study is an open-label, phase 2 multi-center prospective trial (ClinicalTrials.gov NCT05740943) utilizing a Simon two-stage design. Patients diagnosed with potentially resectable or unresectable stage III ALK+ NSCLC were enrolled, with up to 3 cycles of lorlatinib administered, followed by optional local treatment and consolidation lorlatinib for up to 2 years. The primary endpoint was the pathological complete response (pCR) ($H0 \leq 20\%$, $H1 \geq 40\%$, $\alpha=0.05$, $\beta=0.2$, at least 12 pCR events for 43 patients enrolled), while secondary endpoints included major pathological response (MPR), event-free survival (EFS), overall survival (OS), and safety profile. Xenium as well as spatial proteomics was performing on paired samples collected before and after lorlatinib. **Results:** As of January 1, 2026, 43 patients with stage III ALK-fusion NSCLC (19 evaluated as potentially resectable and 24 as unresectable) were consecutively enrolled and received 3 cycles neoadjuvant lorlatinib, with 32 completing surgery (including neck dissection and/or contralateral lymph node dissection), 9 continuing TKI therapy, and 2 undergoing radiotherapy. The most common treatment-related adverse events (TRAEs) included hypertriglyceridemia, hypercholesterolemia, and edema. The confirmed objective response rate (ORR) was 83.7% (36/43), without progressive disease (PD). Among patients who underwent surgery, the R0 resection rate was 96.9% (31/32) and 3 patients experiencing conversion to thoracotomy. pCR and MPR rates were 46.9% (15/32) and 81.3% (26/32), respectively, reaching the primary endpoint. Pathological nodal downstaging was seen in 90.6% (29/32) patients. For those with initially unresectable stage III disease, 75.0% (18/24) achieved conversion surgery through multidisciplinary evaluation after neoadjuvant lorlatinib, while others continued TKI or underwent radiotherapy. With a median follow-up of 13 months, the 1-year EFS rate was 97.1% (95% CI, 91.5-100) and no OS events were observed. Only 3 patients experienced local relapse (regional lymph nodes and/or intrapulmonary metastasis) without distant metastasis; all had initially presented with N3 disease and did not receive adjuvant lorlatinib after surgery. **Conclusions:** Neoadjuvant lorlatinib unveiled overwhelming pathological response and could lead to high conversion surgery for unresectable stage III disease. Further large-scale prospective trial was warranted to testified such treatment modality. Clinical trial information: NCT05740943. Research Sponsor: National Science Foundation of China; National Science Foundation of China.

8003 Oral Abstract Session

Pollution and progression: Air quality and stage of lung cancer diagnosis across the U.S.

Raheem Bell, Peter Graffy, Sanjhai Ramdeen, Mark Siringan, Daniel Horton, William F. Parker, Bryan E. Palis, Ikenna Okereke, David D. Odell; Northwestern University Feinberg School of Medicine, Department of Surgery, Chicago, IL; University of Chicago, Chicago, IL; University of Michigan, Ann Arbor, MI; Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Medicine, Division of Pulmonary / Critical Care Medicine, University of Chicago, Chicago, IL; American College of Surgeons, Chicago, IL; Department of Surgery, Henry Ford Health System, Detroit, MI; University of Michigan School of Medicine, Ann Arbor, MI

Background: Air pollution contributes to increased lung cancer incidence, but whether it accelerates tumor progression, resulting in more advanced stage at diagnosis, is not well understood. Understanding environmental and social factors influencing late-stage presentation can guide targeted prevention efforts. **Methods:** We identified primary lung cancer cases from the National Cancer Database (NCDB; 2010–2023) across 2,803 U.S. counties. Individual-level data were linked to county-level annual averages of $PM_{2.5}$ ($\mu g/m^3$) and NO_2 (ppb). Generalized estimating equation logistic models with county-level clustering assessed associations between chronic pollution exposure and odds of advanced-stage (III–IV vs. I–II) diagnosis, adjusting for median household income and educational attainment. Pollutants were z-score standardized (mean = 0, SD = 1) and summed to create a combined Pollution Burden metric. Effect modification by histology and socioeconomic status was tested. **Results:** Among 1,023,140 patients (mean age 68.5 ± 10.8 years; 51.3% female), 67.1% presented with advanced-stage disease. Each standard deviation increase in $PM_{2.5}$ was associated with 4.8% higher odds of advanced-stage diagnosis (95% CI: 3.5–6.1%; $p < 0.001$; Table 1). In multi-pollutant models, $PM_{2.5}$ remained significant (OR = 1.062, 95% CI: 1.047–1.076; $p < 0.001$), with combined pollution burden linked to a 3.1% increase in odds (95% CI: 1.5–4.7%; $p < 0.001$). Low-SES communities had higher advanced-stage rates regardless of pollution exposure (69.7% vs. 63.6%; $p < 0.001$), equating to approximately 6,100 excess annual diagnoses. Effects varied by histology, with small cell carcinoma showing the highest advanced-stage rate (91.2%), followed by adenocarcinoma (67.3%) and squamous cell carcinoma (58.6%). **Conclusions:** Higher $PM_{2.5}$ exposure and lower socioeconomic status were independently associated with later-stage lung cancer diagnosis across over 1 million cases from 2,803 U.S. counties. Low-SES communities showed 6 percentage points higher advanced-stage rates irrespective of pollution levels. These findings highlight how environmental factors that may accelerate cancer progression and social barriers to accessing care can jointly delay early-stage diagnosis. Targeted pollution control and expanded lung cancer screening in underserved communities could reduce the burden of advanced-stage disease. Research Sponsor: None.

Odds of advanced-stage lung cancer by air pollutant exposure.

Pollutant	Model	Mean ± SD	OR	95% CI Lower	95% CI Upper	P-value
$PM_{2.5}$ ($\mu g/m^3$)	Single-pollutant	8.17 ± 1.58	1.048	1.035	1.061	<0.001
$PM_{2.5}$ ($\mu g/m^3$)	Multi-pollutant		1.062	1.047	1.076	<0.001
NO_2 (ppb)	Single-pollutant	6.93 ± 3.93	1.009	0.993	1.026	0.28
NO_2 (ppb)	Multi-pollutant		0.978	0.963	0.994	0.007
Combined Burden	Z_PM2.5 + Z_NO2		1.031	1.015	1.047	<0.001

8004 Oral Abstract Session

Redefining lung cancer screening eligibility: Smoking duration vs. pack-years in a national VA cohort of nearly 1 million patients.

Brendan Heiden, Daniel B. Eaton Jr., Varun Puri, Whitney S. Brandt, Theodore Seth Thomas, Martin W. Schoen, Haley Tupper, Matthew Paul Smeltzer, Drew Moghanaki, Lawrence Benjamin; Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO; Veterans Affairs, St. Louis Healthcare System, St. Louis, MO; Washington University, St. Louis, MO; Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; Division of Hematology and Medical Oncology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO; Department of Surgery, University of California, Los Angeles, Los Angeles, CA; University of Memphis, School of Public Health, Memphis, TN; UCLA, Los Angeles, CA; Department of Pulmonology, University of California Los Angeles, Los Angeles, CA

Background: Lung cancer is the leading cause of cancer death in the US, yet current lung cancer screening (LCS) criteria based on tobacco pack-years (TPY) miss nearly half of all cases and are difficult to capture reliably in clinical practice. Tobacco smoking duration (TSD) is a simpler, more consistently measurable metric that may better identify high-risk individuals. We evaluated whether TSD improves lung cancer risk prediction compared with TPY in a unique real-world cohort of nearly 1 million patients. **Methods:** We conducted a retrospective cohort study of Veterans aged 50–80 in the Veterans Health Administration. The primary exposure was smoking history quantified as TPY and TSD; the primary outcome was 5-year lung cancer incidence (2021-2025). We compared risk-adjusted 5-year lung cancer incidence based on 2013 USPSTF guidelines (≥30 TPY, quit within 15 years), revised 2021 USPSTF guidelines (≥20 TPY, quit within 15 years), our proposed TSD criteria (≥20 TSD), and never-smoking. We further estimated the impact of switching to TSD-based eligibility on the theoretical number of missed lung cancer diagnoses (i.e., the proportion of lung cancers diagnosed in screening-ineligible individuals) and performed subgroup analyses across race and sex. **Results:** A total of 960,770 Veterans were included in the study, with 340,312 (35.4%) currently smoking, 304,589 (31.7%) formerly smoking, and 315,869 (32.9%) never smoking. The median (SD) age was 64.9 (9.6) years old. Most participants were male (n=876,215, 91.2%) and of white race (n=677,823, 70.6%). 341,061 (35.5%) qualified for 2013 TPY criteria, 437,803 (45.6%) qualified for 2021 TPY criteria, and 571,087 (59.4%) qualified for TSD criteria. Importantly, 127,604 (22.3%) individuals who met TSD criteria did not meet 2021 TPY criteria, suggesting that TSD criteria would increase the eligible screening population by 28.8%. The 5-year incidence of lung cancer was 0.95% (1.87% among 2013 TPY criteria; 1.73% among 2021 TPY criteria; 1.48% among TSD criteria; and 0.13% among never-smoking). The proportion of missed lung cancer diagnoses was 30.3% among 2013 TPY criteria, 17.1% among 2021 TPY criteria, and 7.5% among TSD criteria. Finally, eligibility was higher for TSD vs. TPY criteria in various subgroups, including among black individuals (percent of current or former smokers eligible for screening: 34.7% 2013 TPY; 54.0% 2021 TPY; and 83.7% TSD) and females (38.5% 2013 TPY; 55.1% 2021 TPY; and 83.7% TSD). **Conclusions:** In this nationwide VA cohort consisting of nearly 1 million Veterans, smoking duration performed at least as well as TPY in predicting lung cancer risk and substantially expanded screening eligibility with fewer missed cancers. TSD criteria were also associated with improved equity. These findings support revisiting national lung cancer screening guidelines to prioritize smoking duration over pack-years. Research Sponsor: None.

LBA8005 **Oral Abstract Session**

Concurrent thoracic radiotherapy (TRT), platinum/etoposide chemotherapy, and durvalumab immunotherapy in extensive-stage (ES) small cell lung cancer (SCLC): A phase III trial.

Bjorn Henning Gronberg, Daphne W. Dumoulin, Kersti Oselin, Luigi De Petris, Kirill Neumann, Tesfaye Madebo, Marianne Aanerud, Tarje Onsøien Halvorsen, Johan Isaksson, Maria Moksnes Bjaanæs, Daniel Heinrich, Odd Terje Brustugun, Atle Totland, Siv Gyda Aanes, Øyvind Yksnøy, Andreas Hallqvist, Orvar Gunnarsson, Terje Skraastad, Emelie Gezelius, Kristin Toftaker Killingberg; Department of Oncology, St. Olavs hospital, Trondheim, Norway; Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Department of Chemotherapy, North Estonia Medical Centre, Tallinn, Estonia; Thoracic Oncology Center, Karolinska University Hospital, Stockholm, Sweden; Department of Pulmonology, Akershus University Hospital, Lørenskog, Norway; Department of Pulmonology, Stavanger University Hospital, Stavanger, Norway; Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology and Department of Oncology, St. Olavs Hospital, Trondheim, Norway; Center for Research and Development, Uppsala University/ Region Gävleborg, Gavle, Sweden; Department of Oncology, Oslo University Hospital, Oslo, Norway; Department of Medical and Radiation Oncology and Centre for Palliative Care, Innlandet Hospital Trust, Gjøvik, Norway; Section of Oncology, Drammen Hospital, Vestre Viken HF, Drammen, Norway; Department of Pulmonology, Haugesund hospital, Haugesund, Norway; Department of Oncology and Palliative Medicine, Nordland Hospital Trust, Bodø, Norway; Department of Pulmonology, Ålesund Hospital, Ålesund, Norway; Department of Oncology, Institute of Clinical Sciences, Sahlgrenska University Hospital, Göteborg, Sweden; Department of Oncology, Landspitali, Reykjavík, Iceland; Department of Pulmonology, Hospital of Southern Norway, Kristiansand, Norway; Department of Respiratory Medicine, Skåne University Hospital, Lund, Sweden

Intracranial efficacy of tarlatamab versus chemotherapy (CTx) as second-line (2L) treatment for small cell lung cancer (SCLC): DeLLphi-304 phase 3 post hoc analysis.

Giannis S. Mountzios, Byoung Chul Cho, Phil Lammers, Longhua Sun, Surein Arulananda, Fiona Helen Blackhall, Tatsuya Yoshida, Myung-Ju Ahn, Salman Rafi Punekar, Bo Zhu, Tudor-Eliade Ciuleanu, Julien Mazieres, Antonio Lugini, Pedro Rocha, Ippokratis Korantzis, Martin Schuler, Wei Shi, Ali Hamidi, Diana Gauto, Charles M. Rudin; Fourth Department of Medical Oncology and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Baptist Cancer Center, Department of Medical Oncology, Memphis, TN; The First Affiliated Hospital of Nanchang University, Department of Pulmonary and Critical Care Medicine, Nanchang, China; Monash Health, Clayton, VIC, Australia; The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; NYU Langone Health, New York, NY; The Second Affiliated Hospital of Army Medical University, PLA, Chongqing, China; Prof. Dr. Ion Chiricuta and Universitatea de Medicina si Farmacie Iuliu Hatieganu, Cluj-Napoca, Romania; CHU de Toulouse, Université Paul Sabatier, Toulouse, France; Medical Oncology, Azienda Ospedaliera San Giovanni Addolorata, Rome, Italy; Vall d'Hebron University Hospital, Thoracic Tumors Unit, Barcelona, Spain; Saint Loukas Hospital, Department of Medical Oncology, Thessaloniki, Greece; Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany, National Center for Tumor Diseases (NCT), NCT West, Essen, Germany; Amgen Inc., Thousand Oaks, CA; Fiona and Stanley Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Brain metastases (BM) are common in patients (pts) with SCLC and are associated with poor outcomes. Tarlatamab, a bispecific T-cell engager (BiTE) immunotherapy, demonstrated superior overall survival versus CTx in pts with SCLC following progression on or after platinum-based CTx in the DeLLphi-304 study, including pts with history of BM (prior or current) at baseline (OS HR 0.45 [95% CI: 0.31–0.65]). Here we compare the intracranial efficacy of tarlatamab vs CTx. **Methods:** Pts were randomized 1:1 to receive tarlatamab or CTx (topotecan, lurbinectedin or amrubicin) as 2L treatment for SCLC. Pts with stable asymptomatic brain metastases were eligible; prior CNS treatment was required until protocol amendment 3. Baseline brain imaging by contrast enhanced MRI was mandatory for all pts at screening and repeated at all subsequent imaging assessments for pts with a history of BM at baseline. A post hoc analysis on intracranial efficacy was performed by BICR per mRANO-BM. Given that most pts had prior CNS treatment, specified outcomes were CR, non-CR/non-PD, and PD. **Results:** BM at baseline were present in 98/254 pts (39%) in the tarlatamab arm and 99/255 (39%) in the CTx arm, of whom 75/98 (77%) and 69/99 (70%) had prior CNS treatment, respectively. A CNS full analysis set (FAS) was specified to include pts who had both a baseline scan and ≥ 1 postbaseline scan (tarlatamab-67; CTx-56 pts). In pts in FAS, treatment with tarlatamab resulted in longer CNS PFS than CTx (median: 6.5 mos vs 4.2 mos; HR, 0.40 [95% CI: 0.24–0.66]; Table). CNS tumor shrinkage of ≥30% was observed in 56% of pts with tarlatamab vs 38% with CTx. CNS complete response was observed in 15% of pts with tarlatamab vs 5% with CTx, with longer CNS duration of complete response (DOCR) (not estimable [NE] vs 3.6 mo) and longer CNS duration of disease control (DODC) (8.2 vs 5.2 mo) for pts in the tarlatamab arm. Pts with BM at baseline had longer OS with tarlatamab vs CTx (median OS: 13.9 vs 6.8 mos; HR, 0.51 [95% CI: 0.34–0.74]). In pts with BM at baseline, treatment-emergent adverse events (TEAEs) of any grade (gr)/gr 3/gr 4/gr 5 occurred in 99%/38%/9%/7% for tarlatamab vs 100%/38%/40%/10% for CTx. In pts treated with tarlatamab, the incidence of CRS and ICANS was 54% and 9% in pts with BM at baseline vs 58% and 4% in pts without BM at baseline, respectively. **Conclusions:** Tarlatamab demonstrated increased intracranial efficacy with longer CNS PFS and OS vs CTx in pts with stable, treated and untreated asymptomatic BM. These results affirm tarlatamab as the 2L standard of care for SCLC, even in pts with BM. Clinical trial information: NCT05740566. Research Sponsor: Amgen Inc.

	Tarlatamab n = 67	CTx n = 56
CNS PFS, mos (95% CI)	6.5 (4.3, 13.7)	4.2 (2.9, 5.5)
CNS Complete Response, n (%)	10 (15%)	3 (5%)
CNS DOCR, mos (95% CI)	NE (2.9, NE)	3.6 (3.1, NE)
CNS DODC, mos (95% CI)	8.2 (6.3, NE)	5.2 (4.2, 6.2)
CNS tumor shrinkage of ≥30%, % (n/N)[a]	56% (9/16)	38% (5/13)

[a]Assessed in pts with ≥1 lesion that was ≥ 10 mm.

8007 Oral Abstract Session

Efficacy and safety of ivonescimab combined with liposomal irinotecan in patients with small-cell lung cancer (SCLC) progressing after first-line chemo-immunotherapy: A multicenter, phase 2 study.

Yun Fan, Kaiyan Chen, Hui Li, Zhiyu Huang, Jing Qin, Xinmin Yu, Ying Jin, Youzu Xu, Qiong He, Lan Shao, Zhiyong Shi, Sizhe Yu, Shichao Zhou, Yanjun Xu, Lei Gong, Jun Zhao, Cuiping Gu; Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, China; Zhejing Cancer Hospital, Hangzhou, China; Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China; Zhejiang Cancer Hospital, Hangzhou, China; Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou, China

Background: SCLC patients (pts) progressing after first-line platinum-based chemo-immunotherapy have limited effective treatment options and poor prognosis. This study evaluated the efficacy and safety of ivonescimab combined with liposomal irinotecan in this setting. **Methods:** This phase 2, multicenter, single-arm trial enrolled SCLC pts who progressed during or after platinum-based chemoimmunotherapy. Eligible pts were required to be ≥18 years of age and have an ECOG PS of 0 or 1. Pts received ivonescimab (20 mg/kg, IV, Q3W) plus liposomal irinotecan (56.5 mg/m^2, IV, Q2W) until disease progression or unacceptable toxicity. The primary endpoint was 6-month progression-free survival (PFS) rate (ClinicalTrials.gov: NCT06478043). **Results:** Between October 22, 2024 and August 27, 2025, 60 pts were included in the intention-to-treat population. Median age was 62.0 years (range: 38-75), 56 (93.3%) were male, and 53 (88.3%) had ECOG PS 1. At baseline, 35.0% and 26.7% of pts had liver and brain metastases, respectively. A total of 63.3% of pts had a chemotherapy-free interval of more than 90 days. As of December 15, 2025, with a median follow-up time of 7.3 months (95% CI: 6.0-9.0), the 6-month PFS rate was 72.0% (95% CI: 57.0-82.6). Median PFS was 9.8 months (95% CI: 6.7-13.4), and median OS was not reached. The confirmed objective response rate was 61.7% (95% CI: 48.2-73.9; all partial responses) and the disease control rate was 91.7% (95% CI: 81.6-97.2). In subgroup analysis, the median PFS was 11.9 months (95% CI: 7.3-NE) for patients with a CFI ≥90 days and 7.0 months (95% CI: 4.4-NE) for those with a CFI < 90 days. Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 16 pts (26.7%). The most common grade ≥3 TRAEs were decreased neutrophil count (8.3%), decreased white blood cell count (8.3%), fatigue (6.7%), and diarrhea (3.3%). TRAEs led to treatment interruption in 31.7% and chemotherapy dose reduction in 25.0% of pts. No patient discontinued all treatment drugs due to TRAEs; discontinuation of ivonescimab alone occurred in 6 pts (10%). Immune-related AEs occurred in 33.3 % of pts, with grade 3 events in 8.3%. No grade ≥4 irAEs or treatment-related deaths were reported. **Conclusions:** Ivonescimab combined with liposomal irinotecan demonstrated encouraging antitumor activity with a manageable safety profile as a second-line treatment for SCLC pts after platinum-based chemoimmunotherapy. These results support further investigation in randomized controlled trials. Clinical trial information: NCT06478043. Research Sponsor: None.

ABBV-706 as monotherapy and in combination with budigalimab in patients with relapsed/refractory (R/R) small cell lung cancer (SCLC).

Lauren Averett Byers, Byoung Chul Cho, Alissa Jamie Cooper, Anne C. Chiang, Ji-Youn Han, Daniel Morgensztern, Muhammad Furqan, Afshin Dowlati, Jair Bar, Joo-Hang Kim, Hiroshi Yokouchi, Luis G. Paz-Ares, Tammy Palenski, Guillermo Rivell, Darius Meiman, Ye Zhao, Wijith Munasinghe, Nadine Jahchan, Sreenivasa R. Chandana; The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Thoracic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Yale School of Medicine, Yale Cancer Center, New Haven, CT; National Cancer Center, Goyang, South Korea; Washington University School of Medicine, St. Louis, MO; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Sheba Medical Center, Ramat Gan, Israel; Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, South Korea; National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; Department of Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; AbbVie, Inc., North Chicago, IL; START Midwest, Grand Rapids, MI

Background: SCLC is an aggressive cancer with poor prognosis and limited treatment options. Seizure-related 6 homolog (SEZ6) is overexpressed in SCLC. ABBV-706 is a SEZ6-targeting antibody-drug conjugate with topoisomerase 1-inhibitor payload. Here we report updated data from a phase 1 study (NCT05599984) evaluating ABBV-706 in patients (pts) with R/R SCLC as monotherapy or in combination with budigalimab (Budi), an anti-PD-1 immune checkpoint inhibitor (CPI). **Methods:** The study enrolled pts ≥18 years old with R/R SCLC and Eastern Cooperative Oncology Group performance score ≤1. Pts received either ABBV-706 monotherapy every 3 weeks (Q3W), or in combination with 375 mg Budi Q3W. **Results:** As of Sept. 27, 2025, 124 pts received ABBV-706 monotherapy. Of these, 41 received the recommended phase 3 dose (1.8 mg/kg), with 17 receiving ABBV-706 as a second-line (2L) therapy. Overall, median age was 64 years, and most pts (65%) received at least 2L of prior treatment. The safety profile was comparable with previously reported data. Median follow-up (mFU) was 16.2 months, and median overall survival (mOS) overall (N=124) and among pts receiving 1.8 mg/kg as 2L (n=17) was 11.3 and 14.3 months, respectively. The 15-month OS estimates for the same cohorts were 40% and 50%, respectively. As of Sept. 27, 2025, 11 pts received ABBV-706 (1.8 mg/kg Q3W) + Budi as 2L treatment. Median age was 68 years. No new safety signals were detected as compared to monotherapy, and there were no reports of pneumonitis. Treatment-related adverse events (TRAEs) occurred in 91% of pts, most commonly gastrointestinal (64%) and hematological (64%). TRAEs grade ≥3 occurred in 46% of pts, with anemia (27%) and neutrophil count decreased (18%) being most common. TRAEs led to treatment discontinuation, interruption, or dose reduction in 0%, 64%, and 36% of pts, respectively. No treatment-related deaths were reported. mFU was 9.1 months. Detailed efficacy endpoints are shown in the Table. **Conclusions:** ABBV-706 monotherapy shows promising OS benefit in a heavily pretreated pt population with R/R SCLC and is combinable with a CPI. Clinical trial information: NCT05599984. Research Sponsor: AbbVie Inc.

Efficacy of ABBV-706 in R/R SCLC.

	Monotherapy Total (N=124)	Monotherapy 1.8 mg/kg (n=41)	Monotherapy 1.8 mg/kg as 2L (n=17)	ABBV-706 1.8 mg/kg + Budi (n=11)
Best overall response,[a,b] n (%)				
Complete response	3 (2)	3 (7)	2 (12)	0
Partial response[c]	64 (52)	20 (50)	12 (71)	6 (55)
Stable disease	46 (37)	16 (39)	2 (12)	3 (27)
Progressive disease	6 (5)	1 (2)	1 (6)	1 (9)
NE/not assessed	5 (4)	1 (2)	0	1 (9)
Objective response rate[a] (%)	52	56	82	55
Median duration of response, months	5.3[d]	5.9[e]	6.6[f]	6.7[g]
Median progression-free survival, months	5.4	6.4	6.8	8.1
mOS, months	11.3	12.4	14.3	NE
OS estimate at 15 months, %	40	44	50	NE

[a]Confirmed by investigator per RECIST v1.1.
[b]Percentages may exceed 100% due to rounding.
[c]Includes 2 pts with unconfirmed partial response and ongoing treatment.
[d]n=65.
[e]n=23.
[f]n=14.
[g]n=6.

Complex segmentectomy versus lobectomy in small-sized peripheral non–small cell lung cancer: A post-hoc supplemental analysis of a multicenter, open-label, phase 3 trial (JCOG0802/WJOG4607L).

Atsushi Kamigaichi, Takahiro Mimae, Ryu Nakajima, Masashi Wakabayashi, Noriko Mitome, Hisashi Saji, Masahiro Tsuboi, Hisao Asamura, Kazuo Nakagawa, Yasuhiro Tsutani, Yoshihisa Shimada, Masaya Yotsukura, Kenji Suzuki, Shun-ichi Watanabe, Haruhiko Fukuda, Keiju Aokage, Morihito Okada; Hiroshima University, Hiroshima, Japan; Osaka City General Hospital, Osaka, Japan; Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; St. Marianna University School of Medicine, Kawasaki, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Hakuhokai Tokyo Hikifune Hospital, Tokyo, Japan; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; Kindai University, Osaka, Japan; Tokyo Medical University, Tokyo, Japan; National Cancer Center Hospital, Tokyo, Japan; Juntendo University School of Medicine, Tokyo, Japan

Background: JCOG0802/WJOG4607L confirmed the superiority of segmentectomy on overall survival (OS) over lobectomy for small-sized peripheral non-small cell lung cancer (NSCLC). However, it remains unclear whether technically demanding complex segmentectomy offers therapeutic efficacy compared to lobectomy, similar to simple segmentectomy. This study therefore aimed to evaluate the oncological outcomes of complex and simple segmentectomy compared to those of lobectomy using final analysis data from JCOG0802/WJOG4607L. **Methods:** Simple segmentectomy was defined as resection of the bilateral superior division (S^6), left lingular (S^{4+5}), or superior division (S^{1-3}); all other segmentectomies were defined as complex. The primary outcome was OS, and secondary outcomes were respiratory function, relapse-free survival (RFS), cumulative incidence of locoregional relapse, and lung cancer-specific death. To ensure comparability, a location-adjusted analysis was performed, separately comparing lobectomy to simple segmentectomy in patients with tumors in the bilateral S^6, left S^{1-3}, or S^{4+5}, and to complex segmentectomy in patients with tumors in the right S^{7-10}, S^{1-3}, or left S^{8-10}, S^{1-3}. **Results:** 1106 patients were assigned to either lobectomy (n = 554) or segmentectomy (n = 552) including 318 complex and 234 simple segmentectomies. At a median follow-up of 10.5 years, the 10-year OS was 83.5% (95% CI: 78.8–87.3%), 83.5% (95% CI: 77.7–87.9%) and 79.8% (95% CI: 76.1–83.0%) for complex, simple segmentectomy, and lobectomy, respectively. In the location-adjusted analysis, the 10-year OS were 83.6% (95% CI: 78.9–87.3%) for complex segmentectomy and 79.2% (95% CI: 74.7–82.9%) for lobectomy (HR 0.839 [95% CI 0.608–1.158]). Similarly, 10-year OS were 82.9% (95% CI: 76.9–87.4%) for simple segmentectomy and 78.0% (95% CI: 72.5–82.6%) for lobectomy (HR 0.791 [95% CI 0.540–1.158]). The reduction of median forced expiratory volume in 1 second at 1 year was less after complex (−7.9%) and simple segmentectomy (−9.0%) than lobectomy (−12.0%; $p < 0.001$ and $p < 0.001$, respectively). RFS and lung cancer-specific death were not significantly different among the arms, while the cumulative incidence of locoregional relapse was higher after complex and simple segmentectomy than lobectomy (HR 2.124 [95% CI 1.327–3.339] and HR 1.817 [95% CI 1.071–3.083], respectively). Surgical margins were shorter in complex (median 2.2 cm, $p < 0.001$) and simple (2.5 cm, $p < 0.001$) segmentectomy than lobectomy (4.0 cm). **Conclusions:** Complex segmentectomy showed a trend toward improved OS compared to lobectomy in small-sized peripheral NSCLC similar to simple segmentectomy. However, due to a higher risk of locoregional relapse, complex segmentectomy should be performed with meticulous attention to securing adequate surgical margin. Clinical trial information: UMIN000002317. Research Sponsor: National Cancer Center Research and the Ministry of Health, Labour, and Welfare of Japan.

Perioperative toripalimab in non-small cell lung cancer: Clinical outcomes and safety from a large prospective real-world study.

Pingping Song, Jian Zeng, Tianqing Chu, Ying Liu, Zhengliang Tu, Haitao Li, Weimin Fang, Shi Yan, Jinyou Liu, LI Yu, Hao Zhang, Guangjian Zhang, Xi Zhang, Zhengfu He, Xingping Wu, Dongliang Bian, Jie Luo, ChunXia Su, Kun Li, Chang Chen; Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China; Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, China; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Yantai Yuhuangding Hospital, Yantai, China; The First Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, Zhejiang, China; Hunan Cancer Hospital, Changsha, China; Fujian Cancer Hospital, Fuzhou, China; Peking University Cancer Hospital & Institute, Beijing, China; The Second Xiangya Hospital of Central South University, Changsha, China; Shengjing Hospital of China Medical University, Shenyang, China; Department of Thoracic Surgery, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; Shaanxi Provincial Cancer Hospital, Xi'an, China; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First People's Hospital of Lianyungang, Lianyungang, China; Shanghai Pulmonary Hospital, Shanghai, China; Department of Comprehensive Oncology Center, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Background: The phase III NEOTORCH trial demonstrated that perioperative toripalimab significantly improved event-free survival in stage IIIA–IIIB driver-gene-negative NSCLC, along with a favorable overall survival trend. However, the generalizability of randomized controlled trial (RCT) results to broader, more heterogeneous, real-world populations is uncertain. This study aimed to evaluate the effectiveness and safety of this regimen in routine clinical practice, providing essential evidence for treatment decisions. **Methods:** This nationwide, prospective, observational study in China consecutively enrolled patients with stage II-III NSCLC planned for perioperative treatment containing toripalimab. The primary endpoint was real-world event-free survival (rwEFS). Secondary endpoints included pathological complete response (pCR) rate, major pathological response (MPR) rate, objective response rate (ORR), R0 resection rate, real-world disease-free survival (rwDFS), real-world overall survival (rwOS), and safety. **Results:** Between December 9, 2024, and January 14, 2026, 1727 patients were enrolled from 221 tertiary and secondary hospitals across 28 provinces in China. Baseline characteristics: 82.8% male; 51.4% aged ≥65 years; ECOG PS 0/1/2 in 43.2%/54.4%/2.4%. Histology: 71.4% squamous, 18.3% nonsquamous, 10.3% NSCLC not otherwise specified. Clinical stage distribution: IIA (1.7%), IIB (10.4%), IIIA (52.8%), IIIB (33.0%), IIIC (2.1%). Of all enrolled patients, 542 (31.4%) were pending preoperative assessment. Surgery was not performed in 634 patients (36.7%); reasons included: other causes (64.9%), patient refusal (15.7%), surgical ineligibility (9.3%), disease progression (8.2%), and adverse events (1.9%). Ultimately, 551 patients (31.9%) underwent resection, with 503 having postoperative pathological assessment. The MPR rate was 67.0% (337/503) and the pCR rate was 39.6% (199/503). As of the data-cutoff, investigators reported 20 (1.2%) grade ≥3 or clinically significant treatment-emergent adverse events, with hematologic toxicities being most common. Immune-related adverse events were infrequent (four events: three grade 1–2 pneumonitis, one grade 3 rash). **Conclusions:** This is the largest prospective real-world study of perioperative immunotherapy in NSCLC to date. Its extensive geographic coverage and diverse patient population-including higher proportions of elderly patients, those with ECOG PS 1, and varied histologies-validate the effectiveness and manageable safety of perioperative toripalimab in routine practice beyond RCT settings. The significant pathological response rates observed support the clinical benefit of this regimen for a broad spectrum of stage II-III NSCLC patients, providing crucial evidence for real-world decision-making. Clinical trial information: ChiCTR2400091457. Research Sponsor: the Shanghai Science and Technology Innovation Action Plan; 24SF1900100.

LuSato-1: Phase I study of ^{177}Lu-SSO110 with ^{68}Ga-SSO120 companion imaging in patients with extensive stage small cell lung cancer (ES-SCLC) on maintenance treatment with immune checkpoint inhibition (ICI).

Surein Arulananda, Richard Pham, Aviral Singh, Muhammad Adnan Khattak, Peter Lin, Abhijit Pal, Udit Nindra, Chong Ghee Chew, Nimit Singhal, Stanley Ngai, Kenneth John O'Byrne, Louise Emmett, Venessa T. Chin, Shakher Ramdave, Rodney John Hicks, Jessica Klaver Preston, Pierre Jordaan, Germo H. Gericke, Giuseppe Cardaci; Monash Health, Clayton, VIC, Australia; GenesisCare, Murdoch, Western Australia, Australia; Hollywood Private Hospital and Edith Cowan University, Perth, Australia; Liverpool Hospital, Liverpool, Australia; Royal Adelaide Hospital, Adelaide, SA, Australia; Princess Alexandra Hospital, Brisbane, Australia; Princess Alexandra Hospital, Translational Research Institute and Queensland University of Technology, Brisbane, Australia; St Vincent's Hospital Sydney, Sydney, Australia; The Kinghorn Cancer Centre, Camperdown, Australia; Monash Health, Moorabbin, Bentleigh East, VIC, Australia; Melbourne Innovation Theranostic Centre, North Melbourne, VIC, Australia; Ariceum International AG, Berlin, Germany

Background: Outcomes for pts with ES-SCLC remains suboptimal despite the addition of ICIs to platinum-based chemotherapy. Somatostatin receptor 2 (SSTR2) is expressed in the majority of SCLC lesions. SSTR2 targeted radiopharmaceutical therapy (RPT) has proven safe and effective when used in other neuroendocrine tumors. The multicentre, open-label, phase I LuSato-1 (ACTRN12623000185662) study investigated the use of ^{177}Lu-satoreotide Tetraxetan (^{177}Lu-SSO110) with ^{68}Ga-Satoreotide Trizoxetan (^{68}Ga-SSO120) companion imaging in pts with ES-SCLC, who are on 1L maintenance ICIs. **Methods:** Adult pts with ES-SCLC received 1L induction therapy with carboplatin, etoposide and atezolizumab for 4 cycles. Following induction, eligible pts without PD were enrolled and received up to 4 doses of ^{177}Lu-SSO110 in 6 to 9 week intervals, with up to 3 additional treatments per investigator choice. Activities were escalated from 3.7GBq to 5.2GBq, following a BOIN design with a target DLT rate of 0.30. The primary objective was to investigate the safety and tolerability of ^{177}Lu-SSO110 with ^{68}Ga-SSO120 companion imaging in pts on maintenance ICI, with secondary objective of anti-tumor activity of the combination. Concordance between ^{68}Ga-SSO120 PET/CT and contrast-enhanced CT was an exploratory endpoint. **Results:** Of the 35 screened pts, 20 were deemed eligible (median age 65.5 years (range 47-83), 55% female, 25% brain mets). With a median 11.1 month follow up (data cut off: 08/12/25), the TEAE rate associated with ^{177}Lu-SSO110 was 0% at 3.7GBq (dose level 1), 71.4% at 4.5GBq (dose level 2), and 83.3% at 5.2GBq (dose level 3). The grade 3/4 TEAE rate associated with ^{177}Lu-SSO110 was 0% (dose level 1), 57.1% (dose level 2), and 41.7% (dose level 3). Grade 2 to 4 thrombocytopenia rate related to ^{177}Lu-SSO110 was 45%. Grade 3/4 irAEs related to ICI was 20%. There was 10% pneumonitis rate attributed to ICI. The treatment interruption rate was 50% and treatment discontinuation rate was 10% (2 attributed to ^{177}Lu-SSO110 associated thrombocytopenia). From the start of C1 induction chemoICI, the ORR was 85%, including 1 CR. From the start of maintenance ICI, median PFS was 3.7 months and median OS was 8 months. **Conclusions:** Addition of SSTR2 targeted RPT to maintenance ICI was well tolerated and demonstrated clinically meaningful anti-tumor activity. This supports further investigation of SSTR2-targeted RPT in combination with ICI in patients with ES-SCLC. Clinical trial information: ACTRN12623000185662. Research Sponsor: Ariceum International AG.

ORR, PFS and OS.

Efficacy	ES-SCLC patients N=20
Best response rates (from C1 induction)	
CR	1 (5%)
PR	16 (80%)
SD	3 (15%)
ORR (from C1 induction)	17 (85%)
Median PFS (months) (from C1 maintenance)	3.7 months
Median OS (months) (from C1 maintenance)	8 months

8012 Rapid Oral Abstract Session

Preliminary results from an ongoing phase 1 study of LB2102, a dnTGFBR2-armored DLL3-targeted autologous CAR-T cell therapy, in patients with relapsed or refractory SCLC or LCNEC.

Zhonglin Hao, Alberto Chiappori, Ben C. Creelan, Reinhold Munker, Paul Otto Schwarzenberger, Nitin Patel, Sahista Vahora, Christian Davis, Chuan Wang, Jinghui Zhang, Lijun Xin, Adam Jacob Schoenfeld, Jacob Sands; Markey Cancer Center, Lexington, KY; Moffitt Cancer Center and Research Institute, Tampa, FL; Legend Biotech USA, Inc., Somerset, NJ; Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Delta-like ligand 3 (DLL3) is a promising target for small cell lung cancer (SCLC) and other neuroendocrine tumors. We present results from an ongoing dose-escalation study of LB2102, an autologous CAR-T cell therapy engineered to target DLL3 and armored with a TGF-β receptor blockade to overcome the immunosuppressive tumor microenvironment. **Methods:** This open-label, multicenter, phase 1 study evaluates LB2102 in patients with SCLC or large cell neuroendocrine carcinoma (LCNEC), relapsed or refractory to ≥1 prior line of therapy (LOT). Dose escalation follows an i3+3 design, with dose levels (DL) of 0.3, 1.0, 2.0, 4.0, 8.0, 12.0, and $16.0x10^6$ CAR+ T cells/kg. Subjects received a single infusion of LB2102 after standard lymphodepletion (LD). The primary objectives are to assess safety and tolerability, and to determine the recommended phase 2 dose. **Results:** As of 05-JAN-2026, 20 subjects received LB2102 (DL1–DL5, n = 3 each; DL6 was skipped based on data; DL7, n = 5). Seventeen subjects had SCLC and 3 LCNEC; 13 (65%) had a history of brain metastases. Median age was 56.5 yrs (range 20–73 yrs) with median 1 prior LOT (range 1–7); 95% received bridging therapy between apheresis and LB2102. The most-common grade ≥ 3 LB2102-related adverse events (TRAEs) were hematologic and co-attributed to LD. Four subjects (20%) had cytokine-release syndrome (CRS; 3 Grade 1 and 1 Grade 2); all resolved. Two subjects developed ICANS (1 Grade 1 and 1 Grade 3); both resolved. There were no dose-limiting toxicities (DLTs) or TEAE-related deaths. Other grade ≥ 3 non-hematologic LB2102-related TEAEs were dyspnea, prolonged QT, and hypoxia (all n = 1 at DL7). Of 17 response-evaluable subjects, best overall responses per RECIST1.1 criteria were 3 partial responses (PR, one each at DL3, DL4, and DL7) and 10 stable diseases (SD, at DLs 2–7), for an objective response rate (ORR) of 3/17 (18%) and a disease control rate (DCR) of 13/17 (76%). Median DOR among patients with a PR was 208 days. CAR-T expansion in peripheral blood (measured by qPCR) was observed at DL3 (N = 3), DL4 (N = 3), DL5 (N = 3), and DL7 (N = 5; 1 patient excluded due to incomplete PK profile): median C_{max} was 694, 581, 527, and 2851 copies/μg gDNA; median T_{max} was 15, 15, 6, and 6 days, respectively. Patients with partial responses had relatively higher PK exposure (median C_{max}) compared to the PK exposure of patients with stable diseases and progressive diseases. Median tumor expression of DLL3 at baseline was 97% (n = 16, range 45%–100%) and at Day 29 post-infusion was 90% (n = 8, range 55%–100%). **Conclusions:** LB2102 demonstrated consistent CAR-T expansion and encouraging anti-tumor activity at doses ≥ $2x10^6$ CAR+T cells/kg (ORR 27% and DCR 91%). LB2102 was well tolerated with no DLTs and manageable CRS and ICANs. Clinical trial information: NCT05680922. Research Sponsor: Legend Biotech USA, Inc; Novartis.

8013 Rapid Oral Abstract Session

Autologous natural killer cell infusion as consolidation therapy after first-line chemoradiotherapy for limited-stage small-cell lung cancer: A randomized, controlled, open-label, single-center phase II clinical study.

Jiuwei Cui, Xiao Chen, Rilan Bai, Wei Song, Jin Lu, Huimin Tian; The First Hospital of Jilin University, Changchun, China

Background: Small-cell lung cancer (SCLC) grows rapidly, is aggressive, has a poor prognosis, and tends to recur after treatment. Autologous cellular immunotherapy (CIT) has demonstrated good safety and efficacy across various tumors; however, there are no prospective studies utilizing autologous natural killer (NK) cells for consolidation therapy following first-line chemoradiotherapy for SCLC. **Methods:** This study aimed to evaluate the safety and efficacy of autologous NK cell infusion (administered every 2 weeks for a total of six courses) as consolidation therapy after first-line standard treatment for limited-stage SCLC, compared to routine follow-up in a randomized, controlled, open-label, single-center phase II clinical trial. The primary endpoint was progression-free survival (PFS, assessed according to Response Evaluation Criteria in Solid Tumors version 1.1), while secondary endpoints included overall survival (OS), the 12- and 24-month PFS rate, the 24- and 36-month OS rate and safety. **Results:** Forty-three patients with limited-stage SCLC were included in the final analysis, comprising 21 patients in the treatment group who received autologous NK cell infusion after chemoradiotherapy and 22 patients in the control group who underwent routine follow-up. At 6 months, the response to initial chemoradiotherapy was maintained in 27.3% (6/22) of the control patients and 57.1% (12/21) of the treatment patients. The objective response rate (ORR) and PFS rates at 12 months for controls compared to treatment patients were 0% versus 19.0% (4/21) ($P < 0.05$) and 4.5% (1/22) versus 42.9% (9/21) ($P < 0.01$), respectively. Compared to the control group, the autologous NK cell consolidation group achieved significantly longer PFS (median 6.5 vs. 11.92 months; hazard ratio [HR] 0.38, 95% confidence intervals [CI] 0.18 to 0.79; P = 0.01) and OS (median 15.6 vs. 27.13 months; HR 0.41, 95% CI: 0.19 to 0.87, P = 0.02), with a particularly pronounced PFS benefit when calculated from the end of chemoradiotherapy (median 8.1 vs.16.3 months; HR 0.35, 95% CI 0.17 to 0.72, P = 0.01). Regarding safety, the incidence of all adverse events (AEs) due to any cause was 50.0% (11/22) in the observation group and 47.6% (10/21) in the treatment group, with most being grade 1–2 and considered unrelated to NK cell infusion. NK cell treatment exhibited good overall safety and tolerability. Additionally, we characterized changes in peripheral blood cell subsets and metabolites before and after treatment, as well as the tumor immune microenvironment characteristics in patients from the treatment group. **Conclusions:** Autologous NK cell infusion as consolidation therapy after first-line chemoradiotherapy for SCLC yielded promising preliminary PFS and OS results, with a well-tolerated safety profile. Clinical trial information: NCT03410368. Research Sponsor: National Natural Science Foundation of China; 82273191; Jilin Provincial Science and Technology Department; 20240304037SF.

Transcriptomic analyses of molecular subsets and correlations with clinical outcomes from the phase 3 IMforte study of lurbinectedin (lurbi) + atezolizumab (atezo) maintenance treatment (Tx) in extensive-stage small-cell lung cancer (ES-SCLC).

Luis G. Paz-Ares, Hossein Borghaei, Martin Reck, Solange Peters, Roy S. Herbst, Andrzej Kazarnowicz, Aleksandra Szczesna, Erdem Cubukcu, Saadettin Kilickap, Jin-Seok Ahn, Raffaele Califano, Yu-Feng Wei, Minu K. Srivastava, Barzin Y. Nabet, Vilma Graupner, Ya-Chen Lin, George Cai, Graham Brock, Kamalnayan Bhatt, Stephen V. Liu; Hospital Universitario 12 de Octubre, Universidad Complutense and Ciberonc, Madrid, Spain; Fox Chase Cancer Center, Philadelphia, PA; Lung Clinic Grosshansdorf, Airway Research Center, North, German Center of Lung Research, Grosshansdorf, Germany; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Yale School of Medicine, New Haven, CT; Tuberculosis and Lung Disease Hospital, Olsztyn, Poland; Mazowieckie Centrum Leczenia Chorób Płuc i Gruźlicy, Otwock, Poland; Uludag University, Bursa, Turkey; Istinye University, Istanbul, Turkey; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; The Christie NHS Foundation Trust and Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; E-Da Cancer Hospital, I-Shou University, Kaohsiung, Taiwan; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Jazz Pharmaceuticals, Dublin, Ireland; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Background: Transcriptomic analyses of pre-Tx tumor samples from the Phase 3 IMpower133 study identified 4 molecular subtypes with distinct clinical outcomes to first-line (1L) Tx with atezo and chemotherapy (chemo). Neuroendocrine (NE) tumors with low tumor-associated macrophage (TAM)/high T-effector (T-eff) signal demonstrated longer overall survival (OS) vs non-NE tumors with high TAM/high T-eff, suggesting that TAM contributes to resistance to atezo. Lurbi, an alkylating agent that modifies the tumor microenvironment and synergizes with immune checkpoint inhibitors, could enhance atezo activity. Lurbi + atezo as 1L maintenance Tx significantly improved progression-free survival (PFS) and OS vs atezo in patients (pts) with ES-SCLC in the Phase 3 IMforte study (NCT05091567). We report exploratory biomarker analyses from IMforte. **Methods:** Adults with Tx-naïve ES-SCLC, without disease progression after induction with atezo + chemo, received maintenance Tx of either 3.2 mg/m^2 lurbi + 1200 mg atezo or 1200 mg atezo q3w until unacceptable toxicity or disease progression. Transcriptomic analyses were conducted on pre-induction Tx tumor samples to identify subgroups with concordance to previously reported SCLC subtypes (SCLC-A, -N, -I-NE and -I-non-NE), immune gene expression signatures (TAM, T-eff) and *SLFN11*. Post-hoc exploratory analyses were conducted for correlation with IRF-assessed PFS and OS. **Results:** Of 483 randomized pts, 303 had samples for RNA sequencing. Of 303 tissue samples analyzed, 104 (34.3%) were classified as SCLC-A, 89 (29.4%) as SCLC-N, 46 (15.2%) as SCLC-I-NE and 64 (21.1%) as SCLC-I-non-NE. Clinical outcomes in the 303 pts (median [m] PFS: 5.5 vs 2.4 months [mo], hazard ratio [HR] 0.61; mOS: 13.5 vs 11.7 mo, HR 0.72, for lurbi + atezo [n = 150] vs atezo [n = 153], respectively) were consistent with the full analysis set. PFS and OS benefit from lurbi + atezo were comparable between NE (mPFS: 5.5 vs 2.1 mo, HR 0.58; mOS: 13.5 vs 11.7 mo, HR 0.74, for lurbi + atezo [n = 115] vs atezo [n = 124], respectively) and non-NE subtypes (mPFS: 4.6 vs 2.8 mo, HR 0.73; mOS: not reached vs 12.0 mo, HR 0.68, for lurbi + atezo [n = 35] vs atezo [n = 29], respectively). Pts with high TAM/high T-eff in the atezo arm had shorter OS vs those with low TAM/high T-eff. The addition of lurbi improved OS in the high TAM/high T-eff subgroup vs atezo alone (HR 0.56). SLFN11 expression was high at baseline across subtypes and had no predictive value for lurbi + atezo clinical benefit. **Conclusions:** The prevalence of the 4 SCLC subtypes and the TAM/T-eff pre-Tx data for IMforte are consistent with findings from IMpower133. PFS and OS were longer for lurbi + atezo vs atezo irrespective of molecular subset, though numerical trends suggest that lurbi may overcome TAM-mediated resistance to atezo. Clinical trial information: NCT05091567. Research Sponsor: IMforte is sponsored by F. Hoffmann-La Roche Ltd. and co-funded by Jazz Pharmaceuticals. Third-party medical writing assistance was provided by Rachel Dobb, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

8015 Rapid Oral Abstract Session

Impact of neoadjuvant durvalumab (D) on tumor microenvironment (TME) features and their association with event-free survival (EFS) in patients with resectable NSCLC (R-NSCLC) from the phase 3 AEGEAN trial.

John V. Heymach, Ross Stewart, David H. Harpole, Tetsuya Mitsudomi, Janis M. Taube, Gabriella Galffy, Gabriel Garbaos, Bivas Biswas, Manuel Domine, Bartomeu Massuti, Thomas Winder, Guzel Mukhametshina, Dinh Van Luong, Jeronimo Rafael Rodriguez Cid, Tamer M. Fouad, Allen Chen, Agrin Moeini Mortazavi, Zhou Zhu, Huiling Xiong, Martin Reck; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; AstraZeneca, Cambridge, United Kingdom; Department of Surgery, Duke University Medical Center, Durham, NC; Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD; Törökbalint Institute of Pulmonology, Törökbálint, Hungary; Fundación Estudios Clínicos, Santa Fe, Argentina; Tata Medical Center, Kolkata, India; Department of Oncology, Fundación Jiménez Díaz, Campus Hospitalario, IIS-FJD, Universidad Autónoma de Madrid, Madrid, Spain; Alicante University Dr Balmis Hospital Isabial, Alicante, Spain; Department of Hematology, Oncology, Gastroenterology and Infectiology, Landeskrankenhaus Feldkirch, Feldkirch, Austria; SAHI Republican Clinical Cancer Dispensary, Ministry of Healthcare of the Republic of Tatarstan, Kazan, Russian Federation; Center of Lung Transplantation, Vietnam National Lung Hospital, Hanoi, Viet Nam; Oncology Center, Medica Sur Hospital, Mexico City, Mexico; AstraZeneca, New York, NY; AstraZeneca, Barcelona, Spain; AstraZeneca, Gaithersburg, MD; AstraZeneca, Waltham, MA; Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

Background: In AEGEAN, perioperative D + neoadj CT improved EFS and pathological complete response vs neoadj CT alone in pts with R-NSCLC. Here, we report exploratory transcriptomic analyses of the TME in tumor samples collected at baseline (BL) and surgery (Sx) to investigate the impact of neoadj D on TME features and their association with EFS. **Methods:** AEGEAN is a double-blind PBO-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II–IIIB[N2]) and ECOG PS 0/1 were randomized 1:1 to neoadj platinum-based CT + D or PBO IV (Q3W, 4 cycles) before Sx followed by D or PBO IV (Q4W, 12 cycles) after Sx. EFS was evaluated by BICR (RECIST v1.1) in the modified ITT (mITT) population, which excluded pts with known *EGFR*/*ALK* aberrations. Total RNA was extracted from BL and Sx tumor samples and sequenced (Illumina NovaSeq X Plus). Unsupervised hierarchical clustering of samples was conducted based on previously reported gene signatures reflective of tumor and TME components. **Results:** Transcriptomic data were available from 366 samples in 292 mITT pts across both arms (at BL, 257 pts; at Sx, 109 pts) whose characteristics and outcomes were broadly representative of the mITT population (74 pts with paired samples). At BL, 3 distinct phenotypic clusters (C) based on TME features were identified: an immune desert (C1, 24.9% of pts), characterized by a predominance of proliferating tumor cells; immune suppressed (C2, 39.3%), by elevated levels of suppressive myeloid cells, angiogenesis, and fibroblasts; and immune activated (C3, 35.8%), by high levels of effector T cells. A higher proportion of pts with squamous vs non-squamous tumors had phenotype C1 (37.5% vs 13.9%, respectively) while a lower proportion had C3 (22.5% vs 47.4%). The addition of perioperative D improved EFS across all BL C (C1: HR, 0.43; 95% CI, 0.19–0.94; C2: HR, 0.90; 95% CI, 0.50–1.63; C3: HR, 0.41; 95% CI, 0.20–0.81), with least improvement in C2. The same clusters were detected at Sx (C1, 32.1%; C2, 33.9%; C3, 33.9%) and pts with C1 tumors had the highest risk of progression; 36-month EFS rates (95% CI) were 27.8% (12.1–46.0), 55.7% (33.7–73.0), and 77.2% (59.3–88.0) for C1, C2, and C3, respectively. Neoadj D was associated with higher proportions of pts with C2 and C3 phenotypes at Sx, such that the proportion with poor prognosis C1 tumors at Sx was 17.9% vs 47.2% in the D vs PBO arms, respectively. Among pts with C3 tumors at Sx, EFS benefit in the D vs PBO arm was striking (HR, 0.16; 95% CI, 0.03–0.79). **Conclusions:** The TME before and after neoadj Tx impacts EFS in pts with R-NSCLC, with an immune suppressed phenotype associated with reduced perioperative D benefit. The TME differs between squamous and non-squamous tumors and is influenced by neoadj D, which may promote an immune-activated phenotype associated with prolonged EFS benefit with perioperative D. Clinical trial information: NCT03800134. Research Sponsor: AstraZeneca.

Tumor-naïve multimodal cfDNA MRD assay to predict recurrence in a prospective cohort of patients undergoing curative-intent lung cancer resection.

Di Lu, Yu Du, Shaobin Li, Hao Zhang, Rui Liu, Haimeng Tang, Xiaoxi Chen, Hua Bao, Xue Wu, Lina Shi, Zhiming Chen, Zhizhi Wang, Jianxue Zhai, Yang Shao, Kaican Cai; Department of Thoracic Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China; Nanjing Geneseeq Technology Inc., Nanjing, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China; Department of Thoracic Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background: Tumor-informed circulating tumor DNA (ctDNA) assays can achieve high sensitivity for minimal residual disease (MRD) detection after lung cancer resection but require tumor tissue and individualized assay design, limiting scalability and timeliness in routine practice. Tumor-naïve MRD approaches offer a practical alternative for postoperative surveillance; however, their sensitivity remains constrained. Integrating complementary cfDNA features beyond somatic mutations may enhance tumor-naïve MRD detection and postoperative risk stratification. **Methods:** A prospective cohort of 212 patients with resectable stage I–IV lung cancer, predominantly consisting of stage I disease (146 of 212), was enrolled. Postoperative plasma samples were collected at a landmark timepoint (~1 week after surgery) and longitudinally every 3–6 months for up to 3 years. MRD was assessed using ShieldingUltra, a tumor-naïve multimodal cfDNA assay integrating somatic mutations, copy number variations (CNVs), and fragmentomic features based on ultra-deep UMI-based sequencing of an integrated panel covering >2000 cancer-related genes. MRD positivity was determined from integrated multimodal cfDNA signals. Survival outcomes were evaluated using Kaplan–Meier analysis and Cox proportional hazards models, with subgroup analyses by disease stage, histology, and postoperative adjuvant therapy. **Results:** At the postsurgical landmark timepoint, MRD positivity was strongly associated with an increased risk of recurrence (hazard ratio [HR], 9.72; log-rank $p=2.06\times10^{-8}$). Longitudinal MRD monitoring further improved risk stratification, with MRD-positive patients exhibiting a markedly higher recurrence risk (HR, 16.64; log-rank $p=1.66\times10^{-9}$) while maintaining high specificity (~90%). Among the 27 patients who developed radiographically confirmed recurrence, MRD was detected prior to imaging in the majority of cases (21 of 27), providing a median lead time of 264 days. The prognostic value of MRD status was consistently observed across disease stages, histologic subtypes, and postoperative adjuvant treatment strategies, with particularly robust prognostic discrimination observed in patients with stage I disease. Multivariable analyses confirmed MRD positivity as an independent predictor of recurrence in both landmark and longitudinal settings. **Conclusions:** Tumor-naïve multimodal MRD assessment integrating mutation, CNV, and fragmentomic cfDNA features enables sensitive and clinically informative detection of residual disease after lung cancer surgery. Early and longitudinal MRD monitoring provides robust prognostic stratification and meaningful lead time over imaging, supporting its clinical utility for postoperative surveillance in resectable lung cancer. Research Sponsor: None.

8017 Rapid Oral Abstract Session

Clinical validity of ultrasensitive single-digit parts per million ctDNA detection in non–small cell lung cancer.

James R.M. Black, Jonathan Wan, Charles Abbott, Bailiang Li, Takahiro Karasaki, Alexander A. Azizi, Lydia Y. Liu, Olivia Lucas, Charlotte Grieco, Aino-Maija Leppa, Maise Al-Bakir, Wing Kin Liu, David Moore, Oliver Shutkever, Cian Murphy, Mariam Jamal-Hanjani, Rachel Marty Pyke, Sean Michael Boyle, Richard Chen, Robert Charles Swanton; Francis Crick Institute, London, United Kingdom, London, United Kingdom; Francis Crick Institute, London, United Kingdom; Personalis, Inc., Fremont, CA; University College London Cancer Institute, London, United Kingdom; Personalis, Inc., Menlo Park, CA; The Francis Crick Institute, London, United Kingdom

Background: Circulating tumor DNA (ctDNA) is a promising biomarker for detecting molecular residual disease (MRD) and predicting recurrence after curative treatment in non-small cell lung cancer (NSCLC). Ultrasensitive personalized assays have demonstrated clinical validity at detection thresholds of ~80-100 parts per million (PPM). As this assay can detect ctDNA at concentrations an order of magnitude lower (below 10 PPM), we extend these analyses to explore the clinical outcomes of patients with single-digit PPM ctDNA. In the future, this may guide adjuvant treatment decision-making. **Methods:** We analyzed longitudinal plasma samples from 431 patients with stage IA–IIIB NSCLC enrolled in the TRACERx study and treated with upfront surgery. We achieved ultrasensitive MRD testing with ctDNA limits of detection as low as 1-3 PPM across 2994 plasma samples using NeXT Personal, a personalized liquid biopsy assay which tracks up to ~1,800 patient-specific somatic variants. Plasma samples were classified as preoperative, postoperative landmark (10–120 days), or longitudinal follow-up. Associations with recurrence-free survival (RFS) and overall survival (OS) were assessed. **Results:** Preoperative ctDNA detection below 10 PPM was associated with inferior recurrence-free survival (RFS) and overall survival (OS) compared to undetectable ctDNA in individuals with lung adenocarcinoma (<10 PPM vs. undetected: HR: 3.25, 95% CI 1.52-6.94, p = 0.0024 and HR: 3.49, 95% CI 1.24-9.81, p = 0.018 for RFS and OS). Postoperative ctDNA was detected in 21% of patients. Detection below 10 PPM occurred in 16.7%, 15.5%, and 11.5% of stage I, II, and III patients, respectively. ctDNA detection preceded imaging-confirmed recurrence in 120 individuals. In postoperative landmark plasma samples, 18% of ctDNA detections occurred below 10 PPM and were associated with increased risk for recurrence and death versus undetectable ctDNA (RFS: HR 3.49, 95% CI 1.70–7.17, p=0.00067; OS: HR 2.58, 95% CI 1.09–6.14, p=0.032). Within ctDNA-positive patients, <10 PPM was associated with improved outcomes compared with ≥10 PPM (HR: 0.38, 95% CI 0.19-0.78, p = 0.0086, HR: 0.37, 95% CI 0.16-0.86, p = 0.021). **Conclusions:** Sub-10 PPM ctDNA detection identifies a clinically high-risk subgroup of early-stage NSCLC patients. Notably, this included stage I patients who would not typically be classified as high-risk or considered for adjuvant therapy; ctDNA positivity in this group therefore reveals high-risk disease that would otherwise go unrecognized. Reliable detection of ctDNA at sub-10 PPM levels may refine post-surgical risk stratification beyond conventional staging and imaging, enabling earlier identification of molecular relapse and potentially guiding treatment escalation in future practice. Research Sponsor: None.

Lung cancer stage prediction using longitudinal CT imaging compared with single-timepoint assessment.

Amrik Majumdar, Michael E. Bryan; Westfield High School, Chantilly, VA; Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom

Background: Lung cancer staging guides treatment decisions but is based on single-timepoint imaging, treating tumors as static entities. Screening programs routinely acquire serial low-dose CTs (LD-CTs), yet this longitudinal information is not used for staging. We hypothesized that modelling temporal change would capture tumor evolutionary dynamics predictive of stage beyond volume change alone, reframing staging as a process rather than a snapshot. **Methods:** We identified 236 NLST participants with biopsy-confirmed lung cancer and three pre-treatment LD-CTs (median interval 12 months). Reference staging used AJCC 7th edition criteria, pathologic where available and otherwise clinical, for overall stage (I–IV) and T and N components. We developed a longitudinal 3D residual network with dual attention and interval-aware temporal encoding, trained using nested five-fold cross-validation. Volume doubling time (VDT) was computed to assess whether temporal features provided information beyond growth rate. The primary endpoint was macro-AUC for overall stage. Secondary endpoints included balanced accuracy, weighted κ, calibration (ECE, Brier score), and decision-curve net benefit. External validation is ongoing in NLSTseg (n = 605) and NSCLC Radiogenomics (n = 211). **Results:** The longitudinal model outperformed a single-timepoint baseline, achieving a macro-AUC of 0.86 versus 0.82, Δ +0.04, $p < 0.05$. Improvements were greatest for N-stage (Δ +0.13) and T-stage (Δ +0.11). Compared with a recent foundation model approach (DINOv2 + ABMIL), the model showed superior N-stage discrimination (AUC 0.86 vs 0.70). Temporal features remained independently predictive after adjustment for VDT, indicating capture of biological signal beyond growth rate. Attention maps consistently highlighted lesion margins and peritumoral regions across timepoints, consistent with invasive behavior. Performance was stable across sex, age, and smoking subgroups, and inference was feasible on standard CPUs. **Conclusions:** Modelling longitudinal change across serial LD-CTs captures tumor evolutionary dynamics that predict lung cancer stage independently of growth rate. This reframes staging as a dynamic, evolution-aware process and provides a practical route for integrating artificial intelligence into screening workflows where serial imaging is already available. External validation is underway. Research Sponsor: None.

8019 Poster Session

Rapid multi-task intraoperative diagnosis of lung cancer via deep neural network-driven label-free femtosecond laser imaging (FLI).

Yin Li, Yunlong Wang, Tao Pan, Bowen Ding, Xin Zhu, Yuchen Han, Xinghua Cheng; School of Medicine, Shanghai Jiao Tong University, Shanghai Chest Hospital, Shanghai, China; New Laboratory of Pattern Recognition (NLPR), State Key Laboratory of Multimodal Artificial Intelligence Systems (MAIS), Institute of Automation, Chinese Academy of Sciences (CASIA), Beijing, China; Shanghai Jiaotong University, Shanghai, China; School of Biomedical Engineering, Guangzhou Medical University, Guangzhou, China; Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Shanghai Chest Hospital, Shanghai, China

Background: Rapid and accurate intraoperative pathological diagnosis is critical for guiding surgical margins and preserving lung function during lung cancer surgery. Current frozen-section (FS) analysis is time-consuming and prone to artifacts. Femtosecond label-free imaging (FLI) enables high-resolution, non-destructive tissue visualization without staining or freezing, offering a promising platform for real-time assessment. **Methods:** We developed FastLung, an integrated FLI+AI platform for multi-task diagnosis. Fresh, unprocessed tissue samples (326 paired tumor-normal specimens) from surgical resections were imaged using multimodal FLI. FastLung employs a self-supervised deep learning model trained on ~4 million image patches, with formalin-fixed paraffin-embedded (FFPE) histopathology as ground truth. The system provides malignancy probability maps and categorical outputs within 5 minutes. **Results:** FastLung achieved high diagnostic performance across key intraoperative tasks: benign vs. malignant (AUC = 0.9854 ± 0.01), invasive vs. minimally invasive adenocarcinoma (AUC = 0.9573 ± 0.03), and adenocarcinoma vs. squamous cell carcinoma (AUC = 0.9892 ± 0.009). It significantly reduced diagnostic turnaround time (5–10 min vs. 20–30 min for FS, 60–80% faster) while maintaining accuracy comparable to or exceeding FS. In core needle biopsies (n = 94), accuracy reached 95.8%. The platform also demonstrated consistent performance across operators and time, supporting reliable integration into surgical workflow. **Conclusions:** FastLung combines label-free FLI with deep learning to deliver rapid, accurate, and reproducible intraoperative diagnosis of lung cancer, outperforming frozen sections in speed and multidimensional assessment. Its robust performance in both resection and biopsy specimens highlights its potential to improve surgical decision-making and extend toward pan-cancer diagnostic applications. Research Sponsor: Shanghai Key Laboratory of Thoracic Tumor Biotherapy; 2025SZ1002; Science and Technology Commission of Shanghai Municipality (STCSM); 24JS2840300.

Noninvasive imaging biomarkers for survival risk stratification with tarlatamab in ES-SCLC.

Mohammadhadi Khorrami, Ameish Govindarajan, Juyoung Lee, Sawyer Bawek, Mimi Najjar, Samer Salem, Kainat Warraich, Lukas Delasos, Anant Madabhushi; Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA; Cleveland Clinic, Cleveland, OH; Department of Computer Science and Informatics, Emory University, Atlanta, GA; Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Center, Cleveland, OH; Cleveland Clinic Taussig Cancer Center, Cleveland, OH; Emory University; Atlanta Veterans Affairs Medical Center, Atlanta, GA

Background: Subsequent treatment for extensive-stage small cell lung cancer (ES-SCLC) following platinum-etoposide chemotherapy +/- an immune checkpoint inhibitor was historically limited to alternative forms of chemotherapy with relatively poor clinical outcomes. Bispecific delta-like ligand 3 (DLL3)-targeting T-cell engagers, such as tarlatamab, have since demonstrated clinically meaningful activity with notable improvements in survival. Although there was a modest improvement in median progression-free survival (PFS) with tarlatamab in the phase 3 DeLLphi-304 trial, 20% of patients remained free from disease progression at 12 months. Unfortunately, conventional clinical factors and early radiographic responses are unable to distinguish transient from sustained benefit; thus underlying the need for validated biomarkers to identify patients likely to derive a durable response from tarlatamab. **Methods:** This study sought to evaluate whether radiomic texture and quantitative vessel tortuosity (QVT) metrics derived from baseline CT imaging are associated with PFS and overall survival (OS) in patients with ES-SCLC receiving tarlatamab.50 patients from Cleveland Clinic with ES-SCLC who received tarlatamab after front-line chemoimmunotherapy were included in this study. Radiomic texture and QVT features characterizing intratumoral heterogeneity and vascular architecture were extracted from CT scans obtained before the first dose of tarlatamab (median scan-to-treatment interval: 33.5 days). A least absolute shrinkage and selection operator Cox regression model with cross-validation identified prognostic features for PFS and OS. A radiomic risk score (RRS) was computed as a weighted linear combination of selected features, and patients were stratified into high- and low-risk groups using the median RRS. Cox regression and Kaplan–Meier analyses with log-rank testing evaluated associations with PFS and OS. **Results:** On univariable analysis, RRS was significantly associated with PFS (HR = 2.3, 95% CI 1.36–3.94, P = 0.0019) and OS (HR = 3.9, 95% CI 1.67–9.1, P = 0.0016). Kaplan–Meier analyses demonstrated significantly shorter PFS and OS in the high-risk group. In multivariable models adjusting for age, sex, race, smoking history, COPD, and prior lines of therapy, RRS remained the only factor independently associated with PFS (HR = 2.1, 95% CI 1.16–4.0, P = 0.014) and OS (HR = 5.87, 95% CI 2.0–17.0, P = 0.001). **Conclusions:** Baseline CT-derived radiomic and vascular features represent noninvasive biomarkers for predicting PFS and OS in patients with ES-SCLC receiving tarlatamab. Further validation of these novel features can improve patient selection, treatment sequencing, and optimized utilization of DLL3-targeted therapy in this unique cancer population with otherwise limited treatment options. Research Sponsor: National Cancer Institute; R01CA26820701A1; National Cancer Institute; R01CA249992-01A1; National Cancer Institute; 1U54CA254566-01; National Cancer Institute; 1U01CA239055-01; National Cancer Institute; 1U01CA248226-01; Lung Cancer research Program Career Development Award; HT9425-24-1-0095; Lung Cancer Research Program; W81XWH-18-1-0440.

8021 Poster Session

Development and validation of an artificial intelligence–based deep learning imaging model for early lung cancer detection: DAVINCI, a retrospective study of 8,962 patients.

Syeda Hafsa Noor-AIN, Rakhshanda Khan, Gadugoyyala Guna Sri Phani Ajay, Nimra Shafi, Harshawardhan Ramteke, Zahra Nawaz, Sangeetha Gandhi, Ifrah Khan, Akshaya Junnuthula, Dineshbaba Murugavel, Divya Sree Rapaka, Vishwajeet Ramagiri, Haroon Alamy, Sourav Hazra, Hongwei Ma, Yang Qianyi; Ayaan Institute of Medical Sciences, Srinagar, India; Ayaan Institute of Medical Sciences, Moinabad, India; GSL Medical College and General Hospital (India), Rajahmundry, India; Arnot ogden medical center, Elmira, NY; Rhythm Heart and Critical Care Hospital, Nagpur, India; CMH Lahore Medical and Dental College, Lahore, Pakistan; Mayo Clinic Rochester, Rochester, MN; Baqai Medical University, Karachi, Pakistan; Siddhartha Medical College, Hyderabad, India; Rhythm Heart and Critical Care Hospitals, Nagpur, India; SVS Medical College, Mahabubnagar, India; Desert Regional Medical Center, Inc., Palm Springs, CA; College of Medicine and Sagore Dutta Hospital, Kolkata, North 24 Parganas, India; University of Sydney, Sydney, Australia; School of Computer Sciences, Anhui University, Hefei, China

Background: Lung cancer is the leading cause of cancer-related mortality worldwide, primarily due to delayed diagnosis and diagnostic variability in histopathological assessment. Advances in deep learning applied to medical imaging offer the potential to enhance early detection accuracy, reduce interobserver variability, and improve diagnostic efficiency in lung cancer. **Methods:** In this retrospective study, we evaluated DAVINCI using a dataset of 8,962 patients with confirmed lung malignancies. The model utilizes a specialized architecture combining convolutional neural networks (CNNs) and residual blocks to optimize feature extraction from high-resolution pathological slides. Performance was measured via detection accuracy, recall, specificity, and Area Under the Curve (AUC). **Results:** A total of 8,962 patients were included in the analysis. The DAVINCI model correctly identified lung cancer in 93% of cases, corresponding to 8,334 of 8,962 patients, with a 95% confidence interval (CI) of 86%–100% (7,707–8,962 patients). Model specificity was also 93% (95% CI, 86%–100%), indicating a high true-negative rate. Sensitivity (recall) was 87%, with correct detection in 7,797 patients and a 95% CI of 80%–94% (7,170–8,425 patients). The model demonstrated strong discriminatory performance, achieving an area under the curve (AUC) of 0.91 (95% CI, 0.84–0.98). In comparison, active pathologists achieved a mean diagnostic accuracy of 83%, corresponding to 7,438 of 8,962 cases, with a 95% CI of 76%–90% (6,811–8,066 cases). In terms of efficiency, DAVINCI processed whole-slide images in 16–19 seconds, substantially faster than conventional manual review, which typically requires several minutes per slide. **Conclusions:** DAVINCI demonstrated superior accuracy, robust discriminatory performance, and markedly faster processing compared with human review, supporting its potential role in early lung cancer detection at scale. Research Sponsor: None.

Cross-stage validation of a multimodal machine learning model to predict pathological complete response to neoadjuvant chemotherapy or chemoimmunotherapy in resectable stage III non–small cell lung cancer.

Loïc Ferrer, Ernest Nadal, Thibaut Dejean, Amelia Insa, Philippe Menu, Joaquin Casal, Manuel Domine, Bartomeu Massuti, Margarita Majem, Alex Martinez-Marti, Rosario Garcia-Campelo, Javier de Castro Carpeño, Manuel Cobo, Guillermo Lopez Vivanco, Edel Del Barco Morillo, Reyes Bernabé, Nuria Vinolas, Isidoro Barneto, Thierry Colin, Mariano Provencio; SOPHiA GENETICS, Pessac, France; Thoracic Tumors Unit, Medical Oncology, Catalan Institute of Oncology (ICO). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain; Hospital Clinico Universitario de Valencia, Valencia, Spain; SOPHiA Genetics, Rolle, Switzerland; Hospital Alvaro Cunqueiro de Vigo, Vigo, Spain; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Alicante University Dr Balmis Hospital Isabial, Alicante, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Hospital Universitario A Coruña, A Coruña, Spain; Hospital Universitario HM Madrid Sanchinarro, Madrid, Spain; Hospital Regional Carlos Haya, A Gudiña, Spain; ECO Foundation, Hospital de Cruces, Bilbao, Spain; Hospital Universitario de Salamanca, Salamanca, Spain; Hospital Universitario Virgen del Rocío, Seville, Spain; Hospital Clinic Barcelona, Barcelona, Spain; Medical Oncology Department, Reina Sofía University Hospital, Cordoba, Spain; Hospital Universitario Puerta de Hierro, Madrid, Spain

Background: Pathological complete response (pCR) after neoadjuvant chemoimmunotherapy is associated with improved outcomes in resectable non–small cell lung cancer (NSCLC), yet reliable tools to predict treatment response before surgery are lacking. Machine learning models have shown promise in advanced disease, but their ability to generalize across disease stages remains uncertain. We evaluated the performance of a machine learning model developed in stage IV NSCLC when applied to a cohort of patients with surgically resectable stage III disease treated with neoadjuvant chemotherapy or chemoimmunotherapy. **Methods:** The DEEP-Lung-IV study (NCT04994795) developed and validated machine learning models for personalized risk prediction based on multimodal data in patients with stage IV NSCLC treated with first-line pembrolizumab and/or chemotherapy. The models incorporated multimodal clinical routine data such as clinical, biological and CT-scan images. For the present study, the trained pre-treatment model was applied without retraining to patients enrolled in the NADIM trials (NCT03081689, NCT03081689) who received neoadjuvant chemotherapy alone (CTx), or in combination with nivolumab (Nivo+CTx), followed by surgery. Model performance was assessed using the area under the ROC curve (AUC) by considering only the last chest CT-scan image before surgery, or by combining it with other multimodal data. **Results:** A total of 103 patients with available clinical, biological, imaging data and who experienced surgery was considered for validation analysis (N = 88 patients with Nivo+CTx, N = 15 patients with CTx). When applied to the stage III NADIM cohort, the stage IV–derived model demonstrated strong predictive performance for pCR, with an AUC of 0.68 (95% CI, 0.57–0.78) in all patients using the CT-scan image only, rising to 0.76 (95% CI, 0.67–0.84) when additionaly leveraging on clinical and biological data. Performance was consistent across clinically relevant subgroups, especially in the patients treated with Nivo+CTx, with AUC estimates from 0.65 (95% CI, 0.54–0.76) using CT-scan image alone to 0.72 (95% CI, 0.61–0.82) when combined with the other multimodal data. The model was capable of handling missing predictor values, and preserved predictive value despite differences in disease stage and treatment intent. **Conclusions:** A machine learning model trained in advanced-stage NSCLC accurately predicted pathological response to neoadjuvant chemo- or chemoimmuno-therapy in a resectable stage III cohort, supporting the biological continuity of treatment response across disease stages. This cross-stage generalizability highlights the potential of machine learning–based tools to guide treatment personalization in earlier-stage NSCLC and warrants prospective validation. Research Sponsor: None.

8023 Poster Session

Multimodal intraoperative diagnosis and grading system integrating macroscopic images, CT imaging, and textual reports for adenocarcinoma (MaCTex) in early-stage LUAD: A multicentric diagnostic study.

Yingwei Lu, Lintong Yao, Jinqing Li, Jiaqing Ye, Canjia Cai, Maotao Weng, LuYu Huang, Haiyu Zhou; Guangdong Cardiovascular Institute, Guangzhou, Guangdong, China; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China

Background: Intraoperative frozen section (IFS) analysis is pivotal for guiding surgical strategies in stage IA lung adenocarcinoma (LUAD), specifically the extent of resection and lymph node dissection. However, IFS is constrained by sampling errors and prolonged turnaround times, which can compromise diagnostic precision and surgical efficiency. To address these unmet needs, we developed and validated a multimodal artificial intelligence framework. By integrating preoperative chest CT imaging, unstructured radiology text reports, and intraoperative macroscopic images of resected specimens, this system aims to deliver rapid, precise intraoperative predictions, thereby mitigating reliance on traditional IFS and optimizing surgical decision-making. **Methods:** This retrospective, multicenter study enrolled patients with stage IA LUAD who underwent complete resection between June 2020 and September 2023 across three institutions (Guangdong Provincial People's Hospital, Affiliated Hospital of Guangdong Medical University, and Meizhou People's Hospital). We collected preoperative thin-slice chest CT scans and unstructured text reports within three months prior to surgery. Intraoperative macroscopic images of resected specimens were captured via smartphone under natural lighting. We developed MaCTex, a multimodal AI model, to predict the IASLC grading system (PIL, MIA, IAC G1, G2, G3). Performance was evaluated against the gold standard of postoperative paraffin pathology. The study is registered with the Chinese Clinical Trial Registry (ChiCTR2500111776). **Results:** The cohort included 1,516 patients (yielding 1,638 pulmonary nodules) with matched preoperative CT imagings/reports and 2,344 intraoperative macroscopic images. We developed four distinct models for evaluation: a CT-only model, a CT-Text model, a Gross Image model, and the comprehensive MaCTex framework. The CT-Text model achieved a diagnostic AUC of 0.857, outperforming the unimodal CT model with an AUC of 0.837. The Gross Image model achieved a performance of 0.82 in five-class prediction. Notably, the integration of unstructured CT text reports significantly enhanced model efficacy, underscoring the critical value of radiologist expertise in refining intraoperative diagnostics. **Conclusions:** We established a robust multimodal AI framework integrating radiographic data, clinical text, and macroscopic pathology that enables efficient and accurate intraoperative prediction of IASLC grading in lung adenocarcinoma. By circumventing the sampling limitations of traditional methods, MaCTex serves as a promising alternative or adjunct to intraoperative frozen sections, providing thoracic surgeons with real-time, precise decision support to optimize surgical management. Research Sponsor: None.

A deep learning model for intraoperative diagnosis of lung adenocarcinoma using frozen section whole-slide images (CryoPath): A multicentric diagnostic study.

Jinqing Li, Lintong Yao, Jiaqing Ye, Yingwei Lu, Maotao Weng, Canjia Cai, LuYu Huang, Haiyu Zhou; Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Guangdong Cardiovascular Institute, Guangzhou, Guangdong, China; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China

Background: Intraoperative frozen section (FS) analysis is critical for guiding surgical decision-making in lung cancer. However, its diagnostic accuracy can be limited by time constraints, sampling issues, and inter-pathologist variability. Deep learning-based analysis of whole-slide images (WSIs) offers a new paradigm for real-time, objective intraoperative diagnosis. **Methods:** We developed and validated an artificial intelligence system, CryoPath, for the intraoperative diagnosis of lung adenocarcinoma (LUAD) from FS-WSIs. The system was trained and tested using a large, multicentric, retrospectively collected cohort comprising 3000 LUAD FS-WSI cases from seven medical centers in China. The model architecture is based on attention-challenge multiple instance learning framework with vision transformer for feature extraction. CryoPath was designed for end-to-end prediction of diagnostic subtypes (pre-invasive lesions, minimally invasive adenocarcinoma and invasive adenocarcinoma) and key pathological features such as extent of invasion and lymphovascular invasion from FS-WSIs. **Results:** The study included 1,042 patients, yielding 1,139 WSI with early-stage lung adenocarcinoma from multiple centers, which comprised a total of 637 WSIs with IAC, 402 with MIA, and 100 with PIL. The CryoPath model achieved an AUC of 0.931 for discriminating IAC from PIL/MIA, which achieved a sensitivity of 0.87 and a specificity of 0.85. In clinical decision simulation, the model-assisted strategy increased surgical decision accuracy from 75% to 88%. 15 WSIs classified as PIL on FS but upgraded to IAC on permanent sections by pathologist were corrected by CryoPath and Attention heatmaps generated by the model highlighted histologically relevant regions. CryoPath model achieved an AUC of 0.92 (95% CI: 0.90–0.94) for discriminating IAC from PIL/MIA on the test set. . In clinical decision simulation, the model-assisted strategy increased surgical decision accuracy from 75% to 88. Attention heatmaps generated by the model highlighted histologically relevant regions. **Conclusions:** The CryoPath system demonstrates for the first time that large-scale deep learning-based analysis of FS-WSIs can achieve high-accuracy, real-time, and interpretable intraoperative diagnosis for LUAD. This system has the potential to serve as a powerful adjunct tool for pathologists and surgeons, potentially reducing diagnostic variability, shortening intraoperative wait times, and providing an objective foundation for precise surgical strategy. A prospective, multi-center clinical trial is being planned to further evaluate its clinical utility. Research Sponsor: None.

8025 Poster Session

Intratumoral heterogeneity of *MTAP* loss by immunohistochemistry in non–small cell lung cancer: Implications for clinical outcomes.

Tsuyoshi Hirata, Hibiki Udagawa, Tetsuro Taki, Gaku Yamamoto, Yu Tanaka, Tetsuya Sakai, Hiroki Izumi, Eri Sugiyama, Yoshitaka Zenke, Shigeki Umemura, Shingo Matsumoto, Kiyotaka Yoh, Keiju Aokage, Masahiro Tsuboi, Genichiro Ishii, Koichi Goto; National Cancer Center Hospital East, Kashiwa, Japan; Department of Pathology and Clinical Laboratories, National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Radiation Oncology Division, National Cancer Center Hospital East, Kashiwa-Shi, Japan; Department of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: MTAP-cooperative PRMT5 inhibitors are under development for MTAP-loss solid tumors including non-small cell lung cancer (NSCLC). However, the intratumoral heterogeneity of MTAP loss in NSCLC and its potential implications for clinical outcomes remain incompletely understood. **Methods:** Tumor specimens from patients with NSCLC who underwent surgical resection between January 2019 and October 2019 in our institution were retrospectively collected. MTAP expression status was evaluated in surgically resected specimens using MTAP immunohistochemistry (IHC) 2G5 and categorized as retained (100% positive tumor cells), partial loss (1–99%), or complete loss (0%). MTAP status was confirmed by fluorescence in situ hybridization (FISH). Clinicopathological characteristics and survival outcomes were analyzed according to MTAP expression status. **Results:** MTAP expression status was successfully analyzed in 196 specimens from primary lesion of patients with NSCLC. MTAP expression status was classified as retained in 131 specimens (67%), partial loss in 43 (22%), and complete loss in 22 (11%). Of 14 specimens of which MTAP status was evaluated by FISH, the MTAP status by IHC and FISH were completely consistent. Compared to the patients with retained, the patients with complete loss showed no significant differences in the clinicopathological characteristics, but the patients with partial loss were significantly more frequently associated with adenocarcinoma histology (93% vs 74%, $P = 0.02$) and never-smoker status (51% vs 22%, $P < 0.001$). Among specimens diagnosed as adenocarcinoma, those with partial loss showed a significantly higher frequency of lepidic and papillary predominant patterns compared to those with complete loss (83% vs 50%, $P = 0.02$). Among specimens of which *EGFR* mutation status was analyzed, the frequency of EGFR mutations was significantly higher in specimens with MTAP complete/partial loss compared to MTAP retained (59% vs 30%, $P = 0.03$). There were no significant differences in the recurrence-free survival (RFS) and the overall survival (OS) among the patients with complete loss, partial loss and retained (5-year RFS rates: 82%, 83% vs 76%, 5-year OS rates: 90%, 81% vs 77%). MTAP expression status of corresponding metastatic lymph node (mLN) was evaluated in 6 patients with MTAP partial loss. MTAP expression status for corresponding mLN were consistent with predominant MTAP expression status for primary lesion in 4 patients (67%). **Conclusions:** Intratumoral heterogeneity of MTAP expression was observed in 22% of NSCLC, particularly with adenocarcinoma histology and in never-smokers. Intratumoral heterogeneity of MTAP loss may contribute to inaccurate assessment of MTAP status on small biopsy samples. MTAP expression status was not associated with the prognosis in patients with surgically resected NSCLC. Research Sponsor: None.

Cancer-related overall survival for patients on durvalumab for stage III unresectable non–small cell lung cancer with PD-L1 positive and negative tumors.

Zohra Nooruddin, Corbyn Gilmore, Amanda Moore, Elizabeth M. Burton, Kathleen Franklin, Xavier Jones, Kelly R. Reveles, Ion Cotarla, Daniel Simmons, Christopher R. Frei; University of Texas Science Center at San Antonio, San Antonio, TX; The University of Texas at Austin College of Pharmacy, Austin, TX; UT Health San Antonio, Encinitas, TX; Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; South Texas Veterans Health Care System, San Antonio, TX; The University of Texas Health San Antonio, San Antonio, TX; University of Texas Health San Antonio, San Antonio, TX; AstraZeneca Pharmaceuticals, Gaithersburg, MD; AstraZeneca, Gaithersburg, MD

Background: Durvalumab improves overall survival (OS) and progression free survival (PFS) when used as consolidation therapy for patients with stage III unresectable non-small cell lung cancer (UR-NSCLC) following chemoradiotherapy (CRT). However, it is uncertain if similar benefits are achieved for patients with PD-L1 positive (1% or greater) and negative (<1%) tumors. We previously found no difference in OS, but no study has yet compared cancer-related overall survival (OS). **Methods:** Patients with stage III UR-NSCLC on durvalumab following CRT, at any Veterans Health Administration (VHA) facility, from 1/1/17 to 6/30/20, were included. Patients were followed from durvalumab initiation through the earliest of their last VHA visit, loss to follow up, death, or end of study (6/30/25). Electronic health record data were retrospectively collected to determine durvalumab treatment course, OS, and cancer-related OS—as determined by review of each patient's chart and death certificate. Kaplan-Meier and Cox regression methods were used to compare cancer-related OS. **Results:** Of the 340 eligible patients, 221 (65%) had PD-L1 positive and 119 (35%) had PD-L1 negative tumors. Groups were similar in age, sex assigned at birth, White race, smoking status, marital status, Charlson score, ECOG 1+ status (78% overall), histology, stage, EGFR, and RAS mutations. Patients with PD-L1 positive and negative tumors had similar median (interquartile range [IQR]) number of durvalumab doses (15 [6-24] vs 13 [5-24], p=0.55), months of durvalumab (8 [3-12] vs 6 [2-12]), and months of follow-up (33 [12-69] vs 28 [11-63], p=0.22). OS was similar for patients with PD-L1 positive and negative tumors in a multivariate model accounting for ECOG 1+ status (HR 0.93, 95% CI 0.70-1.24). Likewise, cancer-related OS was similar in the multivariate model (HR 0.87, 95% CI 0.63-1.21). Median OS was 33.3 months (95% CI 29.8-47.3) for patients with PD-L1 positive tumors and 28.5 months (95% CI 21.6-39.7) for patients with PD-L1 negative tumors. Likewise, median cancer-related OS was 20.4 months (95% CI 16.0-25.4) for patients with PD-L1 positive tumors and 20.6 months (95% CI 15.4-28.5) for patients with PD-L1 negative tumors. The table depicts common causes of death. **Conclusions:** In this real-world study of VHA patients on durvalumab for stage III UR-NSCLC, OS and cancer-related OS were similar for those with PD-L1 positive and negative tumors. Research Sponsor: AstraZeneca Pharmaceuticals LP.

Cause of death.

Cause of death	PDL1+, n=221	PDL1-, n=119	P-value
Disease progression	84%	77%	0.19
Bleeding event	4%	3%	0.75
Cardiac event	14%	14%	1.00
Infection/sepsis	19%	6%	0.01
Intracranial embolism/hemorrhage	2%	3%	0.67
Multiorgan failure	1%	2%	0.56
Thromboembolic event	2%	0%	0.30
Unknown	3%	4%	0.73
Other	9%	19%	0.03

Chromosomal instability and integrated tumor-margin immune ecosystem remodeling as drivers of progression of pulmonary ground-glass nodules.

Ruoyi Jin, Jing Bai, Jiaxing Mu, Shanshan Lu, Yao Fu, Kezhong Chen; Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China; Geneplus-Beijing Institute, Beijing, China; Peking University People's Hospital, Beijing, China; Beihang University, Beijing, China

Background: Precise management of pulmonary ground-glass nodules (GGNs) is hindered by an incomplete understanding of the biological determinants driving the transition from indolence to aggressive progression. **Methods:** In a multicenter longitudinal study of 845 patients, we stratified GGNs into three trajectories via serial CT: Stable, ground glass opacity (GGO)-predominant progression, and solid-predominant progression. Integrative profiling was performed using WES, WGS, bulk RNA-seq, Visium HD, CosMx SMI, and imaging mass cytometry. We developed a deep learning model to predict solid-predominant progression using baseline radiographic features. **Results:** During a median follow-up of 55.8 months, our analysis indicated GGNs progression was driven predominantly by chromosomal instability rather than distinct point mutational profiles. Specifically, progressive GGNs harbored catastrophic structural variations, including chromothripsis, kataegis, and extrachromosomal DNA which were absent in stable lesions. Spatially, the immune microenvironments diverged sharply. While stable GGNs were quiescent, GGO-predominant growth lesions were significantly enriched with antigen-presenting macrophages ($p = 0.00054$), which facilitated the spatial aggregation of activated lymphocytes and promoted the formation of early tertiary lymphoid structure (TLS)-like niches through CCL19-CCR7 signaling. Conversely, in solid-predominant aggressive progression nodules, macrophages underwent a phenotypic shift from antigen-presenting toward SPP1+ state, accompanied by a marked reduction in CD74 and HLA-DR expression ($p = 0.0019$). Within the tumor core, SPP1+ macrophages suppressed T-cell effector function via SPP1-CD44 signaling. At the tumor margin, hypoxia-adapted endothelial cells exhibited significant upregulation of CD274 (PD-L1), contributing to T-cell inhibition, while activated fibroblasts deposited dense collagen matrices formed a physical barrier restricting B-cell infiltration. Together, these mechanisms established a coordinated immunosuppressive niche facilitating tumor growth. Leveraging these biological insights, we developed a deep learning model extracting radiomic features from the baseline CT nodule and an extended 2.5mm perinodular margin. This approach significantly outperformed models using the nodule alone or the nodule plus a 1mm margin ($p < 0.05$), achieving AUCs of 0.89 in the training cohort ($n = 471$), 0.85 in the internal test cohort ($n = 202$) and 0.83 in the external cohort ($n = 117$). **Conclusions:** Distinct radiographic progression trajectories of GGNs are underpinned by divergent chromosomal and spatial immune programs at the tumor core and margin, providing a biological foundation for margin-aware AI strategies to predict aggressive progression and guide optimal surgical intervention. Research Sponsor: None.

PSG copy number amplification and association with poor survival in early-stage female lung adenocarcinoma patients.

Jung Hun Oh, Yingjie Zhu, Himangi Srivastava, Leyla Ebrahimpour, Rena Elkin, Charles Davis Kocher, Corey Weistuch, Larry Norton, Nadeem Riaz, Joseph O. Deasy; Memorial Sloan Kettering Cancer Center, New York, NY; Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pregnancy-specific glycoproteins (PSGs) are essential for maintaining maternal immune tolerance by modulating innate and adaptive responses to prevent fetal rejection. Given our prior finding that increased PSG expression is associated with worse outcomes for female lung cancer patients, we aimed to investigate whether copy number alterations (CNAs) show the same sex-dependent effect on survival in early-stage disease. **Methods:** We evaluated the sex-specific impact of PSG CNAs across two lung adenocarcinoma (LUAD) cohorts: The Cancer Genome Atlas (TCGA) (n = 503; 269 females, 234 males) and MSK-IMPACT (n = 3,863; 2,450 females, 1,413 males). CNAs were retrieved from cBioPortal for the TCGA cohort and determined via the FACETS algorithm on BAM files for the MSK-IMPACT cohort. Overall survival (OS) differences between patients with and without PSG copy number amplification were analyzed using Kaplan-Meier curves along with log-rank tests. Additionally, we examined the association between tumor stage and the prognostic impact of PSG copy number amplification. **Results:** In the TCGA cohort, female patients with PSG copy number amplification exhibited significantly worse OS compared to those without (HR = 1.96, p = 0.0039), while no significant survival difference was observed in males (HR = 1.37, p = 0.1902). This sex-specific trend was further validated in the MSK-IMPACT cohort, where the association between PSG copy number amplification and poor OS was highly significant in females (HR = 1.46, $p = 7.5\times10^{-6}$) but relatively weaker in males (HR = 1.29, p = 0.0089). Notably, the prognostic impact of PSG copy number amplification was stage-dependent; while no significant survival differences were found for either sex in Stage 4 disease across both cohorts, the effect was highly pronounced in early-stage female patients. In the TCGA cohort, female patients with early-stage disease showed increasingly significant survival disparities between patients with and without PSG copy number amplification as stage decreased (Stage $\leq$ 3: HR = 1.81, p = 0.0182; Stage $\leq$ 2: HR = 2.03, p = 0.0129; Stage 1: HR = 2.51, p = 0.0047), whereas no such associations were found in males. Similarly, in the MSK-IMPACT cohort where tumor stage was dichotomized (Stages 1–3 vs. Stage 4), female patients with Stage $\leq$ 3 disease showed a strong survival difference between patients with and without PSG copy number amplification (HR = 1.86, $p = 1.79\times10^{-5}$), which remained significantly stronger than the association observed in the male patients (HR = 1.49, p = 0.0129). **Conclusions:** Our findings raise the question of the potential role of PSG-mediated immune modulation in promoting tumor progression in early-stage female lung cancer patients, and suggest that there may be value in sex-stratified approaches to clinical risk assessment and in therapeutic targeting. Research Sponsor: Breast Cancer Research Foundation.

Breath analysis of volatile organic compounds with mid-infrared laser spectroscopy in a cohort of lung cancer patients and control subjects.

Boshi Duan; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

Background: Exhaled volatile organic compounds (VOCs) represent potential non-invasive biomarkers for lung cancer detection. This study assessed a mid-infrared cavity ring-down spectroscopy (CRDS) platform for measuring key breath VOCs in a large clinical cohort including lung cancer patients across stages/histologies, carcinoma in situ, and non-cancer controls. **Methods:** This prospective single-center validation study enrolled 1,041 participants: approximately 500 with pathologically confirmed lung cancer (various stages and histologies), 25 with carcinoma in situ, healthy controls, patients with benign pulmonary diseases, and those with low- and high-risk pulmonary nodules. Breath samples were collected under standardized fasting and mouth-rinsing conditions and analyzed using a self-developed mid-infrared CRDS system targeting isoprene, acetone, and formaldehyde (detection limit < 10 ppb). The primary endpoint was diagnostic accuracy for distinguishing lung cancer (including carcinoma in situ) from healthy controls, measured by area under the receiver operating characteristic curve (AUC). Sample size was powered to detect an AUC difference of ≥ 0.15 from 0.50 (null hypothesis) with $> 85\%$ power at $\alpha = 0.05$. Group comparisons used independent t-tests or Mann-Whitney U tests with Bonferroni correction for multiple testing. Predictive modeling employed logistic regression and machine learning (random forest and XGBoost) with 5-fold cross-validation; feature importance and SHAP values were assessed. Performance metrics included AUC, sensitivity, specificity, and 95% confidence intervals (CI). **Results:** Isoprene exhibited the most consistent group differences across comparisons ($P < 0.001$ in lung cancer vs healthy and carcinoma in situ vs healthy). Random forest and XGBoost models yielded AUC of 0.94 (95% CI, 0.92-0.96) for lung cancer vs healthy controls and 0.97 (95% CI, 0.95-0.99) for carcinoma in situ vs healthy controls. At optimal thresholds, sensitivity and specificity reached 90-96% and 92-95%, respectively, in primary analyses. Subgroup performance remained robust in non-smokers and stage I patients. Decision curve analysis demonstrated net clinical benefit across 1-20% risk thresholds compared with low-dose CT screening strategies. Acetone and formaldehyde provided supplementary contributions in pathological subtype and benign disease distinctions. **Conclusions:** Mid-infrared CRDS-based breath VOC analysis shows feasible diagnostic performance for lung cancer detection, including strong results in carcinoma in situ and early-stage disease, in this large cohort. Multi-center prospective validation is needed to confirm clinical utility and integration into screening strategies. Research Sponsor: None.

8030 Poster Session

Management of pulmonary nodules across Latin America: A real-world observational study.

Danilo Lopes, Luis Fernando Tejado Gallegos, Victor Oyervides, Uttam Barick, Daniel Nieto, Diana Castano, Lucia Viola, Gabriela Chirino, Eldsamira Mascarenhas, Lorena Noriega-Aguirre, Iris Boyeras, Felipe Marques da Costa; Astrazeneca, São Paulo, Brazil; AstraZeneca, Mexico City, Mexico; Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, NL, Mexico; Vista Health Pte Ltd, Singapore, Singapore; AstraZeneca CAMCAR Costa Rica, S.A., Guachipelin, Costa Rica; ASTRAZENECA COLOMBIA S A, Bogota, Colombia; Fundacion Neumologica Colombia - Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center, Bogotá, Colombia; AstraZeneca Argentina, Buenos Aires, Argentina; Instituto D'Or de Pesquisa e Ensino, Salvador, Brazil; Ciudad de la Salud, Caja de Seguro Social (Health City, Social Security System), Panama City, Panama; Sanatorio Trinidad Palermo, Buenos Aires, Argentina; Hospital Beneficencia Portuguesa, São Paulo, Brazil

Background: Lung cancer is the leading cause of cancer-related mortality globally, with lung cancer accounting for 6.8% of all cancer cases in Latin America and the Caribbean. Despite the availability of guidelines, lung cancer early detection and the management of pulmonary nodules across the region are inconsistent, often hindered by limited resources and fragmented health systems. This study aimed to characterize the diagnostic and treatment journey of pulmonary nodules in patients with lung cancer across Latin America. **Methods:** This was a non-interventional observational study that captured retrospective (March 2019 to July 2021) and prospective (July 2021 to March 2023) data across 16 health institutions in Latin America. Participants were followed for at least two years or until treatment initiation or withdrawal. Data were collected from patients' medical records. Patient characteristics and physicians' involvement were summarised descriptively. Median time estimates of receiving diagnostic procedure or examination from nodule identification and estimates on median time of treatment decision from lung cancer diagnosis were analysed descriptively using the Kaplan-Meier (KM) method. **Results:** Among a total of 546 participants (215 prospective; 331 retrospective), 82 were diagnosed with lung cancer during the study period, most commonly with Stage I lung cancer (5.9%). The majority of referrals to dedicated nodule clinics were made by pulmonologists (44.1%) and prompted by incidentally detected pulmonary nodules (83.9%), which were typically solid and ranged from 8mm to 3cm in size (79.5%). The median time to receiving a diagnostic procedure from nodule identification was 10.83 (prospective) and 12.47 (retrospective) months, while the median time to treatment decision post-diagnosis was 1.20 months across both cohorts. Multidisciplinary teams were involved in only 0.3% of diagnostic procedures, but were involved in at least 40% of treatment decisions across different follow-up visits. **Conclusions:** This study reveals substantial delays in diagnostic procedures and limited multidisciplinary team involvement during early patient evaluation phases in Latin America. Compared with international studies, the study population experienced considerably longer delays in receiving diagnostic procedures. These findings underscore the need for structured referral pathways and broader implementation of critical tools across the region. In addition, adherence to established guidelines is critical to improve early detection and treatment outcomes of lung cancer patients. Research Sponsor: AstraZeneca.

8031 Poster Session

Prognostic stratification of early-stage NSCLC patients using preoperative circulating tumor DNA (ctDNA).

Zhicheng Huang, Daoyun Wang, Jiayue Xu, Yadong Wang, Qiancheng You, Zeliang Deng, Meifang Wu, Bowen Li, Zhibo Zheng, Yuxiao Lin, Zhongxing Bing, Yang Song, Chao Gao, Yicheng Liang, Bing Li, Shanqing Li, Bingsi Li, Nan Zhang, Naixin Liang; Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Burning Rock Biotech, Shanghai, China; Emergency General Hospital, Department of Pulmonary and Critical Care Medicine II, Beijing, China

Background: Curative-intent surgery for early-stage non-small-cell lung cancer (NSCLC) is followed by relapse in approximately 20–30% of patients. We previously reported interim results of the prospective MUSETALK-Lung01 study (multiomics sequencing technique application kick-start), showing that pre-operative, ctDNA positivity predicted increased relapse risk. Here we present the final analysis of the full cohort and incorporate pathological risk factors to conduct a more comprehensive prognostic evaluation for early-stage NSCLC. **Methods:** The MUSETALK-Lung01 study is a prospective, longitudinal, observational study designed to evaluate the clinical utility of a tumor-naïve ctDNA assay in patients with early-stage NSCLC. Cell-free DNA (cfDNA) was extracted, and subjected to CanCatch Surf test as described previously. The assay algorithm reports both the ctDNA detection status (positive/negative) and the estimated ctDNA levels. Longitudinal data, including vital status, treatment, relapse, and survival status, were collected over 5 years. The study was approved by the institutional review board or ethics committee at each site, with all participants providing written informed consent. **Results:** The complete cohort of MUSETALK-Lung01 consisted of 455 early-stage NSCLC patients, among whom the median follow-up time was 63 months, with a 2-year recurrence rate of 7.0% and a presurgical ctDNA positivity rate of 6.4%. To identify clinical and biological factors associated with survival, both univariate and multivariate analyses were performed. Presurgical ctDNA positivity was strongly associated with inferior recurrence outcomes (χ^2 $p < 1 \times 10^{-9}$), indicating that tumor burden can be prognostic beyond clinical stage and pathological conditions. Specifically, among clinical stage I lung adenocarcinoma (LUAD) patients, ctDNA detection demonstrated robust prognostic stratification for recurrence risk (2-year RFS: 60% [95% CI: 40%–91%] vs. 96% [95% CI: 94%–98%]; log-rank $p < 1 \times 10^{-7}$). Similar prognostic value of ctDNA was observed in stage II-IIIA LUAD patients, albeit with reduced discriminative power (log-rank $p < 0.01$). After incorporating pathological information, the performance of prognostic stratification was further improved. **Conclusions:** By evaluating ctDNA abundance, we provide highly sensitive and specific prognostic assessments and risk stratification for early-stage NSCLC patients. The non-invasive, nature of this test enables precision peri-operative management and selection of patients who may benefit from innovative treatments, with the potential to improve survival. Research Sponsor: Burning Rock Biotech.

Pseudoprogression after neoadjuvant immunotherapy for resectable NSCLC: Incidence, PET/CT patterns, and differentiation.

Li-Bo Berlin Tang, Yi Pan, Ji Chen, Hui Lin, Hong-Hong Yan, Jun-Xi Zeng, Song Dong, Lixu Yan, Yi Yang, Dong-Jiang Li, Yi-Long Wu; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; School of Basic Medicine, Guizhou Medical University, Guizhou, China; Department of Pathology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; Department of Thoracic Surgery, The Third People's Hospital of Chengdu; Affiliated Hospital of Southwest Jiaotong University; College of Medicine, Southwest Jiaotong University, Chengdu, Sichuan, China; Department of Nuclear Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China

Background: Neoadjuvant immunotherapy combined with chemotherapy is now the standard of care for resectable non-small cell lung cancer (NSCLC). However, evaluating treatment response remains challenging due to the unique response pattern of pseudoprogression associated with immune checkpoint inhibitors (ICIs), which may lead to unnecessary cancellation of curative surgeries. This study aimed to characterize pseudoprogression and investigate strategies for distinguishing pseudoprogression from true tumor progression in the neoadjuvant ICI setting. **Methods:** This retrospective study included 283 patients with resectable NSCLC who underwent neoadjuvant ICI therapy (n=235) or targeted therapy (n=48) between January 2021 and December 2023. PET-CT scans were acquired at baseline and before surgery. Radiological and metabolic responses were evaluated using RECIST 1.1 and EORTC criteria, respectively. Pathological responses were assessed according to IASLC guidelines. Multivariate logistic regression and receiver operating characteristic analyses were performed to identify predictors of pseudoprogression and evaluate diagnostic performance. **Results:** Among 283 patients (ICI 235, TKI 48), 9.2% (26 patients) were classified as having progressive disease (PD) by RECIST 1.1, all in the ICI cohort. According to EORTC on PET-CT, progression increased to 25.1% (71 patients). Despite radiologic progression, all 26 patients underwent R0 resection; pCR and MPR rates were 53.8% and 11.6%. Among patients without radiologic progression, pCR and MPR were 30.0% and 19.1%, with no differences in R0 rate or pathological response ($p = 1.00$ and 0.06). Among 71 patients with progressive metabolic disease (PMD) on PET/CT, 69 (97.2%) achieved R0 resection; 27 (38.0%) achieved pCR and 12 (16.9%) achieved MPR, with similar outcomes by PMD status ($p = 1.00$ and 0.53). In both the ICI cohort and overall population, primary tumor progression was associated with lower MPR rates than lymph node or distant progression (16.7%, 61.2%, and 100%; $p = 0.001$) and worse EFS and OS. In the TKI cohort, imaging-defined progressive or stable disease was associated with lower MPR and worse survival. Pseudoprogression occurred in 7.2% by CT, increasing to 16.2% with PET-CT, predominantly nodal. A $\geq$53.1% reduction in primary-tumor SUVmax identified pseudoprogression (AUC 0.865; sensitivity 73.8%; specificity 88.6%). A multivariable model combining ΔSUVmax, longest diameter change (%), smoking status, and histology showed excellent discrimination (AUC 0.935). **Conclusions:** Pseudoprogression is common in resectable NSCLC treated with neoadjuvant ICI therapy, presenting as nodal or distant lesions without primary tumor progression. A multifactorial model incorporating primary tumor SUVmax changes provides a robust tool for distinguishing pseudoprogression and guiding clinical decision-making. Research Sponsor: None.

8033 Poster Session

Class-specific clinical and molecular features of *SMARCA4* alterations in non–small cell lung cancer.

Chihiro Takemura, Tatsuya Yoshida, Kouya Shiraishi, Yukihiro Yoshida, Jun Miyakoshi, Ryoko Inaba Higashiyama, Yasushi Goto, Noboru Yamamoto, Yasushi Yatabe, Takashi Kohno, Ryuji Hamamoto, Shunichi Watanabe; Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan; National Cancer Center Hospital, Tokyo, Japan; Department of Diagnostic Pathology, National Cancer Center, Tokyo, Japan; Division of Medical AI Research and Development, National Cancer Center Research Institute, Tokyo, Japan

Background: *SMARCA4* mutations occur in 5–10% of non-small cell lung cancers (NSCLCs) and are associated with poor overall survival, especially class I *SMARCA4* alterations (truncating mutations, fusions, and homozygous deletion), which often result in *SMARCA4* loss. However, the biological and clinical significance of *SMARCA4* alteration classes and their distribution among pan-cancers in Asians remain unclear. **Methods:** We analyzed pan-cancer across solid tumors patients enrolled in Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database (approval number CDU2021-001N) between June 2019 and October 2025 and patients with surgically resected NSCLCs at our hospital between 1999 and 2023 (approval number 2005-109) were performed by whole exome sequencing. Somatic mutations were annotated using Annovar and OncoKB. *SMARCA4* mutations were classified into two groups: class I or class II (missense or other). Copy number alterations were detected using facets and GISTIC2. Transcriptomic differences were assessed using RNA sequencing with DESeq2 and gene set enrichment analysis (GSEA). Tumor immune cell composition was assessed using CIBERSORTx. **Results:** In the C-CAT pan-cancer dataset (N=10,155), *SMARCA4* mutations were frequently identified in NSCLC (NSCLC vs. others; 12.3% vs. 4.0%). In NSCLC, *TP53* was the most frequent co-altered gene in patients with class I and class II mutation (73.0% vs. 63.0%). Other major genes did not show clear class-associated differences. In our NSCLC cohort (N=1,166), the frequency of *SMARCA4* class I and II mutation was 2.3% (all truncating) and 2.3% (all missense), respectively. The class I *SMARCA4* alterations were associated with significantly poorer survival outcomes compared with wild- type tumors (OS: HR = 2.04, 95% CI = 1.24–3.12, p = 0.007; RFS: HR = 2.09, 95% CI = 1.28–3.20, p = 0.005), whereas class II alterations were not significantly different in survival (OS: HR =0.50, 95% CI =0.40-0.61, p =0.17; RFS: HR = 0.46, 95% CI = 0.42–0.76, p =0.12). Regarding transcriptomic analysis and genomic profiling, class I tumors showed activation of *ASCL1*-related transcriptional programs, suppression of squamous/basal lineage differentiation, increased $CD8^+$ T-cell infiltration, and recurrent copy number loss of *SMARCA2* and *CDKN2A/B* compared with wild type tumors. In contrast, class II tumors showed limited transcriptomic divergence from wild-type tumors, downregulating *SPRR2E*, *KRT5*, and *KRT13* without a significant $CD8^+$ T-cell difference. **Conclusions:** In NSCLC, class I *SMARCA4* altered tumors are associated with poor survival outcomes, and an immune-active molecular phenotype with recurrent copy number loss of *SMARCA2* and *CDKN2A/B*, whereas class II tumors lack these features and do not show adverse survival compared to wild-type tumors. This highlights the distinct clinical implications of *SMARCA4* alteration class. Research Sponsor: None.

Outcomes of atypical *EGFR* mutations in early-stage *EGFR*-mutated non-small cell lung cancer (NSCLC).

Jacqueline V. Aredo, Surbhi Singhal, Mandeep Banwait, Emily Guo, Zofia Piotrowska, Heather A. Wakelee, Joseph B. Shrager, Mark F. Berry, Billy W. Loo Jr., Maximilian Diehn, Carlos J. Suarez, Gerald Berry, Jonathan W. Riess, Joel W. Neal; Stanford Cancer Institute, Stanford, CA; University of California Davis Comprehensive Cancer Center, Sacramento, CA; Mass General Brigham Cancer Institute, Boston, MA

Background: Adjuvant osimertinib (osi) improves survival outcomes in patients (pts) with early-stage *EGFR*-mutated NSCLC harboring the classical *EGFR* exon 19 deletions (ex19del) or L858R mutation after surgery or chemoradiotherapy. Pts with early-stage NSCLC harboring atypical *EGFR* mutations were excluded from the respective clinical trials. Outcomes in this pt population remain unknown. **Methods:** We conducted a multi-institutional retrospective analysis of pts with stage IA-IIIC *EGFR*-mutated NSCLC (2010-2024) who were classified into two groups: those with tumors harboring classical *EGFR* mutations (c-*EGFR*: ex19del or L858R) or atypical *EGFR* mutations (a-*EGFR*: non-ex19del or L858R). Kaplan-Meier analyses compared disease-free survival (DFS), central nervous system (CNS) DFS, and overall survival (OS). Multivariable Cox regression adjusted for disease stage, definitive therapy, and adjuvant therapy. **Results:** Among 417 pts, 293 had tumors harboring c-*EGFR* and 124 had a-*EGFR* mutations. Baseline characteristics were similar between groups (Table). Median follow-up was 4 years. Among pts not treated with adjuvant osi (n = 346), a-*EGFR* was associated with a significantly lower 3-year DFS compared to c-*EGFR* (52.5% vs 71.2%; HR 1.71, 95% CI 1.21-2.42; P = 0.003). Compared to c-*EGFR*, a-*EGFR* had higher rates of recurrence to the ipsilateral lung (24% vs 14%) and bone (12% vs 6%). A-*EGFR* was associated with a significantly lower 3-year CNS DFS (81.3% vs 87.1%; P = 0.002) and 5-year OS (77.7% vs 85.6%; P = 0.007) compared to c-*EGFR*. Among pts with a-*EGFR* mutations, *EGFR* exon 20 insertions (ex20ins) were associated with a significantly reduced 3-year DFS compared to other alterations (35.9% vs 68.2%; HR 2.04, 95% CI 1.10–3.77; P = 0.013), and with a lower 3-year CNS DFS (70.9% vs 92.2%; P = 0.028) and trend towards lower 5-year OS (71.3% vs 84.4%; P = 0.141). Among pts who underwent surgery for stage IB-IIIA NSCLC (n = 209), adjuvant osi improved 3-year DFS among c-*EGFR* (84.2% with osi vs 63.4% without osi) whereas a-*EGFR* had a lower 3-year DFS (36.4%; P < 0.001), which was driven by *EGFR* ex20ins compared to other alterations (19.9% vs 59.2%; P = 0.003). **Conclusions:** Atypical *EGFR* mutations are associated with inferior survival outcomes compared to classical *EGFR* mutations in early-stage NSCLC. *EGFR* ex20ins appear to drive poor outcomes among the atypical *EGFR* mutations. Novel adjuvant therapy strategies are warranted to improve definitive treatment of early-stage atypical *EGFR*-mutated NSCLC. Research Sponsor: None.

	Classical *EGFR*, N=293 (%)	Atypical *EGFR*, N=124 (%)
Ex19del / L858R	46 / 54	-
Ex20ins / G719X / L861Q / Other	-	49 / 26 / 17 / 8
Stage IA / IB / II / III	35 / 23 / 17 / 25	38 / 14 / 23 / 25
Surgery / XRT / CRT	81 / 8 / 8	82 / 8 / 7
Neoadjuvant Chemo / EGFR TKI	4 / 3	7 / 2
Adjuvant Chemo / EGFR TKI / Osi	26 / 25 / 23	26 / 8 / 4
3-year DFS*	71.2	52.5
3-year CNS DFS*	87.1	81.3
5-year OS*	85.6	77.7

*In non-adjuvant osi cohort (n=346). Statistically significant difference.

8035 Poster Session

Clinical impact of genomic co-mutation profiles including TP53 in resected early-stage *EGFR*-mutated NSCLC: LC-SCRUM-Advantage.

Kiyotaka Yoh, Yoshitaka Zenke, Shingo Kitagawa, Kenta Tane, Toshio Kasugai, Takafumi Hashimoto, Hiroki Matsumiya, Shingo Miyamoto, Atsushi Suzuki, Yoichi Ohtaki, Tomohiro Miyoshi, Yuki Matsumura, Keiju Aokage, Yu Tanaka, Hiroki Izumi, Tetsuya Sakai, Shigeki Umemura, Shingo Matsumoto, Masahiro Tsuboi, Koichi Goto; National Cancer Center Hospital East, Kashiwa, Japan; Nippon Medical School Hospital, Tokyo, Japan; Matsunami General Hospital, Gifu, Japan; Oita Prefectural Hospital, Oita, Japan; School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; Japanese Red Cross Medical Center, Tokyo, Japan; Itami City Hospital, Hyogo, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Adjuvant osimertinib is the standard of care for resected stage IB–IIIA EGFR-mutated non-small cell lung cancer (NSCLC), and its benefit in stage IA2–IA3 disease is being evaluated in ADAURA2. However, the prognostic impact of genomic co-alterations, particularly TP53, in early-stage EGFR-mutated NSCLC remains unclear. This study characterized genomic co-alterations and their association with clinicopathologic features in resected early-stage EGFR-mutated NSCLC. **Methods:** LC-SCRUM-Advantage is a prospective genomic screening program for resected NSCLC. Postoperative tumor specimens were analyzed using the Oncomine Precision Assay to identify co-alterations, including TP53 and other recurrent genes, across major EGFR mutation subtypes. PD-L1 expression was assessed by immunohistochemistry. Clinico-genomic characteristics and survival outcomes were evaluated. **Results:** Among 1052 enrolled patients, 327 had EGFR-mutated adenocarcinoma (19del 42%, L858R 47%, others 11%). Among tumors with common EGFR mutations, single EGFR alterations accounted for 59%, while co-alterations were detected in 41%. Frequent co-alterations included TP53 (19%), CTNNB1 (4%), PIK3CA (4%), additional EGFR mutations (5%), and EGFR amplification (12%). Co-alteration prevalence increased with pathological stage (IA1 25%, IA2–IA3 41%, IB 53%, II 47%, III 46%), with TP53 showing a similar pattern (IA1 8%, IA2–IA3 18%, IB 19%, II 28%, III 27%). PD-L1 positivity also increased progressively with disease stage (I 37%, II 52%, III 73%; p = 0.0002). TP53-mutated tumors showed a significantly higher PD-L1 positivity rate than TP53 wild-type tumors (60% vs. 39%; p = 0.007). Co-alteration frequencies were comparable across EGFR subtypes. With limited follow-up, five recurrences were observed (IB 1, IIA 1, IIIA 2, IVA 1); three involved co-alterations (TP53, EGFR amplification, EGFR E709V). **Conclusions:** Genomic co-alterations, including TP53, were common and increased with pathological stage in early-stage EGFR-mutated NSCLC. Co-altered tumors exhibited features associated with aggressive biology, including higher PD-L1 expression. Early recurrences were frequently observed in patients with co-alterations, underscoring their potential prognostic relevance. These findings highlight substantial molecular heterogeneity within early-stage EGFR-mutated NSCLC and support incorporating co-alteration status into risk stratification and adjuvant treatment planning. Ongoing follow-up from this study will further clarify the prognostic and predictive significance of co-alterations, particularly regarding their implications for adjuvant targeted therapy. Research Sponsor: Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K.

Fusion-positive early-stage and locally advanced lung cancers: A real-world analysis of event-free, disease-free, and overall survival.

Sameh Nabeeh Daher, Jaime Rubio Perez, Matteo Repetto, Jamie E. Chaft, Soo-Ryum Yang, Jason C. Chang, Sabrina T. Lin, Alexia Iasonos, Alexander E. Drilon; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Division of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, NY

Background: Fusion-positive lung cancers are a distinct subset of lung cancers. While outcomes in metastatic disease are comprehensively characterized, data on survival and disease recurrence outcomes after definitive therapy in non-metastatic disease remain limited. **Methods:** This was a single institution, retrospective study, including patients (pts) with *ALK/ROS1/RET/NTRK+* early-stage/locally advanced lung cancer pts diagnosed between 2012-2025. The primary endpoint in pts who underwent curative surgery or stereotactic body radiotherapy (SBRT) was disease-free survival (DFS; time from curative therapy to disease recurrence or death). The primary endpoint in pts initially treated with neoadjuvant therapy prior to surgery or definitive chemoradiation was event-free survival (EFS; time from curative therapy to disease progression, recurrence, failure of treatment or death). Overall survival (OS) from the start of curative therapy was analyzed. **Results:** 179 pts (82 *ALK*, 38 *ROS1*, 55 *RET*, 4 *NTRK*) were identified. Median EFS across all pts for *ALK/ROS1/RET/NTRK* was 4.4yrs (95%CI: 2.8, Not Reached (NR)), 3.4yrs (95%CI: 2.0, NR), 7.4yrs (95%CI: 4.6, NR) and 3.0yrs (95%CI: 0.4, NR), respectively. Median OS for *ALK/ROS1/RET/NTRK* pts was: 13.0yrs (95%CI: 12.0, NR), 12.0yrs (95%CI: 11.0, NR), 14.0yrs (95%CI: 12.0, NR) and NR (95%CI: 5.4, NR), respectively. 132/179 (74%) of all pts were treated with surgery (128 pts) or SBRT (4 pts) first. Median EFS for pts treated with neoadjuvant treatment first (N=26) for *ALK* (n=15)/*ROS1* (n=5)/*RET* (n=6) pts was 0.9yrs (95%CI: 0.8, NR), 0.9yrs (95%CI: 0.7, NR) and NR (95%CI: 0.2, NR), respectively. Median EFS for pts treated with chemoradiation first (N=21) for *ALK* (n=7)/*ROS1* (n=5)/*RET* (n=9) pts was NR (95%CI: 0.5, NR), 0.6yrs (95%CI: 0.5, NR) and 1.0yrs (95%CI: 0.8, NR), respectively. Median DFS for pts treated with surgery/SBRT first (N=132) for *ALK* (n=60)/*ROS1* (n=28)/*RET* (n=40)/*NTRK* (n=4) pts was: 5.1yrs (95%CI: 3.8, NR), 5.2yrs (95%CI: 3.2, NR), NR (95%CI: 6.6, NR) and 3.0yrs (95%CI: 0.4, NR), respectively. **Conclusions:** This is the largest series on outcomes in fusion-positive early stage/locally advanced lung cancers treated with definitive therapy. Prolonged EFS, DFS, and OS were observed. Research Sponsor: None.

8037 Poster Session

Induction chemoimmunotherapy followed by hypofractionated radiotherapy and consolidation immunotherapy for locally advanced unresectable non–small cell lung cancer: A prospective phase II study.

Xiangzhi Zhu, Lijun Zhao, Ning Jiang, Liyue Ma, Cheng Kong, Xue Song, Bing Feng, Feng Jiang, Ming Jiang, Binhui Ren, Yang Zhao, Meiqi Shi, Ming Li, Bo Shen; The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China; Department of Radiation Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China; Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; Jiangsu Cancer Hospital, Nanjing, Jiangsu, China; Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China; Department of Biostatistics, Nanjing Medical University, Nanjing, Jiangsu, China; The Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China

Background: Concurrent chemoradiotherapy followed by consolidation immunotherapy is the standard treatment for unresectable stage III LA-NSCLC; however, many patients in real-world practice are unable to complete concurrent therapy, and locoregional failure remains common. This phase II study evaluated induction chemoimmunotherapy followed by hypofractionated radiotherapy (hypo-RT) and consolidation immunotherapy to improve feasibility and disease control. **Methods:** Patients with newly diagnosed unresectable stage III NSCLC received 3-4 cycles of immune checkpoint inhibitors combined with platinum-based doublet chemotherapy. Patients without progression or grade ≥2 pneumonitis underwent eligibility assessment for hypo-RT based on anatomical suitability and organ-at-risk constraints. Eligible patients received definitive sequential hypo-RT (48–60 Gy in 12–15 fractions based on tumor regression) and consolidation immunotherapy when appropriate. The primary endpoint was progression-free survival (PFS) with secondary endpoints of safety and overall survival (OS). **Results:** Between October 2022 and October 2025, 132 patients received induction chemoimmunotherapy, and 55 underdoing hypo-RT. Median age was 70 years (range, 47–85), and 42 patients (76.4%) had squamous cell carcinoma. Programmed death-ligand 1 (PD-L1) expression ≥1% was observed in 17 patients (30.9%), with unknown PD-L1 status in 14 patients (25.5%). With a median follow-up of 20.1 (95%CI, 17.3-22.9) months, median PFS and OS were not reached. The 1- and 2-year PFS rates were 88.1% (95% CI, 78.8%–98.5%) and 58.5% (95% CI, 43.6%–77.7%), respectively; the 1- and 2-year OS rates were 100% and 77% (95% CI, 61.5%–93.7%), respectively. Isolated in-field recurrence occurred in 4 patients (7.3%). Pneumonitis was the most common acute nonhematologic toxicity, with grade 3 in 4 patients (7.3%) and grade 4 in 1 patient (1.8%). Grade 3 atelectasis occurred in 4 patients (7.3%), and grade 3 radiation esophagitis in 2 patients (3.6%). No grade 5 toxicities were observed. **Conclusions:** Induction chemoimmunotherapy followed by eligibility-adapted hypofractionated radiotherapy showed promising survival and locoregional control with acceptable toxicity in unresectable locally advanced NSCLC, supporting its feasibility as an alternative strategy for selected patients. Clinical trial information: NCT05784142. Research Sponsor: Research Project of Jiangsu Cancer Hospital (No. ZL202301), Jiangsu Cancer Hospital Yishan Fund (YSZD202405), and Jiangsu Cancer Hospital Yishan Fund (YSPY202403).

Analysis of recurrence and risk factors in resectable early-stage adenocarcinoma with uncommon *EGFR* mutations: A comprehensive cohort study in South Korea.

Insu Kim, Jung Seop Eom; Dong-A University Hospital, Busan, South Korea; Pusan National University Hospital, Busan, South Korea

Background: This study aimed to identify clinicopathologic factors associated with recurrence in patients with surgically resected lung adenocarcinoma harboring uncommon EGFR mutations. **Methods:** We conducted a multicenter retrospective cohort study. The study included patients with stage I–III lung adenocarcinoma harboring uncommon EGFR mutations (G719X, S768I, or L861Q) who underwent curative-intent resection between 2010 and 2017 in South Korea. Recurrence-free survival (RFS) and overall survival (OS) were analyzed using Cox proportional hazards models. **Results:** A total of 48 patients were analyzed (stage I: n=33, stage II: n=6, stage III: n=9). The median age was 65 years; 56.3% were female and 66.7% were never-smokers. Mutation distribution was G719X (72.9%), S768I (16.7%), and L861Q (10.4%). Visceral pleural invasion (VPI) and lymphovascular invasion (LVI) were present in 37.5% and 16.7% of cases, respectively. During follow-up, 26 patients (54.2%) experienced recurrence and 21 (43.8%) died. Multivariable analysis identified ECOG performance status ≥1 (HR 4.55, 95% CI 1.226–16.899; P=0.024), stage III vs. I (HR 5.07, 1.181–21.771; P=0.029), and VPI (HR 3.67, 1.030–13.058; P=0.045) as independent predictors of recurrence. EGFR subtype (non-G719X vs. G719X) was not significantly associated with recurrence (P=0.428). **Conclusions:** Patients with surgically resected lung adenocarcinoma harboring uncommon EGFR mutations face a substantial risk of postoperative recurrence. Conventional clinicopathologic factors—particularly ECOG status, advanced stage, and VPI—outperform EGFR subtype as prognostic indicators. These findings support the need for risk-adapted surveillance and prospective evaluation of adjuvant strategies in these high-risk subsets. Research Sponsor: None.

Univariate and multivariate Cox regression analysis for the risk factors associated with recurrence.

Variables	Recurrence rate*	Univariate analysis, HR (95% CI)	*P*-value	Multivariate analysis, HR (95% CI)	*P*-value
ECOG					
0	50.0 (19/38)	-		-	
1≤	70.0 (7/10)	1.64 (0.678-3.955)	0.273	4.55 (1.226-16.899)	**0.024**
EGFR mutation					
G719X	54.3 (19/35)	-		-	
Non-G719X	53.8 (7/13)	0.91 (0.377–2.210)	0.840	0.58 (0.155–2.207)	0.428
Tumor size†					
< 2.0 cm	38.5 (5/13)	-		-	
≥ 2.0 cm	60.0 (21/35)	1.59 (0.599–4.214)	0.353	1.75 (0.434–7.068)	0.431
Clinical stage					
I	48.5 (16/33)	-		-	
II	66.7 (4/6)	1.65 (0.549–4.950)	0.373	1.33 (0.368–4.801)	0.663
III	66.7 (6/9)	2.11 (0.820-5.436)	0.121	5.07 (1.181-21.771)	**0.029**
Lymphovascular invasion					
Absent	52.5(21/40)	-		-	
Present	62.5(5/8)	1.11 (0.420–2.958)	0.827	0.03 (0.001–0.841)	**0.040**
Visceral pleural invasion					
Absent	46.7 (14/30)	-		-	
Present	66.7 (12/18)	1.97 (0.893–4.334)	0.093	3.67 (1.030–13.058)	**0.045**

*Presented as number of recurrences / number of patients (%).
†ROC curve and Youden's index analyses were used to determine the cut-off value of primary tumor size.

8039 Poster Session

Socioeconomic focus in neoadjuvant chemoimmunotherapy: An analysis of pathologic complete response and overall survival in clinical stage II-III NSCLC patients.

Jack William Ibinson, Jorge Raul Vazquez Urrutia, Shinkichi Takamori, Asato Hashinokuchi, Junjia Zhu, Takefumi Komiya; Penn State College of Medicine, Hershey, PA; Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Dana-Farber Cancer Institute, Boston, MA; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Public Health Sciences, Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Penn State Hershey Medical Center, Hershey, PA

Background: In 2022, CheckMate 816 supported neoadjuvant chemoimmunotherapy (CTIO) as standard treatment for clinical stage II-III non-small cell lung cancer (NSCLC). Low socioeconomic status has historically been underrepresented in clinical trials, warranting further analysis of CTIO outcomes in patients from diverse socioeconomic backgrounds. This study aims to assess the role of socioeconomic factors on pathologic complete response (pCR) and overall survival (OS) after CTIO. **Methods:** Data from the National Cancer Database (NCDB) was obtained for patients diagnosed with clinical stage II-III NSCLC between 2022-2023 undergoing CTIO. Complete T, N, and M stage and post-pathologic status (ypT, ypN) were obtained. OS was available for patients diagnosed in 2022. Patients receiving neoadjuvant radiotherapy or with clinical or pathologic metastatic disease were excluded. Group comparisons were based on socioeconomic factors: age (< 75 vs ≥ 75 years), sex, race (Non-Hispanic White vs Other), primary payor at diagnosis, urban/rural, percent no high-school degree quartile, and median income quartile. Primary outcomes were pCR and OS, analyzed via logistic and cox regression models, respectively. All tests were two-sided, and a p-value of < 0.05 was statistically significant. **Results:** 2,819 patients received CTIO from 2022-2023, with 1,134 patients diagnosed in 2022. Univariate analysis showed patients in the two lowest median income quartiles ($46,277–$57,856: OR 1.40, 95% CI 1.08-1.80, p = 0.011; < $46,277: OR 1.70, 95% CI 1.30-2.23, $p < 0.001$) had significantly higher odds of pCR compared with those in the highest income quartile (≥$74,063). This effect persisted in multivariate analysis ($46,277–$57,856: OR 1.59, 95% CI 1.19-2.13, p = 0.002; < $46,277: OR 2.00, 95% CI 1.41-2.83, $p < 0.001$). Univariate analysis showed that other race (HR 0.49, 95% CI 0.29-0.81, p = 0.006) was associated with improved OS compared to Non-Hispanic White, which persisted in multivariate cox analysis (HR 0.50, 95% CI 0.30-0.85, p = 0.010). There were no significant associations for pCR and OS with age, sex, primary payor at diagnosis, urban/rural status, or percent no high school degree quartile. **Conclusions:** Our findings present promising evidence of improved outcomes of neoadjuvant chemoimmunotherapy among groups facing historical marginalization, namely low-income communities and non-white race. These effects were persistent in multivariate regression models controlling for other socioeconomic variables such as age, sex, primary payor, urban/rural, and percent no high school degree quartile. In light of these findings, further studies with diverse patient populations are warranted to examine the benefit of neoadjuvant chemoimmunotherapy on patients with NSCLC. Research Sponsor: None.

An integrated multidisciplinary analysis of pre-treatment cachexia in locally advanced non–small cell lung cancer.

Ernest Nadal, Sara Hijazo-Pechero, Lorena Arribas, Aina Llenas-Bladé, Inmaculada Peiro, Felipe Jiménez, Joaquim Moreno-Caceres, Matías Fernández-Huarte, Ana Regina Gonzalez-Tampan, Miguel Mosteiro, M. Andres Cuellar, Noelia Vilariño, Maria Jove, Ramón Palmero, Miriam Nuñez-Fernandez, Isabel Brao, Monica Arellano, Susana Padrones, Eduard Montanya, Cristina Munoz-Pinedo; Thoracic Tumors Unit, Medical Oncology, Catalan Institute of Oncology (ICO). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain; Preclinical and Experimental Research in Thoracic Tumors (PRETT). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain; Clinical Nutrition Unit. Catalan Institute of Oncology (ICO), Hospitalet De Llobregat (Barcelona), Spain; Thoracic Tumors Unit, Radiation Oncology, Catalan Institute of Oncology (ICO). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Barcelona, Spain; Thoracic Tumors Unit. Catalan Institute of Oncology (ICO). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain; Thoracic Tumors Unit. Hospital Universitari de Bellvitge. Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain; Endocrinology Department, Hospital Universitari de Bellvitge. Bellvitge Biomedical Research (IDIBELL), Barcelona, Spain

Background: Cancer-associated cachexia is underdiagnosed and not routinely captured in cancer registries, despite its negative impact on quality of life and survival. We aim to determine the prevalence of cachexia in patients with locally advanced NSCLC and to perform a multidisciplinary characterization of cachexia to inform the development of future therapeutic interventions. **Methods:** In this prospective study, 51 patients diagnosed with locally advanced unresectable NSCLC candidates to concurrent chemoradiotherapy followed by immunotherapy at the HUB-ICO Comprehensive Cancer Centre (2022-2024) were included. The primary objectives were to (1) determine the frequency of cachexia according to Fearon's criteria and (2) characterize patients before and after completing chemoradiotherapy in terms of nutritional status, metabolic parameters, body composition and circulating cytokine levels. Baseline assessment results are reported here. **Results:** Most patients were male (80%) and ever smokers (98%), with a median age of 68 years. All patients completed the planned concurrent chemoradiotherapy regimen, whereas only 43% initiated durvalumab consolidation therapy. At baseline, 27 patients met the diagnostic criteria for cachexia (53%, 95% CI 39-66) and women were more likely to have cachexia than men (80% vs 46%, respectively), although this difference was not statistically significant. Cachexia was significantly associated with more advanced tumor stage ($p < 0.001$), worse performance status ($p = 0.027$), lower skeletal muscle index ($p = 9e-4$) and reduced total adipose tissue index ($p = 0.004$), elevated C-Reactive Protein blood levels ($p = 0.004$), moderate to severe malnutrition ($p < 0.001$), reduced caloric intake ($p = 0.007$) and decreased physical strength ($p = 0.001$). Cachectic patients had lower fat intake compared with non-cachectic individuals ($p = 0.006$), while protein intake was similar in both subgroups. Proteomic profiling using the O-link platform identified significant differences in circulating cytokine levels between cachectic and non-cachectic patients. Cachexia was associated with significantly increased levels of CCL23, IL-6, C1QA, CSF1, motilin and agouti-related protein (AGRP), among others, which showed varying degrees of correlation with caloric intake. By contrast, GDF-15 was significantly associated with weight loss ($p = 0.00014$) but showed no association with caloric intake or body composition parameters. **Conclusions:** This prospective study reveals that cancer-associated cachexia is highly prevalent in patients with unresectable locally advanced NSCLC before treatment initiation. Beyond previously described inflammatory mediators, we identified several understudied cytokines, which may contribute to the progression of the cachexia phenotype and represent potential targets for future therapeutic interventions. Research Sponsor: None.

Decomposing the co-mutational landscape of NSCLC by unsupervised learning to unveil components with impact on overall survival.

Chidiebube Ugwu, Stefano Polizzi, Martin Metzenmacher, Amin Turki; Jefferson Einstein Philadelphia Hospital, Philadelphia, PA; IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Department of Medical Oncology, West German Cancer Center, University of Duisburg-Ess, Essen, Germany; Computational Hematology Lab, Institute for AI in Medicine (IKIM), University Hospital Essen, Germany, Essen, Germany

Background: The molecular characterization of non-small cell lung cancer (NSCLC) and targeting therapies are improving outcomes for many patients. However, about 40% remain without identifiable molecular drivers. Understanding the co-mutational landscape of NSCLC may contribute to close that gap but has not yet been sufficiently characterized beyond e.g. *TP53* co-mutations that associated with adverse outcome (Galina et al. *J. Thor. Onc.* 2024). Previously, the hierarchical Dirichlet mixture model (HDMM) provided important insight into acute leukemia biology (Papaemmanuil et al. *NEJM* 2016, Turki et al. *EHA plenary abstract* 2025), reason why we adopted this method for the first time to decompose the NSCLC genetics landscape. **Methods:** Here, we leveraged the HDMM with multinomial distribution for unsupervised learning of NSCLC genetics on the large AACR GENIE BPC NSCLC cohort (n = 1,846 patients, Choudhury et al. *Clin. Can. Res.* 2023) including 300 features for 60 genes. Preprocessing excluded columns with < 5 mutations, features duplicating information or with high rates of missingness, leaving the most relevant 85 genetic features for HDMM analysis including single mutations, gene amplifications and deletions. Within UICC stages I, II-III and IV, overall survival (OS) was analyzed with the Kaplan Meier method comparing the new components with the logrank test. **Results:** Among 1926 genetically distinct tumors of 1785 NSCLC patients with detectable genetic alterations, the HDMM identified four components assembling patients with similar landscape. Their driver patterns involved either co-mutated *TP53/KRAS*, *TP53/EGFR* or *PDGFR/KDR* and other mutations including established risk groups, i.e. with amplifications in *ALK*, *BRAFV600E*, *cMET exon 14* or single *EGFR* or *KRAS* mutations, *ROS1* or *NTRK* translocations. As expected, UICC stages I-IV stratified this cohort significantly for OS. Next, we tested whether genetic components refined outcomes within the same UICC stage. Indeed, for stage I NSCLC the genetic components associated with significant OS differences (p = 0.0065). Patients with PDGFR/KDR had the highest OS, while patients of the TP53/KRAS component had the lowest median OS with a Kaplan Meier estimate of 82.4 months as compared to 116.7 in the TP53/EGFR cluster. Also, among patients with stage II-III NSCLC, the three components associated with significant differences in OS (p = 0.023). Not taking into account other driver mutations, the components also associated with distinct OS in patients with stage IV NSCLC (p = 0.0001). **Conclusions:** This analysis of the co-mutational landscape is complementing existing genetic classes in NSCLC. We identified a new *PDGFR/KDR* component and support the relevance of previously described co-occurring *TP53/EGFR* and *TP53/KRAS*. The significantly distinct OS in resectable NSCLC may open new risk adapted treatment strategies. Research Sponsor: None.

Fraction genome altered to predict survival in early-stage non–small cell lung cancer.

Mobina Shrestha, Salina Dahal, Vishal Mandal; Sentara Albemarle Medical Center, USACS, Elizabeth City, NC; The Ohio State University, Columbus, OH; University of Missouri Columbia, Columbia, MO

Background: Patients with stage I-III non-small cell lung cancer (NSCLC) often have very different outcomes, even when they share the same anatomic stage. This suggests that tumor biology plays an important role in prognosis. Fraction genome altered (FGA), a measure of chromosomal instability derived from next-generation sequencing (NGS), is already used in clinical practice but its prognostic value in early-stage NSCLC is not well established. Therefore, we evaluated whether FGA is associated with overall survival (OS) in early-stage NSCLC and whether it provides prognostic information beyond standard clinical factors and tumor mutation burden (TMB). **Methods:** We performed a retrospective analysis of 7,722 patients with NSCLC using clinical-grade targeted NGS with available copy-number data (MSK CHORD 2024). Disease stage was categorized as stage I-III versus stage IV. FGA was analyzed in quartiles, with high FGA defined as the top quartile. OS was assessed using Kaplan-Meier and multivariable Cox proportional hazards models adjusting for age, sex, smoking history, histology group, sequencing panel, stage, and log-transformed TMB. Incremental prognostic value was evaluated using concordance (C-index) and likelihood ratio testing (LRT). The results were validated using several sensitivity/statistical analysis. **Results:** After quality control, 7,722 patients were included (3,934 deaths), including 4,343 with stage I-III disease (1,559 deaths). In early-stage NSCLC, increasing FGA was associated with progressively worse OS across quartiles (log-rank χ^2 = 199.6, $p < 0.0001$). 5-year OS declined from 65.6% in the lowest FGA quartile to 39.6% in the highest quartile. Patients with high FGA had significantly inferior survival compared with low-FGA patients (5-year OS 39.6% vs 63.0%, $p < 0.0001$). In multivariable models restricted to stage I-III, high FGA remained independently associated with mortality (Hazard-Ratio = 1.60, 95% CI: 1.42-1.82, $p < 0.0001$). Adding FGA to clinical models improved survival prediction (C-index = ~0.70) and overall model performance (LRT = 125.9, $p < 0.0001$), and this improvement was greater than that seen with TMB. When both biomarkers were included, FGA continued to provide strong prognostic information, whereas TMB did not improve prediction once FGA was already in the model. We found our results to be consistent across internally validated analysis. **Conclusions:** FGA was strongly associated with OS in stage I-III NSCLC. FGA identified a subgroup of early-stage patients with substantially worse outcomes despite similar anatomic stage, indicating important underlying biologic differences. Since, FGA can be obtained from routine targeted NGS already used in clinical practice, it presents a practical biomarker that may improve risk stratification beyond standard clinical factors and TMB, and help guide surveillance and perioperative trial selection. Research Sponsor: None.

8043 Poster Session

Real-world adoption of comprehensive genomic profiling in a national cohort of patients with resected stage I–III non–small cell lung cancer.

Brendan Heiden, Daniel B. Eaton Jr., Arvind Kumar, Meghna Katta, Nahom Seyoum, Theodore Seth Thomas, Martin W. Schoen, Benjamin D. Kozower, Varun Puri, Whitney S. Brandt; Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO; Veterans Affairs, St. Louis Healthcare System, St. Louis, MO; Saint Louis VA Medical Center John Cochran Division, St. Louis, MO; Division of Hematology and Medical Oncology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO; Washington University, St. Louis, MO

Background: Comprehensive genomic profiling (CGP) is increasingly used in the multidisciplinary management of resectable NSCLC to identify candidates for targeted adjuvant therapies and clinical trials. NCCN and Veterans Affairs (VA) guidelines recommend selective – not universal – testing in early-stage disease, yet real-world use after surgery remains poorly described. Using the VA's highly unique National Precision Oncology Program (NPOP), we evaluated trends in CGP uptake, factors associated with testing, and the biomarker landscape in early-stage NSCLC. **Methods:** We performed a retrospective cohort study of patients with resected pathologic stage I–III NSCLC (2019-2025) within the VA. CGP was defined as next-generation sequencing (NGS) of the primary tumor within 3 months of surgery. We assessed frequency of CGP and clinicodemographic factors associated with GCP via multivariable logistic regression. We also assessed the distribution of potentially actionable genomic alterations. **Results:** A total of 6,605 patients were included (4,686 [70.9%] stage I; 1,255 [19.0%] stage II; 664 [10.1%] stage III). Over the study period, 1,337 (20.2%) patients received NGS testing. CGP utilization increased over time (11.4% in 2019 to 25.8% in 2025), paralleling evolving recommendations regarding adjuvant targeted therapies. Of note, the GCP utilization rate among those with stage Ib-III NSCLC in 2025 was 54.9%. In multivariable models, factors associated with higher CGP use included former smoking status (adjusted hazard ratio [aHR] 1.19, 95% CI 1.02-1.40), never smoking status (aHR 1.31, 95% CI 1.05-1.65), robotic resection (aHR 1.82, 95% CI 1.52-2.18), higher stage (stage II: aHR 4.33, 95% CI 3.72-5.04; stage III: aHR 5.79, 95% CI 4.81-6.98), and more recent treatment year (aHR 1.25, 95% CI 1.20-1.30). Median time from surgery to CGP ordering was 25 days (IQR 10-67). Among tested tumors, key genomic alterations included EGFR exon 19 deletions (2.39%) and L858R (1.20%), ALK fusions (0.52%), KRAS G12C (10.62%), MET exon 14 skipping (2.02%), ERBB2 mutations (3.29%), BRAF V600E (1.05%), and ROS1 fusions (0.53%). **Conclusions:** In this national cohort, CGP use after resection of stage I–III NSCLC increased substantially over time, likely supported by the VA NPOP infrastructure. Testing patterns were largely guideline-concordant, with continued uptake within complex multidisciplinary pathways. These findings reinforce the real-world adoption of genomically informed decision-making in early-stage disease while highlighting opportunities to strengthen implementation and promote wide access to precision oncology. Research Sponsor: None.

Multi-center prospective study evaluating an AI-enabled clinical decision support tool to improve biomarker testing in early-stage NSCLC.

Melina Elpi Marmarelis, Jessica Dow, Journey Penney, Binyam Yilma, Alexis Aiello, Marina Codari, Chithra Sangli, Karen Huelsman, Andrew J. Parchman, Charu Aggarwal, Sarah Grace Thompson, Natraj Reddy Ammakkanavar, George R. Simon, Amol Rao, Gautum Agarwal, Ezra E.W. Cohen, Jyoti D. Patel, Noah Zimmerman; University of Pennsylvania, Philadelphia, PA; Tempus AI, Inc., Chicago, IL; Tempus AI, Chicago, IL; TriHealth Cancer Institute, Cincinnati, OH; Trihealth Cancer and Blood Institute, Cincinnati, OH; Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; YUMA Regional Cancer Center, Yuma, AZ; Community Regional Cancer Care - East, Indianapolis, IN; OhioHealth, Columbus, OH; MemorialCare Cancer Institute, Fountain Valley, CA; Urologic Oncology and Precision Medicine, Mercy Oncology and Hematology—David C. Pratt Cancer Center, St. Louis, MO

Background: Non-adherence to guideline-concordant biomarker testing in non-small cell lung cancer (NSCLC) can limit access to targeted therapies and adversely impact survival. We evaluated an AI-enabled clinical decision support (AI-CDSS) program comprising: (1) education around baseline testing rates; (2) continuous monitoring to generate real-time alerts for eligible patients with missing biomarker testing; and (3) longitudinal feedback via dashboards. Here, we report the effectiveness of this program in identifying and closing biomarker testing gaps for patients with early-stage NSCLC. **Methods:** In this descriptive study, we analyzed patients with confirmed NSCLC across 6 geographically and socioeconomically diverse US community health systems. The AI-CDSS identified early-stage patients eligible for biomarker testing (eNSCLC as AJCC 8th edition Stg IB-IIIB (T3, N2) with planned curative intent treatment). Biomarker testing included EGFR, ALK, and PD-L1. We compared testing adherence between a baseline period (BL: 24 months through 3 months prior to the health system-specific roll-out) and a post-launch period (PL: roll-out through Oct 2025). The AI-CDSS was implemented on a rolling basis across health systems (BL from Feb 2022 - Dec 2024 and PL from Feb 2024 - Oct 2025). Testing rates were calculated as the proportion (%) of patients with testing completed within 90 days of pathologic diagnosis in each period. The improvement in test rates (absolute lift) is calculated as the difference in PL - BL testing percentages in the two periods. **Results:** A total of 662 patients with eNSCLC (270 BL and 392 PL) were included in the analysis. Patients were predominately white (85%), had a history of smoking (88%), with a median age of 70 years at diagnosis. The stage distribution was as follows: Stage III (34%), Stage II (37%), Stage IB (25%), and Stage IB or IIA [indeterminate] (5%). The absolute lift in biomarker testing within 90 days of pathologic diagnosis before vs after intervention was 18% for EGFR, 24% for ALK, and 13% for PDL1 biomarkers. Among patients with molecular testing who received adjuvant treatment, 89% were on guideline-concordant adjuvant treatment. **Conclusions:** Implementation of an AI-CDSS was associated with clinically meaningful improvements in rates of biomarker testing for eNSCLC and resulted in high concordance with guideline-directed adjuvant therapy. Appropriate and timely biomarker testing is essential for perioperative treatment planning. This study provides preliminary evidence that AI can use complex electronic health records to provide real-time interventions that can promote guideline-concordant care. Research Sponsor: None.

Testing gap results.

Biomarker	Baseline N	Baseline Test Rate	Post Launch N	Post Launch Test Rate	Absolute Lift
EGFR	264	49%	392	67%	18%
ALK	270	43%	389	67%	24%
PD-L1	270	59%	389	72%	13%

8045 Poster Session

Non-surgical management and outcome of 1,113 patients with stage I-II non-small cell lung cancer (NSCLC) in a 20-year cohort.

Ping Yang, Cristina Ou, Vinicius Ernani, Jason A. Wampfler, Zhong Gu, Matthew Buras, Steven E. Schild, Jonathan D'Cunha, Terence Tai Weng Sio; Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic Arizona, Phoenix, AZ; Mayo Clinic Rochester, Rochester, MN; Mayo Hospital, Phoenix, AZ; Department of Radiation Oncology, Mayo Clinic Arizona, Phoenix, AZ

Background: Surgical resection is the primary therapy for stage I-II NSCLC but not performed in a subset of patients due to comorbidities or self-election, who instead undergo radiation with or without systemic therapy (RT±ST). Little is known about the demographic, tumoral, therapeutic, and quality-of-life (QOL) characteristics of this non-surgical group. Understanding their differences from the surgical group is essential for developing precision treatment strategies and tailored survivorship guidelines. **Methods:** In a prospectively enrolled (1997-2016) and followed (through 2025) cohort of 20,951 primary lung cancer patients, 6,486 (31%) had stage I-II NSCLC, including 5,359 (83%) treated surgically (Surgical) and 1,113 (17%) otherwise (Non-surgical). Preexisting diseases were grouped into cancer, lung, and other comorbidities. QOL data were available for 40% of all patients. Descriptive analysis of demographics, tumor features, treatment patterns, and QOL metrics, as well as survival analysis (median years and overall survival [OS] rates) were conducted. QOL measures, on overall and 15 symptom and functional domains, were scored 0 (worst) to 10 (best), with 1-unit difference considered clinically and statistically meaningful. **Results:** At time of diagnosis, compared to the Surgical, the Non-surgical patients were older (median 73 v 68 years), more likely to have smoked cigarettes (91% v 83%), squamous cell and unspecified NSCLC (53% v 28%), stage IIB (19% v 12%), and preexisting lung comorbidities (71% v 58%). Non-surgical patients more frequently received RT±ST than the Surgical (70% v 21%) and had shorter median survival (2.5 v 7.8) years. Within the Non-surgical, 28% had no cancer treatment (No-Tx), 44% RT-only, 7% ST-only, and 19% both (RT+ST); their respective median diagnosis ages were 74, 76, 68, 70 years; median survival were 1.7, 2.7, 2.2, 3.2 years; 5-year OS (95%CI) at 25% (21-31), 25% (21-29), 26% (17-38), 30% (25-37); and 10-year OS at 9% (7-14), 7% (5-10), 10% (5-21), 9% (6-14), respectively. RT-only group had highest rates of comorbidities (37-84%) and the No-Tx the lowest (31-66%). Although the overall QOL scored the same for all groups, RT-only patients reported the worst scores on multiple symptoms burden, and the No-Tx reported the least pain and lung cancer symptoms but the worst on mental well-being and social activities. **Conclusions:** Non-surgically managed stage I-II NSCLC cases present clinically distinct patients with the shortest median survival in No-Tx group and highest 5-year survival in RT+ST. RT-only patients were oldest, had the most comorbidities, and reported the worst symptom burdens. These differences highlight the need for more in-depth analyses and studies (considering age, histology, comorbidity, QOL, etc.) to support tailored therapeutic strategies and survivorship care for patients who decline or are not suitable for surgery. Research Sponsor: None.

Influence of neoadjuvant spatially fractionated stereotactic body radiotherapy on antitumor immunity and pathological response to toripalimab-based immunochemotherapy in resectable stage IIA-IIIB non-small cell lung cancer.

Xu Yaping, Deping Zhao, Di Liu, Letong Yang, Shuangyan Yang, Leilei Wu, Xiaoling Xu, Liang Liu, Yun Chen, Fangjuan Li; Department of Radiation Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; Department of Radiation Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; Shanghai Pulmonary Hospital,Tongji University School of Medicine, Shanghai, China; Shanghai Pulmonary Hospital Tongji University, Shanghai, China

Background: Neoadjuvant immunochemotherapy has improved outcomes in resectable non–small cell lung cancer (NSCLC); however, pathological complete response (pCR) rates remain limited, and strategies to further amplify antitumor immunity are needed. Spatially fractionated stereotactic body radiotherapy (SF-SBRT, Lattice) delivers spatially separated high-dose regions "peaks" to promote immunogenic cell death while maintaining low-dose regions "valleys" that preserve the tumor immune microenvironment (TIME). We hypothesized that integrating SF-SBRT with toripalimab-based immunochemotherapy could reprogram the TIME and enhance pathological response in resectable NSCLC. **Methods:** This prospective phase II study enrolled resectable stage IIA–IIIB NSCLC (NCT06293690). Patients received one fraction of Lattice SF-SBRT (12 Gy peak / <4 Gy valley) on Day 1, followed by toripalimab plus chemotherapy on Day 2, administered every 3 weeks for 2 cycles prior to surgery. The primary endpoint was major pathological response (MPR). Secondary endpoints included pCR, radiological response, nodal downstaging, event-free survival, overall survival, and safety. Single-cell RNA sequencing (scRNA-seq) was performed to characterize treatment-associated immune remodeling. **Results:** 20 patients completed neoadjuvant therapy and underwent curative-intent resection, R0 resection was achieved in all patients without treatment-related surgical delays. MPR was observed in 95.0% (19/20) of patients, including a pCR rate of 55.0% (11/20). The radiological objective response rate was 100.0%. Nodal downstaging to ypN0 occurred in 82.4% (14/17) of patients with baseline nodal involvement, corresponding to an overall ypN0 rate of 85.0%. Grade 3–4 treatment-related adverse events occurred in 15.0% (3/20), with no grade ≥2 radiation pneumonitis. scRNA-seq revealed enhanced cytotoxic T-cell activation, reduced immunosuppressive myeloid populations, and coordinated immune remodeling following neoadjuvant treatment. **Conclusions:** Neoadjuvant SF-SBRT combined with toripalimab-based immunochemotherapy was feasible, safe, and achieved high pathological response rates in resectable stage II–III NSCLC. These findings suggest that SF-SBRT may function as an immune-reprogramming strategy that amplifies neoadjuvant immunotherapy efficacy and warrants further validation in randomized clinical trials. Clinical trial information: NCT06293690. Research Sponsor: None.

Characteristics	No. of Patients (%)
Radiological Response (RECIST 1.1)	
CR	2 (10.0)
PR	18 (90.0)
Pathological Response	
Major pathological response (MPR)*	19 (95.0)
└ Pathological complete response (pCR)†	11 (55.0)
ypN0‡	17 (85.0)

*MPR: < 10% residual viable tumor (RVT); †pCR: 0% RVT in primary & nodes; ‡ypN0: 14/17 patients with baseline N^+ achieved downstaging.

Real-world outcomes and prognostic risk stratification of neoadjuvant immunotherapy for stage III lung squamous cell carcinoma.

Wang Yishuo, Qi Fei, Mingming Hu, Ying Wang, Zhidong Liu, Nanying Che, Yi Han, Junzhong Ruan, Tongmei Zhang; Beijing Chest Hospital, Capital Medical University and Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China

Background: While neoadjuvant immunotherapy (nIO) is the standard of care for resectable NSCLC, its efficacy in "potentially resectable" (PR) stage III lung squamous cell carcinoma (LUSC)—specifically patients with T4 invasion or multi-station N2 disease—remains underrepresented in clinical trials. We evaluated whether nIO could facilitate surgical conversion in PR patients comparable to initially resectable (IR) candidates and constructed a multidimensional risk stratification system to optimize decision-making. **Methods:** We retrospectively analyzed patients with stage III LUSC treated with neoadjuvant PD-1/PD-L1 inhibitors plus chemotherapy (January 2019–December 2024). The cohort was stratified into IR and PR groups, with PR defined by complex anatomy (T4 invasion or multi-station N2). Endpoints included surgical conversion, major pathological response (MPR), disease-free survival (DFS), and overall survival (OS). Baseline predictors were identified via logistic regression. A pathological risk score (pRS) was developed using Cox regression based on independent risk factors for DFS in the R0 resection cohort. **Results:** Of 210 evaluable patients, 170 (81.0%) underwent surgery with a 96.5% R0 resection rate. The PR cohort (n = 128) achieved surgical conversion rates comparable to the IR cohort (n = 82) (82.9% vs. 90.7%; P = .19). Notably, PR patients demonstrated superior nodal downstaging (74.5% vs. 58.8%; P = .047) compared with IR patients. Long-term survival outcomes showed no statistically significant difference between PR and IR groups (DFS: HR, 1.25; 95% CI, 0.77-2.04; OS: HR, 1.41; 95% CI, 0.76-2.62). Multivariable analysis identified baseline NLR $\geq$ 2.75 and CYFRA 21-1 $\geq$ 6.0 ng/mL as independent predictors of poor therapeutic benefit. The constructed pRS system (integrating non-MPR status, vascular, and pleural invasion) effectively stratified postoperative recurrence risk ($P <$ .0001; 1-year AUC, 0.73). Analysis of treatment failure (n = 40) revealed that baseline fibrinogen $>$ 3.5 g/L was associated with disease progression, while grade 3–5 pneumonitis was a primary cause of surgical dropout in patients with high PD-L1 expression. **Conclusions:** In this real-world cohort, nIO facilitated high R0 resection rates in complex stage III LUSC, allowing potentially resectable patients to achieve survival outcomes equivalent to initially resectable candidates. Nodal clearance appears to be a key driver of benefit in the PR subgroup. The novel pRS system and biomarkers (NLR, CYFRA 21-1, fibrinogen) provide a robust framework for patient selection and postoperative management. Research Sponsor: None.

Post-progression treatment strategies and immunotherapy rechallenge sensitivity following chemoradiation and consolidation durvalumab in unresectable stage III NSCLC: The POST-PACIFIC study.

Valentina Santo, Nikhil Mankuzhy, Kristi Beshiri, Alix Celarier, Lingzhi Hong, Emanuele C. Mingo, Sagal Pannu, Federica Pecci, Edoardo Garbo, Eleonora Gariazzo, Leonardo Brunetti, Ayesha Aijaz, Federico Monaca, Jamie E. Chaft, Marcelo Corassa, Alessio Cortellini, Natalie I. Vokes, Mihaela Aldea, Narek Shaverdian, Biagio Ricciuti; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Medical Oncology Department, Gustave Roussy, Villejuif, France; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Operative Research Unit of Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; Stephenson Cancer Center, Oklahoma University, Oklahoma City, OK; The Christie NHS Foundation Trust and Division of Cancer Sciences, Manchester, United Kingdom; Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Thoracic Oncology Unit, Beneficência Portuguesa de São Paulo, São Paulo, SP, Brazil

Background: Durvalumab consolidation after platinum-based chemoradiotherapy (CRT) is the standard of care for unresectable stage III non-small cell lung cancer (NSCLC). However, optimal treatment strategies after progression remain undefined, and data guiding post-durvalumab strategies, including immunotherapy rechallenge, are limited. **Methods:** This global retrospective multicenter study included patients with unresectable stage III NSCLC treated with concurrent or sequential CRT who progressed after ≥1 dose of durvalumab consolidation. Survival outcomes were assessed using Kaplan-Meier and Cox methods. Immunotherapy sensitivity was defined by time from durvalumab initiation to progression: refractory (< 12 months) or sensitive (≥12 months) and correlated with outcomes after immunotherapy rechallenge. **Results:** Among 319 patients, median age was 66.5 years; 54.2% were male, and 96.7% had ECOG PS 0-1. Concurrent CRT was delivered in 96.5% (median RT dose 60 Gy). Median follow-up was 62.2 months. Progression pattern included locoregional recurrence in 34.8% and distant relapse in 65.2%. Of 293 patients receiving a first subsequent therapy (FST), chemotherapy (CT) ± VEGF inhibition was most common (31.7%), followed by local ablative therapy (LAT, 30.7%), immunotherapy ± CT (18.4%), targeted therapy (TT, 10.9%), and durvalumab beyond progression (BP) ± LAT (6.5%). When comparing FST, immunotherapy rechallenge demonstrated superiority over CT. Compared with CT ± VEGF inhibition, immunotherapy ± CT was associated with a higher objective response rate (ORR: 40.7% vs. 16.9%, $p < 0.01$) and significantly improved progression-free survival (mPFS2: 8.48 vs. 4.14 months; HR 0.41, $p < 0.01$) and overall survival (mOS2: 23.7 vs. 12.2 months; HR 0.41, $p < 0.01$), findings confirmed in multivariable analyses. Patients with actionable oncogenic drivers or indolent, focal relapses achieved the most favorable outcomes with TT or durvalumab BP ± LAT, respectively, reflecting a disease biology amenable to highly effective systemic or localized interventions. Among patients who received immunotherapy rechallenge, those relapsing ≥12 months after durvalumab initiation experienced higher ORR and numerically longer PFS and OS. Additionally, upfront rechallenge was independently associated with superior survival in multivariable models (PFS aHR: 0.51, $p < 0.01$; OS aHR: 0.46, $p < 0.01$) and with higher ORR (41.5% vs. 17.6%, $p = 0.04$), compared with later-line rechallenge. **Conclusions:** Post-PACIFIC treatment approaches are heterogeneous, but immunotherapy-based strategies provide superior efficacy over CT alone. Patients with prolonged benefit from durvalumab (≥12 months) retain immune sensitivity and derive the greatest benefit from immunotherapy rechallenge, particularly as FST. Research Sponsor: None.

8049 Poster Session

Nodulomics: Histopathologic and genomic heterogeneity among multiple malignant pulmonary nodules sampled by robotic-assisted bronchoscopy.

Jamie Rowell, Yupeng Liu, Rohan Bhargava, Momen Wahidi, Sean Smith, Mohamed E. Abazeed, David Abia Trujillo, Benjamin Seides, Jeffrey Thiboutot, Christopher Kapp; Northwestern University, Chicago, IL; Northwestern University, The Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; Mayo Clinic Florida, Jacksonville, FL; Johns Hopkins University, Baltimore, MD

Background: Multiple pulmonary nodules (MPN) pose significant challenges for accurate staging of non-small cell lung cancer (NSCLC). As next generation sequencing (NGS) technologies have become more widely available on smaller amounts of tissue, the prevalence and clinical implications of heterogeneity between MPNs are poorly understood. This study retrospectively evaluates the histopathological and NGS findings after MPN biopsy in a single robotic-assisted bronchoscopy (RaB) procedure. **Methods:** 191 patients were retrospectively enrolled at 6 geographically diverse centers in the US. All patients had 2+ pulmonary nodules biopsied and staging EBUS in the same procedure. An expert molecular pathologist reviewed NGS data between nodule pairs to determine if they were discordant, concordant, or indeterminate. **Results:** Of 191 patients, 85 patients had 2 malignant nodules with 15 of those demonstrating histopathologic heterogeneity (e.g., one adenocarcinoma, one squamous cell carcinoma). 26 patients with 2 malignant nodules of similar histopathology demonstrated molecular heterogeneity between nodules. These cases were reviewed by an expert molecular pathologist who determined the following breakdown: -15 discordant pairs (57.7%) -3 concordant pairs (11.5) -8 indeterminate pairs (30.8%) Breakdown by nodule density: -Discordant: 7 same density, 8 different density -Concordant: 3 same density -Indeterminate: 5 same density, 3 different density Breakdown by nodule laterality: -Discordant: 7 ipsilateral, 8 contralateral -Concordant: 2 ipsilateral, 1 contralateral -Indeterminate: 4 ipsilateral, 4 contralateral Staging EBUS was performed in all 26 cases with malignancy identified in 2 cases. NGS sufficiency for NSCLC from three sites with standardized NGS reporting was as follows: 1st nodule biopsied: 42/54 (77.8%), 2nd nodule biopsied: 37/51 (72.5%), 3rd nodule biopsied: 2/4 (50%). In total, 90/109 (82.6%) NSCLC samples had adequate tissue for NGS. In 85 cases with 2 malignant nodules, 35 (41.2%) had all nodules Stage IIB or lower. Notably, 25 (29.4%) of the cases did not have NGS available on one or more of the nodules, thus precluding staging. **Conclusions:** This study highlights the frequency and clinical relevance of histopathologic and molecular heterogeneity among synchronous MPNs. Importantly, heterogeneity was not limited to contralateral or anatomically distant lesions, challenging the assumption that spatial proximity implies clonal relatedness. Further, this study shows that relying solely on density or radiographic features of a nodule is an incomplete discriminator between separate primary lung cancers and intrapulmonary metastasis. Our findings support the need for an integrated diagnostic paradigm in which sampling of multiple lesions is used to inform clonality, refine staging, and guide precision therapy. Research Sponsor: None.

Sintilimab plus anlotinib and chemotherapy as first-line treatment for advanced malignant pleural mesothelioma (SACH-MPM): A prospective, single-arm, phase II trial.

Yiyi Huang, Xinyu Wu, Xiaohui Ren, Xianzhen Wu, Rui Wan, Kailun Fei, Boyang Sun, Jiachen Xu, Jia Zhong, Zhijie Wang, Lin Wang, Binbin Shan, Qinxiang Guo, Jie Wang, Jianchun Duan; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital,Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Respiratory Medicine,Shanxi Province Cancer Hospital/ Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, China; Cancer Hospital Chinese Academy of Medical Sciences (Langfang Section), Langfang, Hebei, China; Shanxi Cancer Hospital, Taiyuan, China; Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: Standard first-line treatments for advanced malignant pleural mesothelioma (MPM) include platinum-pemetrexed with bevacizumab or nivolumab plus ipilimumab. While the addition of atezolizumab to chemotherapy and bevacizumab improved PFS in the BEAT-meso trial (9.2 vs. 7.6 m, HR 0.72), it failed to show an OS benefit. Anlotinib is a multi-target TKI targeting VEGFR, FGFR, and PDGFR. We investigated the efficacy and safety of sintilimab (anti-PD-1) combined with anlotinib and chemotherapy as first-line treatment for advanced MPM. **Methods:** This open-label, dual-center, single-arm Phase II study (NCT05188859) enrolled systemic treatment-naive pts with unresectable locally advanced or metastatic MPM. Pts received sintilimab (200 mg D1) and anlotinib (12 mg D1-14) plus chemotherapy (pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 or carboplatin AUC 5, D1) Q3W for 4-6 cycles, followed by maintenance sintilimab, anlotinib, and pemetrexed until disease progression, intolerable toxicity, or up to 24 months. Primary endpoint was ORR per modified RECIST (mRECIST) 1.1 for mesothelioma. A Simon's two-stage design (H0 = 41.3%, H1 = 60%, α = 0.1) planned for 23 evaluable pts, requiring ≥12 responses. **Results:** From Sep 2024 to Jan 2026, 30 pts were enrolled (median age 58.5 y; 76.7% epithelioid, 80% stage IIIB). At data cutoff, 29 pts were evaluable. Median follow-up was 7.4 months (m). The primary endpoint was met, with a confirmed ORR of 65.5% (95% CI: 45.7-82.1). DCR was 100%. Median time to response was 1.4 m; median DoR was not reached (0.7+-8.4+ m). PFS and OS were not mature. The 6- and 12-m PFS rates were 100% and 67.5%, respectively. OS rate was 100% at cutoff. Grade ≥3 TRAEs (36.7%) included neutrophil count decreased (13.3%), platelet count decreased (10.0%), pulmonary embolism (6.7%), diarrhea (6.7%), and hypertension (3.3%; any grade 10.0%). Bleeding events were Grade 1-2 (epistaxis 13.3%). TRAEs led to anlotinib dose reduction or discontinuation in 20.0%. No Grade 5 events occurred. **Conclusions:** Sintilimab plus anlotinib and chemotherapy demonstrated superior ORR compared to historical controls with a manageable safety profile. The study met its primary endpoint, and the high 12-month PFS rate suggests a potential survival benefit. These findings support integrating a multi-target TKI with PD-1 blockade and chemotherapy as a potent first-line strategy for advanced MPM. Clinical trial information: NCT05188859. Research Sponsor: Innovent Biologics (Suzhou) Co.Ltd.; Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Machine learning–integrated transcriptomic clustering for prognostic stratification in epithelioid pleural mesothelioma.

Mario Occhipinti, Arianna Rigamonti, Paolo Ambrosini, Ghazal Farhikhteh, Rebecca Romanò, Silvia Marchesi, Daniele Lorenzini, Rosa Maria Di Mauro, Marta Brambilla, Laura Mazzeo, Teresa Beninato, Anna Ianza, Giulia Corrao, Claudia Proto, Giuseppe Lo Russo, Daniele Giulio Generali, Filippo Guglielmo Maria De Braud, Arsela Prelaj, Monica Ganzinelli; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Advanced Diagnostics Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Oncology Department, University Health Organization Giuliano Isontina, Trieste, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Istituti Ospitalieri di Cremona, Cremona, Italy

Background: Survival outcomes in pleural mesothelioma (PM), particularly within epithelioid PM (ePM), are heterogeneous and inadequately captured by histological classification. We applied machine learning (ML) methods integrating transcriptomic and clinical features to improve prognostic stratification in ePM. **Methods:** RNA sequencing was performed on FFPE tumor samples from 125 ePM patients treated at two Italian centers (2006-2021). Overall survival (OS) was categorized as long (> 36 months), intermediate (12-36 months), or short (≤12 months). Unsupervised clustering of highly variable genes identified transcriptomic subgroups, and GSEA was performed. A previously published 20-gene sarcomatoid-like transcriptional score (S-score), derived from single-cell data was calculated. ML models were developed using age, sex, S-score, and a cluster-derived score related to cell proliferation as input features. Logistic Regression (LR) and Random Forest (RF) classifiers were trained to predict long and short survival, using class-balanced weighting and 5-fold stratified cross-validation. Model performance was assessed using AUC-ROC and balanced accuracy. Model interpretability was evaluated with SHapley Additive exPlanations (SHAP). External evaluation was performed in the TCGA PM cohort with cohort-specific standardization. **Results:** Unsupervised transcriptomic analysis identified three clusters with distinct survival patterns. Cluster 1 was enriched for immune-related pathways and associated with longer survival; Cluster 2 exhibited proliferative and cell-cycle-related programs and was enriched in short-survival patients. Cluster 3 showed immune-related transcripts, with variable expression patterns across histology and survival groups. Given the convergent GSEA results, Cluster 2 was selected as a ML feature. Both the S-score and Cluster 2 score were associated with OS, with stronger survival discrimination for Cluster 2. ML models showed good discriminative performance for long survival prediction (cross-validation AUC-ROC: LR 0.83 ± 0.10; RF 0.83 ± 0.04), with similar results in the TCGA cohort (LR AUC-ROC = 0.84; RF = 0.77). Predictive performance for short survival was moderate. SHAP analysis identified Cluster 2 score as the main contributor to ML predictions, with higher values associated with increased risk of short survival. **Conclusions:** Machine learning models integrating transcriptomic clustering with clinical variables improve prognostic stratification in ePM. ML-based risk prediction builds upon transcriptomic features, capturing survival-relevant heterogeneity beyond histology. These findings support the use of ML as a complementary tool to transcriptomic profiling for prognostic assessment in ePM. Research Sponsor: None.

Tumor methylation subtypes as a predictor of clinical outcome to immunotherapy in pleural mesothelioma patients from the NIBIT-EPI-MESO study.

Luana Calabrò, Francesca Pia Caruso, Alessia Covre, Teresa Maria Rosaria Maria Rosaria Noviello, Maria Fortunata Lofiego, Rossella Tufano, Luigi Ferraro, Piera Grisolia, Antonio De Falco, Vincenzo Lagano, Giovanna Sabella, Giulia Rossi, Giulia Gibilisco, Federica Grosso, Anna Maria Di Giacomo, Massimo Milione, Roberta Mortarini, Andrea Anichini, Michele Ceccarelli, Michele Maio; University of Ferrara, Ferrara, Italy; Biogem Institute of Molecular Biology and Genetics, Ariano Iprino, Italy; University of Siena, Siena, Italy; University of Miami, Miami, FL; Azienda Ospedaliero Universitaria Senese, Siena, Italy; Biogem, Ariano Irpino, Italy; Human Tumors Immunobiology Unit - Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; First Division of Pathology, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Mesothelioma Unit, SS Antonio e Biagio e Cesare Arrigo, Alessandria, AL, Italy; University of Siena, Center for Immuno-Oncology, University Hospital of Siena, NIBIT Foundation Onlus, Siena, Italy; Human Tumors Immunobiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Sylvester Comprehensive Cancer Center and Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL

Background: Pleural mesothelioma (PM) is an aggressive malignancy with a poor prognosis. The clinicalefficacy of standard therapy with immune checkpoint inhibitors (ICI) is limited and heterogeneous acrossPM subtypes. Tumor-intrinsic characteristics (i.e., inflammatory phenotype, molecular features, DNAmethylation) may influence immune responsiveness, but predictive biomarkers of ICI therapy efficacy inPM are still lacking. **Methods:** NIBIT-EPI-MESO is a retrospective, multicenter study, sponsored by theNIBIT Foundation, evaluating biological correlates of clinical outcomes in PM patients (pts) treated withICI (i.e., anti-CTLA-4 plus anti-PD-1, anti-CTLA-4 plus anti-PD-L1, or anti-CTLA-4 monotherapy). Pre-ICI therapy FFPE tumor samples were analyzed by RRBS methylation (n = 83 pts) and RNA-seq (n = 82pts), with methylation subtypes defined by consensus clustering of the top 1% most variable CpGs.Tumor microenvironment (TME) was characterized by multiplex immunofluorescence analysis of CD4,CD8, CD20, CD68, CD163 (n = 35 pts). Integrated multi-omics analyses were used to associate tumorbiology with clinical outcome of PM pts. **Results:** Unsupervised methylation profiling identified four PMsubsets with increasingly global DNA methylation levels: demethylated (DEM), LOW, intermediate (INT),and CpG island methylator phenotype (CIMP). Methylation subtypes were significantly associated withresponse to ICI, with LOW/DEM enriched among responder (R) pts and INT/CIMP in non-R pts (p =0.002); no association of response to ICI was found with PM histotype (p = 0.33). The LOW subsetexhibited the longest median overall survival (mOS) and the highest 3-year OS rate, expressed genesinvolved in pathways associated with innate and adaptive immune responses, and showed an "inflamed"TME (i.e., CD8+ T cells, CD20+ B cells). Conversely, the CIMP subtype had the shortest mOS and OSrate, was characterized by genes enriched in developmental, morphogenetic and cell cycle-relatedprocesses, along with a "desert" TME. Functional characterization of the identified methylation classes ofPM was validated in the MESOMICS dataset. Accordingly, a PM methylation subtype classifier wasdeveloped to predict response to ICI therapy. **Conclusions:** Tumor DNA methylation defines biologicallyand clinically distinct immune phenotypes in PM and robustly predicts clinical response and long-termsurvival in ICI-treated PM patients, regardless of tumor histology. Research Sponsor: Fondazione AIRC; ID.21073; NIBIT Foundation Onlus; Bando Ricerca Finalizzata; NET-2016-02361632; National Center for Gene Therapy and Drugs based on RNA Technology European Union -Next Generation EU, Mission 4, Component 2; Project no. CN_00000041; National Cancer Institute (NCI) of the National Institutes of Health (NIH); P30CA240139.

The role of sarcopenia and adiposity in prognosis of pleural mesothelioma: A CT-based analysis.

Senar Ebinc, Nadiye Akdeniz, Halil Komek; Van Yuzuncu Yil University, Van, Turkey; Gazi Yasargil Education and Training Hospital, Diyarbakir, Turkey

Background: Pleural mesothelioma (PM) is a rare malignancy associated with asbestos exposure and characterized by an aggressive clinical course and poor prognosis. Identifying clinical and biological prognostic markers is of significant clinical importance. Recently, computed tomography (CT) based body composition parameters have been investigated for their association with survival outcomes in cancer patients; however, their prognostic value in PM remains unclear. This study aimed to evaluate the impact of clinical characteristics and CT-derived body composition parameters on survival in patients with PM. **Methods:** This retrospective study included 73 patients diagnosed with pleural mesothelioma. CT images were used to calculate the subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI), total abdominal adipose tissue index (TATI), skeletal muscle index (SMI), and psoas muscle index (PMI). Patients were classified as sarcopenic or non-sarcopenic based on SMI. **Results:** The median age was 60 years, and 57.5% of patients were male. Most patients had good performance status (ECOG 0–1), and the epithelioid subtype was the most common histology. Approximately one-third of patients had a history of smoking or prior surgery. In univariate analysis, age ≥60 years was significantly associated with increased mortality. In multivariate analysis, age ≥60 years (HR 2.45) and male sex (HR 2.13) were identified as independent poor prognostic factors. Non-sarcopenic patients had a significantly lower risk of mortality compared with sarcopenic patients (HR 0.37). Additionally, higher TATI values were associated with increased mortality risk (HR 2.26). Kaplan–Meier analysis demonstrated significantly shorter OS in patients aged ≥60 years (Table). **Conclusions:** In patients with pleural mesothelioma, advanced age and male sex are associated with poorer survival, whereas preserved skeletal muscle mass is associated with improved outcomes. Increased abdominal adiposity is linked to higher mortality risk. CT-based body composition parameters may provide useful prognostic information in patients with PM. Research Sponsor: None.

Evaluation of the association between parameters and survival using univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	P value	HR	95% CI
Age (<60y / ≥60y)	**0.005**	**2.27**	**1.27-4.05**	**0.005**	**2.45**	**1.31-4.61**
Gender (female*/male)	0.06	1.65	0.96-2.83	**0.011**	**2.13**	**1.19-3.81**
ECOG PS (0-1*/2-3)	0.35	1.43	0.66-3.07			
Histological subtypes (epithelioid / non-epithelioid)	0.26	1.42	0.76-2.66			
Stage (I-III*/IV)	0.43	1.26	0.70-2.27			
SMI cm^2/m^2 (sarcopenia*/normal)	0.21	0.70	0.41-1.21	**0.007**	**0.37**	**0.18-0.76**
TATI cm^2/m^2 (low*/high)	0.30	1.36	0.75-2.48	**0.04**	**2.26**	**1.03-4.97**

Response to neoadjuvant chemoimmunotherapy in EGFR- or ALK-mutated non-small cell lung cancer.

Giorgio Caturegli, Ebony Jernigan, Maureen Canavan, Abigail Lynch, Jayaditya Patil, Benjamin Resio, Daniel J. Boffa; Yale School of Medicine, New Haven, CT; Section of Thoracic Surgery, Department of Surgery, Yale School of Medicine, New Haven, CT

Background: The role of immunotherapy in non-metastatic EGFR-and ALK-mutated lung cancer is limited, in part because of a lack of efficacy, and partly because of the high response rates to mutation-targeting therapies. However, a subset of immunotherapy-responsive lung cancers may be cured, but only if immunotherapy is included in the treatment strategy. Therefore, a blanket exclusion of all EGFR-and ALK-mutated patients from immunotherapy may restrict a small subset of patients from a potentially curative option. Our objective was to determine the rate of highly immunotherapy-responsive tumors harboring EGFR and ALK mutations. **Methods:** Adult patients in the NCDB with clinical stage I-III NSCLC diagnosed between 2021 and 2023 and treated with neoadjuvant chemoimmunotherapy followed by definitive surgery (wedge resection, segmentectomy, lobectomy, or pneumonectomy) were included. Outcomes were pathologic complete response (pCR, defined as pathologic T0N0 after definitive resection) and nodal downstaging (pathologic N lower than clinical N stage). Covariates of interest for univariate analyses and multivariable logistic regression were year of diagnosis, region, age, sex, race/ethnicity, insurance, Charlson-Deyo score, clinical stage, and receipt of neoadjuvant immunotherapy. **Results:** Of 3,107 eligible patients, 1,133 (36.4%) were tested for EGFR and/or ALK mutations. Overall, 132 (11.7%) patients were found to have mutation(s) in EFGR (99 patients), ALK (27 patients) or both (6 patients). Among those with cN1-3 tumors, nodal downstaging was observed in 57.4% of patients with EGFR/ALK mutations and 74.2% of wild-type patients ($p<0.001$). The rate of pCR was 16.7% in EGFR-/ALK-mutated patients, and 30.9% in wild-type patients ($p<0.001$). Higher tumor grade was associated with significantly higher odds of pCR in EGFR/ALK wild-type patients (OR 2.448, 95% CI 1.58-3.89, $p<0.001$), but not in EGFR-/ALK-mutated patients (OR 2.63, 95% CI 0.37-18.74, p=0.33). **Conclusions:** While a less common practice, neoadjuvant chemoimmunotherapy in patients with EGFR-/ALK-mutated NSCLC demonstrated a pCR rate of 17% in this large real-world NCDB cohort. Further study on the role of neoadjuvant chemoimmunotherapy for this population is indicated given the potential for curative response, particularly in patients with mutations lacking effective targeted therapy. Research Sponsor: None.

Mutation Type	EGFR/ALK wild-type (n=1152)	EGFR-/ALK- mutated (n=132)	p
EGFR (n=105)			
Exon 18, 19, 20, and/or 21		54 (51.4%)	
Other exon		11 (10.5%)	
ALK (n=33)			
EML4-ALK, KIF5B-ALK, TFG-ALK, and/or KLC1-ALK		13 (39.4%)	
Other rearrangement		10 (30.3%)	
Response Outcomes			
Nodal Downstaging (pN < cN), cN1-3 patients only	482/650 (74.2%)	50/87 (57.4%)	**<0.001**
Complete Pathologic Response (ypT0N0)	356 (94.2%)	22 (16.7%)	**<0.001**

Pathologic complete response with neoadjuvant chemoimmunotherapy in clinical stage II–III NSCLC: A large real-world analysis including older adults.

Jorge Raul Vazquez Urrutia, Jack William Ibinson, Shinkichi Takamori, Asato Hashinokuchi, Junjia Zhu, Takefumi Komiya; Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Penn State College of Medicine, Hershey, PA; Dana-Farber Cancer Institute, Boston, MA; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Public Health Sciences, Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Penn State Hershey Medical Center, Hershey, PA

Background: Neoadjuvant chemoimmunotherapy is now the standard for clinical stage II-III non-small cell lung cancer (NSCLC) following CheckMate 816. However, older adults and socioeconomic factors have been underrepresented in clinical trials. This study aims to evaluate the impact of age and basic socioeconomic factors on pathological complete response (pCR) after neoadjuvant chemoimmunotherapy. **Methods:** Data from the National Cancer Database (NCDB) were obtained for patients diagnosed with clinical stage II-III NSCLC between 2019 and 2023 who underwent neoadjuvant chemotherapy (CT; 2019-2021) or chemoimmunotherapy (CTIO; 2022-2023) with complete T, N, and M staging data, as well as post-pathologic status (ypT, ypN). Those receiving neoadjuvant radiotherapy and with clinical or pathologic metastatic disease were excluded. Groups were stratified based on age (<75 vs ≥ 75 years). Group comparisons were performed using chi-square testing. The primary outcome was pCR, analyzed using univariate and multivariable Cox regression models. A p-value of <0.05 was considered statistically significant. **Results:** A total of 993 patients received CT alone, while 2,819 received CTIO. Among patients ≥ 75 years, pCR rates were significantly higher in the CTIO group compared with CT alone (25% vs 5%, p<0.001). This pattern was similar in patients <75 years (29% vs 8%, p<0.001). Among CTIO receivers, pCR rates did not differ significantly by age (25% ≥75 vs 29% <75; p=0.051) (Table 1). Patients with ≥10 lymph nodes examined had lower pCR rates compared with those with fewer nodes examined (26% vs 37%; p<0.001). On multivariate analysis, higher nodal stage (N1–N3; OR 1.23, 1.02-1.49, p=0.035) and non-adenocarcinoma histologies (OR 1.26, 1.07-1.49, p=0.006) were independently associated with higher odds of pCR. Notably, age, sex, race, and rural/urban residence were not independently associated with pCR, and no significant differences in race or rural/urban status were observed between groups. **Conclusions:** To our knowledge, this is the largest real-world analysis of neoadjuvant chemoimmunotherapy outcomes in older adults with clinical stage II-III non–small cell lung cancer. We found comparable pCR rates across age groups, supporting the use of this approach in older individuals. While racial disparities have been described in access to neoadjuvant therapy, our study suggests similar response rates across racial groups who underwent treatment. Higher nodal status was independently associated with pCR, which may be explained by greater tumor immunogenicity. These findings are hypothesis-generating and warrant validation in further prospective studies. Research Sponsor: None.

Pathologic complete response rate by age status.

Factors	pCR (n=811)	No pCR (n=2008)	P value (Chi-square)
Age			
≥ 75	115 (25%)	345 (75%)	0.051
< 75	696 (29%)	1663 (71%)	

pCR=Pathologic Complete Response.

Prediction of survival outcome in clinical stage II-III non-small cell lung cancer undergoing neoadjuvant chemoimmunotherapy: Role of ypN status vs PCR.

Hannah Hoang, Jorge Raul Vazquez-Urrutia, Junjia Zhu, Shinkichi Takamori, Asato Hashinokuchi, Takefumi Komiya; Department of Internal Medicine, Penn State College of Medicine, Hershey, Pennsylvania, Hershey, PA; Blood and Marrow Transplant Program, Division of Hematology and Oncology, Penn State Cancer Institute, Hershey, PA; Penn State Cancer Institute, Hershey, PA; National Kyushu Cancer Center, Fukuoka-Shi Minami-Ku, Japan; NHO Kyushu Cancer Center, Fukuoka, Japan; Penn State Hershey Medical Center, Hershey, PA

Background: After FDA approval in 2022, neoadjuvant chemoimmunotherapy has become the standard of care for patients with non-small cell lung cancer (NSCLC) due to improved survival outcomes. Pathologic complete response (pCR) is often used as a predictor of patient survival following treatment. However, the role of posttreatment pathological nodal status (ypN) as a treatment predictor remains undefined. This study evaluates the predictive significance of ypN in comparison to established treatment predictors, such as pCR. **Methods:** Patients with clinical stage II-III NSCLC diagnosed in 2022 (n=29,017) who underwent neoadjuvant chemo-immunotherapy and resection (n=1,175) were identified using the National Cancer Database. Those with missing pCR data (n=16), pCR in tumor only (n=18), and those who died within one month of diagnosis were excluded. Chi-square tests were used for comparisons between groups. Survival analysis was performed using the Kaplan-Meier method, along with univariate and multivariable Cox proportional models. All tests were two-sided, and the statistical significance level used was 0.05. **Results:** The final cohort consisted of 720 patients divided into three groups: pCR-both (pCRb; ypT0N0; n=217; 30.1%), pCR-node (pCRn; ypN0; n=265; 36.8%), and residual viable in both (RVb; n=238; 33.1%). The pCRb group had a higher proportion of squamous cell carcinoma compared to the pCRn group (47% vs 34%, $p<0.001$). pCRn patients demonstrated a slightly higher rate of positive surgical margins (3% vs 1%, p=0.03) and subsequent use of adjuvant radiotherapy compared with pCRb (3% vs 1%, p=0.03). Kaplan-Meier analyses and Cox proportional hazards models showed similar overall survival (OS) between pCRb and pCRn groups (HR=1.37; p=0.363), while both had significantly higher OS compared with RVb (HRs 0.26 and 0.36; $p<0.0001$ for both). Subgroup analysis by number of examined lymph nodes showed comparable OS between pCRb and pCRn in patients with ≥10 lymph nodes examined (LN≥10; HR=1.36; p=0.47) and in those with <10 nodes examined (LN<10; HR=1.50; p=0.40). **Conclusions:** In clinical stage II-III NSCLC treated with neoadjuvant chemoimmunotherapy followed by resection, pCRb and pCRn demonstrated similar rates of OS, highlighting the significance of post-treatment pathological nodal status (ypN) as a potential predictor of OS in this population. Since pCRb requires invasive tissue sampling, using ypN as a predictor of OS would allow for more efficient risk stratification with overall less invasive testing. Research Sponsor: None.

8057 Poster Session

Differences in central versus local lab PD-L1 classification in the ALCHEMIST Alliance A151216 non–small cell lung cancer (NSCLC) study.

David E. Kozono, Sharmila Giri, Shauna L. Hillman, Meghana Nair, Jacob Sands, Roberto Gianani, Lynette M. Sholl, Hui Yu, Angelina D. Tan, Mark Watson, Yujia Wen, Lisa Meier McShane, Jamie E. Chaft, David E. Gerber, Ramaswamy Govindan, Fred R. Hirsch, Geoff Oxnard, Shakun M. Malik, Tom Stinchcombe, Sumithra J. Mandrekar; Mass General Brigham Cancer Institute, Boston, MA; Mayo Clinic Rochester, Rochester, MN; Alliance Statistics and Data Management Center, Mayo Clinic Rochester, Rochester, MN; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Flagship Biosciences, Broomfield, CO; Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; University of Colorado Anschutz Medical Campus, Aurora, CO; Washington University School of Medicine, Alliance for Clinical Trials in Oncology, St. Louis, MO; Alliance Protocol Office, University of Chicago, Chicago, IL; National Cancer Institute, National Institutes of Health, Bethesda, MD; Memorial Sloan Kettering Cancer Center, New York, NY; UT Southwestern Medical Center, Dallas, TX; Alvin J Siteman Cancer Center at Washington University School of Medicine in St. Louis, St. Louis, MO; Center for Thoracic Oncology Mount Sinai Health System, New York, NY; BlossomHill Therapeutics, Inc., San Diego, CA; Clinical Investigations Branch, CTEP/DCTD, National Cancer Institute, National Institutes of Health, Rockville, MD; Duke Cancer Institute, Durham, NC

Background: The NCI Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) study tested resected stage II-IIIB(N2) NSCLC for targetable EGFR and ALK alterations and PD-L1 expression to screen patients for biomarker-driven adjuvant therapy trials (NCT02194738). Local lab results were requested when available for comparison to central lab results. **Methods:** We identified patients with both central and local PD-L1 results in the ALCHEMIST adjuvant immunotherapy study screening population. Discrepancies in tumor proportion score (TPS) between central and local PD-L1 were defined using prespecified cut-points (granular: <1%, 1-<5%, 5-<10%, 10-<20%, 20-<30%, 30-<40%, 40-<50%, 50-60%, 60-<70%, 70-<80%, 80-<90%, 90-<100%; clinical: <1%, 1-<50%, 50-100%). Large discrepancies were defined as ≥ 50 percentage point differences; for these cases, local PD-L1 and hematoxylin & eosin-stained slides were requested. These and all central slides were digitally scanned at 40X. Three expert pathologists reviewed the scanned slides in a blinded fashion. Differences between patient or tumor characteristics were assessed by Chi-square and Wilcoxon rank sum tests. Percent agreement was computed within and between the reviewers. **Results:** Central and local PD-L1 results were available for 497 patients. 177 cases (36%) had discrepancies that placed patients in different clinical TPS categories (<1%, 1-<50%, 50-100%). Among these, 43 cases had large TPS discrepancies; 14 had available local testing slides. 46 of the 320 cases without discrepancy were randomly selected as controls. No patient or tumor characteristics were associated with discrepancy, including tumor location, histology, grade or cancer stage ($p > 0.05$). Pairwise comparisons of TPS according to three pathologists re-reading the same scanned PD-L1 slides showed similar levels of disagreement in clinical TPS category whether there was initial discrepancy between central and local results (24%, 34%, and 23%; mean 27%) or not (33%, 30%, and 20%; mean 28%). Among the 14 cases with large initial discrepancies and local slides available, there was agreement in clinical TPS category when the anonymized central and local scanned slides were re-read by the pathologists in 54%, 38%, and 43% of cases, despite 100% non-agreement in initial reads. There were higher rates of agreement when the tested slides both originated from the same (100%) versus different (35%) blocks, when the same (48%) versus different (40%) PD-L1 antibodies were used, and when the cases were of non-squamous (52%) versus squamous (14%) cell carcinoma. **Conclusions:** There are substantial differences in PD-L1 TPS read by pathologists that can result in placement of patients in different categories commonly used for clinical management. These differences have clear implications in clinical trials and routine patient care. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; Alliance for Clinical Trials in Oncology Foundation.

8058 Poster Session

Firmonertinib combined with cisplatin/carboplatin plus pemetrexed as neoadjuvant therapy in resectable stage II-IIIb *EGFR*-mutated non–small cell lung cancer: A single-arm, single-center, open-label phase II study.

Jie Xu, Yameng Cui, Lianmin Zhang, Shengguang Wang, Zhanyu Pan, Zhansheng Jiang, Zhansheng Jiang; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Background: For patients with resectable, locally advanced EGFR-mutated NSCLC, traditional neoadjuvant chemotherapy yields suboptimal efficacy. While EGFR-TKIs are standard in the adjuvant therapy, their role in neoadjuvant therapy is under active investigation. **Methods:** This single-arm, phase II study evaluated neoadjuvant firmonertinib plus platinum-based chemotherapy in patients with stage II-IIIB EGFR-mutated NSCLC. The primary endpoint was major pathological response (MPR), the major second endpoint were pathological complete response (pCR), objective response rate (ORR), R0 resection rate and rate of downstaging. **Results:** Among the 13 patients currently enrolled, 11 completed 4 cycles of neoadjuvant therapy, and 9 underwent radical surgery. The MPR rate and the pCR rate are both currently at 0. The ORR is 77.8%, and the radical resection rate reaches 100%. The TNM tumor stage reduction rate is 66.7%. The incidence of grade 3/4 adverse events is 11.1%, and there are no 5-grade adverse events. **Conclusions:** Firmonertinib with chemotherapy as neoadjuvant in II-IIIB EGFR-mutated NSCLC demonstrated a promising surgical conversion rate and a manageable safety profile, supporting its feasibility for further study. Clinical trial information: NCT06890182. Research Sponsor: None.

8059 Poster Session

RATIONALE-315: Post hoc analysis of event-free survival by surgically relevant subgroups treated with perioperative tislelizumab and neoadjuvant chemotherapy vs neoadjuvant chemotherapy.

Gustavo Schvartsman, Mariano Provencio, Solange Peters, Zhenfa Zhang, Kirsha Naicker, Na Zhao, Xiao Lin, Mesha Austin Taylor, Wenxiang Wang, Qixun Chen, Bentong Yu, Jie Jiang, Jian Hu, Changli Wang; Hospital Israelita Albert Einstein, Sao Paulo, Brazil; Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; Lausanne University, Lausanne, Switzerland; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; BeOne Medicines Ltd, London, United Kingdom; BeOne Medicines Ltd, Shanghai, China; BeOne Medicines Ltd, San Carlos, CA; Hunan Cancer Hospital, Changsha, China; Zhejiang Cancer Hospital, Hangzhou, China; The First Affiliated Hospital of Nanchang University, Nanchang, China; The First Affiliated Hospital of Xiamen University, Xiamen, China; The First Affiliated Hospital, Zhejing University School of Medicine, Hangzhou, China

Background: RATIONALE-315 (NCT04379635) compared the efficacy and safety of perioperative tislelizumab (TIS) or placebo (PBO) + neoadjuvant chemotherapy (CT) in patients (pts) with resectable NSCLC. This post hoc analysis reports correlation of event-free survival (EFS) to key surgical outcomes. **Methods:** Pts with resectable stage II-IIIA NSCLC (N=453) were randomized 1:1 to 3-4 cycles of TIS 200 mg or PBO Q3W with neoadjuvant CT, followed by surgery and ≤8 cycles of adjuvant TIS 400 mg or PBO Q6W. Primary and key secondary endpoints were reported previously. Exploratory endpoints of surgical outcomes are presented here. **Results:** As of March 7, 2025, 190/226 pts in the TIS arm and 173/227 pts in the PBO arm underwent definitive surgery. EFS benefit with TIS vs PBO was observed in all surgically relevant subgroups (HR: 0.62; 95% CI: 0.44-0.88). Although R0 resection rates were similar between treatment arms, TIS showed greater EFS benefit vs PBO (HR: 0.62; 95% CI: 0.43-0.90). A similar trend was observed in R1/R2 pts (HR: 0.75; 95% CI: 0.19-3.05); however, data should be interpreted with caution due to small pt numbers. Pts in the TIS arm who underwent open and minimally invasive surgery (n=179) achieved improved EFS benefit compared with those in the PBO arm (n=157), regardless of disease stage and surgery type (Table). In pts who underwent minimally invasive and open surgery, respectively, grade ≥3 treatment-emergent adverse events occurred in 77.2% and 78.8% of pts in the TIS arm and 71.3% and 81.7% in the PBO arm. In pts who underwent minimally invasive surgery in the TIS arm, grade ≥3 immune mediated adverse events were reported in 11.4% of all pts (13/114), 10.4% of pts in stage II (5/48), and 12.3% in stage IIIa (8/65). **Conclusions:** Perioperative TIS + neoadjuvant CT improved EFS in pts with resectable NSCLC across all surgically relevant subgroups regardless of disease stage or surgery type. These results further support TIS + CT as an efficacious and safe treatment option that may reduce the burden of invasive surgical intervention. Clinical trial information: NCT04379635. Research Sponsor: BeOne Medicines Ltd.

	EFS rate, % (95% CI)					
	12 mo		24 mo		48 mo	
Approach to surgery, NSCLC stage	TIS	PBO	TIS	PBO	TIS	PBO
Minimally invasive						
Overall	89.7 (82.2-94.2)	79.0 (78.0-86.6)	81.0 (72.1-87.3)	63.8 (51.8-73.6)	74.3 (64.0-82.1)	55.4 (42.0-67.0)
Stage II	90.9 (82.8-99.8)	85.0 (73.7-98.0)	83.6 (73.1-95.5)	69.8 (55.8-87.4)	77.0 (64.6-91.8)	66.5 (52.1-84.8)
Stage IIIa	88.7 (77.8-94.5)	73.1 (56.7-84.1)	78.9 (66.5-87.2)	58.0 (41.3-71.4)	72.4 (58.6-82.3)	46.7 (29.0-62.6)
Open						
Overall	78.5 (65.9-86.9)	70.9 (57.8-80.6)	60.2 (46.7-71.2)	47.8 (34.9-59.6)	54.1 (40.4-66.0)	31.1 (17.3-45.8)
Stage II	85.7 (72.0-100)	80.0 (64.3-99.6)	76.2 (60.0-96.8)	55.0 (37.0-81.8)	71.4 (54.5-93.6)	NE (NE-NE)
Stage IIIa	74.1 (57.2-85.2)	66.4 (49.9-78.6)	50.3 (33.7-64.8)	44.3 (28.9-58.6)	NE (NE, NE)	28.7 (13.9-45.5)

NE, not evaluable.

Survival outcomes between neoadjuvant and adjuvant chemo-immunotherapy in patients with stage II–III NSCLC undergoing surgical resection.

Joseph Zouein, Brady Kupersmith, John Aversa, Kinjal Dargan, Polina Khrizman, David Shersher, Veli Bakalov; Department of Medicine, Cooper University Health Care, Camden, NJ; Division of Thoracic Surgery, Cooper University Health Care, Camden, NJ; MD Anderson Cancer Center at Cooper, Camden, NJ

Background: In patients with stage II–III NSCLC, perioperative systemic therapy is recommended; however, the optimal timing of chemo-immunotherapy relative to surgery remains an area of active investigation. The aim of this study was to compare overall survival outcomes between neoadjuvant and adjuvant chemo-immunotherapy in patients with stage II–III NSCLC undergoing surgical resection. **Methods:** We utilized the National Cancer Database (NCDB) and included patients with complete follow-up data, diagnosed between 2018 and 2023 with clinically staged IIA–IIIB NSCLC (cT1–cT4, cN0–cN2, cM0), who underwent definitive surgical resection, and received either neoadjuvant or adjuvant chemo-immunotherapy. Kaplan–Meier analysis and propensity score–adjusted Cox proportional hazards models were used to assess survival outcomes. **Results:** A total of 2,815 patients met the inclusion criteria, including 1,521 (54%) males, with a median age of 66 years. Of these, 1,186 (42%) patients received neoadjuvant therapy and 1,629 (58%) received adjuvant therapy. Median overall survival (OS) was not reached in the neoadjuvant group, compared with 79.4 months (95% CI, 68.1–90.7, $p < 0.001$) in the adjuvant group (Table 1). On propensity score–adjusted Cox regression, neoadjuvant therapy was associated with a significant OS advantage compared with adjuvant therapy (HR 0.71; 95% CI, 0.58–0.87; $p < 0.001$). Neoadjuvant therapy was associated with improved OS among patients with baseline cN2 disease (HR 0.64; 95% CI, 0.45–0.91; p = 0.012). No statistically significant difference in OS was observed among patients with cT3 or cT4 disease (HR 0.95; 95% CI, 0.66–1.36; p = 0.759) and HR 0.67; (95% CI, 0.45–1.01; p = 0.053), respectively. **Conclusions:** In patients with stage II–III NSCLC undergoing surgical resection, neoadjuvant chemo-immunotherapy was associated with improved overall survival compared with adjuvant therapy, particularly among those with a higher nodal or regional tumor burden at presentation. Research Sponsor: None.

Median overall survival and hazard ratios for neoadjuvant versus adjuvant chemo-immunotherapy in stage II–III NSCLC.

	Neoadjuvant Median OS (months)	Adjuvant Median OS (months)	Hazard Ratio (HR)	95% CI	p-value
Overall cohort	NR	79.4 (68.1–90.7)	0.71	0.58–0.87	<0.001
cN2	NR	62.6 (45.4–79.8)	0.64	0.45–0.91	0.012
cT3	NR	76.3 (62.4–90.1)	0.95	0.66–1.36	0.759
cT4	71.0 (62.7 – 79.3)	56.1 (37.6- 74.5)	0.67	0.45–1.01	0.053

Characteristics of patients with resectable early-stage non–small cell lung cancer treated with neoadjuvant chemoimmunotherapy or surgery ± adjuvant therapy.

Pragya Rai, Yu-Han Kao, Ashwini Arunachalam, Jeffrey Thompson, Ayman Samkari, Jay M. Lee; Merck & Co., Inc., Rahway, NJ; Merck & Co., Inc., North Wales, PA; University of California, Los Angeles (UCLA), Los Angeles, CA

Background: The integration of immune checkpoint inhibitors (ICIs) into neoadjuvant, perioperative, and adjuvant treatment strategies for early-stage NSCLC (eNSCLC) has been associated with improved patient outcomes; however, despite these advances, uptake of ICIs in the neoadjuvant/perioperative setting remains limited. This study aimed to characterize differences in patient characteristics between those receiving neoadjuvant chemoimmunotherapy (neoadjuvant ICI+CTx) and those receiving upfront surgery ± adjuvant therapy. **Methods:** Adult patients with stage II-IIIB(N2) NSCLC (AJCC 8th edition) diagnosed between March 2022 and six months before data cut-off (November 2025) were identified in the Flatiron Health database. Patients who received ICI+CTx prior to surgery were assigned to the neoadjuvant ICI+CTx group, and patients that underwent upfront resection following an NSCLC diagnosis with no previous treatment, with or without adjuvant therapy, were assigned to the surgery± adjuvant therapy group. The Pearson chi-square or fisher exact tests were conducted to evaluate differences in baseline characteristics. All statistical analyses were two-sided. **Results:** A total of 1,807 patients were identified with resectable stage II-IIIB(N2) NSCLC, of which 204 (11%) initiated neoadjuvant ICI+CTx and 1,603 (89%) received surgery± adjuvant therapy (583 (36%) with adjuvant therapy; 1,020 (64%) without adjuvant therapy). Of the 204 patients, 144 (71%) underwent surgery and 76 (53% of those undergoing surgery) subsequently received adjuvant therapy. Significant differences were observed in the baseline characteristics between the two groups. Patients who received neoadjuvant ICI+CTx had higher proportion of stage III disease, cN2 status, evenly split histology, higher biomarker (PD-L1, EGFR) testing, PD-L1 positive expression levels, and fewer EGFR mutations while patients who received surgery± adjuvant therapy had higher proportion of stage II disease, cN0 status, non-squamous histology, lower biomarker testing, negative or low PD-L1 expression levels, and higher EGFR mutations (all $p < 0.001$). **Conclusions:** Despite the clear benefit across clinical trials of neoadjuvant and perioperative ICI strategies to treat resectable eNSCLC, their utilization in clinical practice remains limited. This study further demonstrates significant differences in baseline characteristics that might contribute to patient selection for neoadjuvant ICI+CTx versus upfront surgery ± adjuvant therapy as a primary therapeutic approach. Tailored interventions to further educate the medical community on recent clinical trial evidence may facilitate wider implementation of neoadjuvant and perioperative ICI strategies and broaden appropriate patient selection in resectable eNSCLC. Research Sponsor: Merck & Co., Inc., Rahway, NJ, USA.

Impact of adjuvant immunotherapy after pathologic complete response to neoadjuvant chemo-immunotherapy in resected stage II–III non–small cell lung cancer.

Joseph Zouein, Brady Kupersmith, John Aversa, Kinjal Dargan, Polina Khrizman, David Shersher, Veli Bakalov; Department of Medicine, Cooper University Health Care, Camden, NJ; Division of Thoracic Surgery, Cooper University Health Care, Camden, NJ; MD Anderson Cancer Center at Cooper, Camden, NJ

Background: Perioperative chemo-immunotherapy has recently emerged as a new standard of care for patients with resectable non–small cell lung cancer (NSCLC) following positive results from the CheckMate-77T (NCT04025879) and KEYNOTE-671 (NCT03425643) trials. However, whether patients who achieve a complete pathologic response (pCR) after neoadjuvant chemo-immunotherapy derive additional benefit from subsequent adjuvant immunotherapy remains uncertain due to limited available data (only 58 patients achieved pCR in CheckMate-77T and 72 patients in KEYNOTE-671). The INSIGHT clinical trial (NCT06498635) is an ongoing phase III study designed to address this question; however, the trial is expected to be completed in 2039. Therefore, generating additional data in this area is critically important. We performed a retrospective analysis to assess whether the addition of adjuvant immunotherapy improves overall survival (OS) among patients with stage II–III NSCLC who achieve pCR following neoadjuvant chemo-immunotherapy. **Methods:** We conducted a retrospective cohort study using the National Cancer Database (NCDB) and included patients with complete follow-up data who were diagnosed between 2018 and 2023 with clinically staged IIA–IIIB NSCLC (cT1–cT4, cN0–cN2, cM0), underwent definitive surgical resection with pCR (ypT0N0M0), and received either neoadjuvant chemo-immunotherapy alone or neoadjuvant chemo-immunotherapy followed by adjuvant immunotherapy (perioperative chemo-immunotherapy). Survival outcomes were analyzed using Kaplan–Meier methods. **Results:** A total of 1,816 patients were included, of whom 967 (53.2%) were male, with a median age of 65 years (IQR, 60–71). Among these patients, 1,186 (65.3%) received neoadjuvant chemo-immunotherapy alone, and 630 (34.7%) received perioperative therapy. No significant difference in overall survival was observed between the two treatment groups. Median OS was not reached in either group, with a hazard ratio of 1.235 (95% CI, 0.602–2.533; p = 0.565). **Conclusions:** Among patients with stage II–III NSCLC who achieve pCR following neoadjuvant chemo-immunotherapy and undergo surgical resection, we observed no significant difference in overall survival between those treated with neoadjuvant therapy alone versus perioperative chemo-immunotherapy. These findings suggest that neoadjuvant chemo-immunotherapy alone may be sufficient for patients who achieve pCR, and that adjuvant immunotherapy in this setting may not provide additional survival benefit. Research Sponsor: None.

8064 Poster Session

Postoperative re-profiling for identification of missed drivers and a high-risk fusion subgroup in non-pCR lung adenocarcinoma after neoadjuvant immunotherapy: A multicenter retrospective study.

Xin Liu, Haiyu Zhou, Dong Xie, Wanpu Yan, Kun Qian, Zuoqing Song, Hefei Li, Jun Wang, Jian Hu, Xu Li, Xiaolong Yan, Ming Li, Hong Yang, Hao Peng, Richeng Jiang, Changli Wang, Zhenfa Zhang, Dongsheng Yue; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Shanghai, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Surgery I, Peking University Cancer Hospital & Institute, Beijing, China; Xuanwu Hospital Capital Medical University, Beijing, China; Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin, China; Affiliated Hospital of Hebei University, Baoding, China; Department of Thoracic Surgery, Jiangsu Province Hospital and The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; The First Affiliated Hospital of Medical School of Zhejiang University, Hangzhou, Zhejiang, China; Hunan Provincial Cancer Hospital, Changsha, China; The Second Affiliated Hospital of Air Force Medical University of the People's Liberation Army of China (Tangdu Hospital), Xi'an, China; China Jinagsu Province Institute of Cancer Research, Nanjing, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China; Department of Thoracic Surgery, The First People's Hospital of Yunnan Province, Kunming, China

Background: For stage II-III driver-negative non–small cell lung cancer (NSCLC), neoadjuvant chemoimmunotherapy followed by surgery is standard. However, patients without pathological complete response (non-pCR) have suboptimal outcomes and heterogeneous benefit from adjuvant immunotherapy. Baseline driver-negative status may be confounded by false-negative PCR- or DNA-only testing and detecting missed drivers postoperatively could alter adjuvant strategies. This study characterized post-treatment driver alterations and its prognostic value in non-pCR NSCLC after neoadjuvant immunotherapy. **Methods:** The retrospective multicenter study enrolled 247 stage II-III lung adenocarcinoma (LUAD) patients initially tested as EGFR L858R/19del- and ALK-negative and treated with neoadjuvant immunotherapy (2018-2025). 76 lung squamous cell carcinoma (LUSC) cases were included for exploratory analysis. Postoperative samples underwent 35-gene synchronous DNA/RNA next-generation sequencing (DR-NGS) to identify SNV/indel and fusion events and assess prognostic associations. **Results:** Of 247 LUAD cases, 179 passed NGS quality control (QC). Driver alterations were identified in 104 (58.1%) patients, including 26 fusions: RETn = 9), MET ex14 skipping (n = 6), ALK(n = 4), ROS1(n = 3), NRG1(n = 2), MET fusion(n = 1), NTRK(n = 1) and 80 SNVs/indels :EGFR (n = 30), KRAS G12C/D (n = 16), HER2/3 (n = 16), BRAF (n = 2), KRAS non-G12C/D (n = 16). Notably, 10 classic EGFR mutations (19del/L858R) 、 9 rare EGFR mutations and 4 ALK fusions were newly identified, indicating baseline omissions. Driver-positive tumors had significantly higher residual tumor burden(median: 51.8% vs. 35.8%, p = 0.003) and a higher proportion of females (43.3% vs 20.0%, p = 0.001). Median recurrence-free survival (mRFS) differed significantly among fusion-positive, mutation-positive, and driver-negative groups (20.9 vs 41.5 vs 60.3 months; p = 0.024). In patients receiving adjuvant immunotherapy, mRFS was 34.6 months in driver-positive and not reached in driver-negative patients. Driver detection was rare ($<$ 3%) in QC-failed samples (n = 68), which exhibited a higher major pathological response than QC-passed samples (58.1% vs 14.5%), indicating tumor cellularity as critical for detection. Exploratory analysis in 55 QC-passed LUSC samples showed a low driver detection rate (7.3%), suggesting limited utility in this cohort. **Conclusions:** DR-NGS reveals a high prevalence of drivers in non-pCR LUAD after neoadjuvant immunotherapy, with positivity associated with higher residual tumor burden. Fusion-positive patients have the poorest prognosis, identifying a subgroup that may benefit from tailored adjuvant strategies. These findings support routine postoperative molecular re-profiling in non-pCR patients to guide individualized treatment. Research Sponsor: The National Natural Science Foundation of China (grant No.82573102, 82173038, 82273428); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0501700, 2023ZD0501703).

CT-derived visceral fat phenotypes to reveal a metabolically defined TOFI subgroup in a lung cancer screening cohort: An imaging-based framework for evaluating the BMI paradox.

Taofik Ahmed Suleiman, Hilmi Al-Shakhshir, Mendel Lebowitz, Juyoung Lee, Sadeer Al-Kindi, Gourav Modanwal, Mohammadhadi Khorrami, Anant Madabhushi; Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA; Atlanta Veterans Administration Medical Center, Atlanta, GA; Department of Computer Science and Informatics, Emory University, Atlanta, GA; Houston Methodist DeBakey Heart & Vascular Center, Houston, TX; Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, GA; Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta Veterans Administration Medical Center, Atlanta, GA

Background: Body mass index (BMI) imperfectly reflects metabolic health and cannot distinguish subcutaneous from visceral fat, contributing to the long-standing "BMI paradox" in cancer, whereby higher BMI is sometimes associated with better survival. Visceral fat is metabolically active and promotes cancer progression. Individuals with normal BMI but high visceral fat, termed "Thin Outside, Fat Inside" (TOFI) are understudied in cancer populations. These TOFI patients may represent an unrecognized high-risk metabolic phenotype in cancer. We investigated whether CT-derived lower-thoracic visceral fat identifies TOFI as a high-risk subgroup for cancer mortality. **Methods:** Baseline CT scans from participants in the National Lung Screening Trial (NLST; n = 19,140), a lung cancer screening cohort designed to detect NSCLC, were segmented to extract subcutaneous fat, visceral fat, and vertebral levels. Because T9–T12 best captures abdominal visceral adiposity, the percentage volume of visceral fat relative to subcutaneous fat from this region was used for phenotyping. Low (<20%) and high (>40%) visceral fat groups were defined, yielding 9,887 participants. Visceral fat was combined with BMI (<25 vs ≥25) to define four phenotypes: P1 (LowBMI_LowVIS), P2 (HighBMI_LowVIS), P3 (HighBMI_HighVIS), and P_TOFI (LowBMI_HighVIS). Cancer-specific mortality was the primary endpoint, and Cox proportional hazards models were used to compare these phenotypes. **Results:** Distinct phenotypes demonstrated markedly different mortality risks (Table). The TOFI group exhibited the worst survival despite normal BMI, with nearly double the cancer mortality risk compared with the metabolically favorable reference group, P1 (HR 1.95; 95% CI, 1.31-2.91; p = 8.4e-04). In contrast, high-BMI groups showed only modest or no excess risk, supporting the limitation of BMI alone. **Conclusions:** CT-derived visceral fat phenotyping reveals a clinically relevant high-risk group TOFI, individuals who have normal BMI but significantly elevated cancer and all-cause mortality risk compared to even high-BMI patients. This finding directly exposes the BMI paradox, showing that normal BMI does not confer protection when visceral adiposity is high. Because this TOFI phenotype is undetectable by BMI, incorporating visceral fat assessment into lung cancer screening and survivorship models could enable earlier identification of high-risk TOFI patients and guide targeted prevention. Research Sponsor: None.

Phenotype	Cancer Mortality HR (95% CI)	p-value	All-Cause Mortality HR (95% CI)	p-value
P_TOFI (LowBMI_HighVIS)	**1.95 (1.31-2.91)**	**8.4e-04**	**2.42 (1.84-3.18)**	**7.5e-11**
P3 (HighBMI_HighVIS)	1.25 (0.91-1.71)	1.7e-01	1.59 (1.27-1.98)	3.7e-05
P2 (HighBMI_LowVIS)	0.92 (0.64-1.30)	6.2e-01	1.08 (0.84-1.39)	5.4e-01
P1 (LowBMI_LowVIS)	Reference	-	-	-

Stage-dependent divergence of immune prognostic signatures in non–small cell lung cancer.

Praveen Thapa, Trilok Shrivastava, Ashish Nepal, Anupam Raj Upadhyay; Chirayu National Hospital, Kathmandu, Nepal; University of Arkansas Medical Sciences, Little Rock, AR; WellSpan York Hospital, York, PA; Stupa Community Hospital, Kathmandu, Nepal

Background: Tumor mutational burden (TMB) and immune activation are widely studied biomarkers in non–small cell lung cancer (NSCLC), yet their prognostic relevance outside the context of immunotherapy remains unclear. We investigated how age, histology, and disease stage modify the relationships between tumor genomics, immune contexture, and overall survival in NSCLC. **Methods:** We analyzed The Cancer Genome Atlas NSCLC cohort from the "Pan-cancer atlas" (2018) with a total of 1053 patients evaluating TMB, CD8A expression, cytolytic activity score (CYT), age at diagnosis, histology, and overall survival. Associations among continuous variables were assessed using Spearman correlation. Multivariable Cox proportional hazards models adjusted for age, sex, and tumor mutational burden were performed and stratified by stage (I–II vs III–IV). **Results:** Age demonstrated an inverse correlation with tumor mutational burden ($\rho = -0.12$, $P < 0.001$) but was not associated with CD8A expression and showed a weak positive association with CYT, driven by non-squamous tumors. Tumor mutational burden was not associated with overall survival in either early- or late-stage disease. In contrast, immune biomarkers demonstrated marked association with stage of disease. Higher CD8A expression was associated with improved survival in early stage (HR 0.77 per SD, P = 0.021) but not in advanced disease. CYT exhibited a significant interaction with stage with higher CYT showing association with improved survival in early-stage NSCLC (HR 0.79 per SD, P = 0.026) but with worse survival in late-stage disease (derived HR ≈ 1.14). Tumor stage remained the dominant prognostic factor across all models. **Conclusions:** In untreated NSCLC, immune prognostic signatures are strongly stage dependent. Immune infiltration and cytolytic activity confer survival benefits in early-stage disease but not in advanced disease, where cytolytic activity may reflect aggressive tumor-associated inflammation. Tumor mutational burden does not provide prognostic value across disease stages. These findings highlight the importance of disease context when interpreting immune biomarkers and provide critical baseline insight for immunotherapy-era studies. Research Sponsor: None.

Patient characteristics.

Characteristic	Overall (N=1053)	Early Stage (I–II) (N=517)	Late Stage (III–IV) (N=479)
Age, median (IQR)	67	68	67
Sex, % male	40.24 (402)	44.68 (231)	35.69 (171)
Histology, %			
Squamous	46.24 (487)	46 (238)	51.35 (246)
Non-squamous	53.7 (566)	56 (279)	50 (233)
Stage			
I–II	47%		
III–IV	53%		
TMB, median (IQR)	7.3 (3.9-12.1)	7.35 (3.7-12.1)	7.36 (4.2-12.1)
CD8A expression, median (IQR)	232 (112-469)	240 (122-471)	208 (103-460)
CYT score, median (IQR)	183 (103.9-368.3)	191.3 (109.6-368.3)	175.9 (98-370)

8067 Poster Session

Survival outcomes of young patients with non-small cell lung cancer in Latin America: A real-world cohort study.

Cristina Torres-Mallma, Ronald Hernan Calle Valdez, Luis Mas; AUNA, Lima, Lima, Peru; Hospital Alberto Sabogal Sologuren Callao, Bellavista, Peru; Oncosalud-AUNA, Lima, Peru

Background: Young patients with non-small cell lung cancer (NSCLC) represent a distinct biological subgroup, frequently enriched with actionable oncogenic drivers. However, real-world survival data from Latin America are limited. We evaluated survival outcomes and prognostic factors in young versus older patients with NSCLC treated in Peru. **Methods:** We conducted a retrospective cohort study including patients with histologically confirmed NSCLC treated between 2018and 2024 at a national reference cancer center. Patients were stratified by age at diagnosis (<45 vs ≥ 45 years). Overallsurvival (OS) was estimated using the Kaplan–Meier method. Multivariable Cox regression was performed adjusting for sex,ECOG performance status, smoking history, clinical stage, histology, molecular alterations and first-line treatment. **Results:** A total of 317 patients were included; 19.9% were younger than 45 years. The cohort was predominantly female (59.3%),never-smokers (85.5%) and had adenocarcinoma histology (95.6%). Advanced disease (stage III–IV) was present in 94.0% ofcases. Actionable molecular alterations were identified in 69.4% of patients, most commonly EGFR mutations (48.3%).Younger patients showed a higher frequency of actionable mutations compared with older patients (70% vs 56%, p=0.038).After a median follow-up of 40.9 months, 92 deaths (29.0%) were recorded. In adjusted analysis, young age was notassociated with worse OS (adjusted HR 1.32; 95% CI 0.79–2.21; p=0.29). Former smoking history was the only independentpredictor of inferior OS (adjusted HR 2.38; 95% CI 1.16–4.91; p=0.018). **Conclusions:** Young age at NSCLC diagnosis was not associated with inferior survival. Despite advanced-stage presentation, youngerpatients exhibited a high prevalence of actionable oncogenic drivers, supporting routine comprehensive molecularprofiling. These results provide robust regional evidence and reinforce the importance of precision oncology inunderrepresented populations. Research Sponsor: None.

Immune aging within the tumor microenvironment as a predictor of survival in non–small cell lung cancer.

Taeyun Kim, Seokho Yang; Kosin University College of Medicine, Busan, South Korea

Background: Immune aging has been associated with survival outcomes in patients with lung adenocarcinoma (LUAD), but its relevance within the tumor microenvironment (TME) remains unclear. **Methods:** Clinical and RNA-sequencing data from the TCGA LUAD cohort were analyzed. Immune aging within tumor tissue was quantified using a predefined 121-gene immune aging–related signature (IAS-121). For primary analyses, patients were dichotomized into high versus low IAS-121 groups based on the median value. Immune cell composition within the TME was inferred using xCell analysis and compared according to IAS-121 status. Overall survival (OS) was assessed using Kaplan–Meier analysis and Cox proportional hazards models adjusted for age, sex, tumor stage, smoking status, and EGFR mutation status. Sensitivity analyses were performed using quartile-based categorization of IAS-121 (lowest vs highest quartile), and external validation was conducted in two independent LUAD cohorts (GSE68465 and GSE50081). **Results:** A total of 518 patients with LUAD from the TCGA cohort were included. Patients with high IAS-121 had significantly poorer OS compared with those with low IAS-121 (p=0.026). In multivariable analysis using the median cut-off, high IAS-121 showed a non-significant trend toward increased mortality (adjusted hazard ratio [aHR] 1.33; 95% confidence interval [CI], 0.96–1.84). In sensitivity analyses comparing the lowest and highest quartiles of IAS-121, a significant association with OS was observed (aHR 1.87; 95% CI, 1.20–2.92). This association was further confirmed in a pooled analysis of the external LUAD cohorts (GSE68465 and GSE50081), in which higher IAS-121 was independently associated with worse OS (aHR 1.57; 95% CI, 1.02–2.43). Subgroup analyses showed generally consistent associations across age, sex, tumor stage, smoking status, and EGFR mutation status. Tumors with high IAS-121 exhibited reduced enrichment of $CD8^+$ T cells and $CD4^+$ naïve T cells, along with increased neutrophil enrichment. **Conclusions:** Immune aging within TME is associated with poorer survival in LUAD. As this study is hypothesis-generating, further investigations integrating tissue- and blood-based measures of immune aging are warranted to clarify its clinical and biological implications. Research Sponsor: None.

Cox proportional hazards models comparing the lowest versus highest quartile of immune aging score-121 and overall survival in lung adenocarcinoma.

	TCGA		GSE68465 plus GSE50081	
	HR (95% CI)	p	HR (95% CI)	p
Crude	1.648 (1.114 – 2.238)	0.012	2.093 (1.396 – 3.141)	<0.001
Adjusted	1.873 (1.200 – 2.924)	0.006	1.571 (1.016 – 2.429)	0.007

Models adjusted age, sex, tumor stage, smoking status, and EGFR mutation status for TCGA dataset and age, sex, tumor stage for GSE68465 plus GSE50081 cohorts.
LUAD = lung adenocarcinoma; HR = hazard ratio; CI = confidence level.

8069 Poster Session

Age-based differences in outcomes among small cell lung cancer patients treated with tarlatamab.

Raymart Macasaet, Vinit Singh, Grace K. Dy, Doantrang Du; Monmouth Medical Center, Long Branch, NJ; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Tarlatamab has durable antitumor activity in patients with previously treated Small Cell Lung Cancer (SCLC). A rising fraction of SCLC diagnoses is now observed in older patient groups. To assess real-world outcomes, we analyzed a large, multi-institutional database evaluating age-related differences in survival, treatment patterns, and immune toxicities, including Cytokine Release Syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), to clarify factors affecting response and tolerability. **Methods:** A retrospective cohort study was conducted using de-identified data from the TriNetX Research Network. At the time of data analysis, it included 154,537,377 patients across 113 healthcare organizations. We identified adults aged 18 years or older with lung cancer treated with Tarlatamab. Kaplan-Meier analysis assessed overall survival. Statistical comparisons of survival rates between groups were performed using the log-rank test. Propensity matching was used to adjust for age, comorbidities, and lines of treatment. **Results:** A total of 616 patients were identified in the TriNetX cohort, with a mean age of 65.8 ± 9.89 years, and 51.9% were female. Age distribution was as follows: 124 patients (20.13%) were younger than 60 years, 271 (43.99%) were 60–70 years, and 221 (35.88%) were older than 70 years. Brain metastases were present in 53 patients (8.60%) in the <60 group, 116 (18.83%) in the 60–70 group, and 90 (14.61%) in the >70 group. Median overall survival of the entire cohort was 13.32 months; it was not reached in the <60 group, 13.32 months in the 60–70 group, and 12.72 months in the >70 group, with no significant differences across age groups or brain metastasis status. In the propensity score–matched cohorts, survival did not differ significantly between <60 and >70 age groups (HR 0.80 (95% CI 0.34–1.22; p=0.39)), and a similar lack of difference was observed between 60–70 and >70 age groups (HR 0.72 (95% CI 0.48–1.07; p=0.10)). In the overall population, 57 patients (9.25%) experienced ICANS and 67 (10.88%) developed CRS. By age group, ICANS and CRS occurred in 16 (2.60%) and 17 (2.76%) patients <60, 23 (3.73%) and 29 (4.71%) patients 60–70, and 18 (2.92%) and 21 (3.40%) patients >70, respectively. Overall, 91 patients (14.77%) required tocilizumab and 23 (3.73%) required vasopressors, with no significant differences across the three age groups. **Conclusions:** This study offers an extensive evaluation of age-related outcomes with Tarlatamab. Neither age nor brain metastases significantly influenced overall survival, indicating preserved efficacy in older adults. ICANS and CRS were infrequent and evenly distributed across age groups. Tocilizumab and vasopressor use were similar across groups, indicating comparable severity. These results support Tarlatamab's favorable safety, tolerability, and effectiveness across diverse real-world populations. Research Sponsor: None.

SPARK-Lung: A study of patterns and outcomes in young-onset lung cancer.

Teja Voruganti, Yi Lian, Benjamin Aaron Bleiberg, Lauren Reed-Guy, Roger B. Cohen, David John Cantor, Kyle William Robinson, Christopher D'Avella, Christine Agnes Ciunci, Melina Elpi Marmarelis, Aditi Puri Singh, Corey J. Langer, Lova Sun, Charu Aggarwal; Penn Medicine Abramson Cancer Center, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Health System, Philadelphia, PA; Penn Medicine-Abramson Cancer Center, Philadelphia, PA; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Young onset lung cancer patients diagnosed before age 50 appear to have distinct features compared to their older counterparts, including a higher proportion of never-smokers and increased frequency of targetable driver mutations. Yet, the molecular characteristics and survival outcomes of young-onset non-small cell lung cancer (NSCLC) remain poorly defined in U.S. populations. Improved understanding of the demographic and molecular profile of this distinct disease is needed to guide diagnostic testing strategies and personalize treatment. **Methods:** We conducted a retrospective cohort study using the US-based, electronic health record-derived deidentified Flatiron Health Research Database, which included adults diagnosed with NSCLC between 2013 and 2025 who underwent next-generation sequencing. Young-onset NSCLC was defined as age < 50 years and older-onset as ≥ 50 years. Demographics, stage at diagnosis, and prevalence of driver mutations and fusions were compared between age groups. Differences are reported using standardized mean differences (SMD) with SMD ≥ 0.2 indicating significant difference. Treatment patterns and overall survival (OS) were evaluated in metastatic patients adjusting for sex, histology, smoking status, performance status, insurance, and TP53 status. **Results:** Among 3792 young-onset and 120,161 older-onset patients with NSCLC across all stages, young-onset patients were more often female (54.2% vs 51.2%), Asian (5.3% vs 2.4%), Black (12.4% vs 8.1%), or Hispanic/Latino (8.5% vs 3.6%) (SMD 0.38). They were more often treated in academic settings (24.8% vs 16.0%; SMD 0.26) and more likely to have no tobacco history (36.6% vs 13.8%; SMD 0.65). Non-squamous histology predominated in younger patients (85.1% vs 73.1%; SMD 0.29) and actionable driver alterations were more common (47.8% vs 40.5%), particularly ALK (9.3% vs 1.2%; SMD 0.66) and EGFR (17.6% vs 11.0%; SMD 0.21). Young-onset patients were more likely to present with metastatic disease (69.8% vs 49.2%; SMD 0.43). After adjustment, treated young-onset patients received more lines of therapy than older patients (median no. 2 vs 1; incident rate ratio 1.16; 95% CI 1.12–1.20; $p < 0.0001$) and had longer median treatment duration (23.7 vs 14.3 mos, $p < 0.0001$). Among patients with metastatic disease at diagnosis, unadjusted median OS was longer in young-onset versus older-onset patients (2.0 vs 1.1 years), with higher 1-year (72.6% vs 57.2%) and 2-year (56.7% vs 41.8%) OS rates. **Conclusions:** Young-onset NSCLC represents a clinically distinct population in the United States, characterized by higher rates of advanced stage at diagnosis, a higher percentage of actionable molecular alterations and improved survival in the metastatic setting. Recognition of these differences may inform screening, testing, treatment, and survivorship strategies for younger adults with NSCLC. Research Sponsor: None.

Real-world impact of first immunotherapy infusion timing on outcomes in locally advanced non-small cell lung cancer.

Mumtu Lalla, Puneet Dhillon, Brendon Fusco, Chenxin Zhang, Buse Eglenen Polat, Jinal Gandhi, Renuka Ramchandran, Dean Nehama, Xiaonan Xue, Nitin Ohri, Balazs Halmos, Haiying Cheng; Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Department of Epidemiology and Population Health, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Department of Radiation Oncology, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Montefiore Medical Center/ Albert Einstein College of Medicine, Bronx, NY

Background: Emerging evidence suggests that earlier time-of-day (ToD) infusion of immune checkpoint inhibitors (ICIs) is associated with improved progression-free survival (PFS) and overall survival (OS) in patients with advanced non-small cell lung cancer (NSCLC). Although the timing of the initial infusion may be particularly influential, its impact on outcomes in earlier stages of NSCLC remains unclear. We investigated the association between first ICI infusion ToD and clinical outcomes in a racially and ethnically diverse population with locally advanced NSCLC. **Methods:** We conducted a retrospective cohort study of patients with locally advanced NSCLC treated with definitive chemoradiation followed by consolidation durvalumab between 2018-2025. Patient demographics, smoking status, ECOG performance status, PD-L1 tumor proportion score (TPS), lung cancer stage and histology, disease volume (DV), mean heart dose, and clinical outcomes were all obtained using chart review. Neighborhood distress was classified using patient zip codes and the Distress Communities Index. ICI administration timing was categorized into quartiles: ≤11:20 AM, 11:20 AM-12:32 PM, 12:32 PM-13:48 PM, >13:48 PM. Kaplan Meier methods and cox proportional hazards models, adjusted for major patient factors, were used to evaluate OS and PFS. **Results:** Among 109 eligible patients (median age 69.5 years), 55% were male, 42% were Non-Hispanic Black, 30% were Hispanic, 64% resided in distressed ZIP codes. Patients receiving ICIs in the latest ToD quartile (>13:48) had a significantly shorter PFS compared to those treated in the earliest quartile (≤11:20) in both univariate (HR 2.10, p=0.024) and multivariate analysis (HR 3.32, p=.0.0057). A non-significant trend towards inferior OS was also observed with later ToD administration. Higher DV (HR 1.09 per 10 mL, p=0.029) and mean heart dose (HR 1.86, p=0.03) were independently associated with worse OS. **Conclusions:** In this real-world study of a diverse population with locally advanced NSCLC, later ToD ICI administration (>13:48) was associated with a significantly shorter PFS and a trend towards worsened OS. These findings suggest that the timing of ICI delivery may influence outcomes in locally advanced NSCLC, consistent with prior observations in metastatic disease, and highlight the need for prospective trials to validate the impact of infusion timing on survival and clarify the underlying circadian mechanisms contributing to these differences.
Research Sponsor: None.

Multivariable Cox regression analysis.

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
ToD of First Infusion						
≤11:20	-	-	-	-	-	-
11:20-12:32	1.53	0.57,4.10	0.40	1.68	0.75,3.80	0.21
12:32-13:48	0.48	0.15,1.59	0.23	1.30	0.53,3.16	0.57
>13:48	1.66	0.62,4.45	0.31	3.32	1.39,7.92	0.007
Mean Heart Dose (Gy)	1.86	1.06,3.26	0.030	1.54	0.98,2.42	0.060
Disease Volume (mL)	1.09 per 10 mL	1.01,1.17	0.029	1.03 per 10 mL	0.97,1.09	0.29

Trends in income-related lung cancer disparities since the introduction of USPSTF screening guidelines.

Tyler Munchmeyer Healy, Wenqing Yang, Soutrik Mandal, Daniel Jacob Becker; NYU Grossman School of Medicine, New York, NY; NYU Langone Health, New York, NY; Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: In 2013, the USPSTF introduced guidelines for lung cancer screening to promote earlier detection. Prior screening programs have unintentionally widened disparities due to limited access in vulnerable populations. We examined national US administrative data to explore the effect of lung cancer screening according to area levels of income. **Methods:** We studied adults with lung cancer in the SEER 21 Registries Database diagnosed between 2005-2022 over two time periods (pre-screening: 2005-2013; screening: 2014-2022). We evaluated outcomes of survival and stage distribution over varied levels of county median household income (MHI). We calculated descriptive statistics for our sample and used a Cox PH model to evaluate the interaction of time period and MHI while adjusting for other covariates. **Results:** We identified 485,763 cases in the pre-screening era and 487,001 cases in the screening era, with the median age for each group in the 60-69 years range. Sex, race, rurality, MHI and stage are reflective of US lung cancer demographics. Compared to the pre-screening era, cases in the screening era were more likely to be diagnosed at a localized stage in all MHI groups. The lowest MHI group saw a 24.6% increase in proportion of cases detected at a localized stage, while the highest MHI group saw a 37.5% increase. Median survival increased for all MHI groups with a positive association between MHI and survival gains. In a multivariable Cox PH model, a time period and MHI interaction term indicated that the income-related survival disparity between the highest and lowest MHI groups is 12.2% larger in 2014-2022 than in 2005-2013 (HR = 1.122, $p < 0.001$). **Conclusions:** Since the introduction of USPSTF lung cancer screening guidelines in 2013, lung cancers are detected at earlier stages and survival has improved. These changes have been experienced across all income groups, but the income-related disparities in survival have widened. These results indicate a need for additional efforts to ensure that the benefits of lung cancer screening are distributed across all populations regardless of wealth. Research Sponsor: None.

MHI	Year of Diagnosis	3-Year OS	5-Year OS	Median OS (Months)	Change in Median OS (Months)
< $60,000	2005-2013	19.4% (19.2-19.6)	13.8% (13.6-14.0)	8 (7.89-8.11)	2
	2014-2022	25.5% (25.1-25.9)	18.3% (17.9-18.7)	10 (9.84-10.16)	
$60,000 - $69,999	2005-2013	21.8% (21.6-22.0)	15.9% (15.7-16.1)	9 (8.88-9.12)	2
	2014-2022	29.2% (28.8-29.6)	21.8% (21.4-22.2)	11 (10.80-11.20)	
$70,000 - $79,999	2005-2013	22.6% (22.4-22.8)	16.7% (16.5-16.9)	9 (8.89-9.11)	4
	2014-2022	31.4% (31.0-31.8)	23.9% (23.5-24.3)	13 (12.78-13.22)	
$80,000 - $99,999	2005-2013	23.9% (23.7-24.1)	17.7% (17.5-17.9)	9 (8.87-9.13)	6
	2014-2022	33.8% (33.4-34.2)	25.8% (25.4-26.2)	15 (14.77-15.24)	
≥ $100,000	2005-2013	27.3% (26.9-27.7)	20.6% (20.2-21.0)	11 (10.81-11.19)	8
	2014-2022	38.6% (38.2-39.0)	30.1% (29.7-30.5)	19 (18.66-19.35)	

A large prospective patient-advocacy assessment of fears, concerns, and challenges in patients diagnosed with lung cancer in the United States.

Lisa Spain, Peixin Jiang, Sara Patton, Daniel Richard Gomez, Alexandre Reuben, Dhru Deb, Amy Cipau, Hildreth Grossman, Marc Muskavitch, Courtney Brandt, Joan H. Schiller; Rexanna's Foundation, Prosper, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; IASLC, Denver, CO; Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Lung Cancer Research Foundation, New York, NY; Lung Cancer Initiative, Raleigh, NC; Upstage Lung Cancer, Brookline, MA; ALK Positive, Incorporated, Atlanta, GA; Lung Cancer Research Foundation, University of Virginia, Vienna, VA

Background: Studies have been conducted assessing patient (pt) experiences with lung cancer, but minimal data is available on how fears and challenges differ by age, region, and disease stage. Through a pt advocacy organization, we performed a prospective analysis to capture pt and caregiver perceptions. **Methods:** 2055 surveys were sent out by non-profit organizations to US pts diagnosed with lung cancer and caregivers. 46% of the surveys (n = 956) were returned. Respondents included 63% (N = 603) pts (included in this abstract), 35.5% caregivers, and 1.5% medical professionals. Demographics included: ethnicity, time from diagnosis, gender, stage, region of country, age, role, and current disease status. Of 36 survey questions, 27 were multiple choice, 9 were open-ended and analyzed for recurring themes. Results were analyzed by region, stage, and age to determine if these influenced perspectives about living with lung cancer, and challenges with medical care or treatment. Chi-square test was used to assess differences in responses to survey questions across participant groups. Additional analysis was conducted using Fisher's exact test. Responses to each survey question were categorized, and the proportions of the topics were compared between participant groups. **Results:** Overall challenges reported by pts varied significantly by disease stage—both at the time of diagnosis ($p < 0.001$) and during treatment ($p < 0.001$). The fear cited most was disease progression or recurrence, in stage I (25.8%) or stage IV (27%) disease. Significant differences were observed across age groups relating to challenges with medical care or treatment ($p < 0.001$), and fears of living with lung cancer. ($p < 0.001$). Pts older than 45 were more concerned with side effects at diagnosis than younger than 45 (55.1% vs 33%, $p < 0.0001$) and were less concerned with financial issues (25.7% vs 44.7%, $p < 0.0001$) at treatment. Care costs and transportation challenges varied regionally, peaking in the Midwest (60.4%) and Southwest (56.5%). **Conclusions:** Fears, concerns and challenges faced by pts with lung cancer vary significantly by age, disease stage at diagnosis, and during treatment. The findings reveal an opportunity to deliver better support to pts throughout their journey and to allocate resources to address specific concerns. Research Sponsor: None.

Survey Question	Topic	Age: </= 44 (N=219)*	Age: >/= 45 (N=321)*	Fisher's Exact Test
Fears	Progression & Recurrence	10% (21)	29% (94)	$p < 0.0001$
"	Emotional & Psychological	18% (40)	10% (33)	$p < 0.01$
"	Inadequate Information	5% (11)	10% (33)	$p < 0.05$
Challenges at Diagnosis	Varied opinions	34% (75)	20% (63)	$p < 0.001$
"	Financial	40% (88)	24% (78)	$p < 0.0001$
"	Depression	32% (70)	53% (169)	$p < 0.0001$
Challenges at Treatment	Side Effects	33% (73)	55% (177)	$p < 0.0001$
"	Varied opinions	28% (62)	12% (39)	$p < 0.0001$
"	Financial	45% (98)	26% (82)	$p < 0.0001$

*63 patients did not respond to the question on age.

Regional and gender disparities in lung cancer mortality in Guatemala.

Natalia Pineda Grajeda, Alba Kihn-Alarcón; Independent Researcher, Miami, FL; AstraZeneca Central America and Caribbean Region, Guatemala City, Guatemala

Background: Lung cancer is the leading cause of cancer-related deaths worldwide and a major contributor in Latin America, where rates are generally lower. To date, there are no published population analyses describing lung cancer trends in Guatemala. **Methods:** Secondary analysis of publicly available national mortality data (Guatemala's National Institute of Statistics), extracting lung cancer deaths from 2012 to 2022. Deaths were summarized by region, department, year, and sex. Annual crude mortality rates (deaths per 100,000 inhabitants) using corresponding population denominators. **Results:** Between 2012 and 2022 Guatemala recorded 4273 lung cancer deaths (mean age 66,SD:16.17), concentrated in three regions (66.58%,n=2845): Metropolitan, Southwest and Central with the highest department-level counts in Guatemala (37.66%,n=1609), Quetzaltenango (6.53%,n=279), Huehuetenango (5.41%,n=231), San Marcos (5.24%,n=224) and Escuintla (5.29%,n=226). Crude lung cancer mortality ranged from 2.24 to 2.66 deaths per 100,000 inhabitants—highest in 2019 and 2020. Deaths were more frequent among men (54%,n=2,317), but deaths among women increased throughout the study period, resulting in a male-to-female ratio decline from 1.53 in 2012 to 1.07 in 2022. **Conclusions:** Guatemala's lung cancer mortality rates were lower compared to global estimates with nearly two-thirds of deaths concentrated in three regions —especially in Guatemala department— reflecting the concentration of health services in this region. Globally, lung cancer deaths show a marked sex disparity, with men accounting for about 68%. In contrast, Guatemala demonstrated a narrowing sex gap, with male-to-female mortality of nearly 1:1 by 2022, with rising mortality among women. These differences may reflect variations in smoking prevalence, access to early diagnosis, and health system capacity, with post-2020 shifts possibly influenced by COVID-19-related disruptions in diagnosis, treatment, referral pathways, or cause of death-of-death reporting. Research Sponsor: None.

Lung cancer deaths.

Region(Departments)	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	No(%)
Metropolitan(Guatemala)	132	129	121	125	144	148	156	175	182	146	151	1609(37.66)
North(Baja Verapaz, Alta Verapaz)	14	16	8	15	16	14	20	12	14	12	15	156(3.65)
Northeast(Izabal, Zacapa, Chiquimula, El Progreso)	27	32	37	28	44	32	36	35	25	42	30	368(8.61)
Southeast(Jalapa, Jutiapa)	50	33	41	39	33	27	32	45	40	30	33	403(9.43)
Central(Sacatepequez, Chimaltenango, Escuintla)	37	32	54	31	43	42	41	47	56	52	54	489(11.44)
Southwest(Solola, Totonicapan, Quetzaltenango, Suchitepequez, Retalhuleu, San Marcos)	45	70	52	64	82	67	74	70	79	76	68	747(17.48)
Northwest(Huehuetenango, Quiche)	21	28	34	37	29	32	40	43	41	38	28	371(8.68)
Petèn	11	8	15	10	13	13	10	15	10	16	9	130(3.04)
Deaths(Mortality x 100k hab)	337(2.28)	348(2.31)	362(2.37)	349(2.24)	404(2.55)	375(2.33)	409(2.50)	442(2.66)	447(2.65)	412(2.41)	388(2.24)	4273

Surgical resection versus stereotactic body radiation therapy in stage IV non–small cell lung cancer: A large, real-world, propensity-matched survival study.

Harshitha Bandaru, Madho Mal, Sravani Bhavanam, Nayanika Chowdary Tummala, Rithish Nimmagadda, Shiwani Keswani, Bolivia Crocete Aloysia Fernandes, Omar Oudit, Shalin Rawal, Love Kumar, Kushal Kriplani; Dr NTR Univeristy of Health Sciences, Tirupathi, India; Marshall University School of Medicine, Huntington, WV; Brookdale University Hospital and Medical Center, New York, NY; NYMC at St. Mary's General Hospital and Saint Clare's Health, Denville, NJ; One Brooklyn Health - Interfaith Medical Center, New York, NY; Mayo Clinic Arizona, Scottsdale, AZ; The New York Medical College Graduate Medical Education Program at St. Mary's General Hospital and St. Clare's Health, Denville, NJ; One Brooklyn Health System/Brookdale University Hospital and Medical Center Program, Brooklyn, NY; Charleston Area Medical Center (CAMC), Charleston, WV; SUNY Downstate Health Sciences University, New York, NY

Background: The role of definitive local thoracic therapy in metastatic non–small cell lung cancer (NSCLC) remains controversial. While stereotactic body radiation therapy (SBRT) is increasingly utilized, comparative survival outcomes with surgical resection in real-world populations remain limited. We evaluated survival and pulmonary outcomes associated with surgery versus SBRT in patients with stage IV NSCLC. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network including adults (≥18 years) with stage IV NSCLC treated between January 2013 and December 2023 who underwent definitive local thoracic therapy with either surgical resection or SBRT. Patients with small cell lung cancer, prior lung cancer diagnoses, prior thoracic radiation, or incomplete survival data were excluded. Propensity score matching (1:1) was performed to balance demographics, comorbidities, smoking history, and exposure to systemic therapy including chemotherapy and immunotherapy within 6 months of index treatment. Primary outcomes included landmark 1-year all-cause mortality and overall survival. Secondary outcomes included pneumonia and respiratory failure. Kaplan–Meier analysis and Cox proportional hazards regression were performed. **Results:** After matching, 1,934 patients were included (967 per cohort). At 1 year, surgical resection was associated with significantly lower mortality compared with SBRT (17.5% vs 31.4%; RR 0.56, 95% CI 0.47–0.66; $p < 0.001$), corresponding to an absolute risk reduction of 13.9% and an estimated number needed to treat of approximately 7. Kaplan–Meier analysis demonstrated superior survival in the surgical cohort (log-rank $p < 0.001$). Surgical resection remained associated with significantly improved long-term survival, with a 64% lower hazard of death (HR 0.36, 95% CI 0.30–0.44; $p < 0.001$) and prolonged median survival (3,942 vs 1,182 days). Pulmonary outcomes favored surgery. Pneumonia incidence was significantly lower in the surgical cohort at both 1 year (12.9% vs 29.3%; RR 0.44; $p < 0.001$) and 3 years (5.9% vs 14.2%; RR 0.42; $p < 0.001$). Rates of respiratory failure did not differ significantly between treatment groups. **Conclusions:** In this large real-world propensity-matched study, surgical resection was associated with significantly improved survival compared with SBRT in carefully selected patients with stage IV NSCLC. Surgery was additionally associated with lower long-term pulmonary infectious complications without increased respiratory failure risk. These findings suggest a potential role for aggressive local therapy in selected metastatic patients and support prospective trials to refine patient selection strategies. Research Sponsor: None.

Association of carbon tetrachloride with lung cancer incidence and mortality, including effects in low-smoking regions.

Ashish Samaddar, Alexandra Feathers, Srinivas Govindan, Shuyi Chen, Juliet Meir, Nagashree Seetharamu; Donald and Barbara Zucker School of Medicine at Hofstra University, Manhasset, NY; Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra University, Manhasset, NY; Northwelll Health Zuckerberg Cancer Center, New Hyde Park, NY; Northwell Zuckerberg Cancer Center, New Hyde Park, NY; Zuckerberg Cancer Center, Northwell Health, Lake Success, NY

Background: Although cigarette smoking is the main risk factor for lung cancer, 10–20 percent of cases occur in non-smokers, with women disproportionately affected. This pattern suggests that community-level environmental exposures may contribute to lung cancer risk beyond smoking. **Methods:** In this ecologic, county-level study, average age-adjusted lung cancer incidence from 2017–2021 and sex-specific smoking prevalence were obtained from the NCI State Cancer Profiles. County-level exposure data were derived from the EPA National Air Toxics Assessment, with 73 air toxics screened to identify the most strongly associated pollutant. The leading exposure was evaluated in sex-stratified multivariable spatial error regression models adjusting for smoking prevalence and key county-level covariates, including radon, $PM_{2.5}$, Social Vulnerability Index (SVI). Analyses included 2,042–2,238 U.S. counties. Additional models were fit separately within strata of smoking prevalence to compare associations across lower and higher-smoking counties. **Results:** Among 73 EPA-tracked air toxins, carbon tetrachloride (CCl_4) showed the strongest association with lung cancer incidence (population-weighted $r = 0.34$, $p < 0.001$). In fully adjusted spatial models, each standard deviation increase in carbon tetrachloride was associated with a 10.6% increase in lung cancer incidence in women and 10.4% in men, and with a 6.5% and 7.6% increase in lung cancer mortality, respectively. In stratified analyses, associations between CCl_4 and lung cancer incidence were larger in lower-smoking counties (10–12% per SD) than in higher-smoking counties (5–6% per SD), with similar patterns by sex. **Conclusions:** CCl_4, a legacy industrial solvent with ongoing emissions, was the most predictive air toxin associated with population-level lung cancer incidence, showing larger adjusted associations than $PM_{2.5}$ or radon. Although effects were not sex-specific, incidence increases were greatest in lower-smoking communities, suggesting a greater relative contribution of environmental exposures. Research Sponsor: None.

Percent change in lung cancer incidence and mortality per 1 standard deviation increase in covariates.

Variable	Women – Incidence (% per 1-SD)	Men – Incidence (% per 1-SD)	Women – Mortality (% per 1-SD)	Men – Mortality (% per 1-SD)
Current Smoking (Women)	6.7 (5.9, 7.6)	7.0 (6.2, 7.9)	7.3 (6.3, 8.3)	8.3 (7.4, 9.3)
Former Smoking (Women)	4.6 (3.8, 5.3)	1.7 (1.0, 2.5)	5.0 (4.2, 6.0)	1.1 (0.3, 1.9)
Current Smoking (Men)	5.0 (4.2, 6.0)	6.9 (6.1, 7.8)	7.4 (6.3, 8.3)	8.5 (7.6, 9.5)
Former Smoking (Men)	4.0 (3.1, 4.9)	3.3 (2.4, 4.1)	4.9 (3.9, 5.9)	3.9 (3.0, 4.8)
$PM_{2.5}$	0.0 (−0.7, 0.7)	0.3 (−0.4, 1.0)	0.9 (0.1, 1.6)	1.3 (0.5, 2.0)
Radon	0.9 (−0.2, 2.0)	1.8 (0.7, 2.8)	1.1 (0.0, 2.3)	1.9 (0.7, 3.0)
Carbon Tetrachloride (CCl_4)	10.6 (9.1, 12.2)	10.4 (8.9, 12.0)	6.5 (5.1, 7.8)	7.6 (6.2, 9.0)
Counties in model (n)	2,170	2,238	2,042	2,182

Are lobectomy and neoadjuvant therapy the missing link in improving early-stage small cell lung cancer survival?

Yahya Alwatari, Robert A. Vierkant, Mohamed Shanshal, Sahar Saddoughi, Luis Felipe Tapias, Robert Shen, Stephen David Cassivi, Dennis A. Wigle, Janani S. Reisenauer, Carlos Puig; Division of General Thoracic Surgery, Mayo Clinic Rochester, Rochester, MN; Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic Rochester, Rochester, MN; Mayo Clinic Rochester, Rochester, MN; Division of Thoracic Surgery, Mayo Clinic Rochester, Rochester, MN; Division of Thoracic Surgery, Division of Pulmonary and Critical Medicine, Mayo Clinic Rochester, Rochester, MN

Background: Small cell lung cancer (SCLC) is an aggressive malignancy with poor prognosis. This study evaluates national trends in surgical management of early-stage SCLC using the National Cancer Database (NCDB), aiming to identify factors associated with improved outcomes and assess the survival benefit of surgical resection. **Methods:** Patients diagnosed with clinical stage T1–T3 N0 M0 SCLC between 2004 and 2022 were identified from the NCDB. Exclusions included non-SCLC histologies, advanced or missing staging, non-lobectomy surgeries, and incomplete survival data. Propensity score matching (1:1) was used to balance surgical and non-surgical cohorts based on demographic, clinical, and socioeconomic variables. Kaplan-Meier and Cox regression analyses were used to evaluate overall survival, stratified by T stage. **Results:** Among 17,762 patients with early-stage SCLC, 3,234 (18.2%) underwent lobectomy with mediastinal lymph node dissection. Surgical rates increased from 5% in 2004, 17% in 2013 to 24% in 2021. Surgery was more common in T1 (26.5%) than T2 (11.4%) or T3 (4.6%) disease. After matching, surgery was associated with improved survival across all T stages, with no significant interaction between T stage and surgical benefit (p=0.43). Older age, male sex, and higher comorbidity scores predicted worse outcomes. Among surgical patients, 2.3% received neoadjuvant therapy and 71.6% received adjuvant treatment. Systemic therapy-both neoadjuvant (HR 0.63) and adjuvant (HR 0.69)-was significantly associated with improved survival. **Conclusions:** Lobectomy remains underutilized in early-stage SCLC but is linked to significantly improved survival. Albeit small patient's number, neoadjuvant systemic therapy further enhanced survival, supporting broader use of surgery and multimodal treatment in appropriately selected patients Research Sponsor: None.

			Univariable results[1]		Multivariable results[2]	
Characteristic	No. deaths	Person-months	HR (95% CI)	p-value	HR (95% CI)	p-value
Charlson score				<0.001		**<0.001**
0	761	77727	1.00 (ref)		1.00 (ref)	
1	623	60483	1.06 (0.95,1.18)		1.07 (0.96,1.20)	
2 or more	350	27025	1.30 (1.15,1.48)		1.30 (1.13,1.48)	
Clinical T-stage				0.011		**0.014**
cT1N0M0	1266	124916	1.00 (ref)		1.00 (ref)	
cT2N0M0	406	33924	1.18 (1.06,1.32)		1.20 (1.06,1.35)	
cT3N0M0	62	6393	0.96 (0.75,1.24)		1.00 (0.76,1.31)	
Residual disease				<0.001		**<0.001**
No residual tumor	1626	158838	1.00 (ref)		1.00 (ref)	
Residual tumor	92	4699	1.91 (1.55,2.36)		1.91 (1.52,2.40)	
Neoadjuvant systemic treatment				0.253		**0.034**
No	1629	154116	1.00 (ref)		1.00 (ref)	
Yes	30	3495	0.81 (0.56,1.16)		0.63 (0.41,0.97)	
Adjuvant radiation				0.067		**<0.001**
No	1209	118925	1.00 (ref)		1.00 (ref)	
Yes	452	40471	1.11 (0.99,1.23)		1.33 (1.18,1.51)	
Adjuvant systemic treatment				<0.001		**<0.001**
No	563	44045	1.00 (ref)		1.00 (ref)	
Yes	1096	113566	0.75 (0.68,0.83)		0.69 (0.62,0.78)	

Chemoimmunotherapy for large cell neuroendocrine carcinoma (LCNEC) of the lung: A multi-institutional prospective study (NEJ044).

Suguru Matsuda, Tetsuhiko Asao, Takehito Shukuya, Ichiro Nakachi, Satoshi Watanabe, Kazuma Kishi, Tomonori Makiguchi, Tatsuro Fukuhara, Toshiyuki Harada, Kazushi Doushita, Ryotaro Kida, Ryota Saito, Seiji Niho, Shinya Fujioka, Naotake Yanagisawa, Kunihiko Kobayashi, Makoto Maemondo, Kazuhisa Takahashi, The North East Japan Study Group; Department of Pulmonary Medicine, Sendai Kosei Hospital, Sendai, Japan; Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; Pulmonary Division, Department of Internal Medicine, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan; Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Department of Respiratory Medicine, Toho University Faculty of Medicine, Tokyo, Japan; Department of Respiratory Medicine, Hirosaki University Graduate School of Medicine, Aomori, Japan; Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan; Department of Respiratory Medicine, Japan Community Health Care Organization Hokkaido Hospital, Sapporo, Japan; Department of Respiratory Medicine, Asahikawa Medical Center, Asahikawa-Shi, Japan; Division of Respiratory Medicine and Neurology, Department of Internal Medicine, Asahikawa Medical University, Nayoro, Japan; Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University, Mibu, Japan; Medical Technology Innovation Center, Juntendo University, Tokyo, Japan; Department of Respiratory Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Shimotsuke-Shi, Japan

Background: Large cell neuroendocrine carcinoma (LCNEC) is a rare pulmonary malignancy, comprising 1-3% of all lung cancers. It is a high-grade tumor exhibiting heterogeneous characteristics that overlap with both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While chemoimmunotherapy (chemo-IO) has become the standard of care for SCLC and NSCLC, prospective data regarding its efficacy and safety in LCNEC are limited, and the optimal chemotherapy backbone remains unclear. We conducted the NEJ044 study to prospectively evaluate chemo-IO in patients (pts) with advanced LCNEC. **Methods:** This multi-institutional, prospective, observational study enrolled pts with advanced or recurrent LCNEC. Treatment consisted of atezolizumab and carboplatin combined with either etoposide (IMpower133), paclitaxel and bevacizumab (IMpower150), or nab-paclitaxel (IMpower130). The primary endpoint was the 1-year overall survival (OS) rate. Secondary endpoints included OS, progression-free survival (PFS), objective response rate, disease control rate, and safety. **Results:** Between July 2020 and June 2024, 77 pts were enrolled across 31 institutions within the North East Japan Study Group, of whom 76 received treatment. The median follow-up was 29.0 months (mos) (95% CI: 15.2–35.7). Baseline characteristics included: median age 71 years (range 51–83); male, 68 (89%); ECOG PS 0-1, 69 (91%); and postoperative recurrence, 29 (38%). Histology was confirmed as LCNEC in 61 pts (80%) and combined LCNEC in 15 pts (20%). Treatment distribution included the IMpower133 regimen in 56 pts (74%) and IMpower150/130 regimens in 20 pts (26%). The study met its primary endpoint with a 1-year OS rate of 70.1% (95% CI: 58.2–79.2). In the overall population, median OS (mOS) and PFS (mPFS) were 18.5 mos (95% CI: 14.3–22.6), and 6.2 mos (95% CI: 4.8–7.6). Exploratory analysis showed no significant differences in survival by chemotherapy backbone. The IMpower133 cohort demonstrated a 1-year OS of 70.3% (95% CI: 56.1–80.6), mOS of 18.4 mos (95% CI: 13.2-22.3), and mPFS of 5.2 mos (95% CI: 3.9-7.6), compared to a 1-year OS of 69.6% (95% CI: 44.5–85.1), mOS of 19.9 mos (95% CI: 7.3-not evaluable), and mPFS of 7.2 mos (95% CI: 4.3-19.9) in the IMpower150/130 cohort. Grade $\geq$3 non-hematological adverse events occurred in 23 pts (30%), and febrile neutropenia was observed in 9 pts (11%). Biomarker analysis identified oncogenic drivers in 5 pts (including 3 KRAS mutations). PD-L1 expression was $\geq$50% in 12%, 1–49% in 34%, and $<$ 1% in 51%; PD-L1 TPS $\geq$1% was marginally associated with improved OS. **Conclusions:** The NEJ044 study met its primary endpoint, demonstrating that chemoimmunotherapy provides a favorable 1-year OS of approx. 70% with a manageable safety profile in LCNEC. These prospective results support chemoimmunotherapy as a viable standard treatment strategy for this population. Clinical trial information: UMIN000040876. Research Sponsor: Chugai Pharmaceutical.

Real-world (RW) effectiveness and safety of lurbinectedin (lurbi) for previously treated extensive-stage small cell lung cancer (ES-SCLC): Final primary and subgroup analysis results of Jazz EMERGE 402.

Firas Benyamine Badin, Phil Lammers, Geoffrey Liu, Leonid Shunyakov, Shaqil Nadirali Kassam, Mehul P. Patel, Yan Ji, Catherine Labbé, Viral Rabara, Mehmood Hussain Hashmi, Shaker R. Dakhil, Matthias Weiss, Alan C. Gowan, Nicole Bouchard, Badri Rengarajan, Douglas S. Fuller, Navit Naveh, Balazs Halmos; Baptist Health Medical Group, Lexington, KY; Baptist Cancer Center, Memphis, TN; Princess Margaret Cancer Centre, Toronto, ON, Canada; Carrie J. Babb Cancer Center, Bolivar, MO; Southlake Regional Health Centre, Newmarket, ON, Canada; Rochester Regional Health, Rochester, NY; HealthPartners Cancer Center at Regions Hospital, St. Paul, MN; Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec – Université Laval, Québec City, QC, Canada; Carolina Blood and Cancer Care Associates, Rock Hill, SC; Stormont Vail Health, Topeka, KS; Cancer Center of Kansas, Wichita, KS; ThedaCare, Appleton, WI; Baylor Scott & White Medical Center, Temple, TX; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada; Jazz Pharmaceuticals, Palo Alto, CA; Jazz Pharmaceuticals, Philadelphia, PA; Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Lurbi received accelerated approval in 2020 for ES-SCLC that progressed on or after platinum-based treatment (Tx) based on a phase 2 basket trial and full approval in 2025 combined with atezolizumab as 1st-line maintenance Tx for ES-SCLC based on the phase 3 IMforte trial. **Methods:** The phase 4, prospective, observational Jazz EMERGE 402 trial (NCT04894591) evaluated lurbi for previously treated ES-SCLC in RW practice in North America (final data cut: July 17, 2025). The primary endpoint was overall response rate (ORR). Key secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. Effectiveness was assessed in all patients (pts) and in prespecified subgroups. **Results:** At the final data cut, 267 pts had received ≥1 cycle of lurbi. At baseline (BL), median (min–max) age was 67 (29–89) years, 52 (19%) pts had an ECOG PS ≥2, 67 (25%) had brain metastases, 84 (31%) had liver metastases, 88 (33%) had a chemotherapy-free interval (CTFI) <90 days, and 196 (73%) had ES-SCLC as the initial diagnosis. Pts received lurbi as 2nd-line (169 [63%]), 3rd-line (78 [29%]), or later (20 [7%]) Tx. Median (Q1–Q3) number of lurbi Tx cycles and Tx duration were 4 (2–7) and 91 (56–170) days. Granulocyte colony-stimulating factor was used in 99 (37%) pts (71 [27%] as primary prophylaxis). Six (2%) pts were receiving Tx at study completion; 261 (98%) discontinued Tx, with disease progression (183 [70%]) the primary reason. While lurbi was effective among all pts and poor-prognosis subgroups, better outcomes tended to occur in pts with CTFI ≥90 days and ECOG PS <2 (Table). Eighty-eight (33%) pts had Tx-related adverse events (TRAE); anemia (21 [8%]) and neutropenia (19 [7%]) were most common. Rates of serious neutropenic infection (5 [2%]), anemia (4 [1%]), and neutropenia (3 [1%]) were low. **Conclusions:** Lurbi was associated with clinically meaningful effectiveness and predictable/manageable safety in previously treated ES-SCLC in a RW population that included poor-prognosis subgroups. Clinical trial information: NCT04894591. Research Sponsor: Jazz Pharmaceuticals.

Effectiveness among all pts and by subgroup.

	All N = 267	Age <65 Years n = 101	Age ≥65 Years n = 166	CTFI <90 Days n = 88[a]	CTFI ≥90 Days n = 137[a]	Initial LS n = 69[b]	Initial ES n = 196[b]	ECOG PS <2 n = 178[c]	ECOG PS ≥2 n = 52[c]
ORR,[d] % (95% CI[e])	29 (23, 36)	30 (20, 43)	28 (20, 37)	24 (14, 37)	28 (19, 38)	33 (21, 47)	27 (20, 36)	26 (19, 35)	41 (24, 59)
PFS,[d] months, median (95% CI)	3.3 (2.6, 4.1)	4.1 (2.8, 4.5)	2.9 (2.2, 3.8)	2.9 (2.0, 4.1)	3.3 (2.4, 4.2)	4.0 (2.4, 5.8)	3.3 (2.5, 4.1)	3.3 (2.6, 4.2)	2.6 (1.7, 5.2)
OS, months, median (95% CI)	7.6 (6.4, 8.7)	8.2 (7.0, 10.6)	6.6 (5.8, 8.7)	5.8 (4.6, 6.6)	9.3 (7.1, 10.9)	8.7 (6.2, 10.6)	6.8 (6.0, 8.7)	8.1 (6.6, 9.6)	5.2 (2.4, 7.9)

[a]CTFI missing for 42 pts.
[b]Stage missing for 2 pts.
[c]ECOG PS missing for 37 pts.
[d]Per RECIST v1.1 in pts with BL measurable disease.
[e]Estimated using Clopper-Pearson exact method. LS, limited stage.

8080 Poster Session

A retrospective real-world study on the efficacy and safety of anlotinib in combination with immunotherapy as maintenance therapy after standard immunochemotherapy for extensive-stage small cell lung cancer (ALTER-L059).

Yong Fang, Lei Pan, Xin Gan, Junzhen Gao, Baimei He, Cheng Fang, Pin Zhang, Xiting Liu, Huaimin Liu; Sir Run Run Shaw Hospital, affiliated with Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Tangdu Hospital, Xian, China; The First Affiliated Hospital of Nanchang University, Nanchang, jiangxi, China; The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China; Xiangya Hospital of Central South University, Changsha, China; Changzhou First People's Hospital, Changzhou, China; Xinyi City People's Hospital, Xinyi, China; Gansu Cancer Hospital, Lanzhou, China; Henna Cancer Hospital, Zhengzhou, China

Background: Although immune checkpoint inhibitors (ICIs) combined with chemotherapy have become the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC), the use of immunotherapy as a maintenance strategy remains challenging. This study aims to evaluate the efficacy and safety of anlotinib combined with ICIs as first-line maintenance treatment for ES-SCLC. **Methods:** ALTER-L059 was a retrospective, multicenter study conducted at 9 hospitals in China. Eligible patients were 18 years or older with histologically or cytologically confirmed ES-SCLC and had completed 4–6 cycles of first-line immunochemotherapy as induction therapy without disease progression. They subsequently received maintenance therapy with immunotherapy combined with anlotinib. The primary endpoint was progression-free survival from the start of maintenance therapy (PFS2). Secondary endpoints included progression-free survival from the start of induction therapy (PFS), overall survival from the start of maintenance therapy (OS2), overall survival from the start of induction therapy (OS) and safety. **Results:** Between January 2022 and December 2024, a total of 100 patients were enrolled. By the data cutoff date on November 11, 2025, the median follow-up duration was 16.92 months (95% CI: 15.81-18.03). The median PFS2 was 6.05 months (95% CI: 4.83-7.59), and the median PFS was 9.53 months (95% CI: 8.31-11.93). The median OS2 was 17.74 months (95% CI: 15.24-19.71), and the median OS was 21.26 months (95% CI: 18.60-22.60). The incidence of grade 3 or higher treatment-related adverse events (TRAEs) was 30.0%. The most common TRAEs (incidence ≥20%) were hypertension (33.0%), hand-foot syndrome (23.0%), proteinuria (21.0%), and hypertriglyceridemia (20.0%). **Conclusions:** Patients who had been diagnosed with ES-SCLC and had completed 4–6 cycles of immunochemotherapy as induction therapy without disease progression subsequently received maintenance therapy with immunotherapy combined with anlotinib, demonstrating favorable survival outcomes and manageable toxicity. Clinical trial information: NCT06982287. Research Sponsor: None.

8081 Poster Session

A validation study of a novel biomarker-based scoring system (EAST score) for limited-stage small-cell lung cancer: A secondary analysis of JCOG0202 and JCOG1011.

Yu Ito, Yoshitaka Zenke, Noriko Mitome, Shogo Nomura, Miwa Kamatani, Yasushi Goto, Yutaka Fujiwara, Ryo Ko, Takashi Ninomiya, Tsuneo Shimokawa, Haruko Daga, Hidekazu Suzuki, Motohiro Tamiya, Hidetoshi Hayashi, Ryo Toyozawa, Hiroyasu Kaneda, Kyoichi Okishio, Gen Kida, Isamu Okamoto, Koichi Goto; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Department of Thoracic Oncology, Aichi Cancer Center, Nagoya, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Department of Thoracic oncology and Medicine, NHO Shikoku Cancer Center, Matsuyama, Japan; Department of Respiratory Medicine, Yokohama Municipal Citizen's Hospital, Yokohama, Japan; Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan; Department of Thoracic Oncology, Osaka Habikino Medical Center, Habikino, Japan; Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; Department of Thoracic Oncology, NHO Kyushu Cancer Center, Fukuoka, Japan; Department of Clinical Oncology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; Department of Internal Medicine, NHO Kinki Chuo Chest Medical Center, Sakai City, Japan; Department of Thoracic Oncology, Saitama Cancer Center, Saitama, Japan; Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Background: Concurrent chemoradiotherapy (CCRT) followed by prophylactic cranial irradiation (PCI) is potentially curative for limited-stage small-cell lung cancer (LS-SCLC), yet reliable markers for identifying long-term survivors remain undefined. The Enhanced Assessment for SCLC Treatment (EAST) score was originally derived from a retrospective, single-center training cohort for prognostic stratification of LS-SCLC patients receiving CCRT. This score integrates N3 status, serum lactate dehydrogenase (LDH), pro-gastrin-releasing peptide (ProGRP), and cytokeratin 19 fragment (CYFRA 21-1) levels measured at diagnosis. This study (JCOG2401A) validated its prognostic utility using data from two randomized controlled trials (RCTs) of LS-SCLC. **Methods:** The validation cohort comprised patients enrolled in JCOG0202 and JCOG1011: randomized phase 3 and 2 studies, respectively, that compared multiple consolidation chemotherapy regimens following CCRT. External validation of the dichotomized EAST score (low: score 0–1, high: 2–5) was performed by assessing discrimination and calibration for progression-free survival (PFS) and overall survival (OS). Exploratory subgroup analyses were conducted in an integrated cohort of the training cohort (N = 224; median follow-up, 64.5 months) and the validation cohort. Hazard ratios (HRs) for PCI were estimated using propensity score-weighted Cox models. **Results:** Out of 309 patients in these trials, 205 with complete data for EAST score components were included in the validation cohort. Median age was 62 years. Low- vs. high-risk groups showed stage (I-II/III) distributions of 28/72% vs. 11/89%, and tumor response (CR-PR/SD) distributions of 89/3% vs. 91/2%, respectively. The low-risk group (N = 114) showed better outcomes than the high-risk group (N = 91) for both PFS and OS (Table). Integrated cohort analysis revealed a numerical survival benefit from PCI in low-risk patients (N = 214), whereas the benefit was highly limited in the high-risk group (N = 202) (Table). **Conclusions:** The prognostic value of the EAST score was validated even in external RCT datasets. High-risk patients, characterized by early recurrence and inferior OS, derive minimal benefit from PCI. These findings provide a rationale for a planned risk-adapted RCT utilizing the EAST score. Research Sponsor: None.

	Median PFS, months	PFS, HR (95% CI)	Median OS, months	OS, HR (95% CI)
Low- vs. high-risk				
Training cohort (N=107/117)	20.6/9.4	0.48 (0.34-0.67)	53.0/34.2	0.67 (0.46-0.98)
Validation cohort (N=114/91)	25.0/10.7	0.55 (0.40-0.77)	63.2/29.6	0.51 (0.36-0.73)
PCI vs. no-PCI				
All (N=287/129)	14.5/12.9	0.91 (0.65-1.28)	50.0/35.5	0.78 (0.56-1.10)
Low risk (N=152/62)	31.3/14.6	0.86 (0.49-1.48)	67.9/40.1	0.75 (0.43-1.31)
High risk (N=135/67)	10.2/10.6	0.99 (0.71-1.39)	34.2/30.9	0.86 (0.59-1.28)

Prophylactic tocilizumab to mitigate cytokine release syndrome in patients receiving tarlatamab: A single-center exploratory experience informed by bispecific antibody safety data.

Feras Al Moussally, Micheal Bishara, Riya Kumar, Emily McCafferty, Venkataraman Rajagopalan; University of Pittsburgh Medical Center (UPMC), Harrisburg, PA; UPMC, Harrisburg, PA; Drexel University College of Medicine, Harrisburg, PA

Background: Tarlatamab, a bispecific T-cell engager (BiTE) targeting CD3 on T cells and DLL3 on small cell lung cancer (SCLC) cells, represents a major advance in treating relapsed or refractory SCLC. By activating T cells to release cytotoxic cytokines, it induces tumor cell death but carries risks such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). In the phase 2 DeLLphi-301 trial, CRS occurred in up to 53% of patients treated with Tarlatamab. Current inpatient step-up dosing protocols aim to mitigate toxicity but add cost and complexity, particularly for immunocompromised patients. Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor used for CRS, has demonstrated prophylactic benefit in mitigating cytokine-related adverse events with other BiTEs such as teclistamab. We hypothesized that prophylactic tocilizumab could similarly reduce Tarlatamab-related CRS in SCLC without compromising efficacy. **Methods:** We retrospectively analyzed 32 consecutive SCLC patients treated with Tarlatamab at our center. Tocilizumab (8 mg/kg) was administered 1 hour prior to the first Tarlatamab dose when approved by insurance. CRS incidence, grade, rescue interventions, treatment discontinuations, and cost implications were evaluated. CRS grading followed standard consensus guidelines. **Results:** Among 32 treated patients, 29 (90.6%) received prophylactic tocilizumab, and 3 did not. CRS developed in 3 of 29 patients (10.3%) who received pre-treatment—two grade 1 and one grade 2. In contrast, all 3 patients (100%) who did not receive pre-treatment developed CRS—two grade 1 and one grade 2. Overall, CRS occurred in 6 patients (18.8%). All cases resolved after tocilizumab rescue therapy, and no treatment discontinuations occurred. **Conclusions:** Prophylactic tocilizumab substantially reduced CRS incidence among SCLC patients receiving Tarlatamab, suggesting a feasible and safe mitigation strategy. Compared with historical data from DeLLphi-301 (53% CRS incidence), this cohort exhibited markedly lower toxicity rates with prophylactic IL-6 blockade. To our knowledge, this represents the first clinical evidence supporting IL-6 blockade before Tarlatamab administration. Despite the upfront drug cost ($2,800–$5,100 per dose), prevention of CRS-related hospitalizations offers significant economic benefit (estimated $11,000–$200,000 per event based on grade). Limitations include small sample size, lack of randomization, and single-center design. Nonetheless, these findings underscore the potential of integrating tocilizumab prophylaxis into standard Tarlatamab protocols and warrant larger prospective studies to confirm safety, efficacy, and cost-effectiveness. Research Sponsor: None.

Real-world second-line treatment patterns and outcomes by platinum sensitivity in extensive-stage small cell lung cancer in the post-immunotherapy era.

Catherine Rinaldi, Samantha Reiss, Jenna Collins, Karen Schwed, Michael Chiu, Emily Castellanos; Flatiron Health, New York, NY; Flatiron Health, Durham, NC

Background: Platinum-based chemotherapy (PBC) with checkpoint inhibitor (CPI) is standard first-line (1L) treatment for extensive-stage small cell lung cancer (ES-SCLC), though relapse is common. Second-line (2L) treatment selection is determined by platinum sensitivity status, with guidelines based on pre-CPI data, and the benefit of any CPI continuation is unknown. This study examined treatment patterns and real-world (rw) outcomes for patients following 1L PBC +/- CPI among platinum-sensitive (PS) patients, including the impact of continuing a CPI with platinum rechallenge. **Methods:** This retrospective study used EHR-derived US Flatiron Health Research Database. Eligible patients were diagnosed with ES-SCLC between January 1, 2018, and September 9, 2025, received 2L treatment following 1L PBC with a calculable platinum sensitivity and had a minimum potential follow up of 120 days. Platinum sensitivity was defined by a chemotherapy-free interval of ≥ 180 days, based on the last order or administration of 1L PBC to first real-world progression event prior to 2L initiation. Real-world response rate (rwRR), progression free survival (rwPFS) and overall survival (rwOS) were described based on 2L regimen class for patients with PS disease, and were compared via HR for platinum rechallenge with CPI continuation versus without. Time-to-event outcomes were analyzed using Kaplan-Meier methods, with medians and 95% CI reported for the overall cohort and subgroups of interest. **Results:** Among 5,126 eligible patients, 884 (17%) had PS and 4,242 (83%) had platinum refractory (PR) disease. Most patients (73%) received CPI with PBC in 1L. Patients with PR had worse outcomes than PS (rwPFS, 2.7 [95% CI, 2.6-2.8] vs 5.5 [95% CI, 5.3-5.7] mo; rwOS, 4.7 [95% CI, 4.5-4.9] vs 11.2 [95% CI, 10.6-12.4] mo). Among PS patients with 1L CPI exposure (n=666), 48% received 2L PBC, and 41% of 2L PBC continued a CPI. Clinical characteristics in PS disease were similar across classes of 2L regimen. Of patients with PS disease who had 1L CPI exposure, 81% had at least 1 response assessment during the study period. Of PBC patients, rwRR was 52% among CPI treated and 58% without CPI. 2L rwPFS and rwOS were similar regardless of CPI continuation (Table). **Conclusions:** In this large real-world study, nearly half of patients with PS disease were rechallenged with PBC in 2L, and CPI continuation was common despite limited evidence. CPI continuation did not improve response, progression, or survival, suggesting no additional benefit and highlighting the need for prospective data to guide post-CPI treatment in PS ES-SCLC. Research Sponsor: Flatiron Health, Inc.

Outcome	2L rwPFS median, mo (95% CI)	Unadjusted HR (95% CI)	*P* value	2L rwOS median, mo (95% CI)	Unadjusted HR (95% CI)	*P* value
PBC with CPI (n=112)	5.6 (5.4-6.2)	-	-	12.3 (11.0-15.9)	-	-
PBC without CPI (n=149)	6.0 (5.6-6.6)	0.97(0.76, 1.25)	0.80	12.9 (11.0-15.3)	1.04 (0.80, 1.35)	0.80

8084 Poster Session

Antigen presentation suppression as a hallmark of immune evasion and poor outcomes in small cell lung cancer.

Triparna Sen, Elisa Gobbini, Vrinda Jethalia, Subhamoy Chakraborty, Ari Vanderwalde, Balazs Halmos, Hossein Borghaei, Deniz Demircioglu, Dan Hasson, Andrew Elliott; The Ohio State University, Columbus, OH; Icahn School of Medicine at Mount Sinai, New York, NY; Caris Life Sciences, Irving, TX; Montefiore Einstein Comprehensive Center for Cancer Care, Bronx, NY; Fox Chase Cancer Center/Temple Health, Philadelphia, PA; Caris Life Sciences, Phoenix, AZ

Background: Antigen-presenting machinery (APM) is critical for tumor immune recognition. The loss of APM promotes immune evasion and immunotherapy resistance in cancers, including small-cell lung cancer (SCLC). SCLC has a high tumor mutational burden (TMB), and it displays profound APM suppression, explaining its weak response to immune checkpoint inhibitors. We aimed to capture APM gene expression in a large real-world cohort (RWC) and prospective clinical trial datasets to address the clinical implications of APM suppression for current treatment strategies. **Methods:** We calculated a classical antigen-presenting MHCs (CAMs) score using a gene signature comprised of 18 genes closely associated with MHC-I expression and antigen presentation. We evaluated this score in 6,000 real-world lung cancer samples and in the transcriptomic dataset of a Phase III clinical trial evaluating the effect of chemo-immunotherapy as a first-line treatment in extensive-stage SCLC (IMpower133). Transcriptomic, genomic, and proteomic data were collected for analysis. **Results:** Patients with SCLC were stratified into 3 groups according to hierarchical clustering of CAM gene expression for functional enrichment, differential gene expression, response to drug, and survival analyses. CAM expression was markedly suppressed in SCLC compared to other lung cancer histologies. In SCLC, CAM-low accounted for 53% of patients, followed by CAM-intermediate (40%) and -high (7%). We found no statistical difference in TMB-high (³10 mutations/Mb) proportion across CAM groups. CAM-intermediate- and high groups had lower *TP53, RB1,* and *PTEN* mutation rates and a higher *PI3K* mutation rate compared to CAM-low. CAM-low tumors displayed the highest DNA damage response and neuroendocrine signature scores and the lowest *RB1* expression. CAM-low tumors showed the lowest expression of cytokine and cytokine receptors involved in lymphocyte trafficking, as well as the lowest $CD8^+$/Treg and M1/M2 ratios, consistent with a highly immunosuppressive context. CAM-low and intermediate groups had the lower PD-L1 expression and worse overall survival from the start of chemoimmunotherapy in the RWC. Most targetable markers, such as *DLL3,* were down-regulated in CAM-low tumors. We also identified high expression of novel immune targets in the CAM-low population that may inform future drug design. **Conclusions:** We demonstrate that in RWC and clinical trial samples, most patients with SCLC are CAM-low, exhibit immune evasion features, and have poor outcomes, as well as reduced expression of most druggable targets. Our data suggests that SCLC's immunosuppressive microenvironment may lessen the efficacy of new-generation compounds. We highlight potential novel treatment strategies targeting defective APM tumors that may activate the immune microenvironment and augment the effect of existing immunotherapy agents. Research Sponsor: None.

8085 Poster Session

Multiomic spatial analysis of tumor microenvironment during neuroendocrine (NE) transformation in *EGFR*-mutant LUAD.

Elisa Gobbini, Darwin D'souza, Emir Radkevich, Subhamoy Chakraborty, Bi Chongfeng, Chih-wei Fan, Raina Roche, Felix Carl Saalfeld, Deniz Demircioglu, Seunghee Kim-Schulze, Dan Hasson, Zhihong Chen, Martin Wermke, Triparna Sen; The Ohio State University, Columbus, OH; Icahn School of Medicine at Mount Sinai, New York, NY; University Hospital Carl Gustav Carus Dresden, Dresden, Germany; Department of Immunology and Immunotherapy, Icahn School of Medicine at Mount Sinai, New York, NY; TU Dresden University of Technology, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

Background: Histological transformation of *EGFR* mutant lung cancer adenocarcinoma (LUAD) to small-cell lung cancer (SCLC) is a well-known resistance mechanism and has been found in about 14% resistant cases. This phenomenon is associated with extremely poor prognosis and limited therapeutic options. This underscores the need to identify the biological mechanisms triggering lineage plasticity in *EGFR+* LUADs. We and others have shown that several genomic and epigenetic alterations play a central role in the activation of small cell like neuroendocrine (NE) states. However, the impact of these changes on the immune microenvironment and vice versa is not understood, limiting the identification of novel immunotherapy approaches in this setting. **Methods:** We describe the evolution of the tumor microenvironment (TME) during SCLC transformation by comparing tissues from de novo LUAD (n = 10), de novo SCLC (n = 15), and transformed SCLC (n =12) including 11 cases with *EGFR*-mutant LUAD/SCLC mixed histology and 1 pre-transformed LUAD. Additionally, we used de novo lung squamous cancer (LUSC, n = 11), and transformed LUSC (n = 11) including 8 mixed LUSC/LUAD histology and 3 post-transformed samples to inform the LUSC transformation program as a comparator. All samples were analyzed by RNA sequencing, DNA methylation, and whole-exome sequencing. Spatial proteomics (ORION, n = 4) and transcriptomics (XENIUM, n = 6) were performed on pre- and post-transformed paired samples from *EGFR+* patients. **Results:** Differential gene expression and pathway analysis highlight the upregulation of G2M, E2F, and *MYC* targets during both SCLC and LUSC transformation, occurring at an earlier stage for SCLC compared to LUSC. Conversely, a more pronounced and broader and earlier downregulation of immune pathways was detected during SCLC, compared to LUSC, transformation. Analysis of the epigenetic regulators potentially driving these signaling changes pointed to *EZH2* as master regulators of SCLC transformation, while the LUSC program was mainly driven by the *TP63* and *FOXA1* transcription factors. Spatial proteomics and transcriptomics highlighted a decrease in immune-related programs with an increased proportion of immune suppressive subsets and NE features in SCLC-transformed samples compared to baseline specimens. Sub-clustering analysis showed a higher percentage of pro-tumoral macrophages and exhausted T-cells in transformed samples. **Conclusions:** Our results suggest that a broader transcriptional reprogramming is associated with the transition from LUAD to SCLC than from LUAD to LUSC. The TF profile associated with SCLC histological transformation negatively regulates immune pathways leading to profound remodeling of the immune compartment and a cold TME that supports the aggressive phenotype of transformed tumors. Research Sponsor: None.

IMforte: Quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of first-line maintenance (1Lm) treatment (Tx) with lurbinectedin (lurbi) + atezolizumab (atezo) vs atezo in extensive-stage small cell lung cancer (ES-SCLC).

Hossein Borghaei, Luis G. Paz-Ares, Martin Reck, Roy S. Herbst, Solange Peters, Kamalnayan Bhatt, Xiaoyan Wang, Jonathon Gable, Siobhán Connor-Ahmad, Carla Mamolo, Ya-Chen Lin, Stephen V. Liu; Department of Hematology and Oncology, Fox Chase Cancer Center, Philadelphia, PA; Department of Medical Oncology, Hospital Universitario 12 De Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain; Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; Department of Medical Oncology and Hematology, Yale School of Medicine, New Haven, CT; Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Jazz Pharmaceuticals, Philadelphia, PA; Jazz Pharmaceuticals, Palo Alto, CA; Roche Products Limited, Welwyn, United Kingdom; Genentech, a Member of the Roche Group, South San Francisco, CA; Department of Medical Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Background: IMforte (NCT05091567) is the first positive phase 3 study of 1Lm in ES-SCLC to demonstrate statistically significant and clinically meaningful progression-free survival (PFS) and overall survival (OS) benefits (stratified hazard ratios, 0.54 and 0.73) with lurbi + atezo vs atezo. The combination was generally well tolerated based on safety findings and patient-reported outcomes. These data led to the approval of lurbi + atezo as 1Lm Tx for adults with ES-SCLC in the US and Switzerland in 2025. Here, we describe a post hoc Q-TWiST analysis using IMforte data to further elucidate the benefit-risk profile of lurbi + atezo. **Methods:** Eligible pts with ES-SCLC who were progression free after induction with atezo, carboplatin, and etoposide were randomized 1:1 to receive lurbi + atezo or atezo alone every 3 weeks. Survival time was partitioned into 3 health states: toxicity (TOX; time with grade ≥3 adverse events before disease progression), TWiST (time without TOX before disease progression), and relapse (REL; time from disease progression to death). The mean time spent in each health state was estimated using restricted mean survival times, calculated as area under the Kaplan-Meier curve. Q-TWiST was the sum of the mean time in each health state adjusted by respective utility weights, derived from EQ-5D-5L data. **Results:** Analyses were performed on all randomized pts from IMforte (lurbi + atezo, n = 242; atezo, n = 241) as of July 29, 2024, with a median follow-up of 15 months (mo). Utility weights in lurbi + atezo and atezo arms were 0.84 and 0.83 in TWiST, 0.83 and 0.83 in TOX, and 0.78 and 0.76 in REL health states. Pts in the lurbi + atezo arm spent most of their survival time in the TWiST state (66% vs 50% for atezo), and their mean duration of TWiST was substantially longer vs the atezo arm (9.8 vs 6.4 mo; Table). Lurbi + atezo arm pts spent more time in the TOX state vs atezo (0.7 vs 0.3 mo) but less time in the REL state (4.4 vs 6.1 mo). The lurbi + atezo arm had longer mean Q-TWiST vs atezo (12.2 vs 10.2 mo), representing a clinically important 14.9% gain in utility at the maximum follow-up of 26 mo. **Conclusions:** Lurbi + atezo pts had more time without toxicity before disease progression vs atezo and showed a clinically important improvement in quality-adjusted survival, further supporting a favorable benefit-risk profile of lurbi + atezo as 1Lm Tx for ES-SCLC. Clinical trial information: NCT05091567. Research Sponsor: F. Hoffmann-La Roche Ltd and Jazz Pharmaceuticals.

Mean duration of each health state, Q-TWiST, PFS, and OS.

Mo, Mean (95% CI)	Lurbi + Atezo n = 242	Atezo n = 241	Difference	Relative Gain
Q-TWiST	12.2 (11.1, 13.2)	10.2 (9.2, 11.3)	1.9 (0.5, 3.4)	14.9%
TWiST	9.8 (8.4, 11.2)	6.4 (5.2, 7.7)	3.4 (1.5, 5.2)	
TOX	0.7 (0.5, 0.9)	0.3 (0.1, 0.5)	0.4 (0.1, 0.6)	
REL	4.4 (2.8, 6.0)	6.1 (4.6, 7.6)	−1.8 (−4.0, 0.4)	
PFS	10.5 (9.1, 11.9)	6.8 (5.4, 8.1)	3.7 (1.8, 5.6)	
OS	14.8 (13.5, 16.1)	12.9 (11.6, 14.2)	2.0 (0.1, 3.8)	

8087 Poster Session

Impact of DLL3 expression and tumor subtype on response to tarlatamab.

Jessica Ross, Jake June-Koo Lee, Sarah Cascarino, Marina K. Baine, Natasha Rekhtman, Brenden Bready, Andrea Arfe, Robert Michael Daly, Adam Jacob Schoenfeld, Joseph Minhow Chan, Gregory J. Riely, Mark G. Kris, Mark M. Awad, Charles M. Rudin, Alissa Jamie Cooper; Memorial Sloan Kettering Cancer Center, New York, NY; Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Tarlatamab is a DLL3-targeted bispecific T-cell engager used to treat small cell lung cancer (SCLC). SCLC subtypes can be defined by relative expression of master transcription factors (TFs). Whether subtype and DLL3 expression are associated with outcomes on tarlatamab is unknown. **Methods:** We analyzed all patients (pts) with SCLC, including SCLC transformed from lung adenocarcinoma, treated with tarlatamab at Memorial Sloan Kettering prior to October 2025. DLL3 expression and subtyping were determined by IHC by dedicated thoracic pathologists. Expression of subtype TFs ASCL1, NEUROD1, POU2F3, and YAP1 was assessed. "Neuroendocrine (NE)-high" was defined as any ASCL1 or NEUROD1 expression. Pts with any "neuroendocrine (NE)-low" subtype expression—POU2F3 or YAP1—were grouped for analysis. DLL3 fractional expression was dichotomized as "high" (≥50%) or "low" (0-49%). Progression-free and overall survival (PFS, OS) were analyzed with Kaplan-Meier curves and compared with the Cox proportional hazards model. **Results:** We identified 39 pts with SCLC treated with tarlatamab with DLL3 and/or subtyping data available. Median age was 65, 49% were women, and median prior lines of therapy was 1. DLL3 expression was available in 34 pts. Median fractional DLL3 expression was 80% and ranged from 0 to 100%. 7 pts had low expression and 27 had high expression. There were more pts with transformed SCLC in the DLL3-low group (3/7 [43%] vs 1/27 [4%], p=0.02). Among pts with response data available, response was inferior in the DLL3-low group: complete or partial response (CR or PR) in 0/7 (0%; [95% CI, 0 to 35]) vs 12/25 (48%; [95% CI, 30 to 67]); stable disease (SD) in 2/7 (29%) vs 5/25 (20%); progressive disease (PD) in 5/7 (71%) vs 8/25 (32%); p=0.049. Median PFS was 1.4 mos in DLL3-low vs 4.5 mos in DLL3-high disease ($p<0.001$); median OS was 4.7 mos vs not reached (p=0.001). Incidence of CRS and ICANS did not differ (5/7 [71%] in DLL3-low vs 11/29 [38%] in DLL3-high with CRS, p=0.2; 0/9 vs 3/29 [10%] with ICANS, $p>0.9$). 30/39 pts had subtyping data available. 28/30 pts had NE-high tumors (15/28 ASCL1+/NEUROD1+; 11/28 ASCL1+/NEUROD1-; 2/28 ASCL1-/NEUROD1+). 5/30 had subtype biomarkers of NE-low status: 4 YAP1+ and 1 POU2F3+; the 4 YAP1+ tumors also expressed ASCL1. Response rates were similar between pts with and without NE-low expression: 1/5 (20%; [95% CI, 1 to 62]) vs 11/25 (44%; [95% CI, 27 to 63]), p=0.6. PFS was also similar (mPFS 1.1 vs 2.7 mos, p=0.3). **Conclusions:** Low DLL3 expression was potentially associated with inferior response to tarlatamab. A contributing factor may be enrichment of transformed SCLC, which is associated with poor outcomes. We did not detect an impact of POU2F3/YAP1 expression. The majority of pts in this cohort had DLL3-high, NE-high SCLC—in line with prior studies—and they had a response rate of 48%. These data emphasize the need for more discerning predictive biomarkers for tarlatamab in an evolving landscape of treatment options. Research Sponsor: None.

8088 Poster Session

Analysis of corticosteroid exposure on efficacy of tarlatamab in small cell lung cancer: A multicenter retrospective study.

Ty Michael Moore, Courtney C. Cavalieri, Sabrina Cannon, Jessica Campaign Mauser, Emma Jones, Amanda Cass, Alexander Olinger, Bryce Bortka, Allison Schepers, Jacob Hobbs, Lauren Blackwell, Kori Holman, Sarah Blocker, Diana Kim, Chao Hui Huang, Prakash C. Neupane, Sanjana Mullangi, Manidhar Reddy Lekkala, Haoran Li, Timothy J. Schieber; The University of Kansas Cancer Center, Westwood, KS; Hunstman Cancer Institute at The University of Utah, Salt Lake City, UT; Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT; Vanderbilt University Medical Center, Nashville, TN; Nebraska Medicine, Omaha, NE; Saint Luke's Hospital of Kansas City, Kansas City, MO; Michigan Medicine, Ann Arbor, MI; Avera Cancer Institute, Sioux Falls, SD; Medical University of South Carolina, Charleston, SC; Methodist University Hospital, Memphis, TN; University of Kansas Cancer Center, Westwood, KS; University of Kansas Cancer Center, Kansas City, KS

Background: Tarlatamab, a delta-like ligand 3 (DLL3)-targeted bispecific T-cell engager, has shown meaningful activity in small cell lung cancer (SCLC). Immune-mediated toxicities such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are common with T-cell–redirecting therapies and frequently require corticosteroids or cytokine-directed agents like tocilizumab. The impact of lymphodepleting corticosteroid exposure on tarlatamab efficacy remains unclear. **Methods:** We performed a retrospective analysis of patients with SCLC treated with tarlatamab from 2018–2025 across the University of Kansas and nine cancer centers included in the DLL3 PanTUMOR database. The primary endpoint was progression-free survival (PFS) stratified by cumulative dexamethasone dose. Other endpoints included overall response rate (ORR), characterization of CRS and ICANS, and overall survival (OS). A cost analysis of dexamethasone versus tocilizumab was also conducted. **Results:** Among 143 tarlatamab-treated patients, dexamethasone use for CRS or ICANS did not reduce PFS or ORR compared with patients not receiving corticosteroids. Tocilizumab did not reduce steroid needs. Median dexamethasone dose was higher in patients treated with tocilizumab. Severe CRS/ICANS was associated with significantly shorter OS. Cost analysis demonstrates the significant cost savings using dexamethasone compared to tocilizumab for treatment of immune-mediated toxicities. **Conclusions:** Corticosteroid exposure did not compromise tarlatamab efficacy, supporting optimized toxicity management without diminishing antitumor activity of DLL3-targeted T-cell–redirecting therapies. Research Sponsor: None.

Endpoints	Total Number of Evaluable Patients	Outcomes
Median PFS of tarlatamab with cumulative steroid dose **Arm 1: No dex** **Arm 2: 1-40 mg of dex** **Arm 3: 41+ mg of dex**	Arm 1: 66 Arm 2: 42 Arm 3: 16	Arm 1: 2.53 mo Arm 2: 4.70 mo Arm 3: 3.68 mo HR=1.02 95% CI: 0.73-1.42 p=0.31
ORR of tarlatamab with cumulative steroid dose **Arm 1: No dex** **Arm 2: 1-40 mg of dex** **Arm 3: 41+ mg of dex**	Arm 1: 55 Arm 2: 34 Arm 3: 11	Arm 1: 29.1% Arm 2: 47.1% Arm 3: 36.4%
Comparison of ORR with CRS (any grade) versus without CRS	CRS: 58 No CRS: 60	CRS: 34.5% No CRS: 33.3%
Comparison of ORR with ICANS (any grade) versus without ICANS	ICANS: 33 No ICANS: 85	ICANS: 36.4% No ICANS: 32.9%
Did the use of tocilizumab result in lower cumulative steroid use	No tocilizumab: 42 Tocilizumab: 28	Median dex dose without tocilizumab: 10 mg Median dex dose with tocilizumab: 35 mg
Median OS with grade 3+ CRS or ICANS versus with grade 0-2 CRS/ICANS	Grade 0-2: 133 Grade 3+: 10	Grade 0-2: 11.37 mo Grade 3+: 4.19 mo HR=0.34 95% CI: 0.15-0.76 p=0.006
Cost analysis for dex versus tocilizumab **Average wholesale price: tocilizumab $165,724, $3.13 dex10 mg**	CRS: 72 37 doses of tocilizumab	37 doses of tocilizumab substituted with 37 dex 10 mg doses would have saved $173,962

DAREON-8: Updated efficacy and safety from a phase I dose-escalation/expansion trial of first-line (1L) obrixtamig plus chemotherapy and atezolizumab in extensive-stage small cell lung carcinoma (ES-SCLC).

Solange Peters, Rafal Dziadziuszko, Ewa Kalinka, Anas Gazzah, Sophie Cousin, Maria Eugenia Olmedo Garcia, David Vicente, Tirrell T. Johnson, Tatsuya Yoshida, Yiyuan Ma, Nicolas Dorleacq, Dian Yang, Ticiana Leal; Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; Faculty of Medicine, Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdánsk, Poland; Polish Mother's Memorial Hospital, Department of Oncology, Lodz, Poland; Institute Gustave Roussy, Department of Drug Development, Villejuif, France; Institute Bergonié, Department of Medical Oncology, Bordeaux, France; Hospital Universitario Ramón y Cajal, Department of Medical Oncology, Madrid, Spain; Hospital Universitario Virgen Macarena, Medical Oncology Unit, Seville, Spain; Orlando Health Cancer Institute, Department of Medical Oncology, Orlando, FL; National Cancer Center Hospital, Department of Thoracic Oncology, Tokyo, Japan; Boehringer Ingelheim International GmbH, Department of Medical Oncology, Ingelheim Am Rhein, Germany; Boehringer Ingelheim, France S.A.S., Clinical Development and Operation in Oncology, Reims, France; Boehringer Ingelheim (China) Investment Co., Ltd. Department of Medical Oncology, Shanghai, China; Emory Winship Cancer Institute, Atlanta, GA

Background: Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that has shown promising efficacy in ES-SCLC, as monotherapy and in combination with other agents. Due to the aggressiveness of ES-SCLC, early initiation of optimal 1L induction therapy is critical, as many patients (pts) may not reach treatment maintenance. We report updated efficacy and safety data from the ongoing Phase I DAREON-8 (NCT06077500) dose-escalation/expansion trial investigating 1L obrixtamig + induction SoC (carboplatin + etoposide + atezolizumab) and maintenance obrixtamig + atezolizumab in pts with ES-SCLC. **Methods:** Obrixtamig was given IV as step-up dosing followed by target dose (Part A: 3 dose levels [10, 30, 60 mg] guided by a BLRM with overdose control; Part B: selected target dose) + SoC (given per label). After 4 cycles of obrixtamig + SoC, obrixtamig + atezolizumab was continued until disease progression or another reason requiring discontinuation. Primary endpoint: DLTs; secondary endpoints included PFS, DoR, and ORR (RECIST v1.1; investigator assessed). **Results:** As of Dec 17, 2025, 46 pts were treated (Part A/B: n=28/18); 44 pts received ≥1 dose of obrixtamig. Median cycles of obrixtamig: 10 (range: 1–21); median age: 69 yrs (range: 34–76); ECOG PS 0/1: 27%/73%; brain metastasis: 16%. MTD was not reached in Part A; the study continued in Part B with the highest dose level (60 mg). Key efficacy data are in the table. Confirmed ORR: 73% (95% CI: 58–84); DCR: 91% (95% CI: 79–96). mDoR: NC; mPFS: NC; 6- and 9-month PFS rates (95% CI): 76% (62–90), and 61% (44–79), respectively. In the 60 mg cohort, confirmed ORR: 76% (95% CI: 58–88); mDoR and mPFS: NC. Most common G≥3 AEs were cytopenias and were almost wholly related to chemotherapy. Most common obrixtamig-related AE: cytokine release syndrome (52%). SoC discontinuations due to TRAEs: n=2 (G2 asthenia, G2 decreased platelets, G3 anemia). Obrixtamig discontinuations due to TRAEs: n=1 (G2 asthenia). **Conclusions:** Obrixtamig + SoC demonstrated encouraging efficacy, supporting obrixtamig as a combination partner for 1L SoC. The combination showed a safety profile consistent with individual agents, supporting the favorable tolerability of obrixtamig in combination regimens. Updated safety data are consistent with previous findings (Peters S et al, *Ann Oncol* 2025;36: S1466–7), and results warrant further development in Phase III trials. Clinical trial information: NCT06077500. Research Sponsor: Boehringer Ingelheim.

Best confirmed response, n (%)	Obrixtamig 60 mg, n=29*	Total (obrixtamig 10–60 mg), N=44*
CR / PR	4 (14) / 18 (62)	4 (9) / 28 (64)
SD	4 (14)	8 (18)
PD	0 (0)	1 (2)
NE/missing	3 (10)	3 (7)
ORR, % (95% CI)	76 (58–88)	73 (58–84)
DCR, % (95% CI)	90 (74–96)	91 (79–96)
Median PFS, months (95% CI)	NC (NC–NC)	NC (7.2–NC)
6-/9-month PFS rate, % (95% CI)	84 (69–98) / 78 (60–95)	76 (62–90) / 61 (44–79)

*Efficacy-evaluable population.

Clinical outcomes of local treatments for oligoprogressive or oligorecurrent small cell lung cancer.

Adrien Mathieu, Guillaume Pamart, Marion Klotz, Arnaud Scherpereel, Kaoutar Lodyga, Xavier Dhalluin, Eric Wasielewski, Julien Ancel, Simon Baldacci; Université de Lille, CHU Lille, Thoracic Oncology Department, Lille, France; Pulmonology Department, Strasbourg University Hospital, Strasbourg, France; Academic Department of Radiation Oncology, Oscar Lambret Center, Lille, France; CHU Lille, Lille, France; Université de Reims Champagne-Ardenne, INSERM, P3Cell, UMR-S 1250, CHU Reims, Hôpital Cabrol, Service de Pneumologie, Reims, France

Background: The role of local treatments in patients with oligoprogressive or oligorecurrent small cell lung cancer (SCLC) remains unclear. Our study aimed to describe the prognosis of patients with SCLC receiving a local treatment for oligoprogression or oligorecurrence in a real-life setting. **Methods:** The present study included all consecutive patients treated for SCLC at Lille University Hospital or Strasbourg University Hospital between January 2013 and March 2024, for whom local treatment was decided in a Multidisciplinary Tumor Board to control oligoprogression or oligorecurrence. Clinical data and characteristics of the local treatment were collected from medical records. **Results:** Of the 850 patients treated for a SCLC in both centers during the study period, 97 patients were eligible for inclusion. Of those, 84 received local treatment for oligoprogression (n = 47) or oligorecurrence (n = 37). At the time of oligoprogression or oligorecurrence, 82.1% of patients were being treated for extensive-stage disease. The brain was the predominant site of oligoprogression or oligorecurrence (71%) and the most commonly used local treatment was conformal radiotherapy (66.7%), followed by stereotactic radiotherapy (31%) and surgery (2.4%). Grade ≥3 adverse events were observed in only 2.4% of treated patients. After a median follow-up period of 11.9 months, the median overall survival (OS) and median progression-free survival (PFS), measured from the date of initiation of local treatment, were 12.4 months (95% CI: 10.7-18.9), and 3.4 months (95 %CI: 2.4-4.5), respectively. A good performance status (PS 0–1) was associated with better OS (HR 0.50; (95% CI: 0.26–0.97); p = 0.018). PFS was significantly longer in patients with limited-stage SCLC (HR 0.52; (95% CI: 0.31–0.89); p = 0.016) or with five or fewer metastases at the time of local treatment (HR 0.59; (95% CI: 0.37–0.94); p = 0.038). Most progressions observed after local treatment occurred distant from the treated sites (68.8%). **Conclusions:** This study demonstrates that the use of local treatments to control oligoprogression or oligorecurrence in SCLC is not uncommon in routine clinical practice. While this strategy is generally well tolerated, its efficacy remains limited. Further studies are needed to clarify its role in the era of tarlatamab development. Research Sponsor: None.

Paclitaxel, carboplatin, and durvalumab in extensive stage small-cell lung cancer (ES-SCLC; IFCT-2203 TAXIO phase II trial): Can we improve the chemotherapy (CT) immunotherapy combination in SCLC?

Denis Lucien Moro Sibilot, Anne Baranzelli, Etienne Giroux Leprieur, Karim Amrane, Olivier Leleu, Ayoube Zouak, Olivier Molinier, Jacques Henri Le Treut Sr., Pierre-Jean Souquet, Alexandra Langlais, Franck Morin, Alexis B. Cortot, Lionel Falchero; Thoracic Oncology Unit, CHU-Grenoble-Alpes, Grenoble, France; Pneumology Department, Centre Hospitalier Métropole Savoie, Chambery, France; Cancer Institute APHP. Paris-Saclay University, Hôpital Ambroise Paré, Department of Pulmonary Diseases and Thoracic Oncology Respiratory, Boulogne-Billancourt, France; Oncology Department, Centre Hospitalier des Pays de Morlaix, Morlaix, France; Pneumology Department, Centre Hospitalier d'Abbeville, Abbeville, France; Department of Respiratory Diseases, CHU Dijon Bourgogne, Dijon, France; Respiratory Medicine Department, CH Le Mans, Le Mans, France; Thoracic Oncology Department, Hopital Europeen de Marseille, Marseille, France; Pneumology Department, Centre Hospitalier LYON-SUD, Pierre-Bénite, France; Clinical Research Unit, Intergroupe Francophone de Cancérologie Thoracique, Paris, France; Clinical Research Unit, French Cooperative Thoracic Intergroup, Paris, France; Respiratory Medicine and Thoracic Oncology, CHU Lille, Lille, France; Pneumology Department and Thoracic Oncology, Hôpital Nord-Ouest, Villefranche-Sur-Saone, France

Background: Etoposide+platinum-based CT and anti-PD-L1 is the backbone of ES-SCLC treatment. We hypothesize a deleterious action of etoposide on lymphocyte activation. A "proof-of-concept", multicenter and single arm phase II trial was designed to assess the efficacy and safety of an etoposide-free chemotherapy combining durvalumab (Durva) to paclitaxel and carboplatin (Pac-Carbo) CT in ES-SCLC. **Methods:** Patients (pts) with ES-SCLC, PS 0-1 were enrolled and received 4 induction cycles of Durva 1500 mg + paclitaxel 200 mg/m^2 + carboplatin AUC6 (PCD), every 3 weeks followed by single-agent Durva every 4 weeks until progression or unacceptable toxicity. The primary endpoint was overall survival at 12 months (OS@12m), secondary endpoints were overall response rate (ORR), overall survival (OS), OS at 24 and 36 months, progression-free survival (PFS), duration of response, safety (CTC v5.0) and quality of life (EORTC QLQ-C30 LC13). PFS and ORR were also assessed by independent reviewer committee. To reject the null hypothesis and achieve a 12-month survival rate of at least 34 patients (55.7%), 61 patients were required. Safety was assessed in all patients who received at least one dose of their study treatment. **Results:** 68 pts were enrolled between Nov 2023 and Feb 2025. Pts characteristics at baseline were: median age 66.6 years; 51.5% female, 67.6% PS1, 19.1% brain metastasis and 51.5% liver metastasis. The median number of cycles was 4 for chemotherapy and 6 for Durva injections. With a median follow-up of 17.1 months, the primary objective was reached. The OS@12m of the first 61 enrolled pts was 57.4% [IC95%: 44.1-70.0]. Median OS was 14.5 months [IC95%: 9.9-17.6]. ORR was 82.4% [IC95%: 73.3-91.4]. Median PFS was 4.6 months [IC95%: 4.4-4.7]. Treatment-related adverse events (TRAE) of grade 3-5 occurred in 48.5% of pts. TRAE leading to death occurred in 2 pts (sepsis). **Conclusions:** In the IFCT-2203 TAXIO phase 2 trial, the PCD regimen showed a signal of improved OS@12m and reached its statistical objective. Safety findings were consistent with the known safety profiles of all drugs received with no new safety signal for this population. PCD regimen is an active, easy to administer one-day regimen in ES-SCLC and should be integrated in future trials of new IO agents. Pac-Carbo is an alternative to etoposide platinum with potentially better synergy with durvalumab. Clinical trial information: 2023-504670-38-00. Research Sponsor: None.

Sex-specific trends and outcomes in small cell lung cancer (SCLC) in Spain: Insights from the CLARISSE study (2019–2024).

Pilar Garrido, Noemí Villanueva, Reyes Bernabé, Rosario Garcia Campelo, Maria Angeles Sala, Helena Bote-de Cabo, Maria Amelia Insa Molla, Ruth Alvarez, Patricia Cruz, Margarita Majem, María Angeles Moreno Santos, Marta González Cordero, Juana Maria Oramas Rodriguez, Rosa Maria Alvarez Alvarez, Beatriz Alvarez-Abril, Laura Gutiérrez-Sainz, Vanesa Gutiérrez, Nerea Munoz-Unceta, Enriqueta Felip, Dolores Isla; Ramón y Cajal University Hospital, Madrid, Spain; Hospital Universitario Central de Asturias, Oviedo, Spain; Hospital Universitario Virgen del Rocío, Seville, Spain; Hospital Universitario A Coruña, A Coruña, Spain; Hospital Universitario Basurto, Bilbao, Spain; Hospital Universitario 12 De Octubre, Madrid, Spain; Hospital Clínico Universitario de Valencia, Valencia, Spain; Hospital Virgen de la Salud, Toledo, Spain; Hospital Universitario de Cuidad Real, Cuidad Real, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; HU Jerez de La Frontera, Cadiz, Spain; Hospital Universitario de Badajoz, Badajoz, Spain; Hospital Universitario de Canarias, A Gudiña, Spain; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Department of Hematology and Medical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain; Hospital Universitario La Paz, Madrid, Spain; Hospital Regional Universitario de Málaga, Málaga, Spain; Medical Oncology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Hospital Clínico Lozano Blesa, Zaragoza, Spain

Background: SCLC is an aggressive malignancy with poor prognosis. Although overall incidence is declining, cases among women are increasing. European projections show decreasing mortality in men but stable rates in women—except in Spain, where a +2.4% rise is expected—highlighting the need to examine sex-specific trends. **Methods:** CLARISSE is a multicenter, retrospective, observational real-world study conducted in Spain. Data were collected from 29 oncology departments across the country and included adult patients (≥18 years) with histologically confirmed SCLC diagnosed between January 2019 and December 2024. Baseline characteristics, treatment patterns, and survival outcomes were analyzed by sex. **Results:** Among 3,488 SCLC patients, 1,177 (33.8%) were women. The annual distribution of included SCLC cases remained stable over time (15.1%–17.7%), while the proportion of women increased from 29.3% to 39.2% over 6 years. Women were diagnosed at a younger age (mean 64.5 *vs.* 67.8 years). Active smoking was more frequent in women (68.0% *vs.* 54.7%, p<0.001), whereas men showed longer smoking and greater cumulative exposure, with median durations of 45 *vs.*43 years (p=0.02) and median pack-years of 50 *vs.*44 (p<0.001), respectively At diagnosis, 27% had limited-stage (LS) disease, more often in women (29.6% *vs.* 25.7%, p=0.015). Most LS patients received platinum–etoposide plus thoracic radiotherapy. In this population, 1-year overall survival (OS) was 67.9% (95%CI, 64.8-71.0%), with a median OS of 22 months (95%CI, 19.3-24.6 months); women had longer survival than men (Table 1). Systemic first-line (1L) treatment for extensive-stage (ES) consisted predominantly of platinum-based chemotherapy (95.6%; carboplatin 83.0% and cisplatin 12.6%) combined with etoposide (92.1%). Since its approval in September 2021, immunotherapy has been given to 66.3% of patients, more often to women (70.6% *vs.* 63.9%, p=0.013). In the population receiving 1L therapy, 1-year OS was 34.0% (95%CI, 32.1–35.9%), and median OS was 8.5 months (95%CI, 8.1–8.8). Women had longer survival (Table 1). Patients who received 1L immunotherapy had longer OS than those who did not: 10.1 months (95%CI, 9.4–10.7 months) *vs.* 7.2 months (95%CI, 6.6–7.7 months). **Conclusions:** This large multicenter SCLC cohort shows marked sex-related differences in epidemiology, stage distribution, treatment patterns and survival in Spain. Women were increasingly represented over time, diagnosed younger, and experienced longer survival in both LS and ES disease. These results support the importance of integrating sex-specific perspectives in SCLC management and research. Research Sponsor: PharmaMar.

Survival outcomes (CLARISSE study).

	LS-SCLC		ES-SCLC	
	Women	Men	Women	Men
1-year OS (95% CI)	78.1% (73.1-83.1)	62.1% (58.1-66.1)	38.3% (34.9-41.7)	31.7% (29.7-33.7)
Median OS (95% CI) (months)	30.1 (25.4-34.7)	17.3 (14.4-20.3)	9.1 (8.2-9.9)	8.0 (7.6-8.5)

8093 Poster Session

Comparison of real-world overall survival between atezolizumab- and durvalumab-containing first-line induction and maintenance regimens in extensive-stage small cell lung cancer.

Apar Kishor Ganti, Jeremy Snider, Jessie Yan, Catherine Rinaldi, Amy Nguyen, Badri Rengarajan, Deborah Ann Profant, Douglas S. Fuller, Ellen Hu, Trong Kim Le, Navit Naveh, Xiaozhou Fan; Division of Oncology-Hematology, VA Nebraska Western Iowa Health Care System/University of Nebraska Medical Center, Omaha, NE; Flatiron Health, New York, NY; Jazz Pharmaceuticals, Palo Alto, CA; Jazz Pharmaceuticals, Philadelphia, PA

Background: Both atezolizumab (atezo) and durvalumab (durva) are preferred first-line (1L) systemic treatment options for extensive-stage small cell lung cancer (ES-SCLC) with similar efficacy in the IMpower133 and CASPIAN phase 3 trials. There is limited evidence comparing their survival outcomes in the real-world (rw) setting. This study described rw overall survival (rwOS) in patients (pts) with ES-SCLC treated in 1L and 1L maintenance (1Lm) settings and also compared rwOS stratified by cohort and treatment with 1L atezo vs durva in combination with platinum-based chemotherapy (chemo) followed by atezo vs durva as 1Lm immunotherapy (IO). **Methods:** Using the US Flatiron Health Research Database, this retrospective noninferiority study included adults with ES-SCLC across 2 cohorts. The 1L cohort included pts treated with atezo or durva + chemo between Apr 1, 2020, and Sept 30, 2025. The 1Lm cohort included a subset of pts from the 1L cohort who were subsequently treated with atezo or durva monotherapy. The index date was the initiation of atezo or durva in the 1L or 1Lm setting in each cohort. rwOS hazard ratios (HRs) and 95% CIs comparing durva with atezo as reference in the 1L and 1Lm settings were calculated using Cox proportional hazard models, adjusting for prognostic covariates. Based on prior literature, the noninferiority margin was set at HR = 1.25. **Results:** A total of 2063 and 1122 pts were included in the overall 1L and 1Lm cohorts, respectively. In both cohorts, median age was 68 years, ≥20% of pts had an ECOG PS ≥2, and ≥19% had brain metastases at baseline. The 1L cohort had 1614 (78%) pts on atezo + chemo and 449 (22%) on durva + chemo. The 1Lm cohort had 865 (77%) pts on atezo and 257 (23%) on durva. Pt characteristics were generally similar between those treated with atezo vs durva in 1L or 1Lm settings. In the 1L cohort, median OS (95% CI) from the index date was 8.7 (8.2, 9.3) months for atezo and 8.5 (7.9, 9.5) months for durva. In the 1Lm cohort, median OS (95% CI) from index date (start of maintenance) was 9.3 (8.2, 10.2) and 9.2 (7.5, 10.8) months for atezo and durva. In the 1L cohort, the adjusted HR for OS for durva vs atezo was 0.98 (95% CI: 0.86, 1.10; $P = 0.7$), indicating no statistically significant difference between the 2 treatments. In the 1Lm cohort, the adjusted HR for OS for durva vs atezo was 1.04 (95% CI: 0.88, 1.22; $P = 0.7$). In both cohorts, the upper 95% CI was < 1.25, supporting the noninferiority of durva vs atezo. **Conclusions:** In this rw population, atezo and durva offered comparable rwOS, which was shorter than those reported in phase 3 clinical trials, for pts with ES-SCLC when used with chemo in 1L or as monotherapy in 1Lm. Research Sponsor: Jazz Pharmaceuticals.

MC1923: Phase II durvalumab plus lurbinectedin in platinum-resistant relapsed extensive-stage small cell lung cancer after prior chemoimmunotherapy (cohort B).

Konstantinos Leventakos, Anastasios Dimou, Nathan Foster, Brandy L. Jaszewski, Aaron Scott Mansfield, Kaushal Parikh, Janet Lensing, Lynn M. Flickinger, Katherine Emilie Rhoades Smith, Deepti Behl, Mohamed Shanshal, Anna J. Schwecke, Ailsa Luce, Jenesse Nicole Moffett, Ashley Potter, Abdullah Al-Ajmi, Kadi Dick, Dena Weinmann, Julian R. Molina, Alex A. Adjei; Mayo Clinic Rochester, Rochester, MN; Department of Oncology, Mayo Clinic Rochester, Rochester, MN; Department of Oncology, Division of Medical Oncology, Mayo Clinic Rochester, Rochester, MN; Cancer Center Research Office, Mayo Clinic Rochester, Rochester, MN; Cleveland Clinic, Cleveland, OH

Background: Patients with extensive-stage small cell lung cancer (ES-SCLC) who progress after platinum-based chemotherapy plus immunotherapy have limited options. Whether adding lurbinectedin while continuing immune checkpoint blockade at relapse improves outcomes is unknown. We report results for the platinum-resistant cohort (progression ≤3 months from last chemotherapy) of MC1923. **Methods:** MC1923 is a phase II trial using a Simon optimal two-stage design. Patients were assigned to a starting dose of durvalumab 1500 mg IV plus lurbinectedin 3.2 mg/m^2 IV on Day 1 of 21-day cycle. The primary endpoint was the 6-month progression-free survival rate (PFS6). Accrual continued to 22 eligible patients if ≥2/9 achieved PFS6; the regimen would be considered promising if ≥7/22 (32%) were alive and progression-free at 6 months. Secondary endpoints included adverse events (AEs), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Twenty-two patients enrolled (02/04/2022–05/21/2025); all were eligible and treated. Median age was 66 years; 32% were male; ECOG performance status was 0 in 9% and 1 in 91%; 96% had prior atezolizumab. Median cycles delivered were 4 (range 1–13). PFS6 was 4/22 (18.2%; 95% CI, 7.5–44.1%), below the prespecified threshold. Median PFS was 3.1 months (95% CI, 1.6–5.3). ORR was 13.6% (3/22; all partial responses; 95% CI, 2.9–34.9%). At data cutoff (12/18/2025), 4 patients were alive; median follow-up was 16.8 months (range 5.5–39.6). Median OS was 7.4 months (95% CI, 4.3–18.6) and 1-year OS was 33.1% (95% CI, 17.6–61.9%). One (1) patient discontinued treatment with durvalumab due to AE. No treatment-related Grade 5 AEs occurred; Grade 3–4 AEs at least possibly related to treatment occurred in 32% (7/22); Grade 4 AEs occurred in 5% (1/22), all hematologic. Most common Grade 3 AEs were decreased neutrophils and white blood cells (each 9%). **Conclusions:** Durvalumab plus lurbinectedin demonstrated manageable toxicity in platinum-resistant ES-SCLC after chemoimmunotherapy but did not meet the prespecified PFS6 efficacy threshold, supporting the need for alternative strategies in this high-risk population. Clinical trial information: NCT04607954. Research Sponsor: AstraZeneca.

8095 Poster Session

BL0020, a novel tumor microenvironment (TME)-targeting nano-mediated polypeptide-drug conjugate (NMPDC), in patients with advanced solid tumors: Updated results from the small cell lung cancer (SCLC) subset of a phase 1 study.

Shuhang Wang, Charlotte Rose Lemech, Ning Li, Nanya Wang, Xichun Hu, Jian Zhang, Michelle Frances Morris, Weixing Mao, Haoyuan Jiang, Fuyao Zhang; Department of Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Scientia Clinical Research-Prince of Wales Clinical School, Randwick, NSW, Australia; Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; The First Hospital of Jilin University, Jilin, China; Fudan University Shanghai Cancer Center, Shanghai, China; Sunshine Coast University Private Hospital, Sunshine Coast, Australia; Shanghai Best-Link Bioscience, LLC, Shanghai, China

Background: BL0020 is a novel polypeptide-drug nanoconjugate (~10 nm in size) composed of PEG-modified poly(amino acid), enzyme-responsive peptide linkers, and topoisomerase I inhibitor (Topo1i) payloads. It accumulates in the tumor microenvironment (TME), where payloads are continuously released by specific enzymes, penetrate tumor cells, and effectively induce cell death. BL0020 has shown promising efficacy in advanced SCLC. Here, we present updated results from the SCLC subset of an international Phase 1 study of BL0020 (NCT05886868). **Methods:** Patients with locally advanced/unresectable or metastatic SCLC received BL0020 injection (20 mg/m^2 or 25 mg/m^2 IV every three weeks) until disease progression, unacceptable toxicity, or withdrawal of consent. **Results:** As of November 30, 2025, 49 patients were enrolled. Treatment-related adverse events (TRAEs) were consistent with expected payload-related effects, primarily manageable hematological and gastrointestinal toxicities, with no new safety signals identified. Grade 3/4 TRAEs occurring in ≥10% of patients included neutropenia, decreased white blood cell count, and anemia. All SCLC patients had progressed after at least one prior platinum-based chemotherapy regimen, and 61% had received prior anti-PD-(L)1 therapy. The median number of prior lines of therapy was 2 (range: 1–6). Among 13 efficacy-evaluable SCLC patients, the disease control rate (DCR) was 100% and the objective response rate (ORR) was 84.6%, with a confirmed ORR of 76.9%. In addition, eight patients achieved >50% tumor shrinkage. Among SCLC patients with baseline brain metastases, both ORR and DCR were 100%, with brain lesions showing >50% shrinkage or complete disappearance. At a median follow-up of 12.58 months, median progression-free survival (mPFS) was 10.15 months (95% CI: 4.93, not reached), median duration of response (mDOR) was 8.18 months (95% CI: 3.54, not reached), and median overall survival (mOS) was 15.31 months (95% CI: 7.46, not reached). **Conclusions:** BL0020 monotherapy demonstrated a manageable safety profile and promising antitumor activity in patients with advanced SCLC who progressed after at least one prior platinum-based chemotherapy. The therapy showed a high response rate and potential for prolonged PFS compared with standard chemotherapy. Clinical trial information: NCT05886868. Research Sponsor: None.

8096 Poster Session

Updated results of the phase 1 dose escalation and expansion study of alveltamig (ZG006), a trispecific T cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with refractory small cell lung cancer or neuroendocrine carcinoma.

Qiming Wang, Jianhua Shi, Xiaoli Chai, Li Zheng, Lihua Wu, Haibo Mou, Rongbo Lin, Xiujuan Qu, Linlin Liu, Qi Xu, Dan Cao, Yu Yao, Hanli Shui, Hewen Yin, Liqing Wu, Jason Jisheng Wu, Binhua Lv, Andrew X. Zhu; Henan Cancer Hospital Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Second Internal Medicine, Linyi Cancer Hospital, Linyi, Shandong, China; ChangSha TaiHe Hospital, Changsha, Hunan, China; West China Hospital of Sichuan University, Chengdu, China; Shulan Hospital, Hangzhou, Zhejiang, China; Shu Lan Hospital, Hangzhou, China; Department of Gastrointestinal Oncology, Fujian Provincial Cancer Hospital, Fuzhou, China; Department of Oncology, the First Hospital of China Medical University, Shenyang, China; China-Japan Union Hospital of Jilin University, Changchun, China; Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Zelgen, Shanghai, China; Suzhou Zelgen Biopharmaceuticals Co., Ltd., Suzhou, China

Background: Alveltamig (ZG006) is a uniquely designed T cell engager, targeting two distinct delta-like ligand 3 (DLL3) epitopes and CD3 and, thereby bridging tumor cells and T cells together and mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC) or neuroendocrine carcinoma (NEC). **Methods:** This is a multi-center, open-label, phase 1 clinical study of ZG006 as monotherapy in patients with SCLC or NEC who failed or were intolerant to the standard therapies. A standard "3+3" design, with an accelerated titration approach for the first two lower dose levels was used during the dose escalation stage. Here we report the updated results of the efficacy and safety data from the phase I study. **Results:** In this phase I study, patients received ZG006 at 0.1 mg Q2W and escalated at 8 dose levels up to 100 mg Q2W (Wang Q et al, ASCO 2025). A step dose of 1 mg was implemented for higher dose groups starting from 10 mg Q2W. Dose expansion was conducted at dose levels of 10, 30, and 60 mg. A total of 31 patients with SCLC, including 4, 15, and 12 patients from the 10 mg, 30 mg, and 60 mg dose groups respectively, were included in the current efficacy analysis. The overall median follow-up time was approximately 16 months. The median age was 59 years (range, 45.0-72.0), the median number of prior treatment lines was 3 (range,1-4), 80.6% of the patients had received prior immunotherapy, and 90.3% had a baseline ECOG performance status score of 1. The confirmed objective response rate (ORR) assessed by an independent review committee (IRC) was 74.2%. The median duration of response (DoR) was 12.6 months, with 12-month DoR rate at 65.3 %. The estimated 12-month PFS rate was 50.5%. The median overall survival (OS) was not reached yet, however,the 12-month and 18-month OS rates approached 74.2% and 58.6% respectively. Consistent with prior report, the most common adverse events with longer follow-up included CRS, anemia and other conditions, with most being Grade 1 or 2 and occurring during the first two cycles. Overall, ZG006 was well-tolerated and the treatment related adverse events including CRS were manageable. **Conclusions:** With longer follow up from phase I study, ZG006 continued to demonstrate robust antitumor activity in the dose expansion cohorts including high ORR, longer DoR/PFS, and clinically meaningful survival benefits in patients with refractory SCLC. No new safety signal was encountered. These data support ongoing development of ZG006 as monotherapy and in combination with other modalities in SCLC. Clinical trial information: NCT05978284. Research Sponsor: None.

Predictive markers of response and toxicity to tarlatamab in patients with extensive stage small cell lung cancer (ES-SCLC): A multi-institutional real-world analysis.

Graeme Fenton, Daniel Hess, Annie Zhang, Wanru Guo, Curtis Tatsuoka, Alexis Green, Michelle Sittig, Ranee Mehra, Alexandra Simms, Afshin Dowlati, Taofeek Kunle Owonikoko, Katherine Ann Scilla, Melinda Laine Hsu, Laura Alder, Samuel Rosner; University of Maryland Medical Center, Baltimore, MD; Duke University Medical Center, Durham, NC; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Tarlatamab (tarla) is a novel immunotherapeutic agent for the treatment of relapsed ES-SCLC associated with favorable response and survival outcomes. While tarla's unique side effect profile of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) is well described, factors influencing response or toxicity have yet to be fully established. **Methods:** We performed a retrospective, multivariate analysis of patients with ES-SCLC receiving tarla at three NCI-designated comprehensive cancer centers from 7/2024-10/2025. CRS and ICANS were reported using ASTCT consensus guidelines. Dysgeusia was graded using CTCAE v5.0. Overall response rate (ORR) was determined using clinical interpretation of radiographic assessments from patients with available post-treatment imaging. Time to event analyses were performed. Cox Proportional Hazards regression analyses assessed the association between patient characteristics and PFS and OS outcomes. Logistic and ordinal regression analyses evaluated the predictive value of variables contributing to the presence and severity, respectively, of CRS and ICANS. **Results:** 115 patients received at least 1 dose of tarla, with median age of 67 years, 55% female and ECOG PS ranging from 0-3 (median of 1). Rates of observed CRS, ICANS, and dysgeusia were 46%, 28%, and 47%, respectively. ORR was 44% and 6-month PFS/OS rates were 30.4% (95% CI: 22.5-41.1%)/ 54.9% (95% CI: 45.4-66.4%). Excluding patients on tarla <30 days, presence of dysgeusia was associated with a lower rate of progression (HR 0.44, p = 0.00691) and death (HR 0.34, p = 0.0145). Neither CRS nor ICANS were associated with treatment response. Both sum of liver metastasis diameter >10 cm (OR 4.4, p = 0.02) and elevated baseline LDH (p = 0.01) were significantly associated with increased likelihood of CRS, while female sex was a protective factor (OR 0.33, p = 0.01). Increased ECOG PS (OR 2.3, p = 0.02), sum of brain metastasis diameter >2 cm (OR 3.6, p = 0.02), development of CRS (OR 2.8, p = 0.04), elevated baseline LDH (p = 0.04) and elevated baseline ferritin (p =0.004) were all associated with increased risk of developing ICANS. **Conclusions:** In our multicenter cohort of patients with ES-SCLC, tarlatamab continued to demonstrate anticancer activity with similar ORR and 6 month PFS compared to existing DeLLphi-304 data. Importantly, the presence of dysgeusia was found to be a marker of treatment response associated with improved PFS and OS. CRS and ICANS incidence was associated with several baseline patient and disease characteristics. Collectively, these preliminary results identify several predictive biomarkers of toxicity that can be utilized in clinical practice, though validated models are needed to better stratify low and high-risk populations.
Research Sponsor: None.

8098 Poster Session

Monalizumab plus durvalumab plus platinum-based chemotherapy for first-line treatment of extensive stage small-cell lung cancer: Early efficacy results from MOZART trial.

Hirva Mamdani, Hyejeong Jang, Seongho Kim, Muhammad Furqan, William Andrew Zeitler, Misty Dawn Shields, Ryan D. Gentzler, Kristen Pizana, Qura Abid, Shadia Ibrahim Jalal; Department of Hematology and Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI; Biostatistics Core, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI; University of Iowa Hospitals and Clinics, Iowa City, IA; University of Iowa Hospital and Clinics, Iowa City, IA; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; University of Virginia, Charlottesville, VA; Karmanos Cancer Institute, Detroit, MI

Background: Extensive stage small cell lung cancer (ES-SCLC) is an area of unmet need where novel treatment strategies are urgently needed. Preclinical data in SCLC demonstrate higher expression of NKG2A, an immune checkpoint expressed on natural killer (NK) cells and CD8+ T cells, with consequent reduced NK cell mediated anti-tumor activity, substantially enhanced metastatic dissemination of tumor cells, and amelioration of metastasis with hyperactivation of NK cells. We hypothesized that NKG2A inhibitor monalizumab (M) may enhance the efficacy of first-line therapy in ES-SCLC by promoting both NK and CD8+ T cell functions. **Methods:** We conducted a single arm, multicenter, investigator-initiated phase II study with a safety lead-in cohort, evaluating M in combination with platinum (P), etoposide (E), and durvalumab (D) in patients (pts) with previously untreated ES-SCLC. One prior cycle of EP ± D was allowed. Pts received EP + D + M every 3 weeks for 4 cycles followed by D + M every 4 weeks until disease progression or unacceptable toxicity. Primary endpoints were 1-year (yr) progression-free survival (PFS) and safety. Secondary endpoints were objective response rate (ORR), 1-year overall survival (OS) and intracranial PFS (iPFS). We hypothesize that the combination will lead to improvement in 1-yr PFS to 33% compared to historical control of 18% (1-sided alpha:10%, power: 80%). **Results:** 30 pts were enrolled (median age:62.5yrs (range, 53-79)). 10pts (33.3%) were female and 6 (20%) were Black. 14pts (46.7%) received one cycle of EP ± D prior to study entry. ORR was 73.3% (complete response = 3, partial response = 19). At median follow-up of 14.2months (mo) (range, 6.4-not estimable (NE)): estimated 1-yr PFS: 20.6%, 18-mo PFS: 15.5%, median (m) PFS: 4.8mo (4.5-5.3), 1-yr OS: 67.4%, mOS: NE (10.2-NE). Most common site of progression was brain with miPFS of 5.3mo (4.8-10.8); 1-yr iPFS: 21.7%, 18-mo iPFS: 16.3%. 4pts had PFS longer than 1yr, 3 of whom had brain metastasis at baseline. No dose limiting toxicities were identified in the safety lead-in cohort. Treatment related AEs (TRAEs) at least possibly related to D and/or M occurring in ≥10% of pts were fatigue (23%), decreased lymphocyte count (13%), hypothyroidism (10%), decreased neutrophil count (10%), and increased lipase (10%). 5 pts (17%) had grade (G) 3/4 TRAEs: decreased neutrophil count (n = 3), encephalitis (n = 1), acute kidney injury (n = 1). Toxicities solely attributed to M were all G 1: increased lipase (n = 2), headache (n = 1), and increased amylase (n = 1). **Conclusions:** Addition of M to first-line EP + D led to no new severe AEs in patients with ES-SCLC. Estimated 1-yr PFS was not statistically superior to historical control with EP +D, yet a subset of patients including those with baseline brain metastasis derived durable benefit. Long term follow-up and biomarker analysis are ongoing. Clinical trial information: NCT05903092. Research Sponsor: AstraZeneca.

8099 Poster Session

Multicenter phase II trial of atezolizumab plus carboplatin and etoposide for extensive-stage small cell lung cancer older patients who underwent geriatric assessment (OLCSG2002 EPAS Trial).

Yuka Kato, Nobuaki Ochi, Koji Inoue, Toshihide Yokoyama, Shoichi Kuyama, Hirohisa Ichikawa, Naokatsu Horita, Masaaki Inoue, Isao Oze, Akihiro Bessho, Kadoaki Ohashi, Yosuke Togashi, Katsuyuki Hotta, OLCSG; Okayama Lung Cancer Study Group; Department of Thoracic oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama-City, Ehime, Japan; Kawasaki Medical School, Okayama, Japan; Ehime Prefectural Central Hospital Respiratory Medicine, Matsuyama-Shi, Japan; Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan; Department of Respiratory Medicine, Iwakuni Clinical Center, Iwakuni, Japan; Department of Respiratory Medicine, KKR Takamatsu Hospital, Takamatsu, Japan; Kure Kyosai Hospital, Kure, Japan; Department of Chest Surgery, Shimonoseki City Hospital, Shimonoseki, Japan; Division of Cancer Information and Control, Aichi Cancer Center Research Institute, Nagoya, Japan; Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan; Department of Respiratory Medicine and Allergy, Okayama University Hospital, Okayama, Japan; Department of Tumor Microenvironment, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan; Department Hematology and Oncology, Okayama University Hospital, Okayama-Shi Kita-Ku, Japan

Background: Combination therapy with anti-PD-L1 monoclonal antibodies and chemotherapy (ICI-chemotherapy) is the current standard treatment for patients(pts) with extensive-stage small cell lung cancer (ES-SCLC). However, its safety and efficacy in older pts (≥ 71 years) remain limited. Given the pivotal role of geriatric assessment (GA) in the older care, prospective data remain scarce. This study aimed to clarify the efficacy and safety of ICI-chemotherapy in older pts and to evaluate the association between GA and survival. **Methods:** This multicenter prospective study enrolled pts ≥ 71 years with ES-SCLC who received atezolizumab plus carboplatin and etoposide as first-line therapy. The primary endpoint was 1-year survival rate (SR). Based on existing results, the expected value was 60%, the threshold was 40% (α-error = 0.1 [two-sided], power = 0.75). The calculated sample size was 32 pts. A pre-treatment G8 assessment was mandatory for all pts. Secondary endpoints included safety, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Between August 2022 and March 2024, a total of 32 pts were enrolled: median age 77 years (range 71–83); male/female = 27/5; PS 0/1 = 8/24, G8 scores ≥12 / < 12 /not collected were 19/12/1. The 1-year SR was 62.5% (95% confidence interval [CI]: 43.5–76.7). Median OS was 14.6 months (95% CI: 8.2–23.3), median PFS was 5.0 months (95% CI; 4.2–5.9), and ORR was 84.4% (95% CI; 66.3–93.7). Median OS by G8 (score ≥12 vs < 12) was 15.4 vs 12.3 months. Cox regression analysis including clinically important factors for survival (age, PS, G8, bone and brain metastasis at diagnosis) identified brain (HR; 3.1, 95% CI: 1.06 to 8.87; p = 0.039) and bone metastases (HR 3.5, 95% CI: 1.20 to 10.1; p = 0.022) as an independent factor. grade ≥ 3 adverse events (AEs) occurred in 87.5% of pts, and dose reduction was required in 45.1%. The most frequent AE was neutropenia (93.8%); one treatment-related death (stroke) was reported. **Conclusions:** ICI-combined chemotherapy demonstrated efficacy comparable to that in existing studies, but greater caution was required regarding safety in older pts. While G8 status did not affect survival in SCLC pts, the presence of bone or brain metastasis at diagnosis was identified as an independent prognostic factor. Clinical trial information: jRCT1061200024. Research Sponsor: None.

Comparative real-world outcomes of tarlatamab and lurbinectedin in relapsed extensive-stage small cell lung cancer.

Daniyal Aziz Khan, Haris Sohail, Farzeen Fatma Syed, Jennifer Collins, Amir Kamran; Charleston Area Medical Center, Charleston, WV; Charleston Area Medical Center Institute for Academic Medicine, Charleston, WV; Charleston Area Medical Center (CAMC) Cancer Center, Charleston, WV

Background: Extensive stage small cell lung cancer is an aggressive malignancy with rapid progression and poor survival after relapse following platinum-based chemotherapy. Tarlatamab, a DLL3 directed bispecific T cell engager, demonstrated a significant overall survival benefit compared with physician's choice of chemotherapy, including lurbinectedin, in the phase 3 DeLLphi 304 trial. However, access to tarlatamab remains limited in routine clinical practice, and lurbinectedin continues to be commonly used in the post platinum setting. As a result, real world data comparing the effectiveness and toxicity of these agents are needed to better inform treatment decisions for patients with relapsed small cell lung cancer. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, a federated, de-identified electronic health record database. Adults with lung cancer who received platinum-based chemotherapy or immunotherapy as first-line treatment and subsequently initiated tarlatamab or lurbinectedin as second-line therapy between January 1, 2020 and November 1, 2025 were included. Propensity score matching was then performed and overall survival was evaluated using Kaplan–Meier methods. Secondary outcomes included immune- and treatment-related adverse events, including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS/ICE), and corticosteroid use. **Results:** After 1:1 propensity score matching, both groups had 133 patients each with good balance across demographics, comorbidities, metastatic burden, prior therapies, and baseline laboratory. At 1 year, mortality was 33.1% with tarlatamab versus 72.2% with lurbinectedin (absolute risk reduction 39.1%, 95% CI 28.1–50.1; $p< 0.0001$), with improved 1-year survival probability (59.2% vs 17.1%) and superior overall survival (HR 0.46, 95% CI 0.32–0.66; log-rank $p< 0.0001$). The survival benefit persisted at 2 years, with median survival of 417 days versus 149 days and survival probabilities of 47.4% versus 15.9%, respectively (HR 0.48, 95% CI 0.34–0.68; $p= 0.0015$). Tarlatamab was associated with higher corticosteroid use (56.4% vs 33.8%, $p= 0.0002$) and immune-mediated toxicities, including cytokine release syndrome in 45.1% (grade 1: 23.3%, grade 2: 13.5%) and ICANS/ICE in 17.3%, with no grade 4–5 events. **Conclusions:** In this propensity score–matched analysis, tarlatamab demonstrated a significant and durable overall survival advantage over lurbinectedin, with an approximately 50% relative reduction in the risk of death at both 1 and 2 years based on hazard ratios. While tarlatamab was associated with higher rates of expected immune-mediated toxicities, including CRS and ICANS, events were predominantly low-grade, supporting a favorable benefit–risk profile in this heavily pretreated metastatic population. Research Sponsor: None.

Impact of lung cancer screening in patients diagnosed with small cell lung cancer.

Paresh Kumar, Emmalee E. Kiser, Brook Marie Lobsiger, Anthony Alfonso, Weston He, Ahmad Karkash, Mark Botros, Mya Tran, Julian A. Marin-Acevedo, Nasser H. Hanna, Misty Dawn Shields; Indiana University School of Medicine, Indianapolis, IN; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Health North Hospital, Inc., Carmel, IN; IU Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Melvin and Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: The advent of immunotherapy significantly improved overall survival (OS) for limited-stage SCLC (LS-SCLC), highlighting how early detection may drive maximal therapeutic benefit. Lung cancer screening (LCS) with low-dose CT scans (LDCT) in high-risk individuals reduced the risk of lung cancer mortality and identified more Stage I lung cancer (National Lung Screening Trial (NLST), NELSON). Within the NLST, SCLC distribution by stage (I-IV) was similar between LDCT or chest x-ray, thereby limiting the perceived absolute impact of LCS for SCLC detection. Here, we report on the utility of LCS in SCLC in the era of immunotherapy. **Methods:** We retrospectively reviewed the charts of patients diagnosed with SCLC in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by whether SCLC was identified from LDCT or non-screen detected. Kaplan-Meier, Wilcoxon rank sum, Pearson's Chi-squared, and Fisher's exact test were applied. **Results:** Among the 301 LCS-eligible individuals with SCLC, 67 patients (22.3%) received LDCT preceding their diagnosis. With LDCT, a significant shift in stage was observed ($P < 0.001$). In the non-LDCT cohort, 28% were diagnosed with LS-SCLC and 72% with ES-SCLC. In the LDCT cohort, 60% were diagnosed with LS-SCLC and 40% with ES-SCLC. After robust adjustment for confounders in a multivariable logistic regression model, LCS was independently associated with higher odds of LS-SCLC at diagnosis (odds ratio 4.22; 95% CI, 2.20-8.28, $P < 0.001$). Significant delays post-LDCT were noted including time from scan to biopsy (52 vs 10 days, $P < 0.001$) and biopsy to treatment (20 vs 13 days, $P < 0.001$). LCS did not improve response rates, treatment completion rates, or progression-free survival, regardless of stage. At diagnosis, patients with ES-SCLC in the LDCT cohort tended to have less CNS involvement (11% vs 30%, $P = 0.06$) but had more bone metastases (74% vs 45%, $P = 0.006$), compared to non-LDCT. Survival between LDCT and non-LDCT was similar for LS-SCLC (22.9 vs 40.4 months, $P = 0.15$) and ES-SCLC (12.2 vs 10.8 months, $P = 0.89$). To account for stage migration and unequal follow-up between groups (41.4 vs 25.3 months), a pre-specified, stage-agnostic 1-year OS was compared. The LDCT group had a higher 1-year OS compared to the non-LDCT group (69.2% vs 54.6%, $P = 0.03$). **Conclusions:** Use of LCS in eligible patients resulted in a significant "stage-shift" to LS-SCLC for individuals diagnosed with SCLC. At a pre-specified cut-off, LCS significantly improved OS for patients diagnosed with SCLC. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	LDCT (No) (n = 234)	LDCT (Yes) (n = 67)	Overall (n = 301)	*P* value
Age (Q1, Q3)	66 (61, 72)	68 (64, 73)	67 (62, 72)	0.1
Sex (female)	145 (62%)	41 (61%)	186 (62%)	>0.9
ECOG PS (0-1)	150 (70%)	53 (84%)	203 (73%)	0.024
Current tobacco	171 (73%)	50 (75%)	221 (73%)	0.9
COPD	119 (51%)	48 (72%)	167 (55%)	0.003
+FH cancer	128 (59%)	46 (73%)	174 (62%)	0.047
+FH lung cancer	57 (26%)	22 (35%)	79 (28%)	0.2

Comparison by immunotherapy agent of real-world outcomes with chemo-immunotherapy in first-line extensive-stage small cell lung cancer.

Anthony Alfonso, Paresh Kumar, Brook Marie Lobsiger, Emmalee E. Kiser, Weston He, Ahmad Karkash, Mark Botros, Mya Tran, Julian A. Marin-Acevedo, Misty Dawn Shields; Indiana University School of Medicine, Indianapolis, IN; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Health North Hospital, Inc., Carmel, IN; IU Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Melvin and Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Chemoimmunotherapy became the standard of care for extensive-stage small cell lung cancer (ES-SCLC) after two Phase III trials (IMpower133, CASPIAN) demonstrated significant improvement in overall survival (OS) over platinum-based chemotherapy. While both anti-PD-L1 agents provide durable responses in a subset (~10%), the magnitude of benefit with immunotherapy (IO) is similar, suggestive of therapeutic interchangeability. Real-world data (RWD) suggests durvalumab confers superior outcomes in ES-SCLC, compared to atezolizumab. Recently, durvalumab received regulatory approval for limited-stage SCLC, whereas atezolizumab failed to demonstrate benefit after chemoradiation. Here, we investigate whether IO choice impacts outcomes for first-line ES-SCLC. **Methods:** We retrospectively reviewed the charts of patients diagnosed with ES-SCLC in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by receipt of either atezolizumab or durvalumab for first-line chemoIO for comparison of demographics and outcomes. Kaplan-Meier, univariate Cox regression, and Fishers exact test was applied. **Results:** We identified 158 patients diagnosed with ES-SCLC who received chemoIO (Table 1). Platinum-sensitivity and objective response rates were similar between groups ($P = 0.14$ and $P > 0.9$, respectively). The median number of IO cycles received (induction and maintenance) was significant higher with atezolizumab (9), compared to durvalumab (7, $P < 0.001$). Similarly, median progression-free survival (PFS) trended in favor of atezolizumab over durvalumab (6.3 vs 5.2 months, $P = 0.08$). Subsequent therapy post-progression was comparable between groups, including lurbinectedin (31% vs 23%, $P = 0.5$) and tarlatamab (17% vs 23%, $P = 0.4$). The unadjusted median OS for atezolizumab was 16.5 months (95% CI, 13.2-19.5), compared to durvalumab 12.4 months (95% CI, 9.9-17.3) ($P = 0.11$). To account for group imbalances, overlap-weighted multivariable Cox regression was performed, in which ECOG performance status (PS) of 0-1 (HR 0.53, 95% CI, 0.30-0.92, $P = 0.03$) and receipt of atezolizumab (HR 0.56, 95% CI, 0.34-0.93, $P = 0.02$) were independently associated with improved OS. **Conclusions:** In our study, atezolizumab demonstrated improved OS and trended to improve PFS in first-line ES-SCLC, compared to durvalumab. Potential confounders when evaluating the impact of IO agents across RWD studies include ECOG PS, variable use of thoracic radiotherapy, geographical differences, and ethnic distributions. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	Atezolizumab (n = 127)	Durvalumab (n = 31)	Overall (n = 158)	*P* value
Age (Q1, Q3)	66 (61, 73)	68 (63, 73)	67 (61, 73)	>0.9
Sex (female)	79 (62%)	17 (55%)	96 (61%)	0.5
ECOG PS (0-1)	87 (74%)	20 (69%)	107 (73%)	0.6

Demographics and outcomes of individuals with young-onset small cell lung cancer.

Paresh Kumar, Anthony Alfonso, Brook Marie Lobsiger, Emmalee E. Kiser, Kanak Parmar, Weston He, Ahmad Karkash, Alejandra Cardona Perez, Ahmed Abuelgasim, Julian A. Marin-Acevedo, Mark Botros, Mya Tran, Anish Thomas, Misty Dawn Shields; Indiana University School of Medicine, Indianapolis, IN; National Institute of Health, Bethesda, MD; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University School of Medicine, Department of Internal Medicine, Indianapolis, IN; Indiana University Melvin and Simon Comprehensive Cancer Center, Indianapolis, IN; Indiana University Health North Hospital, Inc., Carmel, IN; IU Simon Comprehensive Cancer Center, Indianapolis, IN; National Cancer Institute, National Institutes of Health, Bethesda, MD; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: A diagnosis of lung cancer before the age of 50 is commonly driven by oncogenic alterations and observed in patients without a history of tobacco use. Little is known about the characteristics and outcomes of individuals with young-onset small cell lung cancer (YO-SCLC). **Methods:** We retrospectively reviewed the charts of patients diagnosed with SCLC treated in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by age <50 or >50 years at diagnosis of SCLC for statistical comparison of key variables and outcomes. Fisher's exact and Wilcoxon rank sum tests were applied to categorical and continuous variables, respectively. **Results:** Among 416 individuals with SCLC, we identified 23 patients with YO-SCLC. The incidence of YO-SCLC was 5.5 cases per 100 cases of SCLC (95% CI, 3.7-8.2) with a median age of 47 (40-49). None of the YO-SCLC were detected by lung cancer screening (LCS), compared to 17% in the >50 cohort (Table 1). Patients with YO-SCLC are more likely to have active tobacco use but significantly less pack years, compared to >50. Majority of YO-SCLC (74%) were diagnosed with extensive-stage SCLC, analogous to >50. Extensive-stage YO-SCLC patients had similar platinum-sensitivity and PFS with platinum-based therapy with or without immunotherapy but trended to have improved median OS (24.7 vs 11.1 months, HR 1.67, 95% CI 0.88-3.15, P = 0.12). Limited-stage YO-SCLC patients were more likely to receive prophylactic cranial irradiation (PCI, 67% vs 25%, P = 0.04) but demonstrated no significant difference in PFS or OS with guideline-directed therapy, compared to >50. **Conclusions:** YO-SCLC represents a unique under-recognized population with trends toward improved OS, despite comparable platinum-sensitivity and PFS with chemoimmunotherapy for ES-SCLC. Such patients are currently excluded from LCS due to age. These results suggest eligibility criteria for LCS could be expanded to include individuals <50 with active tobacco use (>20 PY) and a family history of lung cancer to increase detection of YO-SCLC. The molecular underpinnings of YO-SCLC remain to be elucidated. Investigation into the genomic and neuroendocrine subtype composition of YO-SCLC is underway. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	Age <50 (n = 23)	Age >50 (n = 393)	Overall (n = 416)	*P* value
Sex (female)	15 (65%)	231 (59%)	246 (59%)	0.7
Stage (ES-SCLC)	17 (74%)	257 (65%)	274 (66%)	0.5
BMI	33 (23, 38)	27 (23, 32)	27 (23, 32)	0.046
COPD	7 (30%)	207 (53%)	214 (51%)	0.052
Current tobacco use	20 (87%)	247 (63%)	267 (64%)	0.025
Pack years	30 (25, 50)	45 (30, 60)	45 (30, 60)	0.043
Eligible for lung cancer screening	0 (0%)	301 (77%)	301 (72%)	<0.001
Detected by lung cancer screening	0 (0%)	68 (17%)	68 (16%)	0.021
+FH lung cancer	9 (39%)	103 (26%)	112 (27%)	0.14

A multi-institutional, single-arm, phase 2 study of durvalumab plus amrubicin in patients with relapsed extensive-stage small cell lung cancer (Aphrodite trial).

Yuka Kato, Koichi Azuma, Kakuhiro Yamaguchi, Toshihide Yokoyama, Shoichi Kuyama, Kota Sakamoto, Hideki Uno, Michihiro Yoshida, Kadoaki Ohashi; Department of Thoracic oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama-City, Ehime, Japan; Kurume University School of Medicine, Kurume, Japan; Department of Respiratory Medicine, Hiroshima University Hospital, Hiroshima, Japan; Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan; Department of Respiratory Medicine, NHO Iwakuni Clinical Center, Iwakuni, Japan; Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan; Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan

Background: In patients (pts) with sensitive relapsed (SR) and refractory relapsed (RR) small cell lung cancer (SCLC), amrubicin (AMR) is one of the current standard treatments in Japan. However, the overall survival (OS) in RR is particularly poor, with approximately 6-9 months and a 1-year overall survival rate (1yr-OS rate) of 34%, which is not satisfactory. We conducted the phase 2 exploratory proof-of-concept trial based on preclinical results, which showed that the combination of an anti-PD-1 antibody and a topoisomerase II inhibitor had a synergistic effect on cancer cells. This trial was funded by AstraZeneca K.K. **Methods:** This trial enrolled pts with SR or RR SCLC that recurred after first-line chemo-immunotherapy. They were treated with durvalumab (1,500 mg on day1) and AMR (40 mg/m^2 on days1-3), every three weeks until progression. After assessing the safety of the combination therapy in the lead-in cohort, we initiated the phase 2 part of the trial. The primary endpoint was the 1yr-OS rate calculated based on a year consisting of 48 weeks. The secondary endpoints consisted of OS, progression-free survival (PFS), overall response rate (ORR) etc. The expected 1yr-OS rate for SR and RR were 61.1% and 44.4%, respectively, which were 10% higher than the systematic review result for AMR alone in Japanese pts. Based on this review result and considering feasibility, the sample size was planned as 18 pts for each SR and RR. **Results:** Between July 2022 and August 2024, a total of 23 (SR: 5; RR: 18) pts were enrolled. All pts had previously received treatment with platinum-containing drugs and immune checkpoint inhibitors (ICI). The SR group could not be enrolled till sufficient sample size for statistical analysis. The 1yr-OS rate was 80.0% for SR group, which included a complete responder. The efficacy results for the RR group were: The 1yr-OS rate was 44.4% (95% confidence interval (CI): 21.6-65.1). The median PFS and OS were 15.1 weeks (95% CI: 11.0-23.3) and 43.1 weeks (95% CI: 24.6-64.3), respectively. The ORR was 38.9% (95% CI: 17.3-64.3). Grade 3 or higher adverse events were observed in 65.2% of all 23 pts, but no new events beyond those previously reported were identified. The most frequent Grade 3 or higher adverse event was neutropenia (43.5%), with febrile neutropenia occurring in 13.0%. Grade 3 or higher pneumonia was observed in 4.3%, and no treatment-related deaths were reported. **Conclusions:** The combination therapy of durvalumab and AMR suggests favorable efficacy and tolerable safety, particularly in pts with RR, even in those who had already received ICI treatment. Clinical trial information: jRCT2061220036. Research Sponsor: AstraZeneca.

Safety, pharmacokinetic, and preliminary efficacy of SNC115 in patients with relapsed/refractory small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC): A phase 1 study.

Tianqing Chu, Jialin Qian, Chunlei Shi, Yu Dong, Zhiqiang Gao, Liwen Xiong, Yan Zhou, Jiajun Teng, Yanbin Kuang, Runbo Zhong, Hua Zhong, Yu Zhe, Jiuping Ju, Melody Xiong, Zupeng Xu, Limin Wen, Zhuoxiao Cao; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Respiratory and Critical Care Medicine, Shanghai Chest Hospital, Shanghai, China; Shanghai Simnova Biotech Co., Ltd., Shanghai, China

Background: SCLC and LCNEC are characterized by aggressive clinical courses and limited therapeutic options following progression on platinum-based chemotherapy. DLL3(Delta-like ligand 3) is highly expressed and selectively on the surface of these high-grade neuroendocrine tumors, making it an ideal therapeutic target. SNC115 is a novel CAR-T cell armored with CD70 to target DLL3-expressing cells. **Methods:** This phase 1, open-label study utilized an accelerated titration design followed by a standard 3+3 escalation to evaluate the safety, tolerability, and pharmacokinetics of SNC115 in patients (pts) with R/R SCLC or LCNEC who progressed after ≥1 line of standard therapy. Following leukapheresis and a 3-day lymphodepletion regimen (fludarabine/cyclophosphamide), pts received a single infusion of SNC115 at one of five planned dose levels (DL): 1.0×10^5 (DL1), 3.0×10^5 (DL2), 1.0×10^6 (DL3), 3.0×10^6 (DL4), and 6.0×10^6 (DL5) CAR^+ T cells/kg. The primary endpoints were the determination of the maximum tolerated dose (MTD) and the recommended dose (RD). **Results:** As of 23 January 2026, 8 pts with R/R SCLC were treated across four DLs: DL1 (n = 1), DL2 (n = 3), DL3 (n = 2) and DL4 (n = 2). Median age was 53.5 (range 40-69) years, with a median of three prior therapy lines (range 2-6). 6 pts received bridging therapy. SNC115 demonstrated a manageable safety profile. CRS occurred in 3 pts (DL1: 1pt, DL4: 2pts), all Grade 1 or 2 and resolved with tocilizumab/corticosteroids. Grade ≥3 hematologic TEAEs included lymphocyte count decreased (8/8), white blood cell count decreased (2/8) and anaemia (1/8), all attributed to LD. Only one patient (DL4) experienced Grade ≥3 non-hematologic TEAEs related to SNC115, including alanine aminotransferase increased (G3), Gamma-glutamyltransferase increased (G3) and diarrhea (G3), which resolved with symptomatic care. No DLTs, SAEs or ICANS were reported. Among evaluable pts (n = 8), the ORR and DCR were 37.5% and 75%, respectively. All patients (n = 2) in the higher-dose level (DL4) achieved PR. CAR-T cells expansion peaked at a median of 7 days post-infusion, with Cmax ranging from 68.77 to 4359.89 copies/μg DNA. **Conclusions:** SNC115 demonstrated a manageable safety profile and encouraging preliminary antitumor activity in heavily pretreated pts with SCLC. The absence of DLTs and ICANS, combined with low-grade transient CRS, supports continued dose escalation. These early efficacy signals suggest that SNC115 may provide a novel therapeutic avenue for R/R SCLC. Clinical trial information: NCT06384482. Research Sponsor: Shanghai Simnova Biotechnology Co.,Ltd.

Prognostic factors and impact of concomitant medication in extensive-stage small cell lung cancer (ES-SCLC) treated with first-line chemotherapy plus anti-PD-L1: A Spanish multicenter real-world study.

Mikel Portu, Judit Sanz-Beltran, Andrés Pellicer, Blanca Navarro, Alberto Romero Monleon, Patricia Capdevila, Fernando Leopoldo Tallafigo, Teresa Moran, Silvia Catot, Sergio Peralta Munoz, Edurne Arriola, Alfredo Sanchez, Karla Osorio, Amelia Muñoz, Dolores Isla, Beatriz Guarner, Aida Piedra, Sergio Martínez Recio, Andrés Barba, Margarita Majem; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hospital del Mar, Barcelona, Spain; Hospital Provincial de Castellón, Castellón, Spain; Hospital Universitario Lozano Blesa / IIS Aragón, Zaragoza, Spain; Hospital Universitari i Politècnic La Fe, Valencia, Spain; Hospital Universitario Jerez de la Frontera, Jerez De La Frontera, Spain; Hospital Universitari Germans Trias i Pujol / ICO Badalona, Badalona, Spain; Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain; Hospital Universitari Sant Joan de Reus / IOCS, Reus, Spain; Consorcio Hospitalario Provincial de Castellón, Castellon De La Plana, Spain; Hospital Universitario Jerez de la Frontera, Cádiz, Spain

Background: Platinum - etoposide with PD-L1 inhibitors is the standard first-line treatment for ES-SCLC. However, real-world outcome data remain limited, particularly regarding the prognostic impact of frequently used concomitant medications. **Methods:** Retrospective multicenter cohort (9 Spanish centers; Oct 2019 - Apr 2025) of ES-SCLC treated with first-line platinum - etoposide plus anti-PD-L1. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan - Meier. Proton pump inhibitor (PPI), corticosteroid*, and antibiotic use within 30 days before treatment initiation were recorded. Multivariable Cox models were adjusted for Eastern Cooperative Oncology Group performance status (ECOG PS), liver/bone/central nervous system (CNS) metastases (mets), and medications. The immune-related adverse event (irAE) - OS association was explored using time-fixed and 12-week landmark analyses. **Results:** A total of 442 patients were included (median age 66, 67% male, 90% ECOG PS 0–1); PD-L1 inhibitor: atezolizumab 97%, durvalumab 3%, pembrolizumab <1%. Liver, bone, and CNS mets were present in 40%, 34%, and 27%. PPIs, corticosteroids, and antibiotics were used in 51%, 33%, and 26%. Most (77%) completed induction (4 cycles); 79% initiated maintenance (6% after <4 cycles). ORR was 80% and DCR 90% (n=404 evaluable; routine assessment). With median follow-up of 27.2 months (reverse Kaplan - Meier), median PFS was 5.6 months (95% CI 5.3 - 6.1) and median OS 10.2 months (95% CI 8.4 - 11.3); 12-month OS 43%. On multivariable analysis (complete-case n=415; Table), ECOG PS ≥2 and liver/bone/CNS mets were associated with worse OS, while PPIs, corticosteroids, and antibiotics were not. irAEs occurred in 24%; time-fixed analysis suggested improved OS (adjusted HR 0.61; 95% CI 0.45 - 0.81; p<0.001), but this was not confirmed in 12-week landmark analysis (HR 0.84; 95% CI 0.55 - 1.29; p=0.43). **Conclusions:** In this large real-world ES-SCLC cohort treated with first-line chemoimmunotherapy, ECOG PS and metastatic burden remained key prognostic factors. Concomitant PPIs, corticosteroids, and antibiotics were not independently associated with OS, although residual confounding by indication cannot be excluded. The irAE - OS association was not confirmed by landmark analysis, highlighting the importance of time-dependent methods.
Research Sponsor: None.

Multivariable Cox regression for OS (n=415).

Variable	HR (95% CI)	p-value
ECOG PS ≥2 vs 0-1	1.47 (1.02–2.12)	0.039
Liver mets	1.53 (1.22–1.94)	<0.001
Bone mets	1.52 (1.19–1.93)	<0.001
CNS mets	1.41 (1.10–1.81)	0.006
PPI (≤30d)	1.13 (0.89–1.44)	0.311
Corticosteroids (≤30d)*	1.03 (0.79–1.33)	0.842
Antibiotics (≤30d)	1.18 (0.89–1.55)	0.245

*Non-prophylactic systemic corticosteroids (≥10 mg/day prednisone-equivalent).

Tarlatamab in small cell lung cancer with brain metastases: A real-world experience.

Santiago Sucre, Chinmay Jani, Dan Morgenstern, Nelsy Zuniga, Rakhi Modak, Kyle Edwards, Brandon Edward Rose, Subul Malik, Kyle Rowley, Asad Rauf, Gilberto Lopes, Estelamari Rodriguez, Aman Chauhan; Jackson Memorial Hospital, University of Miami, Miami, FL; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; University of Miami Miller School of Medicine, Miami, FL; Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; Department of Internal Medicine, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL

Background: Tarlatamab, a DLL3-directed bispecific T-cell engager, has demonstrated survival benefit in previously treated small cell lung cancer (SCLC) in pivotal clinical trials. However, real-world evidence remains limited, particularly in ethnically diverse populations and in patients with a high burden of central nervous system (CNS) disease who are often underrepresented in clinical trials. We evaluated the safety, radiographic response, and treatment durability of tarlatamab in a real-world cohort treated at a single academic center. **Methods:** We retrospectively reviewed patients with extensive-stage SCLC treated with tarlatamab at Sylvester Comprehensive Cancer Center between January 2024 and October 31, 2025. Demographic, clinical, radiographic, and toxicity data were abstracted from medical records. Radiographic response was assessed per RECIST criteria, with best overall and 6-month responses recorded. Objective Response Rate (ORR) and Disease Control Rate (DCR) were calculated. Progression-free survival (PFS) and Overall Survival (OS) were estimated using Kaplan–Meier methods with multivariable analyses performed using Cox regression. **Results:** Among 23 patients (median age 72 years), male sex, Hispanic ethnicity, and brain metastases were each present in 61% of the cohort at tarlatamab initiation. 43% had received ≥2 prior lines of therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANs) occurred predominantly during cycle 1 and were limited to grade 1 or 2 events, with no grade ≥ 3 toxicities observed. Median time on treatment was 92 days, with a median of 4 cycles. Three patients required treatment discontinuation due to toxicities. Radiographic response was evaluable in 18 patients; five were not evaluable due to early death after cycle 1 day 1 (n=2), loss to follow-up (n=2), and transition to hospice after first cycle (n=1). In those 18 patients, best overall response included partial response in 5 patients (27.7%) and stable disease in 3 patients (16.7%), yielding an ORR of 27.7 % and a DCR of 44.4%. Median PFS was 139 days, and median OS was 323 days (95 % CI, 31 to 614). No variables were independently associated with outcomes on multivariable Cox proportional regression analysis. **Conclusions:** In a predominantly Hispanic, heavily pretreated real-world SCLC population with a high prevalence of brain metastases, tarlatamab demonstrated feasible administration, manageable immune-mediated toxicity, and clinically meaningful antitumor activity. These findings support the effectiveness of tarlatamab beyond clinical trial populations and highlight the importance of real-world evidence in informing care for underrepresented patients. Research Sponsor: None.

Best Overall Response	N (%)
Complete Response	0 (0)
Partial Response	5 (27.7)
Stable Disease	3 (16.7)
Progression of Disease	10 (55.5)
ORR	5 (27.7)
DCR	8 (44.4)

8109 Poster Session

Updated results of the randomized phase 2 dose optimization study of alveltamig (ZG006), a trispecific T cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with advanced small cell lung cancer.

Xinghao Ai, Yan Yu, Tongmei Zhang, Tienan Yi, Mingjun Li, Wenxiu Yao, Liang Han, Longhua Sun, Anwen Liu, Qi Mei, Guang Han, Zhen Zhang, Yinyin Li, Lu Li, Li Zheng, Yong Fang, Yongzhong Luo, Binhua Lv, Andrew X. Zhu, Shun Lu; Shanghai Chest Hospital, Shanghai, China; Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China; Beijing Chest Hospital Capital Medical University, Beijing, China; Oncology Department, Xiangyang Central Hospital, Xiangyang, China; Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Medical Oncology, University of Electronic Science and Technology of China, Sichuan Cancer Hospital and Institute & Cancer, The Second People's Hospital of Sichuan Province, Chengdu, China; Xuzhou Central Hospital, Xuzhou, China; The First Affiliated Hospital of Nanchang University, Nanchang, China; Oncology Department, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; Shanxi Bethune Hospital, Taiyuan, China; Department of Radiation Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Nanyang First People's Hospital, Nanyang, China; Department of Oncology, Shenyang Chest Hospital, Shenyang, China; West China Hospital of Sichuan University, Chengdu, China; Clinical Trial Center, West China Hospital, Sichuan University, Chengdu, China; Medical Oncology, Sir Run Run Shaw Hospital School of Medicine, Zhejiang University, Hangzhou, China; Thoracic Medicine Department I, Hunan Cancer Hospital, Changsha, China; Zelgen, Shanghai, China; Shanghai Chest Hospital, Shanghai, Jiao Tong University, School of Medicine, Shanghai, China

Background: Alveltamig (ZG006) is a trispecific T cell engager (Tri-TE) targeting Delta-like ligand 3 (DLL3) and CD3, designed to bridge tumor cells and T cells by binding to two distinct DLL3 epitopes on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC). **Methods:** This is a multicenter, randomized, open-label, phase 2 dose-optimization study. Patients with SCLC who have failed at least two prior lines of standard therapy are randomized 1:1 to receive ZG006 at either 10 mg or 30 mg Q2W (both with a 1 mg priming dose). Based on the prior data from dose optimization in this study with an objective response rate (ORR) at 53.3% and median progression-free survival (PFS) at 7.03 months in the 10 mg group, 10 mg Q2W was selected as the recommended dose schedule for ongoing pivotal studies in advanced SCLC. Here we present the updated efficacy data with longer follow up and key subgroup analyses from this study. **Results:** This analysis included 60 treated patients (30 each from 10 and 30 mg group). With a median follow-up of about 13.5 months, the median duration of response (DoR) was not mature with 9-month DoR rates reaching 61.6% and 58.4% for 10 mg and 30 mg respectively. Likewise, the median OS for both groups was not reached, however, 12-month OS rates for two groups have approached 65.9% and 59.2% respectively. Based on the IRC data as of Sept 30, 2025, for the 10 mg and 30 mg groups, patients with previously treated and stable brain metastases at baseline achieved a confirmed ORR of 50.0% (4/8) and 44.4% (4/9), respectively, while patients without baseline brain metastases had an ORR of 54.5% (12/22) and 61.9% (13/21). Patients presented with baseline liver metastases achieved an ORR of 58.3% (7/12) and 46.2% (6/13), compared with 50.0% (9/18) and 64.7% (11/17) in patients without liver metastases. While 27 patients in 10 mg and 24 patients in 30 mg had previously received immune checkpoint inhibitors, a notable ORR of 55.6% (15/27) and 58.3% (14/24) was observed. Among patients with exactly two prior lines of systemic therapy, the ORRs were 50.0% (8/16) and 64.7% (11/17), whereas those who had received three or more prior lines demonstrated an ORR of 57.1% (8/14) and 46.2% (6/13) in 10 and 30 mg groups. **Conclusions:** With longer follow up, both ZG006 10 mg Q2W and 30 mg Q2W continued to demonstrate robust antitumor activity with a trend of longer DoR and OS in patients with relapsed or refractory SCLC. Subgroup analyses demonstrated consistent antitumor activity across key prognostic subgroups including those with baseline treated brain metastases, those with baseline liver metastases, and those who received multiple lines of prior systemic treatment. These results also support further development of ZG006 in SCLC with ongoing pivotal studies. Clinical trial information: NCT06283719. Research Sponsor: None.

Evaluation of survival after chemo-immunotherapy in veterans with extensive-stage small cell lung cancer and brain metastases.

Jason Cham, Eunyoung Yang, Jiheum Park, Yeun-Hee Anna Park, Antonio Tito Fojo, Keith Magnus Sigel, Susan Elaine Bates; Division of Hematology Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, NY; James J. Peters Department of Veterans Affairs Medical Center, New York, NY; Department of Medicine, Columbia University Irving Medical Center, New York City, NY; James J. Peters Department of Veterans Affairs Medical Center, Bronx, NY; Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive malignancy with rapid progression and poor long-term survival. For decades, platinum–etoposide chemotherapy has produced high initial response rates, but relapse is nearly universal. The addition of atezolizumab or durvalumab to first-line chemotherapy is now standard of care based on improved survival in the IMpower133 and CASPIAN trials, with reported OS 12.3 and 13 months, respectively. However, these pivotal trials enrolled highly selected populations and largely excluded patients with active brain metastases, limiting generalizability. Veterans are particularly underrepresented in clinical trials due to comorbidities and performance status, leaving the real-world effectiveness of chemo-immunotherapy and immune biomarkers in this population poorly defined. **Methods:** We conducted a retrospective cohort study of Veterans with ES-SCLC treated with first-line chemotherapy alone or chemo-immunotherapy within the Veterans Affairs (VA) health system. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models in propensity-matched cohorts. Prespecified subgroup analyses evaluated whether treatment effects differed by brain metastasis status. Exploratory analyses also assessed the prognostic association between baseline absolute neutrophil-to-lymphocyte ratio (ANC/ALC) and survival. **Results:** In the matched overall cohort (n = 1,250), chemo-immunotherapy significantly improved OS compared with chemotherapy alone (median OS 8.88 vs 7.44 months; HR 0.75, $p < 0.0001$). Among patients who received chemo-immunotherapy (n = 625), 87.0% were treated with atezolizumab and 9.6% with durvalumab. For patients with brain metastases at diagnosis (n = 312), chemo-immunotherapy significantly improved survival (median OS 8.76 vs 5.52 months; HR 0.57, $p < 0.0001$). An elevated pre-treatment absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) ratio > 2.5 was independently associated with worse survival in both chemo-immunotherapy (HR 1.35, p = 0.013) and chemotherapy-only (HR 1.47, p = 0.0004) groups. **Conclusions:** This study represents the largest real-world cohort of Veterans with ES-SCLC and demonstrates a significant overall survival benefit with chemo-immunotherapy. The benefit was particularly pronounced among patients with brain metastases, a group historically underrepresented in clinical trials. Elevated ANC/ALC was identified as a potential prognostic biomarker associated with poor outcomes regardless of treatment. Notably, overall survival in our Veteran cohort remained substantially lower than in registrational trials, highlighting the urgent need for future studies with broader eligibility criteria that better reflect real-world populations. Research Sponsor: None.

8111 Poster Session

An innovative team approach to improve SCLC care across an integrated health system.

Melinda Laine Hsu, Fangzhou Liu, Carley Mitchell, Annie Zhang, Jeffrey Yinhong Zhong, Peronne Joseph, Ravi Kumar Kyasaram, Afshin Dowlati; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH; University Hospitals Seidman Cancer Center, Cancer Informatics, Cleveland, OH

Background: Small cell lung cancer (SCLC) is a highly aggressive cancer, with improved overall survival due to recent advancements in therapy. However, as many as 40% of patients (pts) may not receive guideline-concordant care for SCLC due to barriers including delays in diagnosis and referrals to oncology. We developed and implemented an electronic medical record (EMR) alert system based on ICD codes for early identification of pts with suspected SCLC and early intervention by thoracic medical oncology at University Hospitals Seidman Cancer Center. We hypothesized our intervention would increase rates of guideline concordant care and ultimately improve pt outcomes, compared to historical control. **Methods:** An informatics approach was used to identify pts with possible SCLC from 5/5/2024-5/17/2025 by incorporating Structure Query Language, Server Reporting Services, and text search of the EMR and pathology systems. Daily reports were reviewed by the thoracic medical oncology team, who intervened when needed to ensure appropriate staging and referrals. Clinicodemographic data was collected of pts with confirmed SCLC compared to a historical control of patients diagnosed between 2/5/2019-11/29/2021. Chi-square tests assessed statistical differences between the groups, and Kaplan-Meier (KM) survival analysis estimated overall survival (OS) and progression free survival (PFS). **Results:** 101 pts with SCLC were identified in the current group (C), and 130 pts in the historical group (H). Age, sex, smoking history, and baseline ECOG status, were similar between groups. A numerically higher percentage of pts in C were diagnosed with limited-stage SCLC (38.6%) compared to H (27.7%), p = 0.106). A numerically higher number of pts in C received guideline-concordant baseline imaging (93.1%) compared to H (83.8%, p = 0.05). Among pts who received treatment (tx), median time to tx was longer in C (19 days, interquartile range [IQR] 9-31) than H (13 days, IQR 5-22, p = 0.001). Pts in C were significantly more likely to receive 1st-line guideline-concordant tx than H (94.0% vs 83.3%, p = 0.02), although similar likelihood of enrolling in hospice before any therapy (12.9% vs. 11.5%, p = 0.917). Pts in C with progression were numerically more likely to receive 2^{nd}-line and 3^{rd}-line tx than H (61.3% vs. 57.1%; 78% vs. 53.1%, respectively). Pts in C had statistically significantly improved PFS compared to H (p = 0.008). **Conclusions:** Successful creation of an EMR alert system to identify SCLC significantly increased rates of guideline-concordant tx of SCLC. Although not statistically significant, pts were also more likely to receive guideline-concordant imaging and treatment in the 2^{nd} and 3^{rd} line settings compared to historical control. Research Sponsor: The study is supported by the National Comprehensive Cancer Network (NCCN) through a grant provided by AstraZeneca. Neither NCCN nor AstraZeneca are the sponsor.

Predictive role of immune cell subsets and intestinal flora in immune-related adverse event of small cell lung cancer.

Mei-xi Lin, Man Sun, Dan Zang, Jun Chen; The Second Hospital of Dalian Medical University, Dalian, Liaoning, China; The Second Hospital of Dalian Medical University, Dalian City, Liaoning, China; The Second Affiliated Hospital of Dalian Medical University, Dalian City, Liaoning, China

Background: While immune checkpoint inhibitors (ICIs) have reshaped the therapeutic landscape for extensive-stage small-cell lung cancer (ES-SCLC), they are frequently associated with immune-related adverse events (irAEs) that may lead to treatment disruption. Early prediction of irAEs remains challenging due to their atypical clinical manifestations. This study aimed to identify risk factors and predictive biomarkers for irAEs in ES-SCLC patients undergoing ICIs therapy. **Methods:** 88 patients with ES-SCLC who received ICIs treatment between May 2021 and September 2023 were enrolled. Fecal samples were collected at baseline and before each treatment cycle until therapy discontinuation. The metagenomic and untargeted metabolomic analyses were performed on the fecal samples. Peripheral blood samples were collected from patients for flow cytometry analysis. Tumor response was assessed in accordance with RECIST 1.1 criteria, and irAEs were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Results:** Among 88 patients, 41 developed irAEs (median onset: 118 days), with the most common manifestations being pneumonia (41.5%) and hepatitis (22.0%). Patients who developed irAEs exhibited distinct peripheral immune profiles. Compared to their own baseline levels, these patients exhibited decreased peripheral B-cell counts alongside elevated percentages of activated $CD4^+$ and $CD8^+$ T cells, including early-activated $CD8^+$ T cells ($CD3^+CD8^+CD69^+$ T cells), late-activated helper T cells ($CD3^+CD4^+CD38^+$ T cells), and Th2 cells. Furthermore, at baseline, the irAE group demonstrated a significantly higher percentage of PD-1 in $CD8^+$ T cells compared to the non-irAE group. Metabolomic analyses revealed distinct baseline metabolic profiles between the two groups, *Micrococcus* was significantly enriched at baseline in the irAE group, whereas *Phocaeicola coprocola* and *Oscillibacter* were more abundant in patients without irAEs, and calcitriol was identified as a potential predictive biomarker for irAEs. Following irAE onset, significant enrichment of *Selenomonadaceae*, *Ruminococcus*, *Actinobacteria*, and *Erysipelatoclostridium* was observed, along with significant shifts in metabolites and related metabolic pathways. **Conclusions:** In ES-SCLC patients treated with ICIs, the development of irAEs is associated with distinct alterations in peripheral immune cell subsets, as well as gut microbial and metabolic profiles at baseline. Monitoring these features, particularly PD-1 expression on CD8+ T cells and calcitriol levels, may help predict the risk of irAEs. Dynamic changes in the gut microbiome and metabolome after ICIs initiation further aid in the early recognition of irAEs. Research Sponsor: National Natural Science Foundation of China; 82203056.

Real-world challenges in the adoption of emerging therapies for extensive-stage small cell lung cancer in community settings.

Jacob Sands, Christine L. Hann, Chelsie Anderson, Christina A. Bachmeier, Samuel Dooyema, Jeffrey D. Carter, Cherilyn Heggen Ladda, Kelly E. McKinnon; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; PRIME Education, New York, NY

Background: Despite advances in the treatment of extensive-stage small cell lung cancer (ES-SCLC), outcomes remain poor, and uptake of novel therapies in community oncology settings is inconsistent. As the ES-SCLC treatment landscape rapidly evolves, understanding real-world knowledge gaps, operational barriers, and challenges in patient-centered care is critical to improving evidence-based practice. This study evaluated community oncologists' confidence, practice patterns, and perceived barriers to integrating novel and emerging ES-SCLC therapies. **Methods:** From September–October 2025, 100 US community oncologists completed surveys assessing treatment selection, shared decision-making, adverse event (AE) management, clinical trial referral practices, and system-level barriers to care delivery for patients with SCLC. **Results:** Knowledge and training gaps were the most frequently cited challenges to incorporating novel therapies (55%), followed by electronic medical record workflow limitations (41%) and patient selection complexity (33%). While most oncologists reported a basic understanding of novel antibody-drug conjugates (72%), few actively followed emerging clinical data (19%). Delays in initiating first-line therapy were commonly attributed to unfamiliarity with available treatments or need for academic referral (56%), prolonged staging evaluations (53%), and limited infusion center capacity (39%). AE management represented a major unmet need: 90% reported difficulty educating patients and caregivers on early AE recognition, and 62% reported challenges distinguishing disease progression from treatment-related toxicity. These gaps directly affected patient-centered care, with barriers to shared decision-making including limited clinician knowledge of treatment options (80%) and difficulty tailoring communication to patient preferences (66%). Accordingly, improved AE management was identified as the single greatest opportunity to enhance quality of care (51%). Although most oncologists reported referring patients for clinical trial evaluation after progression most or all of the time (85%; 4-5 on 5-point Likert scale), enrollment was hindered by patient preferences (63%), limited infrastructure to identify and enroll eligible patients (51%), and poor performance status (40%). **Conclusions:** Community oncologists face significant knowledge and operational barriers to integrating novel therapies for ES-SCLC, particularly related to emerging mechanisms of action, AE recognition and management, patient communication, and clinical trial enrollment. Targeted educational and practice-based interventions are needed to support timely, patient-centered, and evidence-based care in the community setting. Research Sponsor: Daiichi Sankyo; Merck Sharp & Dohme LLC; Genentech.

Phenotypic heterogeneity in primary tumors and brain metastases of small cell lung cancer: Insights into tumor microenvironment and metastatic behavior.

Alan Amaral Oliveira, Saulo Brito Silva, Andrea Jazel Rodriguez-Herrera, Alexandre Todorovic Fabro; Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil; Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

Background: Small cell lung cancer (SCLC) is an aggressive malignancy with frequent brain metastases and pronounced phenotypic plasticity. How the tumor microenvironment and phenotypic heterogeneity relate to brain metastases remains poorly understood. **Methods:** We conducted a retrospective study of 124 patients with pathologically confirmed SCLC treated at a tertiary cancer center. In primary tumors, pathological features—including tumor-infiltrating lymphocytes (TILs), morphological patterns (necrosis, hyalinization, desmoplasia), and immunohistochemical characterization of lineage-associated SCLC markers—were assessed on H&E-stained sections. Immune-desert tumors were defined as having no detectable lymphocytic infiltration. Associations between these pathological features and baseline brain metastases were evaluated using appropriate statistical tests for categorical and continuous variables, with available brain metastasis samples also analyzed histopathologically and immunohistochemically to assess spatial heterogeneity and microenvironmental plasticity. **Results:** Among 124 patients, TIL levels were lower in those with baseline brain metastases than without (1.46% ± 4.54 vs 3.04% ± 5.29; p = 0.049), and the immune-desert phenotype was more frequent (88% vs 65%; p = 0.041), indicating a cold tumor microenvironment in patients with brain metastases. Immunohistochemical and morphological patterns were similar regardless of baseline brain metastases. Histopathological evaluation of the two available brain metastases showed marked intralesional heterogeneity. Regions had inflammatory infiltrates, coagulative necrosis, or stromal hyalinization. Tumor cells showed a spiculated growth pattern along the GFAP-positive astrocytic network, suggesting interaction with astrocytes. Synaptophysin expression was higher adjacent to lymphocytes, NEUROD1 predominant near necrotic zones, and POU2F3 higher in hyalinized regions. These findings indicate regional activation of different SCLC transcriptional programs, reflecting microenvironmental plasticity. **Conclusions:** An immune-desert phenotype in primary SCLC tumors is associated with baseline brain metastases, which exhibit pronounced spatial heterogeneity and region-specific tumor programs. These findings suggest that the immune context of the primary tumor may influence microenvironmental plasticity and contribute to brain metastasis development, warranting validation in larger cohorts. Research Sponsor: without funding sources.

8115 Poster Session

Does treatment delay matter?: Impact of time to immunotherapy on survival in extensive-stage small cell lung cancer.

Anand Shah, Pranav Gwalani, Christopher C. Chen, Safia Ansari, Victor Tsu-Shih Chang; Rutgers New Jersey Medical School, Newark, NJ; Icahn School of Medicine at Mount Sinai, New York, NY; Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ; VA New Jersey Health Care System, East Orange, NJ

Background: Immune checkpoint inhibitors (ICI) combined with platinum-etoposide chemotherapy are the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC) based on the CASPIAN and IMpower133 trials. Given the aggressive nature of ES-SCLC, timely initiation of systemic therapy is critical; however, delays in treatment initiation are common in real-world practice. The impact of time to immunotherapy initiation (TTI) on survival has not been well characterized. **Methods:** Adult patients diagnosed with EO-SCLC (2019-2021) who received immunotherapy as part of first-line systemic therapy were identified from NCDB. TTI was defined as the time from diagnosis to first immunotherapy and categorized as ≤30, 31–60, or > 60 days. Association between TTI and OS was analysed using multivariable Cox proportional hazards models adjusting for patient and facility-level factors. A 90-day landmark analysis were performed to mitigate immortal time bias. Multivariable logistic regression was used to identify predictors of delayed initiation (> 30 days). **Results:** A total of 18,630 patients were identified. 2,652 (14.24%) died during follow-up. Median TTI was 29 days (IQR 18–45), with median follow-up of 9.36 months. In multivariable Cox models, TTI was not independently associated with OS (31–60 vs ≤30 days: HR 0.92 [0.84–1.00]; > 60 vs ≤30 days: HR 1.00 [0.89–1.11]). Results were consistent in a 90-day landmark analysis. Increasing age was associated with higher mortality (HR 1.01 per year, p = 0.003). Treatment at academic/research programs was associated with better OS (HR 0.71 [0.61–0.82]), while Medicaid insurance was associated with worse OS (HR 1.31 [1.15–1.49]). Black patients were more likely to receive delayed treatment (OR 1.31 [1.16–1.48]) while Asian patients were less likely (OR 0.74 [0.55–0.98]), when compared with Non-Hispanic White patients. Medicaid (OR 1.36 [1.20–1.53]) and Medicare insurance (OR 1.10 [1.01–1.21]) were associated with increased odds of delay versus private insurance. Higher comorbidity burden (Charlson–Deyo score ≥2 vs 0: OR 1.10 [1.02–1.19]) and treatment at academic centers (OR 1.33 [1.17–1.51]) were also associated with delay. Higher neighborhood income was protective (highest vs lowest quartile: OR 0.86 [0.77–0.95]). **Conclusions:** In a large national cohort of ES-SCLC patients receiving immunotherapy, modest delays in treatment initiation were not associated with OS. However, significant disparities exist in timely access, highlighting opportunities for system-level interventions to improve equity in cancer care delivery. Research Sponsor: None.

Efficacy and safety of second or further line KC1036 in patients with thymoma and thymic carcinoma: A multicenter, single-arm phase II trial.

Wentao Fang, Yongsheng Wang, Zhitao Gu, Tongmei Zhang, Gaofeng Li, Zhiyong He; Shanghai East Hospital, Tongji University, Shanghai, China; West China Hospital, Sichuan University, Chengdu City, China; School of Medicine, Shanghai Jiao Tong University, Shanghai Chest Hospital, Shanghai, China; Beijing Chest Hospital, Capital Medical University and Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China; Yunnan Cancer Hospital, Kunming, China; Fujian Cancer Hospital, Fuzhou, China

Background: Patients with advanced or recurrent thymoma or thymic carcinoma (T/TC) progressing after platinum-based chemotherapy have an unmet therapeutic need. This report assessed the clinical efficacy and safety of KC1036, a novel multi-kinase inhibitor of AXL, VEGFR2, and FLT3, in the treatment of T/TC. **Methods:** This open-label, multicenter, single-arm, phase II study enrolled patients with advanced or recurrent T/TC who had progressed on at least one prior line of chemotherapy. Eligible participants were required to have measurable disease according to RECIST v1.1 and an ECOG performance status of 0 or 1. KC1036 was administered orally at 60 mg QD, every 21 days as a cycle, until disease progression, death or intolerable toxicities. The primary endpoint was investigator-assessed objective response rate (ORR). **Results:** Between February 23, 2023 and January 4, 2024, 6 thymoma (T) and 25 thymic carcinoma (TC) patients were enrolled; all had distant metastases. Median age was 47.5 years (range, 34-71) for T and 57.0 years (37-73) for TC. Most patients had an ECOG PS of 1 (T: 100%; TC: 88.0%). While all T patients received one prior line of therapy, 48.0% of TC patients had received ≥2 prior lines. At the data cutoff of June 9, 2025, with a median follow-up of 19.3 months (95% CI, 13.4-NR), the T cohort achieved 100% SD with a median PFS of 13.6 months (95% CI, 4.1-NR). The TC cohort showed an ORR of 20.0% (n=5, PR) and a DCR of 80.0% (n=15, SD), with a median PFS of 8.2 months (95% CI: 4.1-15.1) and a median DOR of 15.3 months (95% CI: 1.5-NR). Median OS was not reached in either cohort; and the 18-month OS rates were 100% and 75.5% in the T and TC cohorts, respectively. The median duration of treatment exposure was 7.1 months. Treatment-related adverse events (TRAEs) were predominantly Grade 1 or 2. Grade 3 TRAEs occurring in ≥5% of subjects were hypertension (4 [12.9%]) and diarrhea (3 [9.7%]). No Grade 4 or 5 TRAEs were reported. TRAEs leading to dose reduction and treatment discontinuation occurred in 41.9% and 3.2% of patients, respectively. **Conclusions:** KC1036 demonstrated promising antitumor efficacy in patients with advanced or recurrent T/TC. Additionally, KC1036 exhibited a favorable safety profile and tolerability. These encouraging outcomes support further evaluation of KC1036 in a forthcoming phase III trial. Clinical trial information: NCT05683886. Research Sponsor: Beijing Konruns Pharmaceutical Co., Ltd.

Platinum rechallenge versus non-platinum regimens as second-line treatment for advanced thymoma: Analysis of the largest retrospective cohort to date.

Go Saito, Ryo Ko, Koichiro Nozaki, Ryo Koyama, Yutaka Yamada, Mitsuhiro Kamimura, Kenichiro Ito, Ryo Morita, Shiozawa Toshihiro, Kageaki Watanabe, Naruo Yoshimura, Takao Miyabayashi, Shinichiro Iwakami, Kento Kono, Hiroyuki Minemura, Ichiro Nakachi, Rie Sakakibara, Makoto Maemondo, Kunihiko Kobayashi, Takehito Shukuya; Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Department of Respiratory Medicine, Juntendo University Nerima Hospital, Tokyo, Japan; Division of Respiratory Medicine, Ibaraki Prefectural Central Hospital and Regional Cancer Center, Kasama, Japan; Department of Respiratory Medicine, National Hospital Organization Disaster Medical Center, Tokyo, Japan; Department of Respiratory Medicine, KKR Sapporo Medical Center, Sapporo, Japan; Department of Respiratory Medicine, Akita Kousei Medical Center, Akita, Japan; Division of Respiratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; Department of Respiratory Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan; Department of Respiratory Medicine, Niigata City General Hospital, Niigata, Japan; Juntendo University Shizuoka Hospital, Shizuoka, Japan; Department of Internal Medicine, Division of Medical Oncology and Respiratory Medicine, Shimane University Faculty of Medicine, Izumo, Japan; Department of Pulmonary Medicine, Fukushima Medical University School of Medicine, Fukushima, Japan; Pulmonary Division, Department of Internal Medicine, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan; Department of Respiratory Medicine, Institute of Science Tokyo, Tokyo, Japan; Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Shimotsuke-Shi, Japan; Department of Respiratory Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

Background: Although guidelines list platinum-based combination chemotherapy (Pt-rechallenge) as a second-line strategy for patients with thymoma ineligible for curative-intent therapy, evidence is limited to small case series. We investigated the efficacy of Pt-rechallenge versus non-platinum regimens in the largest retrospective cohort of second-line thymoma treatment reported to date. **Methods:** This multicenter study analyzed patients treated at 39 Japanese institutions. Of 157 patients ineligible for curative-intent therapy who initiated palliative platinum-based chemotherapy (2000–2020), 91 patients receiving second-line systemic cytotoxic chemotherapy were evaluated. Efficacy outcomes, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), were compared between second-line Pt-containing (Pt-rechallenge) and non-platinum (non-Pt) regimens. **Results:** Among the 91 patients (median age 59; 91% ECOG PS 0-1) with a median follow-up of 1056 days, 64 (70%) received Pt-rechallenge and 27 received non-Pt regimens (S-1 [tegafur/gimeracil/oteracil], n=15; pemetrexed, n=6; amrubicin, n=5; paclitaxel, n=1). First-line ORR was 51%, and the median chemotherapy-free interval from first-line chemotherapy was 394 days. Pt-rechallenge achieved a significantly higher ORR than non-Pt chemotherapy (40% vs 5%; p=0.0012). Regarding survival outcomes, median PFS was 8.8 months (95% CI, 5.9–11.9) in the Pt-rechallenge group vs 8.0 months (95% CI, 4.8–30.4) in the non-Pt group (HR, 1.29; 95% CI, 0.77–2.18; p=0.325). Median OS was 70.6 months (95% CI, 53.5–82.4) vs 64.4 months (95% CI, 38.7–not estimable) (HR, 1.12; 95% CI, 0.53–2.37; p=0.759); differences in PFS and OS were not statistically significant. In the Pt-rechallenge cohort, outcomes were stratified by anthracycline (A) use in 1st/2nd-line (A→A, n=17; A→non-A, n=28; non-A→A, n=12; non-A→non-A, n=7): ORRs were 50%, 35%, 27%, and 29%; median PFS were 9.3 (95% CI, 4.5–12.2), 6.4 (95% CI, 4.6–10.6), 21.0 (95% CI, 8.7–41.9), and 4.1 (95% CI, 1.8–9.3) months, respectively. Stratified by platinum-free interval (PFI) ($<$6 months, n=15; 6–12, n=10; 12–36, n=27; $\geq$36, n=12), ORR were 14%, 63%, 46%, and 20%; median PFS were 5.8 (95% CI, 1.8–19.8), 7.3 (95% CI, 2.1–14.5), 10.3 (95% CI, 5.5–23.5), and 9.0 (95% CI, 3.1–16.9) months. **Conclusions:** In this largest comparative study to date, platinum rechallenge demonstrated superior response rates compared to non-platinum regimens, particularly in patients with favorable PFI. Study registration: UMIN000048181. Research Sponsor: None.

8118 Poster Session

Cell-free DNA fragmentomics and methylomics for thymic epithelial tumors.

Michael Daniels, Elizabeth R. Francis, Ling Su, Xiaolin Wu, Elsa Bahiru, Shannon Swift, Christine Feierabend, Susan Sansone, Laercio Lopes DaSilva, Eva Szabo, Chen Zhao, Meredith Jo McAdams, Arun Rajan; National Institutes of Health, Rockville, MD; Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, Division of Cancer Prevention, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; Genomics Technology Laboratory, Frederick, MD; CCR Genomics Technology Laboratory, Frederick National Laboratory, Frederick, MD; Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research. National Cancer Institute, National Institutes of Health, Bethesda, MD; Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Institutes of Health, Bethesda, MD; Thoracic and GI Malignancies Branch, Center for Cancer Research and Lung and Upper Aerodigestive Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD; Thoracic and GI Malignancies Branch and Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Development of circulating cell-free (cf) DNA assays for cancer detection and monitoring is an area of active research. Limited data are available on the utility of cfDNA for thymic epithelial tumors (TETs). Evaluation of cfDNA fragmentation patterns (fragmentomics) offers advantages over conventional cfDNA analysis. Studies have shown that concurrent generation of fragmentomics and methylomics features via enzymatic methyl-sequencing (EM-Seq) are highly predictive at classifying cancer vs. non-cancer and capture key cancer-related biological features. We conducted a study to determine the feasibility of fragmentomics and methylomics for evaluation of TETs. **Methods:** cfDNA was extracted from 1-2 mL of plasma EDTA derived from patients with advanced TETs using the QIAamp Circulating Nucleic Acid Kit, underwent enzymatic conversion via the NEBNext Enzymatic Methyl-Seq v2 Kit, and sequenced on a NovaSeq X 10B flowcell. Estimated tumor fractions were generated using *ichorCNA* with low tumor settings and via *fragle*. Recurrent copy number alterations (CNAs) were plotted and compared against external TET copy number datasets. Short fragment percentage (90-150 bps) was calculated and average DELFI scores (DNA evaluation of fragments for early interception) were generated via *FinaleToolkit*. **Results:** Plasma samples from 47 of 50 participants (thymic carcinoma: 26, thymoma: 24; median age: 55 years (range 23-77); females 22; stage distributions: I/II/III/IV = 1/0/1/48) yielded high-quality cfDNA which was sufficient for sequencing. Individuals with thymic carcinoma displayed higher estimated tumor fractions via ichorCNA ($P<0.05$) and Fragle ($P=0.05$). Moreover, although not statistically significant, individuals with thymic carcinoma exhibited a general trend of higher short fragment percentage and higher average DELFI scores. When evaluating recurrent CNAs, individuals with thymic carcinoma displayed greater enrichments in CNAs in general with noted amplifications/gains at chr 1, 5, 12, and 17 and deletions at chr 16, whereas individuals with thymoma showed deletions at chr 3. When grouped and compared to external thymoma tissue CNAs, recurrent CNAs detected in plasma showed partial concordance. Large alterations in fragmentation profiles were also identified across both groups, which showed increased variability near recurrent CNA regions. **Conclusions:** This proof-of-concept study demonstrates that plasma cfDNA is detectable and fragmentomics is feasible among individuals with TETs, thus providing a non-invasive means of capturing cancer-related aberrant signals. Validation of this result in larger studies would establish cfDNA fragmentomics as a novel non-invasive means for disease monitoring and biomarker identification in patients with TETs. Research Sponsor: None.

Surufatinib for advanced or metastatic chemotherapy-refractory thymic epithelial tumor: A single-arm, single-center, phase II study.

Bei Xu, Qing Liu, Xi Guo, Jiahao Jiang, Shuai Wang, Tianshu Liu, Jianyong Ding; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, Shanghai, China; Department of Medical Oncology, Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China; Zhongshan Hospital, Fudan University, Shanghai, China

Background: Thymic epithelial tumors (TETs), though relatively rare, represent the most common anterior mediastinal malignancy in adults. Platinum-based regimens are the standard first-line therapy; however, treatment options for subsequent lines remain poorly defined. Surufatinib, an oral tyrosine kinase inhibitor targeting VEGFR1/2/3, FGFR1, and CSF-1R, exerts both anti-angiogenic and immune-modulating effects. This study aimed to evaluate the efficacy and safety of surufatinib in patients (pts) with type B2/B3 thymoma (TM) or thymic carcinoma (TC), providing a potential new therapeutic strategy for TETs following anthracycline/taxane-based therapy. Here, we report the initial results. **Methods:** This was a single-arm, prospective phase II study. Eligible pts had histologically or cytologically confirmed, unresectable or radiotherapy-ineligible, advanced recurrent or metastatic B2/B3 TM or TC, with progression following at least one prior platinum-based chemotherapy regimen. Pts were aged >18 years and had at least one measurable lesion per RECIST 1.1 criteria. Treatment consisted of surufatinib 300 mg orally once daily in a 4-week cycle. Tumor assessments were conducted every 8 weeks. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), and overall survival (OS). **Results:** As of December 25, 2025, 20 pts were enrolled and evaluated. The median age was 55.5 years (range: 35–69), with 55% being male. Pathological subtypes included B2 TM (30%), B3 TM (15%), and thymic squamous cell carcinoma (TSCC, 55%). Eighteen pts (90%) presented with >5 metastatic sites. Ten pts (50%) achieved a partial response, and ten pts (50%) achieved stable disease. The ORR was 50%, and the DCR was 100%. With a median follow-up of 9.50 months, the median PFS was 11.9 months, and the 9-month PFS rate was 73.5%. Median OS was not reached, with an 18-month OS rate of 91.7%. The most common treatment-related adverse events (TRAEs) of any grade were hypertension (70%), diarrhea (40%), elevated bilirubin (40%), and elevated transaminases (25%). Grade 3 TRAEs included hypertension (15%), diarrhea (5%), and elevated transaminases (5%). No treatment-related deaths were reported. **Conclusions:** Surufatinib monotherapy demonstrated promising antitumor activity and a manageable safety profile in patients with previously treated, advanced recurrent or metastatic TETs, supporting further investigation in this population. Clinical trial information: ChiCTR2600116776. Research Sponsor: None.

Penpulimab (PD-1 inhibitor) combined with platinum-based chemotherapy as induction therapy for newly diagnosed thymic carcinoma: A multicenter, single-arm, phase II trial.

Weixiong Yang, Yao Liu, Sicong Ma, Shuishen Zhang, Bo Zeng, Xin Zhang, Likun Chen, Chao Cheng; The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Thoracic Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Our retrospective study showed that immune checkpoint inhibitors plus chemotherapy had encouraging anti-tumor activity and durable response for unresectable thymic carcinoma (TC). This prospective clinical trial aimed to evaluate the efficacy and safety of penpulimab—a humanized anti-PD-1 monoclonal antibody—in combination with platinum-based chemotherapy as induction therapy for patients with newly diagnosed TC. **Methods:** Patients with histologically confirmed TC at Masaoka stage II–IV, an ECOG performance status of 0 or 1, and no history of prior systemic anticancer therapy were enrolled. Following 4 cycles of induction therapy with penpulimab penpulimab (200 mg), carboplatin (AUC 5 mg/mL per min), and nab-paclitaxel (260 mg/m^2) administered intravenously every 3 weeks, patients were re-evaluated by a multidisciplinary team (MDT). Subsequent treatment was stratified based on resectability: operable patients proceeded to surgery, whereas inoperable patients received standard radiotherapy or chemotherapy. Based on a Fleming two-stage design, the treatment would be promising if at least 10 of the first 18 evaluable patients in stage I or at least 14 of the 36 evaluable patients at the end of stage II have a confirmed response. The primary endpoint was objective response rate (ORR) evaluated by independent central review. **Results:** Between June 2023 and July 2025, 18 eligible patients were enrolled. Fourteen patients (77.8%) had WHO stage IV disease. Ten patients achieved a partial response (PR), meeting the predefined efficacy threshold for early termination according to the Fleming design. The ORR and disease control rate (DCR) were 55.6% and 94.5% respectively in the overall population, with corresponding rates of 57.1% and 92.8% in the subgroup with stage IV disease. Nine patients underwent surgical resection, including 6 with stage IV disease, and an R0 resection was achieved in 7 cases. Among the 9 patients who underwent surgery, one patient (11.1%) with stage III disease achieved a pathological complete response (pCR), and another patient (11.1%) with stage IV disease achieved a major pathological response (MPR). At a median follow-up of 20.15 months, the 1-year relapse-free survival (RFS) and overall survival (OS) rates were 72.2% and 88.9% for the entire population, and 64.3% and 78.6% for patients with stage IV disease, respectively. The most common adverse events of grade 3 or worse were neutropenia (44.4%), anemia (16.7%), and hepatotoxicity (11.2%). One patient died from immune-mediated myocarditis with concurrent hepatitis and myasthenia gravis. **Conclusions:** Penpulimab combined with platinum-based chemotherapy showed promising antitumour activity in previously untreated TC, with vigilance required for immune-mediated myocarditis. Clinical trial information: ChiCTR2300076314. Research Sponsor: National Natural Science Foundation of China; 82373307; the Natural Science Foundation of Guangdong Province; 2024A1515013214; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

Combining SBRT with GM-CSF and Peg-IFNα to induce abscopal effects in previously treated patients with metastatic thymic tumors: A single-institution, phase II trial.

Min Fan, Boyan Wang, Huiting Li, Junmiao Wen, Jiayan Chen; Fudan University Shanghai Cancer Center, Shanghai, China

Background: After the failure of multi-line treatment, patients with metastatic thymic tumors have a poor prognosis and few therapeutic options. Combining stereotactic body radiotherapy (SBRT) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and Pegylated interferon-α (Peg-IFNα) may induce abscopal effects and improve prognosis. **Methods:** We conducted this open-label, single-arm, phase II trial to evaluate SBRT plus GM-CSF and Peg-IFNα in previously treated patients with metastatic thymic tumors. A 21-day treatment cycle consisted of SBRT delivered to one metastatic lesion with 30 Gy in 5 fractions from day 1, synchronous subcutaneous injection of GM-CSF 125 μg/ m^2 once daily for 14 days, and subcutaneous injection of Peg-IFNα 90 μg on day 8. If the patient has more than two metastatic lesions, another treatment cycle was repeated. After the completion of 1 or 2 treatment cycles, Peg-IFNα therapy was maintained for at least half a year with a subcutaneous injection of 90 μg once a month. The two primary endpoints were the proportion of patients with abscopal effects and the objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and therapeutic safety. **Results:** A total of 32 patients from March 2021 to December 2025, were enrolled in this trial, with 2 (6.25%) type A thymoma, 4 (12.50%) type B1 thymoma, 6 (18.75%) type B2 thymoma, 2 (6.25%) type B3 thymoma, 16 (50.00%) thymic squamous cell carcinoma and 2 (6.25%) thymic neuroendocrine tumor. One patient with type B3 thymoma died of cardiac arrest amid the COVID-19 pandemic, rendering tumor evaluation unfeasible. Out of the remaining 31 patients, 9 (29.03%) had abscopal effects, and the ORR was 38.71%. At a median follow-up of 17.20 months, the median OS had not been attained yet. The median PFS was 6.37 months for the whole group. We observed that patients with abscopal effects tended to have longer PFS than those without abscopal effects (13.03 vs. 4.40 months ; $p = 0.003$). 5 patients (16.13%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0), among which cardiac insufficiency compelled 1 patient (3.23%) to drop out of treatment. **Conclusions:** Combining SBRT with GM-CSF and Peg-IFNα was well tolerated with acceptable toxicity and may represent a promising salvage therapy for previously treated patients with metastatic thymic tumors. The occurrence of abscopal effects is likely to improve patient outcomes. Clinical trial information: NCT04517539. Research Sponsor: None.

Development and validation of a preoperative pathological risk prediction model for thymic tumors: A retrospective multicenter diagnostic study.

LuYu Huang, Shaowei Wu, Lintong Yao, Canjia Cai, Guoqing Liao, Weihuan Lin, Daipeng Xie, Haiyu Zhou; Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: The preoperative diagnosis of thymic tumors currently relies on preoperative CT data and the experience of the surgeon, and there is still a lack of highly effective noninvasive radiomic prediction model to assist in clinical decision making. To develop and validate a preoperative CT-based radiomic model to accurately predict the pathological risk staging of thymic tumors. **Methods:** This is a retrospective diagnostic study that included patients from two independent centers Charité Universitätsmedizin Berlin (N = 74) as well as the First Hospital of Zhengzhou University (N = 143) between September 2003 and July 2024. WHO pathological type A, AB, and B1 of the postoperative thymic tumor were divided into low-risk groups (N = 110), and type B2, B3, and C (N = 107) were classified as high-risk groups. The patients were randomly divided into a training group (N = 130) and a validation group (N = 87) in a ratio of 6:4. Preoperative CT imaging of thymic tumor was used to define the tumor area and the peritumoral area (5 mm) and to extract the radiomic features using 3Dslicer software and the in-house pyradiomic software package. Feature selection and model development were conducted using the least absolute shrinkage and selection operator (LASSO) algorithm and logistic regression analysis. **Results:** A total of 217 patients undergoing thymectomy were included in this study. After univariate analysis, patients' age, smoking history, and the presence of combined myasthenia gravis (MG) were included in the clinical model, and the clinical model achieved AUC = 0.75 and 0.65 in the training and validation groups, respectively. The combined radiomic model has better performance than the two radiomic models alone, with AUC values of 0.86, 0.73, respectively. The nomogram model conducted by combined radiomic model with the clinical model achieved the best results in training (AUC = 0.89) and validation cohort (AUC = 0.84). Calibration curve and decision curve analysis (DCA) illustrated the clinical usability and reliability of the model. **Conclusions:** By combining the clinical model with a combined radiomic model, the nomogram model can effectively differentiate pathological risk staging of thymic tumors, providing surgeons with a potential preoperative decision support. Research Sponsor: None.

TPS8123 **Poster Session**

A multi-institutional, randomized, phase III trial comparing anatomical segmentectomy and lobectomy for clinical stage IA3 pure-solid non–small-cell lung cancer: West Japan Oncology Group study WJOG16923L (STEP UP trial).

Atsushi Kamigaichi, Akira Hamada, Morihito Okada, Masaru Takenaka, Tomohito Saito, Tomoyoshi Takenaka, Hidemi Suzuki, Kazuhito Funai, Toshiki Yajima, Seshiru Nakazawa, Kimihiro Shimizu, Shinya Tane, Yoshimitsu Hirai, Hiroyuki Ito, Satoshi Shiono, Masahiro Tsuboi, Kenichi Yoshimura, Hirotsugu Kenmotsu, Nobuyuki Yamamoto, Yasuhiro Tsutani; Hiroshima University, Hiroshima, Japan; Kindai University Faculty of Medicine, Osaka, Japan; Second Department of Surgery (Chest Surgery), University of Occupational and Environmental Health, Fukuoka, Japan; Kansai Medical University, Osaka, Japan; Kyushu University, Fukuoka, Japan; Chiba University, Chiba, Japan; Hamamatsu University, Shizuoka, Japan; Kagawa University, Kagawa, Japan; Gunma University, Gunma, Japan; Shinshu University, Nagano, Japan; Kobe University, Hyogo, Japan; Wakayama Medical University, Wakayama, Japan; Kanagawa Cancer Center, Yokohama, Japan; Yamagata University, Yamagata, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Nagoya City University, Nagoya, Japan; Shizuoka Cancer Center, Shizuoka, Japan; Kindai University, Osaka, Japan

Background: Recent pivotal clinical trials, conducted by the Japan Clinical Oncology Group and West Japan Oncology Group (JCOG0802/WJOG4607L) or Cancer and Leukemia Group B (CALGB140503), have demonstrated the efficacy of anatomical segmentectomy for small-sized early-stage NSCLC measuring ≤ 2 cm. Segmentectomy is gaining attention as an alternative procedure to lobectomy for early-stage NSCLC. However, for tumors larger than 2 cm, particularly those with a pure-solid appearance which indicates higher malignant potential, the efficacy of segmentectomy remains controversial. Therefore, we initiated this randomized phase III trial (WJOG16923L: STEP UP) to confirm the non-inferiority of anatomical segmentectomy to lobectomy for patients with pure-solid NSCLC measuring > 2 cm and ≤ 3 cm.
Methods: This multi-institutional, open-label, randomized phase III study is designed to confirm the non-inferiority of anatomical segmentectomy to lobectomy in terms of overall survival (OS) in patients with clinical stage IA3 pure-solid peripheral NSCLC (tumor's center located in the outer third of the lung field, tumor measuring > 2 cm and ≤ 3 cm, and consolidation-to-tumor ratio = 1). Patients are randomized 1:1 to undergo either lobectomy or anatomical segmentectomy using a minimization method by balancing the arms with the institution, age (≥ 70 or < 70), sex (male or female), location (right upper, right lower, left upper, or left lower lobes), and histological type (adenocarcinoma or non-adenocarcinoma). The primary endpoint is OS in all randomized patients. Secondary endpoints include relapse-free survival, postoperative respiratory function (at 6 months and 1 year after surgery), proportions of patients with respiratory failure and cerebrovascular disease, cumulative incidence of death from other diseases, cumulative incidence of local recurrence, proportion of patients who undergo segmentectomy, number of resected segments, operative time, blood loss, and adverse events. We plan to enroll 520 patients from 64 institutions over a period of 5 years. Enrollment began in January 2024. As of November 2025, 319 patients have been enrolled. This trial is registered with the UMIN Clinical Trials Registry (UMIN000052064). Clinical trial information: UMIN000052064. Research Sponsor: None.

TPS8124 **Poster Session**

CCTG BR.38: Consolidative use of radiotherapy to block (CURB2) oligoprogression in patients with metastatic non–small-cell lung cancer—A randomized phase III trial.

Chiaojung Jillian Tsai, Alexander Sun, Penelope Ann Bradbury, Devin Schellenberg, Houda Bahig, Andrea S. Fung, Jean-Pierre Bissonnette, Jeeban Paul Das, Biniam Kidane, Alexander V. Louie, Joseph Miccio, Meng Xu Welliver, John M. Varlotto, Arya Amini, Ryan Kelly, Keyue Ding, Pierre-Olivier Gaudreau; Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; British Columbia Cancer Agency, Abbotsford, BC, Canada; Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada; University Health Network, Toronto, ON, Canada; Memorial Sloan Kettering Cancer Center, New York, NY; CancerCare Manitoba, Winnipeg, MB, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Penn State Hershey Medical Center, Hershey, PA; Mayo Clinic Rochester, Rochester, MN; Marshall University School of Medicine, Edwards Cancer Center, Huntington, WV; City of Hope Medical Center, Duarte, CA; Queen's University, Canadian Cancer Trials Group, Kingston, ON, Canada; Queen's University, Kingston, ON, Canada; Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada

Background: Immune checkpoint inhibitor (ICI)–based regimens are standard first-line therapy for metastatic non–small-cell lung cancer (NSCLC) without actionable driver mutations; however, most patients experience disease progression within 12 months. A subset develop oligoprogression, defined by progression at a limited number of metastatic sites with otherwise controlled disease. Oligoprogression represents a therapeutic window in which local ablative therapy could be used to prolong disease control. In the prior phase II CURB trial, SBRT was shown to significantly prolong progression-free survival (PFS) in patients with oligoprogressive NSCLC. **Methods:** CCTG-BR38 is an international, multicenter, open-label, randomized phase III trial conducted through the NCI National Clinical Trials Network. Adults with stage IV NSCLC receiving first-line ICI ± chemotherapy who develop ≤5 extracranial oligoprogressive lesions are randomized 1:1 to: (1) switch to second-line standard systemic therapy or (2) SBRT (30 Gy in 3 fractions) to all oligoprogressive sites followed by continuation of the same first-line systemic therapy. Randomization is stratified by type of first-line systemic therapy (ICI alone vs ICI + chemotherapy), number of oligoprogressive lesions (1–2 vs 3–5), and ECOG performance status (0-1 vs 2). Patients with treated, stable brain metastases are eligible. Primary Endpoints: Dual primary endpoints are PFS and overall survival (OS). Secondary endpoints include safety (CTCAE v5.0), patient-reported adverse events (PRO-CTCAE), quality of life (EORTC QLQ-C30/LC13), and cost-effectiveness (EQ-5D-5L; Canadian sites). Optional blood and tissue collection for exploratory biomarker analyses are planned. Statistical Considerations: A total of 320 patients (160 per arm) will be enrolled. The sample size is based on detecting a HR of 0.7 for OS (an improvement in median OS from 10 to 14.3 months) with 80% power using a 1-sided 2% level test (the overall 1-sided 2.5% type I error will be assigned 2% to OS and 0.5% to PFS). Interim analyses for futility and efficacy are planned. Current Status: The trial was centrally activated on April 3, 2025. Accrual is ongoing across Canadian and US NCTN sites. Clinical trial information: NCT06686771. Research Sponsor: National Clinical Trials Network; CA180863; Canadian Cancer Society Research Institute; 707213; University Health Network.

TPS8125 **Poster Session**

InDuRanS: A randomized phase II trial on induction immunochemotherapy followed by surgery or chemoradiotherapy and consolidation durvalumab in stage III NSCLC.

Eleni Gkika, Cornelius Waller, Cas Dejonckheere, Julian Philipp Layer, Jan Meiners, Joachim Schmidt, Peter Brossart, Ernst Rodermann, Anne Sofie Schiefer, Marc Münter, Nils Nicolay, Anca-Ligia Grosu, Andreas Rimner, Severin Schmid; Department of Radiation Oncology, Bonn, Germany; Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; University Hospital Bonn, Bonn, Germany; AstraZeneca, Hamburg, Germany; Department of Thoracic Surgery, Bonn, Germany; University Bonn, Bonn, Germany; Onkologie Rhein-Sieg, Bonn, Germany; Department of Radiation Oncology, Stuttgart, Germany; Department of Radiation Oncology, Leipzig, Germany; Medical Center – University of Freiburg, Freiburg, Germany; University Medical Center Freiburg, Department of Radiation Oncology, Freiburg, Germany; University Medical Center, University of Freiburg, Freiburg, Germany

Background: The optimal local treatment strategy for patients with resectable or borderline resectable stage IIIA/B (N2) non-small-cell lung cancer (NSCLC) remains controversial. Earlier randomized trials comparing surgery with definitive chemoradiotherapy (CRT) failed to demonstrate a survival advantage for either modality; however, these studies predated routine PET staging, modern radiotherapy techniques, and standard-of-care immunotherapy. Consolidation durvalumab after definitive CRT has significantly improved survival in unresectable stage III NSCLC, while neoadjuvant immunochemotherapy has shown promising pathologic and survival outcomes in resectable disease. Whether surgery or definitive CRT provides superior outcomes following induction immunochemotherapy in stage III NSCLC is unknown. The InDuRanS trial aims to address this question in a randomized setting. **Methods:** InDuRanS (ARO-2024-12; NCT06810609) is a prospective, multicenter, open-label, randomized phase II trial conducted across approximately 10 centers in Germany. Eligible patients have (borderline) resectable stage IIIA/B (N2) NSCLC without targetable EGFR or ALK alterations. All patients receive three cycles of induction immunochemotherapy consisting of durvalumab (1,500 mg every 3 weeks) combined with platinum-paclitaxel. Following PET-based restaging, patients with persistent resectable disease are randomized 1:1 to surgery (Arm A) or definitive CRT (Arm B). CRT consists of 60–70 Gy in conventional fractionation with two cycles of concurrent platinum-vinorelbine. Both treatment arms subsequently receive consolidation durvalumab (1,500 mg every 4 weeks) for up to 13 cycles. The primary endpoint is 2-year event-free survival (EFS). Secondary endpoints include overall survival, progression-free survival, treatment-related toxicity, surgical outcomes, and quality of life. Exploratory analyses include radiomics, plasma proteomics, circulating tumor DNA, and immune profiling. A total of 176 patients will be enrolled, with 158 evaluable patients planned for randomization. Interim safety analyses are scheduled after treatment completion in the first 10 randomized patients. The trial is currently open and recruiting. Research Sponsor: AstraZeneca.

TPS8126 Poster Session

Volrustomig, a novel bispecific PD-1/CTLA-4 monoclonal antibody, as single-agent first-line therapy for unresectable pleural mesothelioma: Substudy 5 of the eVOLVE-02 phase 2 study.

Michael Offin, Xiaoling Zeng, Shenqi Wang, Bingying Xie, Melina Elpi Marmarelis; Mesothelioma Program, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY; Clinical Development, Oncology, Oncology R&D, AstraZeneca, Shanghai, China; Biometrics and Data Science, Oncology R&D, AstraZeneca, Shanghai, China; Division of Hematology and Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Standard first-line treatment for unresectable pleural mesothelioma has evolved recently to include anti-PD-1 ± anti-CTLA-4 immunotherapy-based options. Nivolumab + ipilimumab and pembrolizumab + pemetrexed + platinum chemotherapy showed improved survival vs chemotherapy alone, with greater benefit in non-epithelioid compared to epithelioid pleural mesothelioma. However, there is still significant unmet need given the ongoing poor prognosis; further study is needed to optimize dual checkpoint approaches across histologic subtypes and refine regimen selection. Volrustomig is a monovalent, bispecific, humanized IgG1 monoclonal antibody engineered to specifically inhibit PD-1 and CTLA-4, with increased CTLA-4 blockade on PD-1-positive activated T cells compared to PD-1-negative resting peripheral T cells. Volrustomig + chemotherapy is being evaluated as first-line treatment in unresectable pleural mesothelioma in the phase 3 eVOLVE-Meso trial. Volrustomig monotherapy has shown encouraging results in a Phase 1 study of patients with solid tumors; this new eVOLVE-02 (NCT06535607) substudy will evaluate its efficacy and safety as monotherapy in unresectable pleural mesothelioma. **Methods:** ~75 patients with unresectable pleural mesothelioma (epithelioid or non-epithelioid histology) will receive intravenous volrustomig until disease progression, unacceptable toxicity, consent withdrawal, or maximum treatment duration is reached. Eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status 0/1, histologically confirmed pleural mesothelioma with known histology, advanced unresectable disease, measurable disease per mRECIST (modified Response Evaluation Criteria in Solid Tumors) v1.1 (pleural lesions) and/or RECIST v1.1 (metastatic non-pleural lesions), no prior systemic therapy for pleural mesothelioma, and no prior exposure to immune-mediated therapy. The primary endpoint is objective response rate. Secondary endpoints include disease control rate, time to response, duration of response, progression-free survival, and overall survival. eVOLVE-02 is recruiting patients; 3 substudies are ongoing in cervical cancer and head and neck squamous cell carcinoma. Substudy 5 enrollment is planned at sites in 8 countries/regions: Australia, Canada, China, Germany, Italy, Taiwan, UK, and USA. Clinical trial information: NCT06535607. Research Sponsor: AstraZeneca.

TPS8127 **Poster Session**

Neoadjuvant chemo-immunotherapy and surgical resection in locally advanced non-small cell lung cancer with N3 lymph node involvement (NEO-SURG).

Joshua E. Reuss, Chul Kim, Cristina Maria Merkhofer, Ece Cali, Hyein Jeon, Jaeil Ahn, Rebecca Krochmal, Eric D. Anderson, Nitika Paudel, Jillian Thompson, Jay Zeck, Jenny Crawford, Ann Hwalek, Marc Margolis, Edward Chan, Whitney S. Brandt, Linda W. Martin, Ryan D. Gentzler, Stephen V. Liu; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Washington University, St. Louis, MO; Medstar Georgetown University Hospital, Washington, DC; University of Virginia, Charlottesville, VA

Background: The emergence of neoadjuvant and peri-operative chemoimmunotherapy in locally-advanced non-small cell lung cancer (NSCLC) has revolutionized the treatment of resectable NSCLC. Importantly, in multiple phase III trials, patients with multi-station N2 disease derive profound benefit from neoadjuvant chemoimmunotherapy. NSCLC with N3 involvement has been excluded from neoadjuvant/perioperative studies, as these cancers have historically been considered unresectable and treated with definitive chemoradiotherapy (CRT) followed by durvalumab. However, CRT is associated with high rates of treatment-related adverse events and most patients experience disease relapse within 2 years. Whether patients with select N3 lymph node-positive NSCLC may benefit from neoadjuvant chemo-immunotherapy followed by surgery is an important unaddressed question. This phase II trial seeks to evaluate the feasibility and clinical utility of neoadjuvant chemoimmunotherapy followed by surgery in patients with locally-advanced stage III B/C NSCLC with select N3 involvement. **Methods:** This phase II, multi-center, single-arm study is evaluating neoadjuvant chemoimmunotherapy in patients with stage III B/C NSCLC with contralateral mediastinal or ipsilateral supraclavicular (N3) lymph node involvement. Select eligibility criteria include: ECOG performance status 0-1, pathologically-confirmed contralateral mediastinal or ipsilateral supraclavicular N3 disease, ≤2 involved lymph node stations, primary tumor appropriate for resection per multi-disciplinary review (any T stage), physical fitness for resection, wild-type *EGFR/ALK*. Patients will receive neoadjuvant cemiplimab 350mg IV plus histology-specific chemotherapy every 3 weeks for 4 cycles prior to planned surgical resection followed by adjuvant radiotherapy (optional) and 1 year of adjuvant cemiplimab. The primary endpoint is pCR rate defined by IASLC consensus guidelines. Secondary endpoints include objective response rate (per RECIST v1.1), R0 resection rate, major pathologic response (≤10% viable tumor) rate, disease-free survival and overall survival. A total of 21 patients will be enrolled. A Simon-2 stage design will be used such that 12 patients will be enrolled initially and, if at least one pCR is observed, the trial will proceed to the second stage with enrollment of an additional 9 patients. This design yields a type I error rate of 5% and power of 80% when the true pCR rate is 20%. In addition, a Pocock stopping rule at 5% type I error will be deployed to assess feasibility of surgical resection. The study will be halted for futility if 8 of the first 12 patients do not proceed with surgical resection. The study is open for accrual at Georgetown University, University of Virginia, and Washington University. Clinical trial information: NCT06449313. Research Sponsor: Regeneron.

TPS8128 Poster Session

IFCT-2401 SPORADIC trial: Integrating cemiplimab to sequential hypofractionated chemoradiotherapy for unfit or elderly patients with unresectable stage III non–small cell lung cancer.

Sébastien Thureau, Judith Raimbourg, Nicolas Pourel, Hubert Curcio, Marie Wislez, Florian Guisier, Etienne Martin, Jonathan Khalifa, Elodie Amour, Celia Berndt, Alexandra Langlais, Franck Morin, Virginie Westeel, Alexis B. Cortot; Radiotherapy Department, QuantiF AIMS, Centre Henri Becquerel, Rouen, France; Medical Oncology Department, Insitut de Cancérologie de l'Ouest, F44805 Saint-Herblain, France; Radiotherapy Department, Sainte-Catherine, Institut du Cancer Avignon-Provence, Avignon, France; Medical Oncology, Centre François Baclesse, Caen, France; Thoracic Oncology, Hôpital Cochin, Paris, France; Université de Rouen Normandie, LITIS Lab QuantIF team EA4108, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, Rouen, France; Radiotherapy Department, Centre Georges-François Leclerc, Dijon, France; Radiation department, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; Clinical Research Unit, Intergroupe Francophone de Cancérologie Thoracique, Paris, France; Pneumology department, CHU Besançon - Hôpital J. MINJOZ, Besançon, France; Respiratory Medicine and Thoracic Oncology, CHU Lille, Lille, France

Background: Patients with unresectable stage III non-small cell lung cancer (NSCLC) who are elderly or have significant comorbidities are frequently ineligible for concurrent chemoradiotherapy (CCRT). Sequential chemoradiotherapy (seq-CRT) remains the preferred approach in this population. While consolidation immunotherapy after CCRT improves survival, evidence supporting its optimal integration with seq-CRT is limited. Preclinical and clinical data suggest that combining chemotherapy and immunotherapy enhances tumor immunogenicity through increased antigen release, immune priming, and modulation of the tumor microenvironment. Hypofractionated radiotherapy may further potentiate immune-mediated effects while shortening overall treatment duration, which is particularly relevant for frail patients. The IFCT-2401 SPORADIC trial evaluates in unfit or elderly patients a sequential strategy integrating neoadjuvant chemo-immunotherapy prior to hypofractionated radiotherapy, followed by maintenance immunotherapy, in patients with unresectable stage III NSCLC not eligible for CCRT. Exploratory correlative studies include circulating biomarkers, immune profiling, lymphopenia, and metabolic response assessment. **Methods:** IFCT-2401 SPORADIC is a multicenter, randomized, open-label phase II trial (EU-CT 2024-517316-29-00). Patients are randomized in a 2:1 ratio to receive neoadjuvant chemotherapy alone (arm A) or neoadjuvant chemo-immunotherapy (arm B). Neoadjuvant treatment consists of three 28-day cycles of carboplatin (AUC 5, day 1) and paclitaxel (80 mg/m², days 1, 8 and 15). Cemiplimab (350 mg, every 3 weeks) is added in arm B. All patients subsequently receive curative hypofractionated thoracic radiotherapy (55 Gy in 20 fractions), followed by maintenance cemiplimab every 3 weeks for up to 12 months. Eligible patients have unresectable stage IIIA–C NSCLC. Three categories of patients are considered unfit for CCRT: age $\geq$70 years with ECOG performance status (PS) 0 to 1, age $<$ 70 years with ECOG PS 0 to 1 and significant comorbidities or age $<$ 70 years with ECOG PS 2. Key exclusion criteria include actionable oncogenic drivers, prior systemic therapy for NSCLC and active autoimmune disease. The primary endpoint is progression-free survival. A total of 152 patients are planned for enrollment across 25 centers. First patient was enrolled on November 17, 2025. Clinical trial information: EU-CT 2024-517316-29-00. Research Sponsor: None.

TPS8129 **Poster Session**

Beamion LUNG-3: Zongertinib in resectable *HER2*-mutant NSCLC.

Amy Lauren Cummings, Timothy Dudley Clay, Jay M. Lee, Jamie E. Chaft, Elaine Shum, Daniel Shao-Weng Tan, Jordi Remon Masip, Caicun Zhou, Yasuhiro Tsutani, Carlos P. Carrasco, Agnes Tort Piella, Sabina Eigenbrod-Giese, Stephan Luecke, Lukas Lunger, Ernest Nadal; University of California, Los Angeles (UCLA), Los Angeles, CA; St John of God Subiaco Hospital, Perth, WA, Australia; Memorial Sloan Kettering Cancer Center, New York, NY; New York University Langone Health, New York, NY; National Cancer Centre Singapore, Singapore, Singapore; Gustave Roussy, Paris, France; Shanghai East Hospital, Shanghai, China; Kindai University, Osaka, Japan; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; Boehringer Ingelheim Españ̃a, S.A., Sant Cugat, Spain; Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an Der Riss, Germany; Boehringer Ingelheim International GmbH, Ingelheim Am Rhein; and Department of Urology, School of Medicine, and Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany; Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain

Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Based on recent data from the Phase Ib Beamion LUNG-1 trial (NCT04886804), zongertinib was approved in the USA (accelerated), China (conditional), and Japan for previously treated patients with advanced/metastatic *HER2*-mutant NSCLC. Clinically meaningful efficacy has also been seen with zongertinib as first-line therapy in treatment-naïve patients with advanced *HER2*-mutant NSCLC. Beamion LUNG-3 (NCT07195695) is an ongoing, global Phase III trial investigating zongertinib as adjuvant monotherapy compared with SoC (immunotherapy [IO] or observation) in patients with early-stage, resectable *HER2*-mutant NSCLC. **Methods:** Patients with histologically confirmed, resectable, Stage II–IIIB (post-operative, AJCC 9th edition) *HER2*-mutant NSCLC will be enrolled. Patients must be aged ≥18 years, have an ECOG PS of 0 or 1, have tumors that harbor a *HER2* mutation within the tyrosine kinase domain, and have completed 3–4 cycles of neoadjuvant platinum-based chemotherapy + IO or 4 cycles of adjuvant platinum-based chemotherapy (≥2 cycles permitted if discontinued due to toxicity), followed by complete surgical resection. Patients must have a full recovery from surgical procedures and the ability to be randomized within 2–8 weeks of the last treatment for patients who underwent adjuvant chemotherapy, or within 4–10 weeks of surgery for patients who underwent neoadjuvant therapy. Approximately 400 patients will be randomized 1:1 to receive zongertinib 120 mg once daily or physician's choice SoC (observation or IO with nivolumab, pembrolizumab, atezolizumab, or durvalumab). Stratification will be based on tumor stage (II, IIIA, IIIB), pretreatment (neoadjuvant/adjuvant), and physician's choice of SoC (IO/observation). Patients will remain on treatment for up to 3 years (if receiving zongertinib) or up to 1 year (if receiving SoC), or until tumor recurrence, undue toxicity, or any other protocol-defined stopping criterion. The primary endpoint is disease-free survival (DFS) by investigator assessment, defined as the time from randomization until tumor recurrence or death from any cause. Secondary endpoints include overall survival (OS, defined as the time from randomization until death from any cause) and occurrence of grade ≥3 adverse events from first treatment administration (or from randomization for patients in the observation arm) until the earliest of tumor recurrence or 3 years since treatment started. The trial will be conducted at ~200 sites in 32 countries; enrollment is ongoing. Results will inform whether HER2-targeted adjuvant therapy improves DFS and OS in patients with early-stage *HER2*-mutant NSCLC. Clinical trial information: NCT07195695. Research Sponsor: Boehringer Ingelheim.

TPS8130 **Poster Session**

Randomized, double-blind, phase 3 TRUST-IV study of adjuvant taletrectinib vs placebo in patients with stage IB–IIIA ROS1+ non-small cell lung cancer (NSCLC).

Alexander I. Spira, Alexander E. Drilon, Jonathan W. Goldman, Narjust Florez, Petros Christopoulos, Maurice Perol, Dih-Yih Chen, Feiwu Ran, Xianyu Zhang, Geoffrey Liu, Caicun Zhou; Virginia Cancer Specialists and US Oncology, Fairfax, VA; Memorial Sloan Kettering Cancer Center, New York, NY; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; Centre Léon Bérard, Lyon, France; Nuvation Bio Inc., New York, NY; Princess Margaret Cancer Centre, Temerty School of Medicine, University of Toronto, Toronto, ON, Canada; Shanghai East Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

Background: Taletrectinib is a next-generation, CNS-active, selective ROS1 tyrosine kinase inhibitor (TKI) approved by the US FDA for the treatment of locally advanced or metastatic ROS1+ NSCLC. In stage IB–IIIA NSCLC, which represents about 30% of NSCLC cases, the standard of care is surgical resection with perioperative systemic therapy (neoadjuvant or adjuvant). Results from Phase 3 trials have shown significantly improved outcomes for EGFR and ALK TKIs as adjuvant therapy compared with placebo or chemotherapy in early-stage NSCLC with EGFR mutations or ALK fusions, respectively. However, there remains an unmet need for patients with stage IB–IIIA ROS1+ NSCLC. Given the efficacy and tolerability of taletrectinib in advanced ROS1+ NSCLC, there is a rationale for investigating taletrectinib in patients with earlier-stage NSCLC who have undergone complete tumor resection. **Methods:** TRUST-IV (NCT07154706) is a randomized, double-blind, multicenter, Phase 3 study evaluating the efficacy and safety of taletrectinib compared with placebo in patients with stage IB, II, or IIIA ROS1+ NSCLC following curative surgery (negative surgical margins). ROS1 fusions may be detected using validated local tissue or liquid assays but must be confirmed by central tissue testing. Patients may have received prior adjuvant platinum-based chemotherapy ($\leq$4 cycles) if clinically indicated, which must be completed $\geq$7 days prior to randomization. Surgical resection must have occurred 4–16 weeks prior to randomization if no adjuvant chemotherapy was given or 4–30 weeks if adjuvant chemotherapy was given. The estimated enrollment is 180 patients, randomized 2:1 to receive either taletrectinib 400 mg once daily or a matched placebo, stratified by prior adjuvant chemotherapy (yes vs no) and pathological stage (IB vs II vs IIIA). Patients will receive blinded study drug in continuous 28-day cycles until disease recurrence or consent withdrawal, or up to a maximum of 3 years. Contrast computed tomography or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis will be performed at screening, Cycle 4 Day 1 (C4D1), and C7D1, while brain MRI will be performed at screening and C7D1; thereafter, all imaging will be performed every 24 weeks until 5 years and then annually until disease recurrence or end of study. The primary endpoint is disease-free survival (DFS) by investigator assessment. Select secondary endpoints include: DFS rates at 2, 3, 4, and 5 years; DFS by blinded independent central review; overall survival; CNS-DFS; and safety. Exploratory endpoints include patient-reported outcomes for health-related quality-of-life measures and progression-free survival 2. The trial is currently recruiting. Clinical trial information: NCT07154706. Research Sponsor: This study was sponsored by Nuvation Bio Inc. Medical writing support was provided by Caroline Creasey, MSc, and Flaminia Fenoaltea, MSc, of Ashfield MedComms, an Inizio company, and was funded by Nuvation Bio Inc.

TPS8131 **Poster Session**

SWOG S2414 (INSIGHT): A randomized phase III trial incorporating pathologic complete response in participants with early-stage non-small cell lung cancer to optimize immunotherapy in the adjuvant setting.

Jeremy Paul Cetnar, Yingqi Zhao, Raymond U. Osarogiagbon, Bruna Pellini, Theresa A. Boyle, Humberto E. Trejo Bittar, Sanja Dacic, Paul Joseph Hesketh, Krishna Soujanya Gunturu, Ming-Hui Hsieh, Joseph M. Unger, Dwight Hall Owen, Jennifer Marie Suga, Daphna Y. Gelblum, Fred R. Hirsch, Jhanelle E. Gray; Oregon Health and Science University Knight Cancer Institute, Beaverton, OR; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; Baptist Cancer Center, Memphis, TN; Thoracic Oncology Program, Miami Cancer Institute, Baptist Health South Florida, Miami, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL; Department of Pathology, Yale School of Medicine, New Haven, CT; Lahey Hospital and Medical Center, Burlington, MA; Hartford HealthCare Cancer Institute, Hartford, CT; SWOG Statistical Center, Seattle, WA; Ohio State University, Columbus, OH; Kaiser Permanente NCI Community Oncology Research Program and NCORP, Vallejo, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Center for Thoracic Oncology Mount Sinai Health System, New York, NY

Background: Neoadjuvant chemo-immunotherapy (chemo-IO) followed by surgery is a standard of care for resectable clinical stage II-IIIB non-small cell lung cancer (NSCLC). Pathologic complete response (pCR), achieved in roughly 20% of patients, is associated with a favorable overall survival rate, but the benefit of additional adjuvant immunotherapy (IO) after pCR has not been independently studied and remains uncertain. The potential for overtreatment and unnecessary toxicity is a critical question in these patients. SWOG S2414 (INSIGHT) is designed to determine the optimal adjuvant therapy strategy for patients with pCR after neoadjuvant chemo-IO. **Methods:** INSIGHT (NCT06498635) is an open-label, randomized phase III trial, in which patients with clinical stage II-IIIB NSCLC who achieved pCR after standard of care neoadjuvant chemo-IO are randomized to adjuvant durvalumab IV every 28 days for up to 12 cycles (durvalumab, arm A) versus no further treatment (active surveillance, arm B). The primary objective is to compare disease free survival (DFS) between participants in the two arms. Key secondary endpoints include overall survival, event-free survival, and patient-reported quality of life (using the FACT-L and FACT-BRM) and symptoms (using PRO-CTCAE). The total enrollment goal is 306 participants. The design includes 2 interim analyses. Participants must have NSCLC with no known EGFR mutations or ALK fusions, and must have received at least two cycles of an FDA-approved neoadjuvant platinum-based chemo-IO regimen with an anti-PD-1/PD-L1 agent. Pathologic complete response will be confirmed by local pathology. Current Status: S2414 was activated on 3/14/2025, the first patient was registered on 4/1/2025. Enrollment is open and ongoing. Clinical Significance: INSIGHT is a pivotal trial addressing the therapeutic dilemma of adjuvant treatment for early-stage NSCLC patients with pCR after neoadjuvant chemo-IO. The results will help determine whether adjuvant IO provides a significant DFS benefit over surveillance in patients with a pCR, potentially leading to de-escalation of therapy and reduced toxicity. Funding: NIH/NCI grants U10CA180888, U10CA180819; additional support by AstraZeneca. Clinical trial information: NCI-2024-05588. Research Sponsor: NIH/NCI grants U10CA180888, U10CA180819; additional support by AstraZeneca.

TPS8132 Poster Session

Randomized multicenter phase II trial of radioimmunotherapy versus chemo-immunotherapy followed by surgery for c-stage IB-III NSCLC (RICHIS trial).

Jonathan Villena-Vargas, Jeffrey L. Port, Dan Jones, Oliver S. Chow, Sebron W. Harrison, Benjamin E. Lee, Christine A. Garcia, Ashish Saxena, Nicholas J. Sanfilippo, Raphael Bueno, David R. Jones, Silvia Chiara Formenti, Nasser K. Altorki; Weill Cornell Medicine, New York, NY; Weill Cornell Medicine/NewYork-Presbyterian, New York, NY; Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY; NewYork-Presbyterian Hospital/Weill Cornell Medicine, New York, NY; NewYork-Presbyterian/Weill Cornell Medicine, New York, NY; Brigham and Women's Hospital, Boston, MA; Memorial Sloan Kettering Cancer Center, New York City, NY; NewYork-Presbyterian Hospital, Weill Cornell Medical Center, New York, NY; Weill Cornell Medicine, NewYork-Presbyterian Hospital, New York, NY

Background: Chemotherapy combined with PD-1 or PD-L1 blockade (chemo-immunotherapy, ChemoIO), administered in the neoadjuvant, adjuvant, or perioperative setting, has become standard of care for surgically resectable non-small cell lung cancer (NSCLC). However, ChemoIO may be associated with significant toxicity that may limit treatment delivery and compromise surgical fitness. Preclinical data demonstrate that non-ablative stereotactic body radiotherapy (SBRT) can synergize with immunotherapy by enhancing tumor antigen release, interferon signaling, T-cell priming, and systemic antitumor immunity. We previously completed a phase II trial comparing neoadjuvant non-ablative SBRT (24 Gy) plus immunotherapy (SBRT-IO) versus immunotherapy alone, demonstrating favorable tolerability and higher rates of major and complete pathological response (MPR, pCR) in the SBRT-IO arm. SBRT-IO may therefore represent a neoadjuvant alternative for selected patients, with the potential to reduce treatment-related toxicity. **Methods:** RICHIS (NCT06623656) is an open-label, multicenter, randomized phase II trial enrolling approximately 112 patients with histologically confirmed, surgically resectable clinical stage IB-III (N2) NSCLC. Eligible patients are ≥18 years old, have ECOG performance status 0-1, and lack EGFR mutations or ALK fusions. Participants are randomized 1:1 to receive neoadjuvant SBRT-IO (SBRT 8 Gy × 3 fractions plus up to three cycles of cemiplimab) or standard ChemoIO (platinum-based doublet chemotherapy plus up to three cycles of cemiplimab). Randomization is stratified by tumor PD-L1 expression (< 1% vs. ≥1%) and clinical stage (IB/II vs. III). Following neoadjuvant therapy, all patients undergo surgical resection and receive adjuvant cemiplimab for up to 12 months; patients in the SBRT-IO arm may additionally receive adjuvant chemotherapy. The primary endpoint is pCR. Key secondary endpoints include grade 3-5 adverse events (neoadjuvant and postoperative), event-free survival, MPR, and postoperative length of stay. Correlative immune and molecular biomarker studies are planned. Trial enrollment began on 2/4/2025 and is currently enrolling across 2 sites, with planned enrollment at 5 US sites. 19 of 112 patients are currently accrued. Clinical trial information: 24-02027124. Research Sponsor: Regeneron Pharmaceuticals.

TPS8133 Poster Session

A double-blind, double-dummy, randomized, controlled phase 3 trial of iparomlimab and tuvonralimab (QL1706) vs QL1604 as consolidation therapy following concurrent or sequential chemoradiotherapy (cCRT/sCRT) in patients (pts) with limited-stage small-cell lung cancer (LS-SCLC).

Linlin Wang, Chunling Liu, Fangling Ning, Hongxu Liu, Jiuwei Cui, Wenzhong Su, Xiang Song, Yan Yang Wang, Qingshan Li, Yu Changhua, Xianping Cheng, Xiaomin Dang, Furong Hao, Tao Wei, Yang Wei, Huayuan Wang, Jie Wang, Xiusong Qiu, Xiaoyan Kang, Jinming Yu; Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China; Affiliated Cancer Hospital of Xinjiang Medical University, Urumqi, China; Binzhou Medical University Hospital, Binzhou, China; Liaoning Cancer Hospital & Institute, Shenyang, China; Department of Oncology, The First Hospital of Jilin University, Changchun, China; Department of Respiratory, Shanxi Provincial Cancer Hospital, Taiyuan, China; Second Hospital of Shanxi Medical University, Taiyuan, China; General Hospital of Ningxia Medical University, Yinchuan, China; Oncology Department, Affiliated Hospital of Chengde Medical University, Chengde, China; Huai'an First People's Hospital, Huai'an, China; Anhui No. 2 Provincial People's Hospital, Hefei, China; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Weifang People's Hospital, Weifang, China; Anyang Tumor Hospital, Anyang, China; Sichuan Cancer Hospital, Chengdu, Sichuan, China; Qilu Pharmaceutical Co., Ltd., Jinan, China

Background: LS-SCLC is a highly aggressive malignancy with poor prognosis. Positioning effective consolidation strategies is a key focus to improve long-term patient outcomes. Prominently, immune checkpoint inhibitors (ICIs) have emerged as consolidation therapy after cCRT or sCRT for LS-SCLC. QL1706 is a bifunctional antibody against both programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4, and iparomlimab (QL1604) is an anti-PD-1 agent. In previous studies, both QL1706 and QL1604 demonstrated manageable safety profiles. Notably, QL1706 also showed encouraging preliminary anti-tumor signals in SCLC, which indicated the potential as consolidation therapy (Zhao et al. 2023; Huang et al. 2023). This trial aims to compare the efficacy and safety of QL1706 and QL1604 as consolidation therapy in pts with LS-SCLC without progression after cCRT or sCRT. **Methods:** In this multicenter double-blind double-dummy randomized controlled phase 3 trial (NCT06789796), pts with pathologically-confirmed LS-SCLC per AJCC 8^{th} edition are recruited. Pts are eligible if aged $\geq$18 years, with adequate organ function, ECOG PS scored 0 or 1, and do not have disease progression after completion of the requested cCRT or sCRT. Prophylactic cranial irradiation (PCI) is permitted before randomization. Approximately 636 pts are planned to be randomized 1:1 to receive either QL1706 (at 5 mg/kg) plus QL1604 placebo or QL1604 (at a fixed dose of 200 mg or at 3 mg/kg for pts weighing $<$40 kg) plus QL1706 placebo via intravenous infusion on day 1 in a 21-day cycle. Treatment will be continued until disease progression, intolerable toxicity, initiation of new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, trial termination, or up to 24 months, whichever occurs first. Randomization is stratified by disease stage (I/II vs. III), receipt of PCI (yes vs. no), and the type of CRT (cCRT vs. sCRT). The co-primary endpoints are progression-free survival (PFS) per RECIST v1.1 assessed by blinded independent central review (BICR), and overall survival (OS). Secondary endpoints are investigator-assessed PFS, 1-year and 2-year PFS rates assessed by BICR and investigator, objective response rate, disease control rate, duration of response, 1-year and 2-year OS rates, safety, pharmacokinetics, and immunogenicity. Exploratory endpoints are biomarker assessments and their relationship to efficacy and prognosis, as well as patient-reported outcomes. Overall two-sided Type I error (α=0.05) controlled by fixed-sequence testing: BICR assessed PFS will be tested first, followed by OS if significant. An interim analysis is planned. The study will be conducted across around 79 sites in China, and enrollment is ongoing. Clinical trial information: NCT06789796. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS8134 Poster Session

TIGOS-LS, an open-label, randomized study of BMS-986489 (atigotatug + nivolumab fixed-dose combination) vs durvalumab as consolidation therapy following chemoradiotherapy in limited-stage small-cell lung cancer.

Melissa Lynne Johnson, Jerome H. Goldschmidt, Ticiana Leal, Sarah Yue Wang, William E. Brady, Maen A. Hussein, Caressa Lietman, Hillarie Windish, Christophe Y. Calvet, Lola Dosunmu, Alisha Maniar, LaRee Tracy, Neal E. Ready; Sarah Cannon Research Institute, Nashville, TN; Sarah Cannon Research Institute at Blue Ridge Cancer Care, Blacksburg, VA; Emory Winship Cancer Institute, Atlanta, GA; Texas Oncology-Northeast Texas/Sarah Cannon Research Institute, Tyler, TX; Florida Cancer Specialists/Sarah Cannon Research Institute, Leesburg, FL; Sarah Cannon Development Innovations, Nashville, TN; Bristol Myers Squibb, Princeton, NJ; Duke Cancer Institute, Durham, NC

Background: Durvalumab consolidation was added to concurrent chemoradiotherapy for standard-of-care treatment of limited-stage small-cell lung cancer (LS-SCLC) in 2024. Although durvalumab improves overall survival (OS) and progression-free survival (PFS; Cheng et al. 2024), other agents may provide further improvement. BMS-986489 is a first-in-class fixed-dose combination of atigotatug and nivolumab. Atigotatug binds to fucosyl-monosialoganglioside-1 (fuc-GM1), which is highly expressed on SCLC cells and often absent in normal tissues. This binding causes tumor cell death via antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity. These processes trigger T cells, whose activation is also potentiated by nivolumab, which is hypothesized to improve outcomes after chemoradiotherapy. In a randomized Phase II study in extensive-stage SCLC, adding atigotatug to carboplatin, etoposide, and nivolumab (CE/NIVO) improved median OS vs CE/NIVO alone (15.6 months vs 11.4 months; Kalinka et al. 2024).
Methods: TIGOS-LS is an open-label, randomized study evaluating the safety and efficacy of BMS-986489 vs durvalumab consolidation after chemoradiotherapy in LS-SCLC. Approximately 250 participants will be enrolled at 70 sites within the US. Eligible participants are adults with an Eastern Cooperative Oncology Group performance status of 0 or 1, histologically or cytologically confirmed SCLC evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 before standard treatment was initiated, LS disease determined by PET scan at the time of initial diagnosis or justified by the participant history, and inoperable disease, if Stage I/II. All participants must have completed concurrent chemoradiotherapy without progression. Prophylactic cranial irradiation (PCI) is permitted before study treatment. Expression of fuc-GM1 is not required; participants can enroll regardless of tissue availability for the trial. Participants requiring chronic systemic corticosteroids equivalent to >10 mg of prednisone at the time of enrollment are excluded. Stratification factors include disease stage (I/II vs III) and receipt of PCI. Randomization is 1:1 to BMS-986489 or durvalumab. BMS-986489 or durvalumab is administered intravenously at a fixed dose once every 4 weeks for up to 2 years or until discontinuation criteria are met. Response is evaluated by RECIST v1.1. Survival follow-up occurs every 12 weeks for up to 3 years. The primary endpoint is OS. Secondary endpoints include PFS, objective response rate, clinical benefit rate, disease control rate, duration of response, and safety parameters. TIGOS-LS (NCT06773910) opened to enrollment in March 2025; 232 enrollment slots remain. Clinical trial information: NCT06773910. Research Sponsor: Bristol Myers Squibb.

TPS8135 Poster Session

SEZanne: A phase 2 randomized, open-label, multicenter study to evaluate the optimal dose, safety, and efficacy of ABBV-706 in combination with atezolizumab (atezo) versus standard of care (SOC) in patients (pts) with previously untreated extensive-stage (ES) small cell lung cancer (SCLC).

Kristof Cuppens, Lauren Averett Byers, Yasushi Goto, Andrea Ardizzoni, Luis G. Paz-Ares, Caicun Zhou, Afshin Dowlati, Alissa Jamie Cooper, Jair Bar, Se-Hoon Lee, Nadine Jahchan, Ye Zhao, Darius Meiman, Fang Fang, Guillermo Rivell, Tammy Palenski, Anne C. Chiang; Jessa Hospital, Hasselt, Belgium and Faculty of Medicine and Life Sciences LCRC, UHasselt, Diepenbeek, Belgium; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; Hospital Universitario 12 de Octubre, H12O-CNIO Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain; Shanghai East Hospital, Shanghai, China; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Dana-Farber Cancer Institute, Boston, MA; Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; AbbVie, Inc., North Chicago, IL; Yale School of Medicine, Yale Cancer Center, New Haven, CT

Background: SCLC is a neuroendocrine tumor accounting for ~15% of lung cancers, with a 5-year survival rate of ~7%. Platinum-based chemotherapy (PCT) remains the 1L SOC, achieving response rates of 60–70% in pts with ES-SCLC, though durable responses are rare. Adding a PD-L1 inhibitor (atezo or durvalumab) to PCT only modestly improves survival, and novel therapies are needed. Seizure-related homolog 6 (SEZ6), a neuroendocrine lineage marker highly expressed in SCLC, represents a promising target. ABBV-706, a SEZ6-directed antibody-drug conjugate with a topoisomerase 1 inhibitor payload, has shown promise as monotherapy in pts with relapsed SCLC, with an ORR of 57.3% (Byers et al. *J Thorac Oncol.* 2025;10:S23). The phase 2 SEZanne study (NCT07155174) evaluates the dose optimization, safety, and efficacy of ABBV-706 + atezo as a 1L regimen vs SOC. **Methods:** This global, open-label, randomized phase 2 study (~75 sites; up to 180 pts) compares ABBV-706 + atezo vs SOC. Eligible pts (≥18 years) have ES-SCLC requiring 1L therapy, ECOG 0–1, measurable disease per RECIST v1.1, and are candidates for PCT. Primary objectives are to evaluate safety/tolerability, identify the recommended phase 3 dose, and assess PFS of ABBV-706 in combination with atezo. Secondary objectives are to further evaluate efficacy (ORR, DOR, DCR, OS) and characterize the PK/immunogenicity of the combination. The study consists of 2 parts: a safety lead-in (~30 pts) and a dose optimization (~150 pts) stage. During safety lead-in, pts are randomized 1:1:1 to 2 doses of ABBV-706 Q3W + atezo or SOC. SOC includes 4 cycles of PCT (carboplatin) + etoposide + atezo followed by atezo maintenance; lurbinectedin may also be used in maintenance where locally approved. After the safety lead-in, additional pts will be randomized to the ABBV-706 + atezo arms that were deemed safe, or the SOC arm. Treatment continues until progression, intolerable toxicity, or other discontinuation criteria are met. The study is enrolling. Clinical trial information: NCT07155174. Research Sponsor: AbbVie Inc.

TPS8136 **Poster Session**

A randomized, open-label, phase 3 study of ZL-1310, a DLL3 antibody-drug conjugate (ADC), compared to investigator's choice therapy in participants with relapsed small cell lung cancer (DLLEVATE).

Afshin Dowlati, Raffaele Califano, Koichi Goto, Maurice Perol, Yi-Long Wu, Ralph V. Boccia, Paul A. S. Fishkin, John Turner Hamm, Benjamin Jacobs, Melissa Lynne Johnson, Gopal Kunta, Santosh Nair, Manish R. Patel, Caleb Joshua Smith, Yifan Tu, Jun Zhang, Pingkuan Zhang, Renke Zhou, Luis Paz-Ares Rodriguez; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Department of Medical Oncology, The Christie NHS Foundation Trust, The University of Manchester and Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom; National Cancer Center Hospital East, Kashiwa, Japan; Centre Leon-Berard (CLB) - Centre de Recherche en Cancerologie Lyon-Est (CRCL), Lyon, France; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Center for Cancer and Blood Disorders, Bethesda, MD; Illinois CancerCare, P.C., Peoria, IL; Norton Cancer Institute, Louisville, KY; Alliance Cancer Specialists (SCRI), Horsham, PA; Sarah Cannon Research Institute, Nashville, TN; Medical Oncology, Clermont Oncology Center, Clermont, FL; Mid Florida Cancer Centers, Orange City, FL; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Missouri Cancer Associates, Columbia, MO; Mercy South, Springfield, MO; OSF HealthCare Cancer Institute, Peoria, IL; Zai Lab (US) LLC, Cambridge, MA; Hospital Universitario 12 de Octubre, Madrid, Spain

Background: Small Cell Lung Cancer (SCLC) is a neuroendocrine tumor with high proliferation rate, early metastasis and poor prognosis. DLL3 is a validated target for neuroendocrine tumor and is highly expressed in SCLC. ZL-1310 is a novel antibody-drug conjugate (ADC) that employs the TMALIN (Tumor Microenvironment Activable LINker-payload) platform, an anti-DLL3 monoclonal antibody linked to a topoisomerase I inhibitor payload via a protease-cleavable linker. ZL-1310 has demonstrated encouraging systemic efficacy in heavily pre-treated ES-SCLC and showed intracranial activities. **Methods:** DLLEVATE is a randomized, open-label phase III study to further evaluate the efficacy and safety of ZL-1310 compared to investigator's choice of locally approved and available single agent therapy (ICT). This multi-country Phase III study (NCT07218146) enrolls adults with Extensive Stage (ES)-SCLC patients (pts) who have progressed after platinum-based first-line (1L) therapy or after tarlatamab as second-line (2L) therapy. Those with stable or asymptomatic BM are eligible (including those with no prior brain radiotherapy). The eligible pts are randomized at 1:1 according to presence/absence of brain metastasis, sensitivity to prior chemotherapy and with/without prior tarlatamab. ZL-1310 is given intravenously every 3 weeks until disease progression or unacceptable toxicity. Systemic efficacy is assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Intracranial efficacy is assessed by blind independent radiologists using Modified Criteria for Radiographic Response Assessment in Neuro-Oncology (mRANO). The study has one interim analysis based on Objective Response Rate (ORR) assessed by Blind Independent Review Committee (BIRC) and the primary analysis based on Overall Survival (OS). Enrollment is underway, and is planned at ~250 sites across several continents. Clinical trial information: NCT07218146. Research Sponsor: Zai Lab (Shanghai) Co., Ltd.

TPS8137 Poster Session

A phase 3 study of sacituzumab govitecan in patients with previously treated extensive-stage small cell lung cancer.

Afshin Dowlati, Myung-Ju Ahn, Alan Arrieira Azambuja, Lauren Averett Byers, Raffaele Califano, Federico Cappuzzo, Ying Cheng, Nicolas Girard, Lizza Hendricks, Brett Gordon Maxwell Hughes, Giannis S. Mountzios, Takayuki Takahama, Michael Thomas, James Chih Hsin Yang, Mike Vigliotti, Joseph Park, Tia Wu, Luis G. Paz-Ares; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Centro Gaúcho Integrado de Oncologia e Hematologia, Porto Alegre, RS, Brazil; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medical Oncology, The Christie NHS Foundation Trust, The University of Manchester and Division of Cancer Sciences, The University of Manchester, Manchester, United Kingdom; Istituto Nazionale Tumori Regina Elena, IRCCS, Rome, Italy; Jilin Cancer Hospital, Jilin, China; Institut du Thorax Curie Montsouris, Institut Curie, Paris, France; Maastricht University Medical Center, Maastricht, Netherlands; The Prince Charles Hospital, Chermside, Australia; Henry Dunant Hospital Center, Athens, Greece; Kindai University Hospital, Osaka, Japan; Thoraxklinik, Heidelberg University Hospital and National Center for Tumor Diseases, NCT Heidelberg, partnership between DKFZ and Heidelberg University Hospital; Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany; National Taiwan University Cancer Center, Taipei, Taiwan; Gilead Sciences, Inc., Foster City, CA; Department of Medical Oncology, Hospital 12 de Octubre, Madrid, Spain

Background: Treatment options for 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 are limited. Despite the evolving treatment landscape for ES-SCLC, toxicities and poor clinical outcomes with the current globally approved standard of care (SOC), topotecan, highlight the unmet need for novel agents. Sacituzumab govitecan (SG), a Trop-2–directed antibody-drug conjugate, demonstrated encouraging antitumor activity and manageable safety as a second-line treatment for ES-SCLC in the phase 2, open-label TROPiCS-03 study. At a median study follow-up of 12.3 months in TROPiCS-03, the 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; 1 treatment-related TEAE caused death. EVOKE-SCLC-04 (NCT06801834) is a randomized, phase 3, open-label, multicenter study evaluating the efficacy and safety of SG versus SOC (topotecan, lurbinectedin [in countries/regions where approved], or amrubicin [Japan only]) in patients with previously treated 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, and disease progression after 1 prior line of platinum-containing therapy with or without anti–PD-(L)1 therapy. Prior tarlatamab treatment is allowed. Patients with untreated central nervous system (CNS) metastases and/or carcinomatous meningitis are excluded unless these are asymptomatic and immediate CNS-specific treatment is not required. Patients will be randomized 1:1 to either SG (10 mg/kg on Days 1 and 8) or SOC: topotecan (1.5 mg/m^2 daily on Days 1–5), lurbinectedin (3.2 mg/m^2 on Day 1), or amrubicin (40 mg/m^2 daily on Days 1–3) administered as intravenous infusion in 21-day cycles, until progressive disease (assessed by investigator review 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 endpoint is OS; secondary endpoints include progression-free survival, ORR, 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 plans to enroll 695 patients from approximately 275 sites globally. Clinical trial information: NCT06801834. Research Sponsor: Gilead Sciences, Inc.

TPS8139 Poster Session

Durvalumab plus chemotherapy prior to chemoradiotherapy and followed by durvalumab as consolidation for patients with limited-stage small cell lung cancer (CONCUR study).

Qian Chu, Shanshan Huang, Fangfang Liu; Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Oncology, Tongji Hospital, Tongji Medical College, Huauhong University of Science and Tech, Wuhan, China

Background: The ADRIATIC study demonstrated that durvalumab consolidation therapy following concurrent chemoradiotherapy (CRT) significantly improved both progression free survival (PFS) and overall survival (OS) in patients with inoperable limited-stage small-cell lung cancer (LS-SCLC), establishing the standard of care for this population. Building on emerging immune checkpoint inhibitor (ICI) strategies (pre-CRT induction, post-CRT consolidation or concurrent ICI-CRT), CONCUR study innovatively introduces durvalumab plus chemotherapy as induction to synergize early immune priming with cytotoxic effects, aiming to enhance responses during subsequent CRT while preserving safety, with potential to reshape the treatment landscape for LS-SCLC. **Methods:** Approximately 100 eligible patients (aged $\geq$ 18 years) with histologically or cytologically confirmed LS-SCLC, ECOG 0-1, at least one measurable lesion (RECIST 1.1), having received no prior thoracic radiotherapy or chemotherapy will be enrolled in this multi-center, phase II study. Patients will receive durvalumab (1500mg day[D] 1) combined with cisplatin (75 mg/m^2 D1 or 25 mg/m^2 D1-3) or carboplatin (AUC 5-6 D1 or AUC 2.5-3 D1 and D8) and etoposide (100 mg/m^2 D1-3) every 3 weeks for 2 cycles as induction therapy, followed by concurrent or sequential CRT. Thoracic radiotherapy will be delivered as 60 $\pm$ 6 Gy (1.8-2 Gy/day) or 45 $\pm$ 1.5 Gy (1.5Gy twice daily), with optional prophylactic cranial irradiation per clinical indication and local clinical practice. Patients showing at least stable disease after the definitive CRT will continue durvalumab (1500 mg every 4 weeks) until disease progression, unacceptable toxicities, or for up to 24 months (whichever occurs first). The primary endpoint is PFS by investigator per RECIST 1.1. Secondary endpoints include OS, objective response rate, duration of response, and safety. The primary analysis on PFS will be performed at approximately 60% data maturity. Assuming the median PFS is 16 months (defined from first dose of treatment), with an enrollment period of 12 months and drop-out rate of 7%, 100 patients and 60% PFS maturity will provide a precision of $\pm$ 4.8 months with 95% CI (11.6m, 21.1m) estimated by Kaplan-Meier method using Brookmeyer and Crowley method. Enrollment is ongoing. Clinical trial information: NCT07055581. Research Sponsor: None.

TPS8140 **Poster Session**

A phase II trial of ivonescimab for previously treated thymic carcinoma: UCLA L-11.

Jonathan Boiarsky, Chi-Hong Tseng, Zhaohui Arter, Matthew A. Gubens, Chul Kim, Jennifer A. Marks, Surbhi Singhal, Christine Kivork, Larissa Ikenouye, Jonathan W. Goldman; University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; University of California, Irvine, Chao Family Comprehensive Cancer Center, Irvine, CA; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Georgetown University, Department of Hematology and Oncology, School of Medicine, Washington, DC; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: Thymic carcinoma (TC) is a rare and aggressive thymic epithelial tumor (TET), accounting for approximately 20% of thymic neoplasms. TC is often more invasive and less responsive to standard therapy than other TETs, with a 5-year survival rate of 30-50% in the advanced/metastatic setting. Effective treatment remains limited following progression with platinum-based chemotherapy. Programmed Death-(Ligand) 1 (PD-(L)1) inhibition demonstrates modest activity in recurrent TC, with an objective response rate (ORR) of 19.5-22.5% with manageable toxicities [Cho, *Clin Oncol*. 2019; Giaccone, *J Thorac Oncol.* 2021]. Moreover, vascular epithelial growth factor (VEGF) inhibition with sunitinib or lenvatinib achieved ORRs of 26-38% in second line therapy and beyond (Thomas, *Lancet Oncol.* 2015; Sato, *Lancet Oncol.* 2020). Combination of lenvatinib and pembrolizumab as second line therapy and beyond has shown an ORR of 22.5%, with a median duration of response of 8.2 months (Remon, *Lancet Oncol. 2025*). Ivonescimab is a humanized bispecific monoclonal antibody targeting both PD-1 and VEGF and shows favorable safety and efficacy in non-small cell lung cancer. In light of the known benefit of VEGF and PD-(L)1 blockade in TC, this study aims to evaluate the safety and efficacy of ivonescimab in patients with previously treated TC. **Methods:** This study is a multicenter, open-label, single-arm Phase II trial enrolling adults with histologically or cytologically confirmed unresectable/metastatic TC whose disease has progressed following systemic therapy. Key inclusion criteria include one-prior line of treatment, ECOG performance status ≤1, and adequate organ function. Exclusion criteria include prior treatment with PD-(L)1 inhibitors, positive paraneoplastic serologies, or autoimmune disease requiring active systemic therapy. Ivonescimab is administered intravenously on D1 of a 21-day cycle until disease progression, unacceptable toxicity, withdrawal, or loss of follow up. The primary endpoints are investigator confirmed ORR via RECIST 1.1 and safety/tolerability of ivonescimab. Secondary endpoints include progression-free survival, duration of response, time to response, and overall survival. Exploratory analyses will evaluate correlation of antitumor activity with tissue and blood-based biomarkers, such as PD-L1 expression and circulating tumor DNA (ctDNA). The study uses a Simon's two stage design: in stage 1, 15 patients will be enrolled. The study will be stopped if ≥ 5 treatment-related serious adverse events or if ≤1 patient achieves an objective response within the first three months of treatment. Otherwise, an additional 10 patients will be enrolled in stage 2. The design has 80% power with a 5% Type I error to detect an ORR of 30% over the null hypothesis of 10%. The study is currently enrolling patients. Clinical trial information: NCT06980077. Research Sponsor: Jonsson Comprehensive Cancer Center.