LBA8500 **Oral Abstract Session**

Sunvozertinib monotherapy versus platinum-based chemotherapy as first-line treatment for advanced NSCLC with EGFR exon20ins: Primary analysis of a multinational phase 3 randomized study (WU-KONG28).

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8501 Oral Abstract Session

Overall survival of first-line amivantamab plus lazertinib in atypical *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): Updated results from the CHRYSALIS-2 study.

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Background: Patients with atypical *EGFR*-mutated advanced NSCLC have worse long-term outcomes with EGFR-targeted therapies than classical exon 19 deletion/L858R mutations (c*EGFR*). Afatinib, approved for atypical *EGFR*-mutated NSCLC, showed a median overall survival (OS) of 19.4 months among 38 participants (pts) with atypical *EGFR*-mutations globally (Yang *Lancet Oncol* 2015). Amivantamab (ami)-based regimens are approved across multiple lines of therapy in different settings for c*EGFR* and exon 20 insertion (Ex20ins)-mutated advanced NSCLC. In MARIPOSA, first-line (1L) ami plus lazertinib (ami-laz) significantly prolonged OS vs osimertinib (HR, 0.75; *P*=0.005) in c*EGFR*-mutated NSCLC. In an earlier report of 49 pts with atypical *EGFR*-mutated advanced NSCLC who received 1L ami-laz, objective response rate (ORR) was 57%, median response duration was 20.7 months, median progression-free survival (PFS) was 19.5 months, and OS was still immature (Tomasini *JCO* 2025). Here we report OS data with longer follow-up for pts with atypical *EGFR*-mutated NSCLC who received 1L ami-laz. **Methods:** Cohort C of the global, phase I/Ib CHRYSALIS-2 study (NCT04077463) enrolled pts with atypical *EGFR* mutations, excluding Ex20ins and co-mutations with c*EGFR*, who were previously untreated or had ≤2 prior lines of therapy, which may have included a $1^{st}/2^{nd}$-generation EGFR TKI. All enrolled pts received intravenous ami-laz. The primary endpoint was ORR by investigator per RECIST v1.1, which has been previously reported. Here we report OS, a key secondary endpoint, in the treatment-naïve population (n=49). **Results:** As of Oct 31, 2025, the median follow-up was 31.3 months (range, 0.1–53.2). The median OS was 41.0 months (95% CI, 27.7–not estimable), with 55% alive at 3 years and 46% alive at 4 years. As of data cutoff, 20% (10/49; 6 were confirmed responders and 4 had stable disease) of pts were still ongoing 1L treatment (range, 2.5–4.4 years), with 7 pts receiving ami treatment for >3 years. Safety profile was consistent with prior reports; no additional safety signals were identified with longer-term follow-up. Among pts whose disease had progressed and discontinued 1L treatment, 71% (20/28) received subsequent therapy. The most common subsequent regimens included platinum-based chemotherapy agents (55%). **Conclusions:** 1L treatment of atypical *EGFR*-mutated advanced NSCLC with ami-laz resulted in a clinically meaningful median OS of nearly 3.5 years. Many pts were able to stay on 1L treatment long term, with 20% still ongoing. Ami-laz has now shown substantial survival benefit in both 1L c*EGFR*- and atypical *EGFR*-mutated disease. The recently FDA-approved subcutaneous formulation of ami may further simplify the overall treatment experience for this regimen. Clinical trial information: NCT04077463. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

8502 Oral Abstract Session

Lorlatinib vs crizotinib as first-line treatment for advanced *ALK*+ non-small cell lung cancer: 7-year update from the phase 3 CROWN study.

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Background: Median progression-free survival (PFS) was not reached (NR) with lorlatinib in the phase 3 CROWN study after 5 yrs of f/u, representing the longest PFS reported in advanced non-small cell lung cancer (NSCLC). Due to the unprecedented PFS benefit with lorlatinib after 5 yrs of f/u and the decreased event rate after the first 24 mos in the study, we aimed to quantify long-term outcomes at 7 yrs. **Methods:** 296 treatment-naive patients (pts) with advanced *ALK*+ NSCLC were randomized 1:1 to receive lorlatinib 100 mg once daily (n=149) or crizotinib 250 mg twice daily (n=147). This post hoc analysis presents investigator-assessed efficacy outcomes, safety, and biomarker analyses. Formal statistical testing between arms was not performed. **Results:** As of October 31, 2025, 66 of 149 pts (44%) vs 4 of 142 (3%) were receiving lorlatinib vs crizotinib. With a median f/u for PFS (95% CI) of 83.0 (81.2-86.3) and 77.2 mos (36.8-not evaluable), respectively, median PFS (95% CI) was NR (68.5-NR) with lorlatinib and 9.1 mos (7.4-10.9) with crizotinib (HR, 0.19; 95% CI, 0.13-0.26); the 7-yr PFS (95% CI) was 55% (46-63) and 3% (1-8). In the lorlatinib arm, pts without a PFS event at the end of 24 mos had a 79% probability of survival without progression at yr 7. PFS benefit was consistent across all prespecified subgroups. No new intracranial (IC) progression events occurred after the first 30 mos on lorlatinib. Median time to IC progression (95% CI) was NR (NR-NR) with lorlatinib and 16.4 mos (12.7-21.9) with crizotinib (HR, 0.06; 95% CI, 0.03-0.12). The number of overall survival (OS) events for a protocol-specified analysis has not been met; OS f/u is still ongoing. The safety profile was consistent with the 5-yr results, with all-cause grade 3/4 adverse events (AEs) in 77% of pts with lorlatinib and 57% with crizotinib. Treatment-related AEs (TRAEs) led to permanent treatment discontinuation in 5% of pts with lorlatinib and 6% with crizotinib. No new permanent discontinuations due to TRAEs occurred after the first 26 mos with lorlatinib. Dose reductions were reported in 34% of pts in the lorlatinib arm (17% had 1 dose reduction and 17% had 2 reductions). Long-term efficacy was similar between pts with and without dose reduction. Exploratory translational analyses of outcomes in pts with different molecular subtypes and resistance mechanisms at the end of treatment are ongoing. **Conclusions:** With median PFS yet to be reached after 7 yrs of f/u in CROWN, lorlatinib continues to show unprecedented and highly durable benefit in treatment-naïve pts with advanced *ALK*+ NSCLC. In pts without a PFS event at 24 mos, the probability of survival without progressive disease at 7 yrs was 79%. Longer f/u showed very few additional PFS events, no new IC progression, and no new treatment-related discontinuation, suggesting long-term substantial benefit with lorlatinib for the majority of pts with advanced *ALK*+ NSCLC. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

8503 Oral Abstract Session

ALKOVE-1: Efficacy and safety of neladalkib in patients with advanced *ALK*+ NSCLC.

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Background: Neladalkib is an investigational ALK TKI designed for inhibition of ALK single and compound resistance mutations, brain penetrance, and sparing TRK. We report the first analyses of phase 2 TKI pre-treated patients (pts) and preliminary data in TKI-naïve pts with *ALK*+ NSCLC. **Methods:** The global, single arm phase 1/2 ALKOVE-1 trial (NCT05384626) enrolled pts with advanced/metastatic *ALK*+ NSCLC. Key study endpoints are objective response rate (ORR, RECIST v1.1 by BICR), duration of response (DOR), intracranial ORR (IC-ORR) and safety. Efficacy analyses included TKI pre-treated pts who initiated neladalkib 150 mg QD by 30 Sep 2024 or all treated TKI-naïve pts. Data cut: 29 Aug 2025. **Results:** 656 pts with *ALK*+ NSCLC received neladalkib. Efficacy-evaluable TKI pre-treated pts (n=253) had received a median of 3 prior anticancer therapies (range 1-11, 51% prior chemo). 78% of pts received ≥2 (range 2-5) prior ALK TKIs, of whom 91% had prior lorlatinib. 19% had single or compound ALK G1202R resistance mutations. 40% had CNS disease by BICR. ALK TKI pre-treated results are reported in the Table. In a preliminary analysis of TKI-naïve pts, ORR was 86% (38/44, 2 uPRs); 12-month DOR rate was 91%. IC-ORR was 78% (7/9) with no CNS progression events as of data cutoff. **Conclusions:** In this ALK TKI pre-treated data set, neladalkib demonstrated clinically meaningful activity, including in pts with CNS disease, ALK G1202R single or compound mutations, and prior lorlatinib. Encouraging preliminary activity was also observed in TKI-naïve pts. Neladalkib's safety profile was consistent with its ALK-selective, TRK-sparing design. Clinical trial information: NCT05384626. Research Sponsor: Nuvalent, Inc.

Efficacy Parameter (RECIST v1.1, BICR)	All ALK TKI Pre-treated ± chemo	ALK TKI Pre-treated, Lorlatinib-naïve ± chemo
ORR % (n/N)	31 (79/253)[a, b]	46 (29/63)[c]
95% CI	26, 37	33, 59
% DOR ≥ 12 m (95% CI) / 18 m (95% CI) [d]	64 (51, 75) / 53 (34, 68)	80 (58, 91) / 60 (19, 85)
G1202R Mutation		
ORR % (n/N)	68 (32/47)[e,f]	83 (10/12)
95% CI	53, 81	52, 98
% DOR ≥ 12 m [d] **(95% CI)**	80 (61, 91)	77 (34, 94)
Intracranial Activity		
IC-ORR % (n/N)	32 (29/92)[g, h]	63 (15/24)[g]
95% CI	22, 42	41, 81
% IC-DOR ≥ 12 m [d] **(95% CI)**	71 (48, 85)	92 (57, 99)

m, months; NE, not estimable.
[a]Includes 2 unconfirmed partial responses (uPRs).
[b]Pts with prior lorlatinib: ORR 26% (50/190, including 2 uPRs) and mDOR 17.6 m (95% CI: 6.9, NE).
[c]Pts with 1 prior 2nd generation ALK TKI (alectinib, n=44; brigatinib, n=2) ± chemo: ORR 48% (22/46) and DOR ≥ 12 m of 74% (95% CI: 48, 88).
[d]Estimated by Kaplan-Meier analysis.
[e]Single or compound G1202R resistance mutations may be present.
[f]Includes 1 uPR.
[g]Includes 2 IC-uPRs.
[h]Pts with prior lorlatinib: IC-ORR 21% (14/68) and IC-DOR ≥ 12 m of 55% (95% CI: 26, 77).

Efficacy and safety of pralsetinib as first-line treatment of *RET* fusion–positive advanced or metastatic non–small cell lung cancer (NSCLC): The phase 3 AcceleRET-Lung study.

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Background: Pralsetinib, an oral tyrosine kinase inhibitor, selectively and potently targets oncogenic *RET* fusion and mutation proteins. Pralsetinib is FDA approved to treat adults with metastatic *RET*-altered NSCLC. We present efficacy and safety of pralsetinib vs standard of care (SOC) in first-line *RET* fusion-positive NSCLC from a randomized phase 3, open-label study, AcceleRET-Lung (NCT04222972). **Methods:** AcceleRET-Lung was conducted at 74 sites in 22 countries. Adults with *RET* fusion-positive advanced or metastatic NSCLC received pralsetinib 400 mg/d or platinum-based SOC therapy. Crossover to pralsetinib was optional upon progression. The primary end point was progression-free survival (PFS) per RECIST v1.1. Secondary end points included overall response rate (ORR), overall survival (OS), duration of response (DOR), and safety. Efficacy was evaluated in randomized patients (intent-to-treat population [ITT]). Safety was assessed in patients receiving ≥1 dose of study drug. **Results:** 223 ITT patients were randomized to pralsetinib (n=110) or SOC (n=113). Pralsetinib and SOC groups had similar baseline characteristics (median age: 62 and 63 y, respectively; female: 48% and 57%; median lesions: both 4; brain metastases: 15% and 16%). The study was terminated early per sponsor decision on January 27, 2025. ITT patients in the pralsetinib group had significantly greater median PFS vs SOC (18.7 vs 9.0 mo; P=0.003), ORR (65.5% vs 41.6%; P<0.001), and median DOR (20.6 vs 9.7 mo; P=0.004; Table). Safety was generally consistent with the known pralsetinib profile except for a higher rate of infection in the pralsetinib group vs SOC (71.3% vs 51.9%), including pneumonia (19.4% vs 5.8%), urinary tract infections (17.6% vs 7.7%), and opportunistic infections (9.3% vs 1.0%). There were 32 (30.0%) and 26 (25.0%) deaths in the pralsetinib and SOC groups, respectively, with 8 (7.4%) and 0 due to infection. Common grade ≥3 TRAEs in the pralsetinib vs SOC groups were hypertension (11.1% vs 0), neutropenia (10.2% vs 8.7%), anemia (8.3% vs 10.6%), and decreased neutrophil count (7.4% vs 4.8%). **Conclusions:** In a Phase 3 study, pralsetinib met the primary PFS end point and had a significantly greater and more durable ORR vs SOC, confirming the clinical utility of pralsetinib in *RET* fusion-positive NSCLC. Monitoring for infections with pralsetinib is warranted. Clinical trial information: (1) NCT04222972; (2) 2023-505035-12-00; (3) 2019-002463-10. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy outcomes.

	Pralsetinib (n=110)	SOC (n=113)	Stratified hazard ratio/odds ratio (95% CI)	*P* Value
Duration of follow-up, mo, median (range)	20.5 (0, 49.8)	16.0 (0, 42.3)	-	-
PFS, mo, median (95% CI)	18.7 (11.1, 25.2)	9.0 (7.1, 11.5)	0.59 (0.42, 0.84)	0.003
ORR, % (95% CI)	65.5 (55.8, 74.3)	41.6 (32.4, 51.2)	2.81 (1.61, 4.93)	<0.001
OS, mo, median (95% CI)	NR (29.6, NR)	39.8 (39.8, NR)	1.09 (0.65, 1.85)	0.742
DOR, mo, median (95% CI)	20.6 (17.2, 31.8)	9.7 (7.6, 15.9)	0.48 (0.28, 0.80)	0.004

8505 Oral Abstract Session

Efficacy and safety of lunbotinib (A400/EP0031), a next-generation selective RET inhibitor (SRI), from a pivotal phase II study in patients with advanced *RET* fusion–positive non–small cell lung cancer (NSCLC).

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Background: RET-fusion positive NSCLC accounts for 1-2% of all lung cancers. Lunbotinib is a next gen brain-penetrant SRI with high potency against RET fusion and mutant proteins (*Zhou et al., 2023*; *Alonso et al., 2025*). We report findings from a pivotal phase II study in advanced RET-fusion positive NSCLC in China (NCT05265091). An ongoing study is assessing lunbotinib alone or in combination with chemotherapy in Western patients (pts) (NCT05443126). **Methods:** The phase II part enrolled two single-arm cohorts: cohort 1 included pts with prior platinum-based chemotherapy and immunotherapy (pre-treated), and cohort 2 included treatment-naïve pts. All pts received oral lunbotinib 90 mg once daily in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was ORR assessed by an independent review committee (IRC) per RECIST v1.1. **Results:** As of Oct 29, 2025, 71 pre-treated pts and 92 treatment-naïve pts were enrolled, with median follow-up of 22.6 and 20.7 mos, respectively. Among pre-treated and treatment-naïve pts in full analysis set (FAS), ECOG PS 1 rates were 90% and 80.2%, and metastases involving ≥3 organ sites were observed in 75.7% and 57.1%. IRC-assessed confirmed ORR was 87.1% (95% CI: 77.0-93.9) in pre-treated pts and 81.3% (95% CI: 71.8-88.7) in treatment-naïve pts. mPFS was 27.5 mos and NR, respectively. Among pts with baseline CNS metastases (23 pre-treated, 16 treatment-naïve), ORR was 82.6% and 75.0%, respectively, and 6 pts in each cohort had complete intracranial response. Full efficacy data are in Table. Treatment-related AEs (TRAEs) occurred in 98.8% of pts, the most common were AST (72.4%), ALT (68.1%), anemia (63.2%), urinary retention (45.4%), dry eye (43.6%), and increased blood creatinine (42.9%). Grade ≥ 3 TRAEs observed in 40.5%. Two pts (1.2%) discontinued due to TRAEs. No fatal TRAEs occurred. **Conclusions:** Lunbotinib demonstrated robust efficacy in pts with advanced RET-fusion positive NSCLC, with high ORR and prolonged PFS in both pre-treated and treatment-naïve populations, and notable intracranial activity. Safety profile was manageable, with no new signals identified. These data support the potential of lunbotinib as a valuable therapeutic option for this population. Clinical trial information: NCT05265091. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

	Pre-treated pts (Cohort 1) N=71	Treatment-naïve pts (Cohort 2) N=92
Confirmed ORR[a]/DCR[a], % (95% CI)	87.1 (77.0, 93.9)/ 91.4 (82.3, 96.8)	81.3 (71.8, 88.7)/ 92.3 (84.8, 96.9)
mDoR[a] (95% CI), mo	25.7 (14.8, NE)	NR (NE, NE)
24-mo DoR rate, % (95% CI)	55.4 (41.1, 67.5)	NE
mPFS (95% CI), mo	27.5 (16.1, NE)	NR (19.4, NE)
24-mo PFS rate, % (95% CI)	52.1 (39.3, 63.5)	59.9 (47.8, 70.0)
mOS (95% CI), mo	NR (26.1, NE)	NR (NE, NE)
24-mo OS rate, % (95% CI)	65.7 (51.5, 76.6)	74.1 (62.1, 82.8)
Baseline CNS metastases, n	23	16
ORR, % (95% CI)	82.6 (61.2, 95.0)	75.0 (47.6, 92.7)

[a]In FAS; N was 70 and 91.

Sacituzumab tirumotecan (sac-TMT) plus pembrolizumab (P) versus pembrolizumab (P) as first-line treatment for PD-L1–positive advanced non-small cell lung cancer (NSCLC): Results from the randomized phase 3 OptiTROP-Lung05 study.

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Background: Pembrolizumab has been the standard first-line treatment for PD-L1 positive advanced NSCLC. Sac-TMT, a TROP2-directed antibody-drug conjugate with a unique bifunctional linker, and PD-1/L1 inhibitors demonstrate complementary mechanisms that enhance antitumor activity in the first-line treatment of NSCLC (*Hong et al., Nat Med, 2025*). Here, we report the results from the planned interim analysis for PFS in this phase 3 OptiTROP-Lung05 study (NCT06448312). **Methods:** Eligible patients (pts) had treatment-naïve, locally advanced or metastatic NSCLC without *EGFR/ALK* alterations and positive PD-L1 expression (defined as TPS ≥1%, 22C3 assay). Pts were stratified by PD-L1 (TPS 1-49% vs ≥ 50%), histology (squamous vs non-squamous) and ECOG (0 vs 1) and then randomized (1:1) to receive sac-TMT 4 mg/kg Q2W plus P 400 mg Q6W or P 400 mg Q6W. The primary endpoint was PFS per RECIST 1.1 assessed by blinded independent central review (BICR), and the key secondary endpoint was OS. **Results:** A total of 413 pts (median age 65 yrs; 84.5% ECOG 1; 40.0% squamous; 40.0% PD-L1 TPS ≥ 50%) were randomized to receive sac-TMT + P (n = 208) or P (n = 205). As of Sep 29, 2025, the median follow-up was 10.5 months. PFS by BICR was significantly longer in the sac-TMT + P group than the P group (median, not reached vs 5.7 months; HR, 0.35; 95% CI, 0.26-0.47; $p< 0.0001$). The data for OS were not mature, and a favorable trend was observed in the sac-TMT + P group (HR, 0.55; 95% CI, 0.36-0.85). The BICR-assessed ORR was 70.2% in the sac-TMT + P group versus 42.0% in the P group. In the pre-specified PD-L1 subgroups, the HRs for PFS in pts with TPS 1-49% and TPS ≥ 50% were 0.28 (95% CI, 0.19-0.41) and 0.47 (95% CI, 0.29-0.77). In the pre-specified histology subgroups, the HRs for PFS in pts with non-squamous and squamous were 0.28 (95% CI, 0.18-0.43) and 0.44 (95% CI, 0.29-0.66). Grade ≥ 3 TEAEs were 55.3% in the sac-TMT + P group and 31.4% in the P group. Most common grade ≥3 TEAEs of special interest for sac-TMT were neutrophil count decreased (17.3%), anemia (9.1%), and stomatitis (5.3%). TEAEs led to discontinuation of sac-TMT/pembrolizumab in 3.8%/5.3% of pts in the sac-TMT + P group while discontinuation of pembrolizumab occurred in 4.9% of pts in the P group. **Conclusions:** To our knowledge, this is the first phase 3 study to demonstrate the significant PFS benefit of an antibody-drug conjugate plus pembrolizumab in the first-line treatment of PD-L1 positive advanced NSCLC compared to pembrolizumab. The safety profile of sac-TMT + P was generally manageable and consistent with the safety profile of the components. No new safety signals were seen. These results from phase 3 OptiTROP-Lung05 study support sac-TMT + P as a potential new treatment option for this population. Clinical trial information: NCT06448312. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

LBA8507 **Oral Abstract Session**

A randomized, open-label, parallel-controlled phase 3 trial of benmelstobart plus chemotherapy and anlotinib for first-line treatment of advanced non-squamous non–small cell lung cancer.

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8509 Clinical Science Symposium

Neoadjuvant almonertinib followed by chemo-immunotherapy in II-IIIb EGFR-mutant NSCLC: A single arm, phase II study (NEOVADE).

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Background: Neoadjuvant target therapy has improved objective response rate (ORR) or major pathological response (MPR) of stage IIA-IIIB non-small cell lung cancer (NSCLC) with EGFR mutation. EGFR-TKI-induced evolution indicated a hot-tumor status in residual disease. However, the role of immunotherapy in this phrase remained unclear. Here, we present the results of a phase II, open-label study investigating the efficacy and safety of sequential almonertinib and chemo-immunotherapy (IO) in potentially resectable stage IIA-IIIB EGFR-mutant NSCLC patients. (NCT06300424). **Methods:** Untreated patients with II-IIIB NSCLC were enrolled in this study. Patients received almonertinib for 6 weeks, followed by 3 cycles of adebrelimab and chemotherapy before surgery. Primary end point was MPR, Secondary end points included pathological complete response (PCR), ORR, event-free survival (EFS), overall survival (OS) and safety. **Results:** A total of 32 patients were enrolled from Apr 2024 to Aug 2025. EGFR mutation subtype was 19del in 16 (50.0%) patients, L858R in 11 (34.4%) patients, others in 5 (15.6%) patients. All the patients completed neoadjuvant almonertinib, 30 (93.8%) patients completed 3 circles of chemo-IO and underwent surgery, R0 was achieved in 29 (96.7%) patients. ORR was 46.9% (15/32) and 59.4% (19/32) after target therapy and chemo-IO, respectively. MPR was documented in 13 (40.6%) patients, including PCR in 5 (15.6%) patients. In patients underwent resection, MRP and PCR rate were 66.7% and 33.3% in patients with PD-L1≥1%, compared with 21.4% and 0% in PD-L1 < 1% subgroup, respectively, N downstage was confirmed in 44.8% (13/29) patients. After a median follow-up of 13.5 months (interquartile range [IQR], 7.5–16.1 months), 31 (96.9%) patients were alive. Median EFS and OS were not reached. One-year EFS and OS rate was 89.5% and 95.2%, respectively. Grade ≥ 3 AEs occurred in 28 (87.5%) patients during neoadjuvant therapy. **Conclusions:** This study met its primary endpoint, indicating almonertinib followed by chemo-IO was a feasible neoadjuvant treatment in patients with resectable stage IIA-IIIB EGFR-mutant NSCLC, especially in patients with PD-L1 expression. The study was partially supported by Jiangsu Hengrui Pharmaceuticals and Hansoh Pharmaceutical Group Co. Ltd. Clinical trial information: NCT06300424. Research Sponsor: None.

Primary and secondary outcomes.

Outcomes	ITT (N=32)	Resection (N=29)
Major pathological response rate	40.6% (13/32)	44.8% (13/29)
PD-L1 < 1%	18.8% (3/16)	21.4% (3/14)
PD-L1≥1%	62.5% (10/16)	66.7% (10/15)
Complete pathological response rate	15.6% (5/32)	17.2% (5/29)
PD-L1 < 1%	0.0% (0/16)	0.0% (0/14)
PD-L1≥1%	31.3% (5/16)	33.3% (5/15)
After receiving neoadjuvant TKI		
ORR	46.9% (15/32)	44.8% (13/29)
DCR	93.8% (30/32)	96.6% (28/29)
After receiving neoadjuvant TKI+IO		
ORR	59.4% (19/32)	58.6% (17/29)
DCR	100.0% (32/32)	100.0% (29/29)

TKI: Tyrosine kinase inhibitor; IO: Immunotherapy.

First-line (1L) divarasib plus pembrolizumab (pembro) in advanced or metastatic *KRAS* G12C+ non–small cell lung cancer (NSCLC): Results from the Krascendo-170 study.

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Background: Krascendo 170 (NCT05789082) is an open-label, phase Ib/II, dose-finding and -expansion study of divarasib, an oral next-generation KRAS G12C inhibitor, with/without other anti-cancer therapies in 1L *KRAS G12C*+ NSCLC. We report the primary analysis for pts receiving divarasib plus pembro in the programmed death-ligand 1 (PD-L1)-positive cohort (tumor cell [TC] ≥1%; cohort A1) and key preliminary data for the PD-L1-negative cohort (TC <1%; cohort A2). **Methods:** Eligible pts were aged ≥18 years with untreated advanced or metastatic *KRAS G12C*+ NSCLC and ECOG PS ≤1. All pts received oral divarasib once daily plus intravenous pembro 200 mg once every 3 weeks until loss of clinical benefit, disease progression, study withdrawal or unacceptable toxicity. In cohort A1, pts were randomized 1:1 to receive divarasib 200 or 400 mg. In cohort A2, all pts received divarasib 400 mg. We present data only from pts receiving divarasib 400 mg. Primary endpoints were safety and tolerability. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and duration of response (DOR; all investigator-assessed per RECIST v1.1). **Results:** At data cutoff (Oct 29, 2025), 59 pts were enrolled to receive divarasib 400 mg in cohort A1 and 23 pts in cohort A2. In cohort A1 (median duration of divarasib treatment 10.6 months [range 0.3–24.3]), treatment-related AEs (TRAEs; divarasib- or pembro-related) were reported in 98% of pts; 65% of pts had grade (gr) 3/4 TRAEs and 0% had gr 5 TRAEs (Table). The most common TRAEs were diarrhea (75%; gr 3/4 16%), nausea (64%; gr 3/4 2%), vomiting (49%; gr 3/4 2%), ALT increase (49%; gr 3/4 20%) and AST increase (47%; gr 3/4 18%). In cohort A1, confirmed ORR was 73%, no patients had progressive disease as their best response, median DOR was not reached and median PFS was 19.3 months (95% CI 12.4–not estimable [NE]). In cohort A2 (median duration of divarasib treatment 2.8 months [range 0.5–8.8]), TRAEs were reported in 100% of pts (65% gr 3/4; 0% gr 5) and unconfirmed ORR was 70%. **Conclusions:** In Krascendo 170, divarasib 400 mg once daily plus pembro had a manageable safety profile. Promising efficacy was shown in pts with advanced *KRAS G12C*+ NSCLC in both PD-L1- positive and -negative cohorts. A global, phase III trial investigating divarasib 400 mg in 1L advanced *KRAS G12C*+ NSCLC (Krascendo 2; NCT06793215) is currently enrolling. Clinical trial information: NCT05789082. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd.; Third-party medical writing assistance, under the direction of the authors, was provided by Tahmina S. Alam, MA, and Rebecca Benatan, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	Cohort A1, n=59*,†	Cohort A2, n=23
Median follow-up, months	12.2	3.4
Safety, n (%)		
Any gr TRAE	54 (98)	23 (100)
Gr 3/4 TRAE / serious TRAE	36 (65) / 19 (35)	15 (65) / 3 (13)
TRAE leading to	28 (51) / 40 (73)	13 (57) / 14 (61)
Dose reduction / interruption	14 (25)	3 (13)
Discontinuation		
ORR, % (95% CI)	73 (60–84)	70‡ (47–87)
Median PFS, months [95% CI]	19.3 [12.4–NE]	–

*3 pts did not receive treatment, 1 pt received divarasib 200 mg; †safety analysis comprised all pts treated with divarasib 400 mg (n=55); ‡unconfirmed.

Elisrasib (D3S-001), a next-generation GDP-bound KRAS G12C inhibitor, as first-line therapy for *KRAS* G12C mutation–positive non–small cell lung cancer (NSCLC).

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Background: Elisrasib (D3S-001) is a next-generation KRAS G12C inhibitor (G12Ci) designed to improve target engagement (TE) efficiency and overcome growth factor-induced nucleotide exchange. This unique MoA distinguishes elisrasib from prior G12Ci and has demonstrated robust and durable anti-tumor activity in PDX models, and in combination with immunotherapy (IO) in immunocompetent models. Current ongoing phase 1/2 trial (NCT05410145) evaluates elisrasib as monotherapy (mono) or combination (combo) with pembrolizumab as first line (1L) therapy for advanced NSCLC harboring G12C mutation. **Methods:** Treatment naïve patients (pts) with G12C mutant advanced stage NSCLC were eligible. Elisrasib is administered 600mg QD orally in a 21-day cycle as mono or combo with pembrolizumab i.v. 200mg Q3W. The key objectives included safety and efficacy. ctDNA dynamic was analyzed by Guardant360 CDx or OncoCompass Target panels. **Results:** As of 06 Jan 2026, 43 pts and 52 pts received mono and combo. Median study follow up was 8.5m and 5.7m in mono and combo, respectively. In mono, 41 (PD-L1 TPS [22C3]: 21 <1% and 20 ≥1%) out of 43 pts were efficacy evaluable. Overall ORR was 78.0% (32/41). Subgroup ORRs in TPS <1% and ≥1% were 76.2% and 80.0%, respectively. Median PFS and DOR were immature. 6m PFS rate was 68.9% and 6m DOR rate was 77.2%. Above results provide first time evidence of G12Ci monotherapy in 1L NSCLC. In combo, 48 (PD-L1 TPS [22C3]: 17 <1%, 11 1-49%, and 20 ≥50%) out of 52 pts were efficacy evaluable. Overall ORR was 81.2% (39/48). Subgroup ORRs in TPS <1%, 1-49%, and ≥50% were 70.6%, 72.7% and 95.0%, respectively. Median PFS and DOR in the overall combo population were immature. 6m PFS rate was 74.6% and 6m DOR rate was 80.5%. Toxicity profile is summarized in Table. Baseline ctDNA G12C+ was detected in 90% (37/41) of mono and 80% (37/46) of combo. 35 mono and 25 combo pts completed on-treatment ctDNA analysis, with 83% and 100% achieved molecular response (≥90% G12C MAF reduction), respectively. PK at 600mg QD achieved C_{trough} exposure of ~5nM and ~3nM with mono and combo, respectively, with overlapping variabilities at steady state, both well above the required exposure (1nM) for complete TE. **Conclusions:** Both elisrasib monotherapy and in combination with pembrolizumab show strong efficacy and good tolerability as 1L treatments for G12C-mutant NSCLC, warrant for randomized study to evaluate elisrasib as a potential new standard of care. Clinical trial information: NCT05410145. Research Sponsor: D3 Bio.

TRAEs*	1L NSCLC Mono (N=43)	1L NSCLC Combo (N=52)
Any Grade	41 (95.3%)	48 (92.3%)
≥G3	3 (7.0%)	17 (32.7%)
LFT TRAEs* by PT (≥G3)		
ALT increased	0	4 (7.7%)
AST increased	0	3 (5.8%)

*TRAEs for combo cohort is related to elisrasib and/or pembrolizumab.

Efficacy and safety of HLX43 (anti–PD-L1 ADC) in patients with advanced non–small cell lung cancer.

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Background: HLX43 (a PD-L1 ADC) has demonstrated encouraging efficacy with a manageable safety in a phase 1 study. Here, we present the pooled findings from patients with NSCLC in a phase 1 study (HLX43-FIH101) as well as a global phase 2 study investigating HLX43 in NSCLC (HLX43-NSCLC201). **Methods:** The phase 1 study included a dose-escalation phase in patients with advanced solid tumors (0.5–4.0 mg/kg Q3W), followed by a dose-expansion phase in patients with advanced or metastatic NSCLC at doses of 2.0, 2.5, and 3.0 mg/kg Q3W. The phase 2 study was conducted in NSCLC and comprised two parts: Part A was dose-exploration for patients who had failed prior first-line therapy and had no actionable genomic alterations, to receive HLX43 at 2.0 or 2.5 mg/kg Q3W; Part B was dose-expansion in which patients received HLX43 at the recommended dose determined from Part A. This analysis integrated data from heavily pretreated NSCLC patients enrolled across both studies. Efficacy and safety outcomes were evaluated in the pooled population. **Results:** As of December 31, 2025, 205 patients were enrolled and received HLX43 at 1 mg/kg (n = 3), 2 mg/kg (n = 89), 2.5 mg/kg (n = 85), 3 mg/kg (n = 23), and 4 mg/kg (n = 5). Patients received a median of 2 lines of prior antitumor therapy (range, 1–9). Among the 161 response-evaluable patients (2, 69, 64, 21, and 5 in the 1, 2, 2.5, 3, and 4 mg/kg groups, respectively), the investigator-assessed ORR was 31.1%. In the 2.0 mg/kg group, investigator-assessed ORR was 36.4% for squamous NSCLC (n = 33); among these patients, ORR was 40.0% for those who previously failed docetaxel (n = 15). ORR was 47.4%, and 50.0% for patients with EGFR-wildtype (n = 19), and EGFR-mutant (n = 16) nonsquamous NSCLC receiving HLX43 at 2.5 mg/kg. Biomarker exploratory analyses showed that efficacy was not associated with PD-L1 expression, with ORRs of 30.1% and 32.1% in patients with PD-L1-positive (n = 83) and PD-L1-negative tumors (n = 78), respectively. Overall, 199 (97.1%) patients experienced treatment-related adverse events (TRAEs), of whom 88 (42.9%) had grade ≥3 in severity. Most common Grade ≥3 TRAEs (incidence ≥10%) included lymphocyte count decreased (n = 47, 22.9%), white blood cell count decreased (n = 27, 13.2%), anemia (n = 25, 12.2%), and neutrophil count decreased (n = 23, 11.2%). TRAEs led to treatment discontinuation in 17 (8.3%) patients. **Conclusions:** HLX43 exhibited promising efficacy in patients with heavily pretreated advanced NSCLC, regardless of histology subtypes, and PD-L1 expression, along with manageable tolerability. Further investigation is warranted. Clinical trial information: NCT06115642 (HLX43-FIH101-phase 1 study), NCT06907615 (HLX43-NSCLC201- phase 2 study). Research Sponsor: Shanghai Henlius Biotech, Inc.

8513 Rapid Oral Abstract Session

Phase 2 data from ROSETTA Lung-02, a global randomized phase 2/3 trial of pumitamig (PD-L1 × VEGF-A bsAb) + chemotherapy in 1L NSCLC.

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Background: Pumitamig (BNT327/BMS986545) is an investigational PD-L1 × VEGF-A bsAb designed to restore effector T-cell function by binding PD-L1 and localizing VEGF-A neutralization within the tumor microenvironment. We present the prespecified interim analysis of the Phase 2 dose-optimization part of the global Phase 2/3 ROSETTA Lung-02 trial (NCT06712316) evaluating the recommended Phase 3 dose of pumitamig + chemotherapy in 1L NSCLC. **Methods:** The Phase 2 part of ROSETTA Lung-02 enrolled pts with treatment-naïve advanced NSCLC, no actionable genomic alterations, regardless of PD-L1 status, ECOG PS ≤1, and ≥1 measurable lesion per RECIST v1.1 into two substudies based on histology (nonsquamous [NSQ] and squamous [SQ]). Pts were randomized 1:1 to 1400 mg (dose level [DL] 1) or 2000 mg (DL2) pumitamig + histology-specific chemotherapy Q3W (NSQ: carboplatin + pemetrexed; SQ: carboplatin + paclitaxel). Primary endpoints were safety, overall response rate (ORR), and best percentage change in tumor size from baseline. Key secondary endpoints include duration of response (DOR) and disease control rate (DCR). **Results:** The Phase 2 part enrolled 44 pts (NSQ n=23; SQ n=21; data cutoff Nov 21, 2025). Median age was 66 y (range: 41–87), and 27 (61.4%) pts had ECOG PS 1. Among 40 response-evaluable pts, best overall response was CR in 2 pts, PR in 26, and SD in 12, for an ORR of 70.0% (28/40; confirmed ORR was 52.5% [21/40], 5 pending confirmation) and DCR of 100%. DOR data were not mature at the time of data cutoff. Median best change in tumor volume was -38.2% (NSQ -36.6%; SQ -39.7%). In NSQ NSCLC, ORR was 66.7% (14/21) and, by pumitamig dose, it was 72.7% for DL1 (8/11) and 60.0% for DL2 (6/10). In SQ NSCLC, ORR was 73.7% (14/19), 81.8% for DL1 (9/11) and 62.5% for DL2 (5/8). Central PD-L1 levels were available for 35 pts (PD-L1 <1% [n=20], 1–49% [n=9], ≥50% [n=6]), with activity across PD-L1 levels. Circulating tumor DNA dynamics were assessed. Median treatment duration was 4.5 mo (range: 0.1–8.8) with 30 (69.8%) pts still on treatment. In the safety set (N=43), 40 (93.0%) pts had a treatment-related adverse event (TRAE). Grade ≥3 TRAEs were reported in 19 (44.2%) pts and were considered pumitamig-related in 8 (18.6%). Pumitamig-related TRAEs led to treatment discontinuation in 2 (4.7%) pts. Immune-related AEs (irAEs) occurred in 6 (14.0%) pts and grade ≥3 irAEs in 1 (2.3%). Bleeding events were reported in 7 (16.3%) pts, with only 1 event being grade 3. **Conclusions:** In these first global data for a PD-(L)1 × VEGF-A bsAb in 1L NSCLC regardless of PD-L1 status, pumitamig + chemotherapy showed encouraging efficacy with a manageable safety profile. Efficacy of the lower dose + chemotherapy was particularly encouraging (ORR 72.7% in NSQ, 81.8% in SQ) and is being evaluated vs pembrolizumab + chemotherapy in the ongoing Phase 3 part of the trial. Clinical trial information: NCT06712316. Research Sponsor: BioNTech.

8514 Rapid Oral Abstract Session

Updated results from a phase 2 trial of SSGJ-707 (PF-08634404), a PD-1/VEGF bispecific antibody, as monotherapy in patients with advanced non-small cell lung cancer (NSCLC).

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Background: SSGJ-707 is a fully human IgG4 bispecific antibody that simultaneously binds PD-1 and VEGF. In the phase 2 study (NCT06361927), SSGJ-707 monotherapy demonstrated promising efficacy and manageable safety in first-line NSCLC with PD-L1 tumor proportion score (TPS) ≥1%. We report updated results from this study with the FDA-aligned pivotal dose of 10 mg/kg Q3W. **Methods:** Patients (pts) with treatment-naive advanced NSCLC (without actionable genomic alterations and PD-L1 TPS ≥1%) were enrolled to receive SSGJ-707 at 5 mg/kg, 10 mg/kg, 20 mg/kg, or 30 mg/kg Q3W until disease progression or unacceptable toxicity. Primary endpoint is objective response rate (ORR) per RECIST 1.1. Secondary endpoints include safety, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and correlation between circulating tumor DNA (ctDNA) and efficacy. **Results:** As of Nov 28, 2025, 83 pts received ≥1 dose of SSGJ-707, of which 27.7% remained on treatment. In pts treated with the FDA-aligned dose of 10 mg/kg Q3W (n = 34), 41.2% remained on treatment and median duration of follow-up was 15.2 mos (95% CI, 14.3-16.2). In the 10 mg/kg group, confirmed ORR was 67.6% (95% CI, 49.5-82.6%), median DOR was not reached (NR; 95% CI, 10.9-NR), median PFS was 12.4 mos (95% CI, 8.2-NR), and median OS was NR (95% CI, 14.8-NR). High efficacy was noted for the 10 mg/kg Q3W dose irrespective of histology and TPS (table). Among all treated pts (n = 83), treatment-related adverse events (TRAEs) occurred in 92.8%; grade ≥3 TRAEs occurred in 42.2%. The most common grade ≥3 TRAEs (≥5%) were pneumonia (8.4%), hypertension (7.2%), and hemoptysis (6.0%). VEGF-related AEs occurred in 62.7% (grade ≥3, 18.1%) of pts; immune-mediated AEs occurred in 37.3% (grade ≥3, 8.4%). In the 10 mg/kg group, TRAEs led to permanent discontinuation in 1 pt (2.9%) and none had grade 5 TRAE. In pts with detectable ctDNA at baseline (n = 65), median PFS was NR (95% CI, 12.4-NR) in pts with nondetectable ctDNA at C3D1 (n = 19) compared to 7.6 mos (95% CI, 5.6-9.4) in those with detectable ctDNA at C3D1 (n = 33). **Conclusions:** With longer follow-up, SSGJ-707 monotherapy continues to show promising efficacy with a manageable safety profile in pts with treatment-naive advanced NSCLC across histology and PD-L1 expression subgroups. These results supported initiation of the phase 3 study (Symbiotic-Lung-01) of SSGJ-707 with platinum-based chemotherapy in 1L squamous (SQ) and nonsquamous (NSQ) NSCLC irrespective of TPS (NCT07222566). Clinical trial information: NCT06361927. Research Sponsor: Pfizer.

	n=34	Confirmed ORR, % (95% CI)	DOR, mos, median(95% CI)	PFS, mos, median (95% CI)	OS, mos, median(95% CI)
Histology					
SQ	12	75.0(42.8-94.5)	6.2 (4.1-NR)	8.9 (2.7-NR)	NR(4.9-NR)
NSQ	22	63.6(40.7-82.8)	NR(10.9-NR)	12.4 (8.2-NR)	NR(14.8-NR)
TPS					
1%-49%	21	61.9(38.4-81.9)	NR(4.1-NR)	9.6 (7.6-NR)	NR(12.1-NR)
≥50%	13	76.9(46.2-95.0)	NR(5.6-NR)	12.4(5.9-NR)	NR(NR-NR)

8515 Rapid Oral Abstract Session

Tremelimumab (T) + durvalumab (D) + chemotherapy (CT) vs pembrolizumab (P) + CT in 1L non-squamous (NSQ) metastatic NSCLC (mNSCLC) with *STK11*, *KEAP1*, and/or *KRAS* mutations (mut): Interim analysis (IA) of the phase 2b TRITON study.

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Background: Pts with *STK11*, *KEAP1* and/or *KRAS*-mutated mNSCLC may benefit from the addition of anti-CTLA-4 to anti-PD-(L)1-based chemo-immunotherapy. In the phase 3 POSEIDON study, 1L T+D+CT significantly improved OS vs CT in pts with mNSCLC. Exploratory analyses showed sustained OS improvement with T+D+CT vs CT in subgroups with *STK11*, *KEAP1* and/or *KRAS* mut; in each mut subgroup, magnitude of OS benefit with T+D+CT vs CT was numerically greater than with D+CT vs CT. The phase 2b, open-label, multicenter, US-based TRITON study is comparing 1L T+D+CT vs P+CT in pts with NSQ mNSCLC and *STK11, KEAP1* and/or *KRAS* mut. Here we report results of a planned IA (data cutoff [DCO] 15 mo after 1st pt randomized) of objective response rate (ORR), duration of response (DoR) and safety. **Methods:** Pts with treatment [tx]-naïve, *EGFR*/*ALK* wild-type, NSQ mNSCLC and *STK11*, *KEAP1* and/or *KRAS* mut (ECOG PS 0/1) were randomized 1:1 to T+D+CT or P+CT. T+D+CT arm: T 75 mg + D 1500 mg + pemetrexed-platinum Q3W for 4 cycles, then maintenance D + pemetrexed Q4W until disease progression (PD); additional doses of T given at week 16 and, optionally, at mo 24. P+CT arm: P 200 mg + pemetrexed-platinum Q3W for 4 cycles, then maintenance P + pemetrexed Q3W until PD, for up to 24 mo. Randomization was stratified by mut type and tumor PD-L1 expression (≥1% vs <1%). The primary endpoint is PFS (RECIST v1.1; investigator-assessed) with planned sample size ~100 pts. Key secondary endpoints include OS, ORR, DoR and safety. **Results:** At DCO (12 Nov 2025), 41 pts were randomized to T+D+CT and 43 to P+CT. Overall, 27.4%, 21.4% and 78.6% of pts had *STK11*, *KEAP1* and *KRAS* mut (not mutually exclusive); 39.3% had PD-L1 <1%. In the T+D+CT vs P+CT arms, median (range) age was 69 (47–82) vs 69 (51–86) y, 48.8% vs 62.8% pts were male, 70.7% vs 72.1% were White and 14.6% vs 20.9% Black or African American, 78.0% vs 62.8% had ECOG PS 1. Median (range) safety follow-up for D/P was 5.6 (0.0–14.0)/5.1 (0.0–17.5) mo; median no. of D/P doses was 8/7. ORR (95% CI) was 39.0% (24.1–54.0) in the T+D+CT arm vs 34.9% (20.6–49.1) in the P+CT arm [unconfirmed ORR 48.8% (33.5–64.1) vs 41.9% (27.1–56.6)]. Median DoR (95% CI) was not reached (6.3–NR) vs 6.4 (4.2–NR) mo; 100% vs 58.3% pts remained in response at 6 mo. In *KRAS* mut-only pts (n=52; exploratory), ORR was 48.0% (12/25) with T+D+CT vs 33.3% (9/27) with P+CT. The sponsor remains blinded to PFS at this IA. With T+D+CT vs P+CT, 41.5% vs 41.9% of pts had Grade 3/4 AEs possibly related to tx (TRAEs); 2.4% vs 4.7% had TRAEs leading to tx discontinuation and 0% vs 2.3% had TRAEs leading to death. **Conclusions:** At IA, ORR and DoR results from the prospective TRITON study support a role for the addition of anti-CTLA-4 (T) to 1L anti-PD-L1 (D) + CT in pts with *STK11*, *KEAP1* and/or *KRAS*-mutated mNSCLC. Safety was similar in the two arms and consistent with known safety profiles. Clinical trial information: NCT06008093. Research Sponsor: AstraZeneca.

A phase 1/2 study of TSN1611, a highly selective oral KRAS G12D inhibitor, in solid tumors: Efficacy and safety in *KRAS* G12D–mutated NSCLC patients.

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Background: There remains an unmet clinical need for effective therapies targeting KRAS G12D mutation in patients (pts) with advanced non-small cell lung cancer (NSCLC) refractory to prior treatments. TSN1611 is a novel oral small-molecule inhibitor designed to bind both the active GTP-bound (ON) and inactive GDP-bound (OFF) conformations of KRAS G12D, providing a differentiated mechanism of action and broad antitumor activity in preclinical models. **Methods:** This multi-regional Phase 1/2 study enrolled pts with advanced solid tumors harboring KRAS G12D mutation. Phase 1a dose-escalation part evaluated TSN1611 at 50–1200 mg twice daily (BID). A subsequent Phase 1b dose-optimization part evaluated 800 mg and 1200 mg BID. In Phase 2, efficacy is being further explored across multiple tumor types at the recommended Phase 2 dose of 1200 mg BID. **Results:** As of Jan 23, 2026, 117 pts received TSN1611 across all dose levels in Phase 1/2. Tumor types included NSCLC (n = 26), pancreatic adenocarcinoma (n = 50), colorectal cancer (n = 35), and others (n = 6). Median age was 62 yrs (range 22-81). The median prior lines of systemic therapy were 2 (range 0-7). The most common (≥10%) treatment-related adverse events (TRAEs) in all treated pts were diarrhea (53.0%), nausea (48.7%), vomiting (46.2%), anemia (17.9%), decreased white blood cell count (16.2%), decreased neutrophil count (13.7%), increased ALT (12.8%), decreased appetite (12.0%), decreased platelets (11.1%), fatigue and increased AST (10.3% each). Grade 3 TRAEs occurred in 9.4% of pts; these were all single events (0.9% each) except for anemia, diarrhea, and asymptomatic lipase elevation, which occurred in 1.7% of pts each. TRAEs led to dose interruption in 17.1% pts and dose reduction in 7.7% pts; no treatment discontinuations due to TRAEs occurred. Among 26 NSCLC pts, all had stage IV metastatic disease; 22 (84.6%) had received prior chemotherapy and/or PD-1/PD-L1 inhibitors, and 9 (34.6%) had received prior anti-angiogenic therapy. Among 20 response-evaluable NSCLC pts treated with TSN1611 at 600–1200 mg BID, 10 achieved partial response, 8 had stable disease, and 2 had progressive disease, yielding an objective response rate (ORR) of 50% (95% CI 27.2–72.8) and a disease control rate (DCR) of 90% (95% CI 68.8–98.3). Median time to response was 1.4 months (range 1.2–3.5). In addition to extracranial responses, rapid intracranial responses were observed. Median progression-free survival (PFS) was not mature yet (range 1.3+ to 12.9+ months), with a 9-month PFS rate of 54.5% (95% CI 24.4–77.0). Enrollment continues and updated data will be presented at the conference. **Conclusions:** TSN1611 demonstrated a favorable safety profile and clinically meaningful antitumor activity in pts with KRAS G12D mutated NSCLC. Further development of TSN1611 as monotherapy and in combination regimens is ongoing. Clinical trial information: NCT06385925. Research Sponsor: Tyligand Pharmaceuticals (Suzhou) Limited.

8517 Rapid Oral Abstract Session

Prophylactic peptide vaccine targeting resistance mutations in advanced ALK-positive lung cancer: Primary analysis from the ARCHER trial.

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Background: Acquired resistance to targeted therapy remains a major challenge in ALK-positive NSCLC and is often mediated by mutations in the ALK kinase domain. Prophylactic immune targeting of common ALK resistance mutations represents a novel strategy to delay or prevent the emergence of ALK inhibitor resistance. **Methods:** We conducted a first-in-human phase 1b clinical trial of a prophylactic peptide vaccine (ALK-Vac) in advanced ALK-positive NSCLC patients without progression on standard-of-care tyrosine kinase inhibitor (TKI) therapy. Patients continued their ALK TKI and received ALK-Vac, consisting of synthetic long peptides targeting seven common ALK resistance mutations (I1171T, I1171N, I1171S, L1196M, G1202R, D1203N, E1210K) plus poly-ICLC adjuvant. ALK-Vac was administered subcutaneously on days 1, 4, 8, 15, and 22 (priming) and weeks 12 and 20 (boost). Primary objectives were safety and vaccine-specific T cell responses assessed by IFN-γ ELISpot. Exploratory objectives included molecular and immune-phenotype dynamics assessed by ultrasensitive cell-free DNA (cfDNA) duplex sequencing and CyTOF mass cytometry. **Results:** Fifteen patients were enrolled and all completed the planned ALK-Vac regimen. Most patients (13/15, 87%) were receiving first-line TKI therapy. Concomitant TKIs included alectinib (7/15, 47%), lorlatinib (5/15, 33%), and brigatinib (3/15, 20%). At enrollment, median TKI duration was 43.7 months (range 4.6-74.2) and 67% of patients had no measurable disease. Treatment-related adverse events (TRAEs) were primarily grade 1 (93% of patients); most commonly injection site reactions (93%), fatigue (60%), and flu-like symptoms (40%). No grade $\geq$ 3 TRAEs were observed. T cell responses ($\geq$2-fold increase in SFU) were detected in 71% (10/14) of evaluable patients, with a median 11.9-fold increase. Responses were observed to G1202R, L1196M, and D1203N (each 10/14, 71%), E1210K (9/14, 64%), and I1171N/S/T (each 7/14, 50%). With a median follow-up of 11.5 months, the disease control rate was 93% (14/15). One patient who achieved robust immune response against multiple resistance mutations developed oligoprogression on alectinib 8.5 months after starting ALK-Vac; molecular profiling of this lesion identified an emergent KRAS G12D mutation without detectable ALK resistance mutation. **Conclusions:** ALK-Vac was well-tolerated and induced vaccine-specific T cell responses in a minimal residual disease setting, demonstrating feasibility of prophylactic targeting of ALK resistance mutations as an adjunct to TKI therapy and supporting a broader immune-interception framework potentially applicable to other oncogene-driven NSCLC. Comprehensive cfDNA and immune-phenotyping analyses will be reported. Clinical trial information: NCT05950139. Research Sponsor: None.

LBA8518 **Rapid Oral Abstract Session**

Phase 3 clinical trial of the combination of erlotinib plus ramucirumab compared with osimertinib in untreated advanced or recurrent non-small cell lung cancer with EGFR L858R mutation: The REVOL858R trial (WJOG14420L).

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8519 Rapid Oral Abstract Session

Safety and efficacy results of the phase 2 study of silevertinib (BDTX-1535) in treatment-naïve patients with non-small cell lung cancer with non-classical EGFR mutations.

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Background: Non-classical mutations (NCM) of epidermal growth factor receptor (EGFR) represent a broad group of oncogenic mutations in non-small cell lung cancer (NSCLC), often associated with resistance to osimertinib (e.g., P-loop and αC-helix compressing [PACC] mutations). Patients (pts) with NCM have inferior clinical outcomes with a high incidence of CNS metastases (CNSm). Silevertinib (BDTX-1535) is a fourth-generation, covalent EGFR TKI with high CNS penetrance targeting both EGFR classical mutations and NCM. The anti-tumor activity and safety of silevertinib in pts with advanced NSCLC were evaluated in a Phase 2 trial (NCT05256290). **Methods:** Pts with advanced EGFR NCM NSCLC who received no prior systemic therapy were enrolled (Cohort 3) based on a local molecular test. Silevertinib 200 mg was administered orally once daily. The primary endpoint of objective response rate (ORR) was assessed using RECIST v1.1. CNS ORR was assessed using Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) in pts with no prior CNS therapy. Secondary endpoints include progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and safety. **Results:** From February 2024 to July 2025, 43 pts with 35 unique NCMs (including 25 pts with PACC mutations) were enrolled in Cohort 3: median age 70.0 years, 72% female, 74% white, and 42% never smoked cigarettes. As of November 3, 2025, median follow-up was 7.2 months. ORR by RECIST v1.1 is shown in the table. Sixteen pts (37%) had CNSm, including 7 pts (16%) with measurable CNS disease. RANO-BM CNS response was 86% (n=6/7). Complete clearance of EGFR VAF ctDNA was observed in 21/26 (81%) evaluable pts. Serious treatment-related adverse events (TRAEs) were reported in 5 pts (12%), and 4 pts (9%) discontinued treatment due to TRAEs. The most common TRAEs included rash (19%, grade 3), diarrhea (19%, grade 3), stomatitis (9%, grade 3), and paronychia (5%, grade 3). While 77% of pts had a dose reduction, 19/22 (86%) patients with a radiographic response maintained or deepened their response after dose reduction, including all patients with CNS response. **Conclusions:** Silevertinib demonstrated robust antitumor activity in treatment-naïve pts with a broad spectrum of NCM EGFR driver mutations with high intracranial activity in pts with brain metastases. The safety profile was consistent with the known AEs of the EGFR TKI class. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

Data as of November 3, 2025	N	ORR n (%) 95% CI	DCR n (%) 95% CI
ITT Population*	43	26 (60) (44.4, 75.0)	39 (91) (77.9, 97.4)
PACC mutations	25	14 (56) (34.9, 75.6)	22 (88) (68.8, 97.5)
Compound mutations†	16	11 (69) (41.3, 89.0)	15 (94) (69.8, 99.8)

*No pts with classical (E746_A750del or L858R) mutations were enrolled.
†Presence of ≥ 2 NCMs.
As of December 27, 2025, the 6-month PFS rate was 86% overall and 80% in pts with CNSm; available PFS and DOR data will be presented.

DZD6008, a fourth-generation EGFR TKI, in pretreated NSCLC patients with *EGFR* C797X mutations: Results from phase 1/2 studies.

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Background: Patients with EGFR-mutant NSCLC whose disease progresses on or after 3rd generation EGFR TKI treatment often acquire resistance mutations, among which EGFR C797X is one of the most frequently reported. DZD6008 is a 4th generation EGFR TKI, designed to target classical EGFR sensitizing mutations (L858R/19del), as well as resistant double (T790M and L858R/19del) and triple mutations (C797X, T790M and L858R/19del), with preclinical data showing high selectivity over wild-type EGFR and other kinases and full blood-brain-barrier (BBB) penetration. Here we report results in pretreated NSCLC patients with EGFR C797X mutations (C797X+) from phase 1/2 studies. **Methods:** TIAN-SHAN1 (NCT06905197) and TIAN-SHAN2 (NCT06813365; CTR20241790) are ongoing, multicenter phase 1/2 studies evaluating the safety, tolerability, and anti-tumor activity of DZD6008 in EGFR-mutant NSCLC patients, conducted in the US/Australia and China, respectively. The efficacy endpoints include objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) by investigator per RECIST v1.1, and safety endpoints include treatment-related adverse events (TRAEs) per CTCAE 5.0. **Results:** As of December 19, 2025, a total of 24 patients with confirmed C797X+ NSCLC were treated with once daily (QD) oral DZD6008 (20 mg, n=1; 40 mg, n=13; 60 mg, n=10), and had at least 1 post-baseline tumor assessment. The median age was 66.5 years, 58.3% were female, 91.7% were Asian, 58.3% had ECOG PS of 1. All patients had metastatic disease upon study entry and received median 2 (range 1 - 6) lines of prior therapies. Across all dose levels, tumor shrinkage was observed in 75% of patients, with an ORR of 41.7%. Intracranial anti-tumor activity was observed in patients with baseline brain metastasis. The doses of 40 mg and 60 mg QD were defined as the recommended phase 2 doses (RP2Ds). The ORRs were 23.1% and 60.0% at these two dose levels, respectively. The median DoR and median PFS were not reached for either dose. The 9-month PFS rates were 54.5% and 64.8%, respectively. DZD6008 was well tolerated at the doses evaluated, with no dose limiting toxicities observed. The majority of TRAEs were grade 1 or 2. The TRAEs with grade ≥3 included lymphocyte count decreased (8.3%), anemia, malaise, fatigue and amylase increased (all 4.2%). There were no Grade 5 TRAEs. **Conclusions:** DZD6008 demonstrated promising and durable anti-tumor activity in patients with EGFR C797X+ NSCLC with a manageable safety profile, supporting its potential use as a later line treatment option after 3rd generation EGFR TKI failure. The updated data will be presented at the meeting. Clinical trial information: NCT06905197, NCT06813365. Research Sponsor: None.

8521 Poster Session

Amivantamab in *EGFR*-mutated NSCLC with refractory brain or leptomeningeal metastases: A multi-center real-world study.

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Background: The central nervous system (CNS), particularly after progression on third-generation EGFR TKIs, represents a common yet challenging scenario. While recent trials establish amivantamab-lazertinib for EGFR-mutant NSCLC, their real-world applicability is limited by patient complexity and access barriers, highlighting an urgent need for flexible, real-world solutions. **Methods:** To evaluate the intracranial efficacy of amivantamab, used as monotherapy or in combination, we conducted a multi-center, retrospective study of patients with EGFR-mutated NSCLC and brain parenchymal metastases (BM) and/or leptomeningeal metastases (LM) treated with amivantamab monotherapy or combination based on routine clinical practice. The cohort included two key populations: heavily pretreated patients with sensitizing exon19del/L858R mutations after progression on third-generation EGFR TKIs, and treatment-limited patients with atypical mutations. Efficacy endpoints included intracranial progression-free survival (PFS) and intracranial objective response rate (ORR) by RANO-BM and/or RANO-LM. Exploratory endpoints included symptom improvement, and longitudinal cerebrospinal fluid (CSF) biomarker dynamics. **Results:** Thirty-one patients from seven centers were included (BM, n=13; BM+LM, n=18). Most (25/31, 80.6%) harbored EGFR sensitizing mutations and had progressed on third-generation EGFR TKIs; six (19.4%) carried atypical EGFR mutations. Over half (17/31, 54.8%) had received ≥4 prior lines. Amivantamab monotherapy was received in 10/31 patients (32.3%). Median intracranial PFS was 10.3 months (95% CI, 4.5-16.1). Among 24 evaluable patients, intracranial ORR was 25.0% (n=6), and disease control rate was 91.7% (n=22). CNS-related symptoms improved in 26/31 (83.9%). CSF analyses showed decreased pressure and CEA, reduced EGFR amplification, and clearance of EGFR C797S. **Conclusions:** In real-world settings, amivantamab-based regimens demonstrate promising intracranial efficacy in EGFR-mutated NSCLC patients with refractory brain or leptomeningeal metastases. These findings support the use of amivantamab as a viable therapeutic strategy in this challenging population and suggest that CSF biomarkers can serve as a valuable tool for monitoring treatment response. Research Sponsor: National Natural Science Foundation of China.

Sigvotatug vedotin (SV), an investigational integrin beta-6 (IB6)—directed antibody-drug conjugate (ADC), plus pembrolizumab: Updated results from the phase 1 study (SGNB6A-001).

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Background: IB6 is overexpressed in many tumors, such as non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). SV, an IB6-directed ADC, demonstrated encouraging antitumor activity and manageable safety as monotherapy or in combination with pembrolizumab (SV+P) in advanced NSCLC (aNSCLC) in the ongoing phase 1 SGNB6A-001 study. We report updated results for SV+P. **Methods:** SGNB6A-001 (NCT04389632) is an open-label, multicenter, dose-escalation and -expansion study evaluating safety, pharmacokinetics, and antitumor activity of SV. SV+P is being evaluated in safety and expansion cohorts of treatment-naive locally advanced, unresectable, or metastatic NSCLC across PD-L1 scores and HNSCC CPS ≥1. Additional cohorts currently enrolling are not included in this analysis. We describe patients (pts) who received SV 1.8 mg/kg AiBW (adjusted ideal body weight) IV Q2W and P 400 mg IV Q6W. Primary endpoint is safety; secondary endpoints include efficacy, such as confirmed objective response rate (cORR) per RECIST v1.1 by investigator. **Results:** 71 pts across cohorts received ≥1 SV+P dose (37 aNSCLC, 33 HNSCC, 1 esophageal cancer). As of Sep 30, 2025, 34 pts were on treatment. Overall, any-grade (Gr) and Gr ≥3 treatment-emergent adverse events (TEAEs) occurred in 96% and 59% of pts, respectively; treatment-related any-Gr and Gr ≥3 TEAEs occurred in 85% and 44% of pts, respectively. Most common TEAEs (> 30%) were alopecia, decreased appetite, fatigue, and nausea. In the expansion cohort, 35 pts with aNSCLC were treated, with median follow-up of 10.6 mo (95% CI, 7.6-11.9). In the efficacy-evaluable pts, cORR was 50% in both the PD-L1 TPS < 1% (n = 10) and ≥1% (n = 18) subgroups, with 1 additional partial response (PR) pending confirmation in the PD-L1 TPS ≥1% subgroup (Table). In 5 pts with PD-L1 TPS ≥50%, cORR was 80%, with 1 additional PR pending confirmation. Regardless of TPS, cORR was numerically higher in pts with nonsquamous (n = 19 [53%]) vs squamous (n = 9 [44%]) histology. **Conclusions:** SV+P continued to show manageable safety and encouraging antitumor activity in treatment-naive NSCLC across PD-L1 TPS and histologies. This supports the ongoing phase 3 SigVie-003 study (NCT06758401) of SV+P vs P for treatment-naive aNSCLC with PD-L1 TPS ≥50% as well as further investigation in the enrolling phase 1 cohorts and future studies. Clinical trial information: NCT04389632. Research Sponsor: Pfizer.

	PD-L1 TPS <1% (n=10)	PD-L1 TPS ≥1% (n=18)	NSQ (n=19)	SQ (n=9)
cORR (95% CI), %	50 (19-81)	50 (26-74)	53 (29-76)	44 (14-79)
BOR, %				
CR	0	6	5	0
PR	50	44	47	44
SD	40	44	42	44
NE/no assessment	10	6	5	11
ORR (95% CI), %	50 (19-81)	61 (36-83)	63 (38-84)	44 (14-79)
DCR (95% CI), %	90 (56-100)	94 (73-100)	95 (74-100)	89 (52-100)
mDOR (95% CI), mo	NR (2.9-NR)	8.1 (4.2-NR)	8.1 (2.9-NR)	NR (4.2-NR)

8523 Poster Session

Dose-escalation results from a phase I study of FZ-AD004, a TROP2-directed ADC, in patients with advanced solid tumors.

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Background: FZ-AD004 is an ADC (antibody-drug conjugate) targeting Trop-2 (trophoblast cell-surface antigen 2), an intracellular calcium signaling transducer overexpressed on many epithelial tumors. It delivers the topoisomerase inhibitor DXd. This first-in-human study evaluated the safety and efficacy in patients(pts) with advanced solid tumors, mainly in non–small-cell lung cancer (NSCLC). **Methods:** PTs with unresectable, treatment-refractory or relapsed solid tumors received FZ-AD004 intravenously on days 1 of 21-day cycles. The primary objectives were to determine maximum tolerated dose (MTD), safety, and tolerability; secondary objectives included efficacy, pharmacokinetics, and immunogenicity of FZ-AD004. Pts were eligible regardless of TROP2 level. **Results:** As of November 28, 2025, 22 pts were treated with ≥1 dose of FZ-AD004 (median age: 61.5 years [range from 45-75], male: 77.3%, EOCG PS 1: 100%, prior lines of anticancer treatment ≥ 2: 77.3%). Diagnoses included NSCLC (n=21) and SCLC (n=1). Doses evaluated were at 3.2 (n=3), 5.6 (n=3), 6.4 (n=3), 8.0 (n=4), 10.0 (n=3), and 12.0 mg/kg (n=6). No dose-limiting toxicity (DLT) was observed across all dose levels.19 pts (86.4%) discontinued (15 (68.2%) due to disease progression per RECIST v1.1). Treatment emergent adverse events (TEAEs) regardless of causality were reported in all of 22 pts (100%; 10 pts [45.5%] experienced ≥grade 3, 5 pts [22.7%] had serious adverse events). Treatment-related AEs (TRAEs) occurred in all pts (100%; grade ≥3 in 36.4%; serious TRAEs in 13.6%). Grade ≥3 TRAEs included stomatitis (13.6%), decreased lymphocyte count (9.1%), nausea (4.5%), hypokalemia (4.5%), and keratitis (4.5%).Among 12 efficacy-evaluable pts at doses ≥8.0 mg/kg, the objective response rate (ORR) was 50.0% and the disease control rate (DCR) was 83.3%. Responses were observed in pts harboring KRAS G12C (n=1), EGFR mutations (n=3), and without AGA mutations (n=2). The longest duration treatment was 11.4 months. **Conclusions:** FZ-AD004 demonstrated a manageable safety profile with no DLTs observed up to 12.0 mg/kg and promising antitumor activity in heavily pretreated NSCLC patients, particularly at doses of 8.0 and 10.0 mg/kg. These doses are being further explored in the expansion phase. Clinical trial information: NCT05914545. Research Sponsor: None.

Impact of *MET* amplification (amp) on telisotuzumab vedotin (Teliso-V) efficacy and safety in 2L+ non-squamous (NSQ) *EGFR* wild-type (WT) NSCLC with c-Met protein overexpression (OE).

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Background: Teliso-V is a c-Met–directed antibody-drug conjugate comprising telisotuzumab and the microtubule polymerization inhibitor monomethyl auristatin E (MMAE) payload. In the Ph2 LUMINOSITY study (NCT03539536), Teliso-V showed durable responses and manageable safety (Camidge et al, JCO 2024;42:3000-11) resulting in its accelerated approval in locally advanced/metastatic NSQ NSCLC with high c-Met protein OE (3+, ≥50%), as determined by an FDA-approved test. *MET* amp is a negative prognostic risk factor in advanced NSCLC, frequently associated with recurrent disease. High levels of *MET* amp and c-Met OE are hallmarks of *MET*-addicted tumors. Here, we analyzed the effects of *MET* amp on clinical responses to Teliso-V in LUMINOSITY. **Methods:** *MET* amp was evaluated by FISH and ctDNA in baseline samples from 108 NSQ *EGFR* WT NSCLC pts with c-Met OE (3+, ≥25%). *MET* amp by FISH was defined as having focal *MET* amp (MET/CEP7 ≥2.0) with *MET* gene copy number (GCN) ≥4. *MET* amp *(focal)* by ctDNA was defined as having plasma *MET* GCN ≥4 with no co-amplification in *CDK6* and *EGFR.* c-Met OE by Immunohistochemistry (IHC; SP44) was defined as 3+ tissue staining intensity in ≥25% tumor cells (high c-Met OE: 3+, ≥50%; intermediate [int] c-Met OE: 3+, 25% to 49%). Exploratory analysis of tumor response was assessed in 76 efficacy evaluable pts with c-Met OE and *MET* amp assay results. **Results:** *MET* amp was detected in 34% (37/108) of pts with c-Met OE (3+, ≥25%) and was enriched by c-Met levels: 22% (11/50) in pts with Int c-Met OE (3+, 25% to 49%) and 45% (26/58) in pts with high c-Met OE (3+, ≥50%). The effects of *MET* amp on tumor response in LUMINOSITY are shown in Table 1. The majority of c-Met OE pts (79%) with PFS ≥10 mo (n=14) had GCN ≥10 and/or c-Met IHC 3+ ≥50%. No new safety signals were reported in pts with c-Met OE and *MET* amp. **Conclusions:** *MET* amp is more common in pts with high c-Met OE in this retrospective subgroup analysis. Tumor activity with Teliso-V was observed regardless of *MET* amp status. The impact of *MET* amp in pts with c-Met OE will be further evaluated in ongoing Phase 3 study (NCT04928846). Research Sponsor: None.

Teliso-V efficacy in NSQ *EGFR*-WT NSCLC pts with c-Met OE with or without *MET* amp in LUMINOSITY.

	Total c-Met OE (3+, ≥25%)	Total c-Met OE (3+, ≥25%)	Intermediate c-Met OE (3+, ≥25%-49%)	Intermediate c-Met OE (3+, ≥25%-49%)	High c-Met OE (3+, ≥50%)	High c-Met OE (3+, ≥50%)
***MET* amp (N)**	**No** (N=53)	**Yes** (N=23)	**No** (N=30)	**Yes** (N=7)	**No** (N=23)	**Yes** (N=16)
ORR % (95% CI)	**28** (18.0, 41.6)	**39** (22.2, 59.2)	**23** (11.8, 40.9)	**57** (25, 84.2)	**35** (18.8, 55.1)	**31** (14.2, 55.6)
PFS, median, mo (95% CI)	**5.26** (3.71, 8.11)	**8.02** (4.47, 14.65)	**5.32** (2.69, 8.11)	**7.52** (4.47, NA)	**4.17** (3.25, 8.87)	**8.02** (3.06, 25.92)
OS, median, mo (95% CI)	**14.5** (8.18, 17.38)	**13.86** (6.54, 22.24)	**14.03** (3.65, 17.02)	**9.79** (6.54, NA)	**16.26** (5.59, 36.44)	**13.86** (3.06, 30.29)

SHR-1826, a c-MET directed antibody-drug conjugate (ADC), in advanced solid tumors: Updates from a phase 1 study.

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Background: SHR-1826 is a novel ADC comprising a humanized IgG2 monoclonal antibody targeting c-MET, conjugated via a cleavable peptide-based linker to a topoisomerase I inhibitor payload. We conducted a multi-center, first-in-human, phase 1 trial of SHR-1826 in patients with advanced solid tumors. Here we report updated results, with a focus on patients with *EGFR*-mutated (*EGFRmut*) lung adenocarcinoma (LUAD). **Methods:** The study consisted of dose-escalation (i3+3 design), dose-expansion and efficacy-expansion phases. Patients with advanced solid tumors harboring MET alterations, who had failed standard therapy or had no available standard treatment options, were enrolled and received SHR-1826 intravenously at 2.2–6.0 mg/kg Q3W. In patients with *EGFRmut* LUAD, 4.0 and 5.0 mg/kg Q3W were evaluated during dose and efficacy expansion. **Results:** As of Dec. 3, 2025, 195 patients with lung (n=126), colorectal (n=40), gastric (n=22), liver (n=5), or pancreatic (n=2) cancer were treated. Median age was 59.0 yrs; 89.7% had ECOG performance status 1. Among 36 patients with *EGFRmut* LUAD, median number of prior lines of therapy was 2 (range 1–9); 97.2% had previously received EGFR-TKI (3rd generation, 88.9%) and 75.0% received platinum-based chemotherapy. As of data cutoff, median follow-up was 14.4 months. Efficacy in *EGFRmut* LUAD across doses is shown in Table 1. Overall, the confirmed objective response rate (ORR) was 41.7% (95% CI 25.5–59.2) and median duration of response (DoR) was 14.1 months (95% CI 5.6–not reached [NR]). Median progression-free survival (PFS) was 9.8 mo (95% CI 5.8–15.4). Median overall survival (OS) was not reached; 12-month OS rate was 67.4% (95% CI 48.9–80.5). In all 195 patients, grade ≥3 treatment-related adverse events (TRAEs) were reported in 129 patients (66.2%), with all occurring in ≥5% being hematological toxicities. Interstitial lung disease occurred in 4 (3.1%; grade ≥3, n=2 [1.6%]) patients. TRAEs led to treatment discontinuation in 8 (4.1%) patients. No treatment-related deaths were reported. **Conclusions:** SHR-1826 demonstrated encouraging activity with manageable safety in heavily pretreated patients with MET-altered *EGFRmut* LUAD. Multiple trials are ongoing to assess SHR-1826 combined with other anti-tumor therapies in NSCLC. Clinical trial information: NCT06094556. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy outcomes in *EGFRmut* LUAD.

	4.0 mg/kg (n=16)	5.0 mg/g (n=18)	All patients (n=36)
Confirmed ORR (n/N; 95% CI), %	31.3 (5/16; 11.0–58.7)	50.0 (9/18; 26.0–74.0)	41.7 (15/36; 25.5–59.2)
DCR (n/N; 95% CI), %	87.5 (14/16; 61.7–98.4)	100.0 (18/18; 81.5–100.0)	94.4 (34/36; 81.3–99.3)
Median DoR (95% CI), mo	NR (8.6–NR)	9.7 (4.2–NR)	14.1 (5.6–NR)
Median PFS (95% CI), mo	12.4 (2.6–NR)	8.4 (4.5–15.4)	9.8 (5.8–15.4)
12-mo OS (95% CI), %	67.0 (37.9–84.7)	69.1 (40.7–85.9)	67.4 (48.9–80.5)

Data are based on the full analysis set. DCR, disease control rate.

8527 Poster Session

SHR-A2102 in combination with adebrelimab as first-line treatment in patients with locally advanced or metastatic squamous or non-squamous non-small cell lung cancer (NSCLC): Results from a phase 1b/2 study.

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Background: SHR-A2102 is a novel antibody-drug conjugate composed of a monoclonal antibody targeting nectin-4, a cleavable linker, and a topoisomerase I inhibitor payload. Here, we report the preliminary efficacy and safety of SHR-A2102 plus adebrelimab (an anti-PD-L1 antibody) as first-line therapy in patients with locally advanced or metastatic squamous or non-squamous NSCLC. **Methods:** This is a multicenter, open-label phase 1b/2 study (NCT06512051). In the phase 2 part, patients aged 18-70 years with ECOG PS 0-1 and histologically/cytologically confirmed stage IIIB-IV squamous (cohort A) or non-squamous (cohort B) NSCLC who had received no prior systemic therapy were enrolled. All patients received intravenous SHR-A2102 (8 mg/kg, day 1 Q3W) plus adebrelimab (1200 mg, day 1 Q3W) until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). **Results:** Between Dec 13, 2024 and Nov 19, 2025, 67 patients were enrolled and received treatment (27 with squamous NSCLC and 40 with non-squamous NSCLC). In cohort A, 92.6% were male, the median age was 64 years (range 42-70), 14 patients had PD-L1 TPS 1-49%, and 13 patients had PD-L1 TPS ≥50%. In cohort B, 60.0% were male, the median age was 62 years (range 42-70), 7 patients had PD-L1 TPS <1%, 20 patients had PD-L1 TPS 1-49%, and 13 patients had PD-L1 TPS ≥50%. Efficacy was evaluated in 26 and 33 patients from cohorts A and B, respectively, while all patients were included in the safety analysis. As of Nov 30, 2025, the median follow-up was 9.1 months (range 2.0-11.1), with 9.9 months (range 3.0-11.0) with squamous NSCLC and 9.0 months (range 2.0-11.1) with non-squamous NSCLC. Antitumor activities are shown in Table 1. In patients with PD-L1 TPS ≥1%, ORR was 80.8% (95% CI 60.6%-93.4%) for squamous NSCLC and 69.2% (95% CI 48.2%-85.7%) for non-squamous NSCLC. Grade ≥3 treatment-related adverse events (TRAEs) were reported in 53.7% (36/67) of patients. The most common Grade ≥3 TRAEs were decreased neutrophil count (32.8%), decreased white blood cell count (14.9%), and anemia (9.0%). **Conclusions:** These results suggested the combination of SHR-A2102 and adebrelimab as the first-line therapy is a promising treatment strategy in patients with squamous or non-squamous NSCLC, supporting further investigation. Clinical trial information: NCT06512051. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy summary.

	Squamous NSCLC (N=26)	Non-squamous NSCLC (N=33)	Total (N=59)
ORR, % (95% CI)	80.8 (60.6-93.4)	69.7 (51.3-84.4)	74.6 (61.6-85.0)
DCR, % (95% CI)	96.2 (80.4-99.9)	97.0 (84.2-99.9)	96.6 (88.3-99.6)
DoR (months), median (95% CI)	NR (4.4-NR)	NR (5.7-NR)	NR (6.5-NR)
6-month PFS rates, % (95% CI)	64.1 (42.3-79.5)	78.9 (58.9-90.0)	71.8 (57.6-81.9)

Necitumumab plus pembrolizumab and chemotherapy for untreated advanced squamous NSCLC: Phase I/II NEJ048A/NEXUS.

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Background: EGFR blockade enhances tumor antigen presentation and may potentiate PD-1 inhibition. This phase I/II study evaluated the safety and efficacy of adding necitumumab to pembrolizumab plus platinum-based chemotherapy in patients with previously untreated advanced squamous non–small cell lung cancer (NSCLC), a population with limited biomarker-driven treatment options. **Methods:** Patients received necitumumab (400–800 mg on days 1 and 8), pembrolizumab (200 mg on day 1), nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15), and carboplatin (AUC 5 on day 1) every 3 weeks for four cycles, followed by necitumumab plus pembrolizumab maintenance. Phase I used a standard 3+3 dose-escalation design. Per protocol amendment, patients treated at the recommended dose (RD) in phase I (n = 6) and all phase II patients (n = 6) were pooled for efficacy analyses (n = 12). Tumor assessments were performed every 6 weeks per RECIST v1.1. Primary endpoints were safety and objective response rate (ORR). Data cutoff was September 14, 2025. **Results:** Twenty-one patients were enrolled, including 15 in phase I (400 mg, n = 6; 600 mg, n = 3; 800 mg, n = 6). One dose-limiting toxicity (DLT) occurred in the 800 mg cohort, which was determined as the RD and maximum tolerated dose (MTD). Among the 12 patients treated at the RD, the ORR was 75.0% (9/12; 95% CI, 42.8–94.5), with partial response in 9 patients, stable disease in 1 patient, and progressive disease in 2 patients. The disease control rate was 83.3%. The 24-week survival rate was 95.2%. Median progression-free survival and overall survival were not reached at the time of analysis. The most frequent adverse events (AEs) in 21 patients were hypomagnesemia (66.7%), acneiform dermatitis (66.7%), neutropenia (61.9%), decreased appetite (52.4%), anemia (52.4%), constipation (47.6%), stomatitis (42.9%), and leukopenia (42.9%). Grade 3 and 4 AEs occurred in 66.7% and 28.6% of patients, respectively, with no grade 5 events. **Conclusions:** The addition of necitumumab to pembrolizumab and platinum-based chemotherapy demonstrated manageable toxicity and resulted in a high ORR in patients with untreated squamous NSCLC. These findings support the potential activity of EGFR blockade–based immunochemotherapy and warrant further clinical investigation. Clinical trial information: 2031210387. Research Sponsor: Nippon Kayaku Co., Ltd.

First-in-human study of DM005, an anti-EGFR/c-MET bispecific antibody-drug conjugate, in patients with advanced solid tumors.

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Background: DM005 is a bispecific ADC (BsADC) conjugated to BLD1102, a linker/payload system composed of a linker and a DNA topoisomerase I inhibitor (BCPT02), targeting EGFR and c-MET with an average DAR value of 4. EGFR and c-MET are highly co-expressed in NSCLC, SCLC, HNSCC, breast cancer, gastric cancer, colorectal cancer, and some other solid tumors, for which DM005 has demonstrated robust anti-tumor activity in PDX/CDX models. **Methods:** This is a First-in-human dose-escalation study (NCT 06515990). Patients (pts) with advanced solid tumors received DM005 by IV administration from 0.5 to 6.5 mg/kg Q3W. The classical "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. Tumor response was evaluated by the Investigators based on RECIST v1.1. A Safety Monitoring Committee (SMC) was established to determine the dose levels, dose regimen, and the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE). **Results:** As of 2 Jan 2026, a total of 45 pts from China, United states of America and Australia were enrolled and received ≥1 dose of DM005 across 8 dose cohorts. Median age was 59 years (range 40-76). Baseline ECOG scores were 0 (n = 7), 1 (n = 38) with all pts progressed after an average of 3 (range 1-7) prior lines of available standard therapy. There were no dose limiting toxicities (DLT) observed up to 6.5 mg/kg. The MTD was not reached. Thirty-six pts (80%) experienced treatment-related adverse events (TRAEs), the most common TRAEs (≥10%) including: nausea (28.9%), anemia (28.9%), fatigue (26.7%), decreased appetite (26.7%), leukopenia (20%), aspartate aminotransferase increased (15.6%), lymphopenia (13.3%), constipation (11.1%). Most TRAEs were Grade 1-2 and Grade ≥3 TRAEs reported in 10 pts (2 lymphopenia, 1 neutropenia, anemia, leukopenia, nausea, stomatitis, vomiting, fatigue, pain, urinary tract infection, hypoxia, hypotension). No ILD or Infusion reaction were observed. Among 32 patients evaluable, there were 8 PRs, including 1pt with NSCLC EGFR-mutant (NSCLCm) at 3.3 mg/kg, 4 pts with NSCLCm and 1pt with SCLC at 4.2 mg/kg, and 1pt with NSCLCm and 1pt with NSCLC EGFR wildtype (NSCLCw) at 5.2mg/kg, and 14 pts with stable disease (SD). In the 3.3/4.2/5.2 mg/kg dose groups, a total of 13 NSCLCm pts underwent imaging tumor assessment, with 6 subjects achieving PR, and 5 subjects achieving SD. The unconfirmed objective response rate (ORR) is 46.2%, and the disease control rate (DCR) is 84.6%. **Conclusions:** DM005 is safe and tolerable up to 6.5 mg/kg dose level. In both NSCLCm and NSCLCw pts, and SCLC pts, DM005 has demonstrated an encouraging efficacy with a manageable safety profile. The putative RDE ranges from 4.2 to 6.5 mg/kg which will be further evaluated in phase II trials. Clinical trial information: NCT06515990. Research Sponsor: None.

8531 Poster Session

The efficacy of trastuzumab deruxtecan after HER2-TKI exposure in HER2 exon 20 insertion–positive non–small cell lung cancer: Results from a large-scale nationwide genomic screening (LC-SCRUM-Asia).

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Background: Although reduced efficacy of HER2-TKIs after trastuzumab deruxtecan (T-DXd) has been reported in HER2 exon 20 insertion–positive non–small cell lung cancer (NSCLC), the efficacy of T-DXd following prior HER2-TKI exposure remains unclear. **Methods:** We identified patients with HER2 exon 20 insertion–positive NSCLC treated with T-DXd from two cohorts: the National Cancer Center Hospital East (N = 26,971) and the LC-SCRUM-Asia (N = 20,902). Clinical outcomes (ORR, DCR, and PFS) were evaluated across three groups based on prior HER2-TKI therapy: (1) HER2-TKI-naïve patients (naïve cohort), (2) those treated with selective HER2-TKIs (zongertinib or severtinib) (selective TKI cohort), and (3) those treated with non-selective pan-HER2-TKIs (such as poziotinib, afatinib, and others) (non-selective TKI cohort). **Results:** Of 77 patients (0.2%) included, 60 in the naïve cohort, 7 in the selective TKI cohort, and 10 in the non-selective TKI cohort. Overall, the median age was 60 years (range, 44–76), and 56% of patients were female. By NGS analysis, all tumors harbored ERBB2 exon 20 insertions within the tyrosine kinase domain; the YVMA subtype was the most common (57%). T-DXd was administered as a median fourth-line therapy (range, 2–8). Baseline clinical and genomic characteristics were generally comparable across the three groups. According to prior HER2-TKI exposure, the ORR was 60% (36/60) in the naïve cohort, 29% (2/7) in the selective TKI cohort, and 60% (6/10) in the non-selective TKI cohort. The DCRs were 83% (50/60), 71% (5/7), and 80% (8/10), respectively. Median PFS with T-DXd was 9.9 months in the naïve cohort, compared with 6.5 months in the selective TKI cohort and 5.3 months in the non-selective TKI cohort. The 6-month PFS rate was 72%, 71%, and 50%, respectively. Among 10 patients who did not achieve an objective response to prior HER2-TKIs (best response of stable or progressive disease), 6 achieved a partial response with subsequent T-DXd. **Conclusions:** Although prior HER2-TKI exposure, particularly selective HER2-TKIs, may attenuate the efficacy of T-DXd in HER2 exon 20 insertion–positive NSCLC compared with HER2-TKI–naïve patients, T-DXd retained clinically meaningful activity in a subset of patients, including those who did not achieve objective responses to prior HER2-TKIs. Research Sponsor: Astellas Pharma Inc.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Company Limited; Chugai Pharmaceutical Co., Ltd.; Eli Lilly Japan K.K.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Pfizer Japan Inc.; Bristol-Myers Squibb K.K.; Merck Serono Co., Ltd.; Janssen Pharmaceutical K.K.; AstraZeneca K.K.; Sumitomo Pharma Co., Ltd.; Bayer, Ltd.; AbbVie GK; Nippon Kayaku Co., Ltd.; Merus N.V.; Amgen K.K.; Medical & Biological Laboratories Co., Ltd. (MBL); Eisai Co., Ltd.; MSD K.K.; Ono Pharmaceutical Co., Ltd.; Kyowa Kirin Co., Ltd.; Daiichi Sankyo Co., Ltd.

8532 Poster Session

Integrating tumor growth models to improve late-stage lung cancer outcome prediction using early-stage clinical trial data.

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Background: Immunotherapy has substantially improved clinical outcomes but poses distinct challenges for response assessment due to heterogeneous and non-monotonic tumor kinetics. RECIST 1.1 rely on unidimensional lesion measurements that may incompletely capture spatial heterogeneity which can result in limited characterization of tumor growth. Tumor growth modeling provides a complementary, quantitative framework for capturing longitudinal tumor dynamics. Different frameworks have been proposed to model total disease progression and response to treatment from total tumor volume. However, model selection may be challenging with each model capturing distinct growth mechanisms. In this work, we present a framework integrating complementary tumor growth models using a neural network classifier to predict late-stage outcomes from early-stage timepoints. **Methods:** We retrospectively aggregated deidentified data from 417 anonymized subjects with metastatic non-small cell lung cancer (NSCLC) treated with immunotherapy. Serial CT datasets were acquired at five timepoints over a 30-week period and lesions were annotated by expert radiologists according to RECIST 1.1 criteria. Tumor burden was derived from radiologist annotations using a previously validated AI method that reconstructs 3D lesion volumes from bidimensional data. For each subject, Modified Gompertz (MG) and Stein-Claret (SC) models were implemented to estimate intrinsic tumor growth parameters. Both models were fitted using early on-treatment data up to 21 weeks and used to predict response to treatment at week 30. To evaluate complementarity and the ability of early tumor dynamics to predict radiological response, model parameters were combined and used to train a two-layer neural network for radiological outcome classification. Performance of the combined MG+SC was compared with single-model classifiers on response (CR/PR) vs non-response (SD/PD) and progression (PD) vs non-progression (CR/PR/SD) using accuracy and sensitivity metrics. **Results:** The cross-validated accuracy in classifying responders and non-responders at week 30 was 81.1% from the combined MG+SC model (sensitivity=79.2%; specificity=83.0%), higher than both individual models (accuracy = 77.8% and 68.0% for MG and SC respectively). The combined modeling framework confirmed higher accuracy (70.7%) when distinguishing progressive disease from the non-progressor group (sensitivity=64.5%, specificity=76.5%) when compared to both MG (69.1%) and SC (66.8%). **Conclusions:** This work showed that integrating early-stage dynamics from complementary mechanistic growth models improves week-30 radiographic outcome prediction over individual models in metastatic NSCLC immunotherapy trials. This framework can enable earlier identification of patient-level response that may support treatment adaptation. Research Sponsor: None.

8533 Poster Session

GEMINI-NSCLC: Multiomics and single-cell spatial profiling to benchmark, back-translate, and build digital twins of IO response.

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Background: Response to first-line standard-of-care (SoC) chemo-immunotherapy (IO) for patients with NSCLC without targetable mutations is heterogeneous, highlighting the need for predictive biomarkers. GEMINI (NCT05236114) integrates real-world outcomes, whole exome sequencing (WES), single-cell spatial transcriptomics (SpTx), and AI-pathology to establish a benchmarking resource and patient-level digital twins, enabling back-translation into testable hypotheses. With >4 million cells from 53 biopsies, GEMINI is one of the largest single-cell spatial datasets linked to IO outcomes. **Methods:** Patients with metastatic NSCLC were analyzed for outcome associations. Progression-free survival (PFS) was defined from IO start to progression, next regimen, last follow-up, or 2 years. Patients were classified as fast progressors (<3 months PFS) or slow progressors (>3 months PFS). Baseline biopsies (n=53) underwent WES and SpTx. Neural networks traced single-cell boundaries on H&E to quantify gene expression; cells were annotated via clustering and LLM-assisted labeling. AI-, manual-, and digital-pathology (DSP) defined tumor, immune, and stroma regions. Cohort-level benchmarking was integrated into patient-level digital twins to back-translate spatial-genomic features into individualized risk and mechanism hypotheses. **Results:** WES revealed expected mutation frequencies: *STK11* 15%, *TP53* 73%, *KEAP1* 21%, *KRAS* 46%, supporting cohort representativeness. Stroma-associated TIL counts were higher in slow versus fast progressors by AI-path (p=0.034) and manual-path (p=0.014). DSP showed immune aggregates in slow progressors were lymphocyte-diverse, whereas fast progressors were enriched for five macrophage subtypes consistent with immunosuppressive niches. Spatial proximity of lymphocytes and stroma to a tumor subcluster (C2) predicted progression (p<0.01). Immunoglobulin light-chain expression localized to the tumor core in slow progressors, suggesting tumor–B cell interactions with disease arrest. Differential expression identified 14 EMT/ECM genes overexpressed in fast-progressor stroma, implicating stromal barrier/ECM remodeling in IO resistance. Digital twins captured these spatial-omic signatures to forecast risk and generate patient-specific, testable hypotheses. **Conclusions:** GEMINI provides a large single-cell spatial transcriptomic benchmark linked to IO outcomes for patients with NSCLC and enables AI-driven digital twins for clinical decision support. Fast progressors show stromal EMT/ECM programs and immunosuppressive myeloid niches; slow progressors exhibit lymphocyte diversity and tumor–B cell interactions near subcluster C2. Findings support multimodal risk stratification and nominate stromal EMT/ECM targeting to overcome IO resistance, with prospective validation via digital-twin biomarkers. Clinical trial information: NCT05236114. Research Sponsor: AstraZeneca; Tempus AI.

AI-derived CD8⁺ cytotoxic T-cell immune signatures from baseline H&E images to predict immunotherapy benefit over chemotherapy in non–small cell lung cancer: Blinded validation in CheckMate-227 (CM227).

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Background: Immunotherapy (IO) has transformed treatment for non–small cell lung cancer (NSCLC), but not all patients (pts) benefit, underscoring the need for predictive biomarkers to guide IO versus chemotherapy (Ch). CheckMate 227 (CM227; NCT02477826) showed a survival benefit of first-line nivolumab plus ipilimumab (nivo+ipi) over Ch in stage IV NSCLC. CD8⁺ T cells are key mediators of antitumor immunity and are associated with IO benefit. We developed an artificial intelligence (AI)–based pipeline (VIGOR-CD8) that predicts spatial CD8⁺ immune signatures from routine baseline H&E whole-slide images using histopathology foundation model embeddings (H-Optimus-0) and virtual gene expression modeling (HE2Gene), and evaluated its ability to identify pts who do and do not derive IO benefit over Ch in CM227. **Methods:** 1,598 pts with advanced NSCLC were analyzed, including multi-institutional retrospective cohorts (n = 487; 65 for patch-level CD8⁺ prediction and overall survival (OS), 422 for patient-level OS) and a blinded CM227 validation subset (n = 1,111). For orthogonal validation, 86,470 H&E patches were co-registered with quantitative CD8⁺ immunofluorescence. H-Optimus-0 and HE2Gene immune-related embeddings were used to train a random forest classifier to predict patch-level CD8⁺ probability. Patch-level probabilities were aggregated into a patient-level CD8⁺ signature and dichotomized into biomarker-positive (B^+) and biomarker-negative (B^-) groups by the training-set median. Cox models assessed the impact of VIGOR-CD8 on OS. In CM227, prognostic and predictive utility were evaluated using treatment-specific analyses; investigators were blinded to outcomes, and models were trained on independent, non-overlapping cohorts. **Results:** VIGOR-CD8 was associated with longer OS in the testing cohort (n = 422; HR 0.68, 95% CI 0.53–0.87, p = 0.00163) and CM227 (n = 1,111; HR 0.8, 95% CI 0.67–0.96, p = 0.016), irrespective of treatment type and PD-L1 expression. Among pts with evaluable PD-L1, B^+ pts treated with nivo+ipi had superior OS versus Ch (n = 617; HR 0.72, 95% CI 0.58–0.90, p = 0.003), while in B^- pts there was no significant OS difference between treatment arms (n = 130; HR 1.18, 95% CI 0.79–1.75, p = 0.436), supporting a predictive rather than purely prognostic role for VIGOR-CD8. **Conclusions:** An AI-derived CD8⁺ immune signature from routine baseline H&E slides was associated with favorable OS in CM227 and predicted differential benefit from nivo+ipi versus Ch. VIGOR-CD8 may help identify advanced NSCLC pts most likely to benefit from first-line dual IO, but further validation in independent and prospective trials is warranted. Research Sponsor: National Cancer Institute; R01 CA249992 - 01A1, R01 CA216579 - 01A1, R01 CA257612 - 01A1, R01 CA264017 - 01, R01 CA268287 - 01A1, U01 CA113913 - 16A1, U01 CA239055 - 01, U01 CA269181 - 01, U24 CA274494 - 01, U54 CA254566 - 01; VA Biomedical Laboratory Research and Development Service; I01CX002622, I01CX002776, IK6BX006185; VA Research and Development Office through the Lung Precision Oncology Program; LPOP-L0021; Office of the Assistant Secretary of Defense for Health Affairs through the Prostate Cancer Research Program; W81XWH-15–1-0558, W81XWH-20–1-0851, W81XWH-21-1-0160; Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Cancer Research Program; W81XWH-16-1-0329; Kidney Mapping and Atlas Project (KMAP); U01DK133090-01; and sponsored research agreements from Astrazeneca, Bristol Myers Squibb, the Prevent Cancer Foundation, Innovation in Cancer Informatics, and the Scott Mackenzie Foundation.; National Heart, Lung and Blood Institute; R01 HL151277 - 01A1, R01 HL158071 - 01A1; National Institute of Allergy and Infectious Diseases; R01 AI175555; National Institute of Dental and Craniofacial Research; R21 DE032344 - 01; National Library of Medicine; R01 LM013864 - 01A1; National Institute on Aging; R01 AG089759; National Institute of Diabetes and Digestive and Kidney Diseases; R01 DK118431; Kidney Mapping and Atlas Project (KMAP); U01 DK133090 - 01; United States Department of Veterans Affairs VA Merit Review award; IBX004121.

8535 Poster Session

Impact of NCCN-guided training on large language model performance in mNSCLC.

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Background: Publicly available large language models (LLMs) such as ChatGPT may support clinical decision-making in precision oncology by rapidly synthesizing complex information. We previously evaluated ChatGPT's ability to generate NCCN-concordant first-line (1L) treatment recommendations for metastatic non-small cell lung cancer (mNSCLC) using a novel Generative AI Performance Score (G-PS). We evaluated whether NCCN-guideline–based training improves LLM treatment recommendations across multiple lines of therapy and targetable genotypes in metastatic NSCLC. **Methods:** NCCN Guidelines (v3.2025) were reviewed and eight driver alterations with FDA-approved therapies were selected: EGFR Ex19del, BRAF V600E, ALK fusion, KRAS G12C, NTRK1/2/3 fusion, ROS1 fusion, RET fusion, and MET exon 14 skipping. Standardized prompts requesting 1L, second-line (2L), and third-line (3L) recommendations were generated and run through ChatGPT-5.2. Prompts included information on patient demographics, disease stage, and prior therapy where appropriate. Each scenario was repeated five times per line of treatment (N = 15 per mutation). In trained sessions, the LLM was explicitly instructed to defer to an uploaded PDF copy of the NCCN guidelines prior to generating recommendations. Responses were scored using the G-PS, which quantifies guideline concordance on a continuous scale from -1 (all hallucinations) to 1 (all correct answers) based on alignment with NCCN-recommended therapies. Additionally, we calculated ratios for the mean trained G-PS and untrained G-PS across groups, to estimate the relative fold change effect of training on ChatGPT performance (called the "Training Ratio"). **Results:** A total of 240 prompts were analyzed (120 untrained, 120 trained). NCCN-guided training significantly improved overall LLM guideline concordance (mean G-PS 0.462 vs 0.313, $p = 0.049$) and reduced irrelevant recommendations (mean irrelevant rate of 23.7% vs 39.8%, $p < 0.001$) but did not significantly affect the rate of hallucinations (10.4% vs 8.1%, $p = 0.297$). 1L responses demonstrated significantly higher mean G-PS than 2L ($p < 0.001$) or 3L ($p < 0.001$) for both trained and untrained sessions. Training also significantly improved the mean G-PS of 1L responses compared to untrained responses (0.902 vs 0.647, $p < 0.001$) but not in 2L or 3L. The overall Training Ratio was 1.48, with the greatest Training Ratio seen in EGFR Ex19del and ALK fusion (> 4) and the poorest in NTRK fusions (0.53). **Conclusions:** While guideline-based training improves ChatGPT's overall performance and reduces irrelevant outputs, recommendation quality declines substantially beyond the first line of therapy and shows marked variability by mutation. These findings highlight important limitations of LLMs in complex oncology decision-making and reinforce that clinicians must independently verify recommendations against established guidelines. Research Sponsor: None.

8536 Poster Session

A triage-aware neuro-symbolic approach for clinical trial matching in oncology: Real-world validation in lung and genitourinary cancer.

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Background: Low clinical trial accrual remains a critical barrier in oncology, driven by fragmented electronic health records (EHRs), limited trial awareness, and the substantial time required for manual eligibility screening. While large language models (LLMs) can extract clinical information from unstructured data, their probabilistic nature limits direct use for eligibility decisions that require protocol-level determinism and auditability. We developed a neuro-symbolic clinical trial matching platform that combines LLM-based information extraction with explicit rule-based eligibility reasoning, augmented by an uncertainty-aware triage strategy to safely integrate automation into real-world workflows. **Methods:** Unstructured EHRs were processed using a large language model (Llama 3.1–70B) to extract key clinical variables, which were normalized to a domain ontology. Trial eligibility was evaluated using deterministic inclusion and exclusion criteria encoded directly from full trial protocols, producing per-criterion explanations and an overall classification (eligible, not eligible, or indeterminate). A triage module quantified evidentiary completeness and logical consistency, categorizing cases into low-uncertainty confidence results suitable for automated screening, moderate and high-uncertainty cases requiring clinician review. Performance was assessed against clinician-validated ground truth in a real-world cohort of 107 patients, including advanced lung cancer patients and an independent genitourinary cancer validation cohort. **Results:** Among matchable patients (n = 79), the system achieved perfect Top-1 accuracy and Recall@3 of 1.00, with all eligible patients correctly identified within the top three trial recommendations. Thirty-nine patients (49%) were triaged as low-uncertainty and suitable for automated screening, while the remainder were appropriately flagged for clinician review. Among non-matchable patients (n = 28), no false-positive eligibility assignments were observed (false-positive rate 0.0). Triage correctly identified high-uncertainty cases, minimizing unsafe automation. In indeterminate cases (ground truth unknown, n = 6), the system deferred to manual review in two-thirds of cases, with zero unsafe automated classifications. Median end-to-end processing time was under one minute per patient. **Conclusions:** This neuro-symbolic, triage-aware approach enables transparent and deterministic clinical trial matching in oncology. By combining automated eligibility assessment with uncertainty-based triage, the system reduces manual screening burden while preserving clinician oversight, supporting scalable and trustworthy trial enrollment in real-world practice. Research Sponsor: None.

8537 Poster Session

Discrepancy between plasma cell-free DNA and tissue-based analysis for detection of gene amplifications in non–small cell lung cancer.

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Background: Therapeutic strategies have been developed in patients with non-small cell lung cancer (NSCLC) harboring gene amplifications (amp) such as *MET* and *HER2*. Although both plasma cell-free DNA (cfDNA) and tissue-based next-generation sequencing (NGS) are available for the detection of gene amp, the concordance between plasma cfDNA and tissue-based analysis for the detection of gene amp remains unclear. **Methods:** We investigated plasma cfDNA and tissue-based NGS concordance for detection of gene amp in NSCLC using a large-scale screening cohort (LC-SCRUM-Liquid). Paired blood samples were prospectively collected within 4 weeks of corresponding tumor tissue sampling from patients with advanced NSCLC. Guardant360 panel or Oncomine Precision Assay panel was used for plasma cfDNA NGS. Oncomine Comprehensive Assay panel or Oncomine Precision Assay was used for tissue-based NGS. The concordance of *EGFR*, *MET* and *HER2* gene amp were evaluated. **Results:** A total of 1,133 pairs of blood and tissue samples were successfully analyzed between December 2017 and December 2024. The median age of the patients was 69 years (range 25-91), 60% were male, 68% were ever smokers, and 79% had a histopathological diagnosis of adenocarcinoma. The positive percent agreement (PPA) and positive predictive value (PPV) of plasma cfDNA analysis relative to tissue-based analysis are shown in the table. For detecting *MET* amp, the PPA of plasma cfDNA analysis relative to tissue-based analysis tended to be lower in the patients with metastases involving fewer than two organs compared to those with metastases involving two or more organs (25% vs. 63%, P = 0.07). Among the patients with *EGFR*, *MET*, or *HER2* amp detected by either tissue-based or plasma cfDNA analysis, the correlation of the copy number variants between tissue-based and plasma cfDNA analysis was very weak (r = 0.20). **Conclusions:** The concordance between plasma cfDNA and tissue-based analysis for detecting gene amp is markedly low, particularly in patients with a low tumor burden. Detection of gene amp using plasma cfDNA analysis may be insufficient for accurately evaluating the efficacy of targeted therapies for patients with lung cancer harboring gene amp. Research Sponsor: AbbVie GK, Amgen K.K., Astellas Pharma Inc., AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd., Bristol-Myers Squibb K.K., CHUGAI PHARMACEUTICAL CO., LTD.; the Japan Agency for Medical Research and Development (AMED); the National Cancer Center Research and Development Fund; DAIICHI SANKYO COMPANY, LIMITED, Eisai Co., Ltd., Guardant Health Inc., Janssen Pharmaceutical K.K., Kyowa Kirin Co., Ltd., Life Technologies Japan Ltd., Merck Biopharma Co., Ltd.; MEDICAL & BIOLOGICAL LABORATORIES CO., LTD., MSD K. K., Nippon Kayaku Co., Ltd, Novartis Pharma K.K., ONO PHARMACEUTICAL CO., LTD., Pfizer Japan Inc., Sumitomo Pharma Co., Ltd.; TAIHO PHARMACEUTICAL CO., LTD., Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., Merus N.V. and Takeda Pharmaceutical Co., Ltd.

Concordance of gene amp between plasma cell-free DNA and tissue-based analysis.

			Tissue		PPA	PPV
			+	-		
cfDNA	*EGFR* amp	+	9	37	13%	20%
		-	60	1027		
	MET amp	+	9	7	38%	56%
		-	15	1102		
	HER2 amp	+	0	4	0%	0%
		-	3	1126		

Smoking signature as used to define a genomically distinct subset of class I BRAF-mutant NSCLC.

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Background: Class I *BRAF* mutant (*BRAF* mut) non–small cell lung cancer (NSCLC) is biologically heterogeneous, occurring in both smokers and never-smokers with disparate benefits from immunotherapy (IO). Genomically defined tobacco-induced damage may better identify biologically and clinically distinct subsets than self-reported smoking history. We evaluated COSMIC mutational signature-SBS4 as a genomic surrogate of smoking exposure and examined its association with molecular features, tumor microenvironment (TME) and outcomes in *BRAF* mut NSCLC. **Methods:** Retrospective review of 33,217 NSCLC specimens that underwent whole exome and whole transcriptome sequencing at Caris Life Sciences. Mutation profiles of specimens were deconvolved using the COSMIC SBS4 signature to estimate tobacco-associated mutational exposure (filter: total mutation count>=200, Nfiltered=26448; *BRAF* mut = 276). TME was estimated using QuanTIseq method. Overall survival (OS) and survival on IO (IO-OS) were obtained from insurance claims and calculated from date of tumor biopsy (for OS) or initiation of IO (for IO-OS) to last contact using Kaplan-Meier estimates and Cox proportional hazards models. Statistical significance was determined by Fishers Exact, chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($P<0.05$). **Results:** Among 6,405 patients with smoking history and SBS4 data, SBS4+ (SBS4>0) was strongly associated with smoking (OR 11.2, $P<0.001$). SBS4+ tumors exhibited elevated TMB (mean:13 vs 9 mut/Mb, and TMB-High [>=10 mut/Mb], $P<0.05$, Table). SBS4+ *BRAF* mut tumors had a lower prevalence of mutations in *SETD2* (OR 0.33), *PIK3CA* (OR 0.26) and *SMAD4* (OR 0.25, all $P<0.05$). Regardless of SBS4 status, *BRAF* mut tumors were more often PD-L1+ (OR 3.2, TPS>=1), while mutations in *STK11, KEAP1*, and *SMARCA4* were less frequent (OR 0.07-0.37, all $P<0.05$). Evaluation of the TME revealed that SBS4+ *BRAF* mut were enriched for regulatory T cells (vs. SBS4-,1.44 fold, $P<0.05$). In metastatic disease, *BRAF* mut showed improved OS (HR 0.8[0.66-0.97], $P=0.03$) and IO-OS (HR 0.8[0.66-0.99], $P=0.04$) compared to WT. The OS benefit was preserved in the SBS4+ tumors (HR 0.64[0.43-0.95], $P=0.03$), but not in SBS4- tumors. No difference in IO-OS was observed in SBS4+ subgroups likely due to small size. **Conclusions:** SBS4 identifies biologically distinct subsets in class I BRAF mut NSCLC, with differences in mutational landscape, TMB, and TME. SBS4+ tumors show a survival benefit over WT disease, whereas SBS4- tumors do not. These findings support SBS4 as a genomic marker of smoking-related biology and a potential tool to refine therapeutic decision-making between targeted therapy and IO in NSCLC and potentially other smoking-associated cancers. Research Sponsor: None.

Smoking signature in BRAF mut NSCLC (% prevalence and OS).

Characteristics	SBS4 +	SBS4 -
SETD2	20	43
PIK3CA	6	19
SMAD4	3	12
TMB-high	41	18
OS (months)	29.9 vs. 11.9 ($P=0.03$)	16.0 vs. 10.9 ($P=0.47$)

A real-world analysis of ctDNA methylation-based histology prediction and associated clinical characteristics in non–small cell lung cancer (NSCLC).

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Background: The treatment of NSCLC differs by histologic subtype, though traditional histologic review faces several challenges including insufficient tissue and intratumoral heterogeneity. The circulating tumor DNA (ctDNA) assay Guardant360 Liquid (G360) now includes a molecular tumor type (TT) and lung subtype (ST) predictor based on DNA methylation patterns. This study aimed to evaluate the concordance between G360 TT/ST prediction and tissue-based histology in a real-world sample of patients (pts) with NSCLC. A comparative analysis was conducted to understand differences in clinical characteristics between pts with and without G360 TT/ST prediction. **Methods:** This retrospective study included pts with NSCLC who underwent G360 testing from May to October of 2025. G360 predicted TT and ST (proportion of adenocarcinoma (AD), squamous cell carcinoma (SQ), and small cell carcinoma (SC)). Dominant TT was defined as the top cancer of origin prediction. Dominant ST was defined as a proportion >80%. G360 TT/ST was compared to tissue histology to determine concordance using Cohen's kappa coefficient. Demographic and clinical characteristics were collected, and statistical differences ($p<0.05$) between pts with and without TT/ST prediction were evaluated. **Results:** Of 145 pts who underwent a combined 176 G360 assays, 47 (32%) had assays predicting TT/ST, including 9 pts with TT prediction only and 38 with both. Of these 38 pts, 32 had tissue-proven AD, 3 had SQ, and 3 had poorly differentiated NSCLC. The overall accuracy of G360 TT prediction was 100% (47/47). The accuracy of ST prediction, excluding the 3 pts with poorly differentiated NSCLC, was 94% (33/35, k=0.72), with 2 discordant cases. One case was a pt with AD whose G360 at diagnosis predicted AD, but 4 months later predicted a SC component (40%). Both pts with discordant subtyping died within 4 months of their G360 result. Pts with TT/ST prediction were statistically younger, had more advanced disease, higher extra-thoracic metastatic burden, and higher ctDNA tumor fraction (TF) than pts without TT/ST prediction (Table 1). **Conclusions:** In this real-world analysis, G360 TT/ST prediction demonstrated good concordance with tissue-based histology, though prediction was more likely in pts with more advanced disease and higher TF. In the future, ctDNA-based TT/ST prediction may be a useful noninvasive tool to confirm primary lung cancer, classify histologic subtype, and identify histologic transformation, particularly during periods of disease progression, leading to better therapeutic decisions. Research Sponsor: None.

Baseline pt characteristics.

	(+) G360 TT/ST prediction (n=47)	(-) G360 TT/ST prediction (n=98)	*P*-value
Median age (IQR)	68 (64-77)	71 (60-74)	0.03
Female (%)	27 (57.4)	60 (61.2)	0.66
Stage III/IV (%)	46 (97.9)	67 (68.4)	<0.0001
Extra-thoracic metastases (%)	35 (74.5)	20 (20.4)	<0.0001
TF (%)	3.9	0.7	0.01

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Longitudinal circulating tumor DNA surveillance as predictor of progression in advanced non-small-cell lung cancer with long-term benefit to immunotherapy.

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Background: Radiographic assessments often lag behind biological progression, and reliable biomarkers to stratify the post-treatment progression risk remain lacking in advanced non-small-cell lung cancer (NSCLC). The clinical utility of minimal residual disease in advanced solid tumors also requires further evaluation. We investigated ctDNA-based post-immunotherapy molecular residual disease (ctDNA-iMRD) in advanced NSCLC with long-term benefit from immunotherapy and assessed its predictive value for subsequent progression. **Methods:** This prospective, observational, multicenter CR1STAL study, is designed to evaluate whether longitudinal ctDNA-iMRD surveillance can can stratify progression risk in advanced NSCLC patients with long-term benefit from immunotherapy (defined as non-PD at 12 months after treatment initiation). The primary endpoint was progression-free survival (PFS), defined as the time from enrollment to radiographic progression or death. For ctDNA detection, tumor-informed and tumor-agnostic approaches were selected according to tumor tissue availability. ctDNA-iMRD positive was defined as detectable ctDNA at at any surveillance timepoint. **Results:** A total of 97 advanced NSCLC patients were included, comprising 46 in the tumor-informed cohort and 51 in the tumor-agnostic cohort. At median follow-up of 36.4 months and a median ctDNA-iMRD surveillance duration of 10.5 months, 49 patients (50.5%) were classified as ctDNA-iMRD positive during longitudinal monitoring. Patients who were ctDNA-iMRD positive had a significantly shorter median PFS than those who remained ctDNA-iMRD negative (10.1 months vs not reached; HR = 4.85; 95% CI, 2.66 to 8.82; $p < 0.001$). ctDNA-iMRD detectable preceded radiographic progression by a median of 5.9 months. The positive and negative predictive values of longitudinal ctDNA-iMRD surveillance were 85.1% and 72.7%, respectively. Between ctDNA detection approachs, ctDNA-iMRD positive was strongly associated with increased progression risk in both the tumor-informed (HR = 6.29; $p < 0.001$) and tumor-agnostic (HR = 3.67; $p < 0.001$) cohorts. In addition, longitudinal ctDNA-iMRD negative was associated with long-term overall survival (HR = 0.22, 95% CI, 0.09 to 0.55; $p < 0.001$), with 2-year and 3-year OS rates of 97.2% and 89.8%, respectively. Furthermore, ctDNA clonal status and high ctDNA growth rates were correlated with early progression. **Conclusions:** Both tumor-informed and tumor-agnostic ctDNA-iMRD approaches showed strong predictive performance. Longitudinal ctDNA-iMRD surveillance effectively stratified advanced NSCLC patients at high risk of progression after achieving long-term benefit from immunotherapy, supporting its potential role in enabling earlier, risk-adapted intervention in future prospective studies. ClinicalTrials.gov Identifier: NCT05198154. Research Sponsor: None.

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Association of gut microbiota and peri-initiation proton pump inhibitor/antibiotic exposure with outcomes of atezolizumab-bevacizumab-carboplatin-paclitaxel regimen in patients with advanced non-squamous NSCLC: Prospective phase II study (K-TAIL-201).

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Background: Concomitant medications that alter gut microbiome composition, such as proton pump inhibitors (PPIs) and antibiotics, have been suggested as possible modifiers of immune checkpoint inhibitor outcomes; however, there is a paucity of prospective data with pre-specified exposure windows during atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP) treatment. This study investigated the associations between peri-initiation PPI/antibiotic exposure and gut microbiota with clinical outcomes. **Methods:** K-TAIL-201 is a prospective, single-arm, phase II study (jRCT031200088) that enrolled Japanese patients with previously untreated advanced non-squamous non-small cell lung cancer (NSCLC) who received an induction ABCP regimen, followed by maintenance with atezolizumab plus bevacizumab. The primary endpoint was six-month progression-free survival (PFS) rate. PPI/antibiotic exposure was evaluated in two pre-specified windows: pre-treatment (up to 21 days before ABCP) and early on-treatment (the first 21 days of treatment). Longitudinal fecal samples were collected and analyzed using 16S rRNA gene sequencing. Exploratory analyses were conducted to investigate the relationships between exposure/microbiota features and outcomes. **Results:** Thirty-two patients were enrolled, with a median follow-up period of 20.6 months. The 6-month PFS rate was 59.4% (95% confidence interval (CI), 40.6–76.3), objective response rate was 50.0% (95% CI, 31.9–68.2), median PFS was 7.1 months (95% CI, 5.9–9.6), and the median overall survival (OS) was 24.3 months (95% CI, 18.7–not reached). Early on-treatment PPI exposure was associated with poorer outcomes, including shorter PFS (hazard ratio [HR] 7.07, $p < 0.001$) and OS (HR 5.66, $p = 0.009$), whereas pre-treatment PPI exposure was not associated with PFS of at least six months. Early on-treatment antibiotic exposure was associated with a lower 6-month PFS rate (21% versus 89%, $p < 0.001$), but showed no association with time-to-event PFS (HR 1.62, $p = 0.41$). Microbiota analyses revealed no significant differences in alpha or beta diversity by outcome or exposure group. However, *Bifidobacterium* was more frequently detected among responders. **Conclusions:** Early on-treatment (but not pre-treatment) PPI exposure is strongly associated with inferior PFS and OS in patients with advanced non-squamous NSCLC on ABCP regimen, supporting the clinical relevance of exposure timing. These findings suggest careful PPI use during the induction phase and warrant validation in larger prospective cohorts. Clinical trial information: 031200088. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

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USP10 activity as sensitizer of lung adenocarcinoma to immune checkpoint inhibitors: Upregulating PD-L1 via the ANT3-mediated activation of the cGAS-STING pathway.

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Background: Although immune checkpoint inhibitors (ICIs) have reshaped the treatment landscape for advanced lung adenocarcinoma (LUAD), response heterogeneity remains substantial. The cGAS–STING pathway plays a pivotal role in activating antitumor immune responses, yet its upstream regulatory mechanisms remain poorly defined. This study investigated the role of the deubiquitinating enzyme USP10 in remodeling the LUAD immune microenvironment and its mechanistic link to PD-L1 expression via the cGAS-STING axis to establish its potential as a predictive biomarker for ICIs efficacy. **Methods:** Interactions between USP10 and the mitochondrial protein ANT3 were characterized using Co-IP, LC-MS/MS, and in vitro deubiquitination assays. Mitochondrial DNA (mtDNA) leakage and cGAS-STING activation were assessed via immunofluorescence and qPCR. The therapeutic impact of USP10 on PD-1 blockade was evaluated in an orthotopic murine LUAD model. Furthermore, Furthermore, a clinical cohort of 228 patients with advanced driver-gene negative LUAD receiving first-line ICIs treatment was analyzed to correlate USP10 expression with objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). **Results:** Mechanistically, USP10 directly interacts with mitochondrial adenine nucleotide translocase 3 (ANT3) and stabilizes its protein level by removing K48-linked ubiquitin chains. USP10-mediated ANT3 accumulation triggers mitochondrial stress and promotes mtDNA release into the cytosol, thereby activating the cGAS-STING-TBK1-IRF3 signaling pathway and ultimately driving transcriptional upregulation of PD-L1. In orthotopic LUAD models, USP10-overexpressing tumors exhibited an "inflamed" phenotype characterized by a significant increase in CD8+ T cell infiltration. USP10 expression levels sensitized tumors to immunotherapy; USP10-high tumors demonstrated dramatic regression upon anti-PD-1 treatment compared to controls. In the cohort of 228 patients, high USP10 expression was identified as a robust predictor of superior clinical benefit to first-line ICIs treatment . Patients in the USP10-high group achieved significantly prolonged PFS ($p = 0.028$), higher ORR ($p = 0.037$), and improved DCR ($p = 0.041$) compared to the USP10-low group. **Conclusions:** Our study identifies a novel USP10-ANT3-cGAS-STING-PD-L1 regulatory axis that converts "cold" tumors into "hot" tumors. By inducing a pro-inflammatory TIME, USP10 enhances the sensitivity of LUAD to ICIs. These findings establish USP10 as a promising predictive biomarker and a potential therapeutic target to optimize immunotherapy strategies in lung adenocarcinoma. Research Sponsor: None.

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Smoking–genomic discordance in metastatic non–small cell lung cancer.

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Background: Smoking is the dominant risk factor for lung cancer, yet clinical smoking history does not consistently align with the presence of tobacco-associated mutational patterns (C > A transversions). We hypothesized that smoking-genomic discordance identifies a biologically distinct subset of tumors arising through endogenous, aging-enriched mutational processes. **Methods:** We analyzed metastatic NSCLC patients with documented smoking history and tumor sequencing from a discovery cohort (n = 111) and an independent Dana-Farber validation cohort (n = 2,680). Tumors were stratified by presence or absence of C > A tobacco transversions. Endpoints included C > T transition burden as a surrogate for aging-related mutational processes, transition-to-transversion (Ti/Tv) ratio for endogenous mutational contribution, tumor mutational burden (TMB), oncogenic driver distribution, and first line treatment outcomes. Multivariable regression models adjusted for age, sex, smoking intensity, and driver genotype. **Results:** Among patients with smoking history, 30% of the discovery and 15.2% of the validation cohort lacked detectable C > A transversions, including 29% with > 30 pack-years. Smoking intensity correlated with C > A but not C > T burden, while C > T increased with age in binomial models, consistent with clock-like aging accumulation. C > A negative discordant tumors had higher C > T fractions and Ti/Tv ratios than both concordant smokers and never smokers ($p < 0.001$). After multivariable adjustment, discordance was independently associated with higher C > T fractions ($\beta = 0.21$, $p < 2\times10^{-16}$) and increased odds of aging-dominant profiles defined by C > T quartiles (OR = 9.2, $p < 2\times10^{-16}$). Associations varied by driver (interaction $p = 0.007$), with EGFR mutant and oncogene fusion driven tumors enriched for C > T high discordant profiles and weak coupling between smoking intensity and C > A burden. Discordance differed by age ($p = 7.6\times10^{-4}$): among patients < 50 years, discordant smokers paradoxically had highest C > T fractions, whereas never smokers showed greatest C > A transversions, suggesting bidirectional smoking-genomic mismatch. C > A negative discordant tumors had lower TMB and depletion of KRAS/STK11/KEAP1 alterations. PD-L1 and TMB predicted immunotherapy PFS only in C > A positive tumors, suggesting limitations of conventional biomarkers in discordant cases. Conversely, C > A presence correlated with shorter targeted therapy PFS across oncogenic drivers. **Conclusions:** Clinical smoking history alone does not capture the dominant mutational processes shaping NSCLC. Smoking–genomic discordance identifies a biologically coherent phenotype with endogenous aging-associated patterns, driver- and age- related heterogeneity, and distinct therapeutic vulnerabilities. These findings motivate research into germline susceptibility and environmental exposures that may underlie tobacco-independent mutagenesis. Research Sponsor: None.

STK11 and/or KEAP1 alterations in KRAS-mutant NSCLC treated with immune checkpoint inhibitors or chemotherapy: An episode-based Project GENIE analysis.

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Background: STK11 and KEAP1 alterations are linked to aggressive biology in KRAS-mutant NSCLC and have been proposed to confer immune resistance and inferior outcomes with immune checkpoint inhibitor (ICI) though data remains inconsistent. We evaluated whether STK11 and/or KEAP1 alterations are associated with inferior overall survival (OS) and whether outcomes differ by treatment class (ICI vs chemotherapy) in a real-world clinic-genomic cohort. **Methods:** Using GENIE BPC NSCLC v2.0-public data, we created an episode-based cohort of KRAS-mutant NSCLC treatment regimens categorized as ICI or chemotherapy. STK11 and/or KEAP1 alteration status (single or dual) was the primary exposure. OS was measured from regimen start and analyzed with multivariable Cox models using patient-level clustering, adjusting for available covariates (age, sex, histology, tumor mutational burden [TMB], and KRAS G12C). We tested effect modification with an interaction term (STK11/KEAP1 $\times$ ICI). Sensitivity analyses included 3-, 6-, and 12-months landmark models and inverse probability of treatment weighting (IPTW). PD-L1, ECOG PS and line of therapy were not available. **Results:** We identified 542 treatment episodes from 293 patients (ICI = 149; chemo = 393) including 181 episodes that were STK11/KEAP1-altered. In the main cluster-robust model, STK11/KEAP1 alterations were associated with worse OS (aHR 1.68, 95% CI 1.27 - 2.24; $p < 0.001$). ICI (vs chemo) was associated with higher hazard ratio (aHR 1.76, 95% CI 1.42 - 2.18; $p < 0.001$) likely reflecting later-line use of ICI. The STK11/KEAP1 $\times$ ICI interaction was not significant as aHR 1.13, 95% CI 0.76 - 1.67; p = 0.559). In the 3-month landmark analysis STK11/KEAP1 remained adverse (aHR 1.61, 95% CI 1.19 - 2.18; p = 0.002), and the interaction estimate shifted below 1.0 (aHR 0.86, 95% CI 0.55 - 1.35; p = 0.519) suggesting a possible trend toward relatively greater ICI benefit among altered patients who survive beyond early attrition. Results were directionally consistent across 6- and 12-month landmark and IPTW analyses. **Conclusions:** In this real-world KRAS-mutant NSCLC cohort, STK11 and/or KEAP1 alterations were consistently associated with worse OS across treatment classes, supporting a primarily prognostic role. We did not find evidence of ICI-specific resistance by STK11/KEAP1 status, although modest interaction effects may be underpowered. Unmeasured confounding (ECOG PS, PD-L1 and line of therapy) remains a key limitation highlighting the need for larger, highly annotated datasets.
Research Sponsor: None.

Model	STK11/KEAP1 aHR (95% CI); p	ICI vs Chemo aHR (95% CI); p	Interaction aHR (95% CI); p
Main	1.68 (1.27–2.24); <0.001	1.76 (1.42–2.18); <0.001	1.13 (0.76–1.67); 0.559
3-mo Landmark	1.61 (1.19–2.18); 0.002	1.76 (1.39–2.23); <0.001	0.86 (0.55–1.35); 0.519
IPTW	1.68 (1.27–2.24); <0.001	1.76 (1.42–2.19); <0.001	1.13 (0.75–1.70); 0.546

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AI-powered characterization of the tumor microenvironment landscape in HER2-overexpressing non–small cell lung cancer.

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Background: Antibody-drug conjugate (ADC) targeting HER2 in NSCLC is an opportunity for biomarker-guided therapy independent of oncogenic driver status. As such, HER2 overexpressing (OE) tumors remain a clinically relevant yet under-characterized subgroup of NSCLC patients. Given the role of the tumor microenvironment (TME) in modulating response to ADCs, we applied AI-powered spatial analysis to comprehensively characterize the immunological landscape of NSCLC stratified by HER2 expression. **Methods:** We performed a retrospective analysis of a proprietary dataset comprising 2,054 H&E whole-slide images (WSIs) of NSCLC cases collected globally and enriched for HER2 OE tumors. HER2 OE was defined as IHC 3+ by pathologist reading based on ASCO/CAP guidelines and compared against IHC 0-2+. An AI-powered H&E analyzer (Lunit SCOPE IO) was used to quantify tumor-infiltrating lymphocytes (TILs) in the epithelial and stromal compartments. Immune phenotypes were classified as inflamed, excluded, or desert. For a subset of 1,099 cases with paired HER2 IHC WSIs, the proportion of tumor cells with 3+ intensity was quantified using an IHC analyzer (Lunit SCOPE HER2). Findings were further validated using 318 H&E WSIs and differential gene expression analysis of the TCGA Lung Adenocarcinoma (LUAD) cohort, stratified by ERBB2 protein expression (RPPA). **Results:** Of the 2,054 NSCLC cases, the primary analysis focused on adenocarcinoma cases (n = 1,641), which included 229 (14.0%) HER2 OE tumors. These tumors exhibited a significantly lower proportion of inflamed immune phenotype compared to the non-OE group (10.2% vs 22.1%, $P < 0.0001$). Intratumoral TIL and stromal TIL densities were reduced by 26.1% ($P < 0.0001$) and 14.7% ($P < 0.001$), respectively. Notably, even among HER2 OE tumors, a subset with high 3+ cell proportion (≥50% 3+ tumor cells) demonstrated a dose-dependent trend with an even lower inflamed proportion (3.7% vs 14.0%, $P = 0.004$) and reduced intratumoral TIL density (-36.7%, $P < 0.001$). The non-adenocarcinoma cohort (n = 413), where HER2 OE was present in 57 (13.8%) cases, showed a trend towards reduced intratumoral TIL density (-20.6%, $P = 0.080$). Analysis of H&E WSIs in TCGA LUAD validated that ERBB2-high tumors had significantly lower intratumoral TIL density (-16.1%, $P = 0.027$). Furthermore, gene expression analysis revealed that these tumors had downregulation of immune effector (GZMB, PRF1) and exhaustion (LAG3) markers, while maintaining an epithelial phenotype (OCLN, CDH1) with decreased mesenchymal markers (CDH2). **Conclusions:** NSCLC with HER2 OE is characterized by a distinct, immune-cold phenotype that is more pronounced with higher HER2 expression. These findings highlight a unique TME landscape that warrants further investigation to understand its potential impact on therapeutic responses. Research Sponsor: None.

8546 Poster Session

Comparing becotarug plus osimertinib with a real-world osimertinib therapy cohort in platinum-refractory, advanced non–small cell lung cancer with EGFR exon 20 insertion.

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Background: EGFR exon 20 insertion (20ins)-positive non-small-cell lung cancer (NSCLC) is a rare subtype with limited therapeutic options and poor prognosis. Becotarug plus osimertinib showed encouraging activity and acceptable safety in a phase 1 study (NCT04448379). To assess its efficacy in EGFR 20ins-positive NSCLC, a phase 2 single-arm trial (NCT05132777) was initiated. To provide a comparator, a multicenter retrospective real-world study (NCT05513664) was served as an external control arm. **Methods:** Eligible patients in the phase 2 study had unresectable stage IIIB–IV NSCLC with EGFR exon 20 insertion mutations and ≥1 prior platinum-based chemotherapy; those relapsing within six months after neoadjuvant or adjuvant chemotherapy were also eligible. The external control comprised a real-world cohort treated with osimertinib, matched 1:1 on age, sex, stage, ECOG PS, brain metastases, and number of prior systemic therapies. The primary endpoint was independent review committee (IRC)-assessed objective response rate (ORR) in the trial arm and real-world ORR in the control arm. Secondary endpoints included disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS). Safety was evaluated by incidence and severity of adverse events. **Results:** Of the 126 and 96 patients enrolled in the trial and control arms, respectively, 112 and 91 patients met criteria for the pre-matching cohort. After 1:1 propensity-score matching, 158 patients (79 per arm) comprised the post-matching population. Baseline characteristics were well balanced between arms, with 62.0% and 60.8% of patients, respectively, having received ≤1 prior line of systemic therapy. The IRC-assessed ORR was 46.8% (95% CI, 36.24–57.73) in the trial arm versus 7.6% (95% CI, 3.53–15.60) in the control arm. Notably, the lower bound of the trial-arm 95% CI (36.24%) exceeded the control-arm point estimate (7.6%). The absolute ORR difference was 39.2% (95% CI, 25.96–50.87; $P < 0.0001$), corresponding to an odds ratio of 10.72 (95% CI, 4.18–27.51). Furthermore, in a propensity score–matched analysis restricted to patients receiving osimertinib monotherapy (64 per arm), the combination therapy produced a greater ORR (42.2% [95% CI, 27.5-54.8], $P < 0.0001$). Higher DCR were achieved in trial arm compared to control arm (77.2% [95% CI, 66.8-85.1] vs 64.6% [95% CI, 53.6-74.2], $P = 0.080$). The median PFS in trial arm was significantly longer than that in control arm (6.9 vs. 4.8 months, $P = 0.007$). Other efficacy endpoints showed consistent trends favoring the combination therapy. The most common adverse events were EGFR-related mucocutaneous toxicities in both arms. **Conclusions:** This study further supports the efficacy and tolerability of becotarug plus osimertinib in patients with platinum-refractory, EGFR 20ins-positive NSCLC. Clinical trial information: NCT05513664; NCT05132777. Research Sponsor: Shanghai JMT-BIO Technology Co., Ltd.

8547 Poster Session

Genomic characterization of *SMARCA4*-mutant versus wild-type non–small cell lung cancer in a Chinese population: A large-scale next-generation sequencing study.

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Background: SMARCA4 is a core component of the SWI/SNF chromatin remodeling complex and plays a critical role in transcriptional regulation and tumor suppression. SMARCA4 mutations define a biologically aggressive subset of lung cancer; however, their genomic landscape and clinical implications in Chinese patients with non–small cell lung cancer (NSCLC) remain incompletely characterized. This study aimed to comprehensively compare the genomic alteration profiles between SMARCA4-mutant and SMARCA4–wild-type NSCLC to better define distinct molecular subtypes and potential therapeutic implications. **Methods:** A total of 2,362 Chinese patients with NSCLC underwent comprehensive next-generation sequencing (NGS) using a 733-gene DNA panel. The prevalence and mutation spectrum of SMARCA4 were analyzed. Genomic alteration profiles, including co-occurring mutations, tumor mutational burden (TMB), and microsatellite instability (MSI) status, were systematically compared between SMARCA4-mutant and wild-type tumors. **Results:** SMARCA4 mutations were identified in 29 of 2,362 patients (1.23%). The mutation spectrum included frameshift (10.34%), non-frameshift (10.34%), nonsynonymous missense (51.72%), stop-gain (24.14%), and synonymous (3.45%) alterations. SMARCA4-mutant tumors exhibited a distinct genomic profile compared with wild-type tumors. Several genes were significantly enriched in the SMARCA4-mutant group, including STK11 (25.0% vs 5.8%, $P < 0.001$), FAM135B (25.0% vs 8.2%, $P = 0.0068$), CDH10 (17.9% vs 4.2%, $P = 0.0063$), and FUBP1 (7.1% vs 0.3%, $P = 0.0036$), suggesting increased genomic instability and aggressive tumor biology associated with chromatin remodeling dysfunction. In contrast, EGFR mutations were significantly enriched in the SMARCA4–wild-type group (49.1% vs 14.3%, $P < 0.001$), indicating a strong mutual exclusivity between SMARCA4 alterations and classical EGFR-driven oncogenesis. SMARCA4-mutant tumors also demonstrated a significantly higher tumor mutational burden compared with wild-type tumors (7.8 vs 3.1 muts/Mb, $P < 0.0001$), whereas no significant difference in MSI status was observed between the two groups. **Conclusions:** SMARCA4-mutant NSCLC represents a distinct molecular subtype characterized by enrichment of tumor suppressor gene alterations, chromatin remodeling dysfunction, and elevated TMB, while SMARCA4–wild-type tumors are predominantly driven by canonical tyrosine kinase oncogenes such as EGFR. These findings highlight fundamental differences in tumor biology and suggest divergent therapeutic strategies, with SMARCA4-mutant NSCLC potentially benefiting from immunotherapy-oriented approaches rather than traditional targeted therapies. Research Sponsor: None.

Effect of gut microbiota–derived testosterone on distant metastasis in non–small cell lung cancer.

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Background: Distant metastasis is the major cause of poor prognosis in non–small cell lung cancer (NSCLC). Emerging evidence suggests that gut microbiota and their metabolites influence tumor progression, but their role in NSCLC metastasis remains unclear. This study aimed to characterize gut microbiota and metabolic features associated with NSCLC metastasis and to elucidate the role and mechanism of the key metabolite testosterone. **Methods:** Fecal samples from 60 NSCLC patients (48 with distant metastasis, 12 without) were analyzed using metagenomic sequencing and untargeted metabolomics. Multi-omics integration with machine learning identified metastasis-associated metabolites. The effects of testosterone on NSCLC cell migration, invasion, and epithelial–mesenchymal transition (EMT) were evaluated in vitro (PC9, A549, H1299) and in vivo using a mouse metastasis model. Molecular mechanisms were investigated by Western blot, transcriptomics, Mendelian randomization analysis, and functional studies of FGF21. Finasteride was used as a pharmacologic antagonist. **Results:** Patients with metastatic NSCLC showed distinct gut microbiota profiles, with increased alpha diversity and altered community structure compared with non-metastatic patients. Opportunistic pathogens including Oscillospiraceae, Ruminococcus, and Actinobacteria were enriched in metastatic patients, while Fusobacteria was enriched in non-metastatic patients. Metabolomic analysis revealed significant enrichment of steroid-related metabolites in metastatic NSCLC, with markedly elevated testosterone levels. Testosterone demonstrated good predictive value for metastasis (AUC = 0.761). Testosterone significantly enhanced NSCLC cell migration and invasion and induced EMT, characterized by decreased E-cadherin and ZO-1 and increased N-cadherin and Snail expression. In vivo, testosterone promoted liver metastasis and EMT marker expression. Mechanistically, testosterone activated AKT/mTOR signaling, showed a causal association with AKT phosphorylation, and upregulated FGF21. Functional assays confirmed that FGF21 promoted EMT and metastasis via AKT/mTOR activation. Finasteride reversed testosterone-induced EMT, signaling activation, and metastasis by inhibiting the FGF21/AKT/mTOR axis. **Conclusions:** Metastatic NSCLC is associated with a distinct gut microbiota and metabolic profile. Gut microbiota–derived testosterone is a key metabolite that promotes NSCLC distant metastasis by activating the FGF21/AKT/mTOR pathway and inducing EMT. Finasteride effectively antagonizes this process, suggesting potential therapeutic value. The testosterone/FGF21/AKT/mTOR axis may serve as a biomarker and therapeutic target for metastatic NSCLC. Research Sponsor: National Natural Science Foundation of China; 82203056.

8549 Poster Session

Baseline CT-derived QVT score as predictor of bevacizumab benefit in advanced non-squamous NSCLC: A retrospective biomarker analysis of SWOG S0819.

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Background: Despite two decades of anti-angiogenic therapy in NSCLC, no predictive biomarker identifies which patients benefit. As VEGF-targeted combinations advance in clinical development, patient selection biomarkers remain a critical unmet need. QVT (Quantitative Vessel Tortuosity) Score is an automated imaging biomarker measuring chaotic tumor vasculature from baseline CT scans and has been shown to be associated with immune checkpoint inhibitor (ICI) outcomes. We hypothesized that QVT Score could identify patients with chaotic angiogenesis tumors and greater sensitivity to anti-angiogenic therapy. **Methods:** We analyzed a subset of 334 patients from the SWOG S0819 (NCT00946712) trial with treatment-naïve stage IV non-squamous NSCLC receiving carboplatin/paclitaxel with (56%) or without (44%) bevacizumab. QVT Scores were derived from baseline CTs based on radiologist-defined tumor annotations and radiomic features of tumor vasculature (e.g. vessel twisting, curvature, and branching). Overall survival (OS) was evaluated as the primary endpoint using Cox proportional hazards models with QVT $\times$ bevacizumab interaction terms. Bevacizumab was non-randomized in S0819 (physician/patient discretion): to address this, we employed doubly robust estimation combining inverse probability of treatment weighting (IPTW) with multivariable covariate adjustment for age, performance status, histology, smoking history, and stage. **Results:** The QVT Score $\times$ bevacizumab interaction was significant (p=0.007, doubly robust estimation) and stayed consistent across sensitivity analyses (p=0.017 multivariable; p=0.047 IPTW), suggesting differential treatment benefit based on pre-treatment vascular phenotype. QVT Score was strongly OS-associated without bevacizumab (HR=3.03, p=0.003) but not with bevacizumab (HR=1.71, p=0.079), consistent with mitigation of high-risk biology. Bevacizumab benefit increased across QVT quartiles (Table 1): patients in the highest quartile had a 60% reduction in mortality (HR=0.40, p<0.001), while patients in the lowest quartile showed no OS benefit (HR=0.89, p=0.64). **Conclusions:** Despite unfavorable prognosis on standard-of-care therapies (chemotherapy, ICIs), we found that patients with elevated baseline QVT Score may benefit from the addition of anti-angiogenic agents. As VEGF-targeted combinations including bispecific antibodies enter development, radiomic biomarkers may play a crucial role in enriching trial populations and enabling mechanistic longitudinal monitoring. These findings warrant prospective validation in independent randomized clinical trials. Research Sponsor: None.

Bevacizumab treatment effect by QVT score quartile.

QVT Score Quartile	N	Bevacizumab effect (Hazard Ratio)	P
Q1	84	0.89 (0.56 -1.42)	0.64
Q2	83	0.70 (0.44-1.12)	0.14
Q3	83	0.54 (0.34-0.85)	0.01
Q4	84	0.40 (0.24-0.65)	0.0003

Impact of *KRAS* co-mutations on the efficacy of durvalumab in patients with locally advanced non–small cell lung cancer (LA-NSCLC) treated with concurrent chemoradiotherapy (ChRT).

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Background: Durvalumab improves survival after platinum-based ChRT in LA-NSCLC. Although immunotherapy is effective in KRAS-mutant tumors across treatment lines, co-mutations are associated with poorer prognosis and treatment resistance. Data efficacy in this context remains limited. **Methods:** We conducted a retrospective, single-institution analysis of patients with locally advanced NSCLC to evaluate the impact of KRAS mutations on progression-free survival (PFS) and overall survival (OS) after concurrent chemoradiotherapy (ChRT) and durvalumab, accounting for key clinical factors and co-mutations (TP53, STK11, KEAP1). Patients with other actionable genomic alterations (EGFR, ALK, ROS1, BRAF, MET, HER2, RET, FGFR) were excluded. PFS was defined from the first durvalumab dose to progression or death and estimated using the Kaplan–Meier method with comparisons by log-rank test. **Results:** A total of 290 patients were included (113 KRAS-mutant, 177 non-KRAS [non-AGA]). Median age was similar (69.7 vs 68.5 years), and baseline characteristics were comparable, except that KRAS-mutant patients were more often female(65% vs 38%, $p < 0.001$) and enriched for adenocarcinoma histology (90% vs 42%; squamous 2.7% vs 49%; $p = 0.009$) and PD-L1 expression (negative: 34% vs 48%; 1–49%: 25% vs 28%; ≥50%: 41% vs 34%). No significant differences in PFS were observed between KRAS and non-KRAS patients (median PFS: 22.9 months [95% CI, 16.0–29.2] vs 19.6 months [95% CI, 13.4–35.2]; log-rank $p = 0.087$), nor in overall survival (OS) (median OS: 44.5 months [95% CI, 34.4–NR] vs 40.9 months [95% CI, 30.0–59.4]; log-rank $p = 0.40$). In contrast, PFS differed significantly across KRAS-mutant subgroups: isolated KRAS mutations (median PFS 23.9 months [95% CI, 17.4–30.0]), KRAS with STK11 or KEAP1 co-mutations (8.3 months [95% CI, 3.8–20.8]), and concurrent KRAS/STK11/KEAP1 mutations (3.0 months [95% CI, 2.7–NR]; log-rank $p < 0.0001$). OS showed a similar numerical trend without statistical significance (49.4 months [95% CI, 37.4–NR], 27.3 months [95% CI, 18.4–NR], and 10.0 months [95% CI, 6.7–NR], respectively; log-rank $p = 0.08$). **Conclusions:** While KRAS mutations alone were not associated with inferior outcomes with durvalumab, concurrent STK11 and KEAP1 co-mutations were associated with markedly worse clinical outcomes. Research Sponsor: None.

8551 Poster Session

Serial ctDNA genomic profiling integrated with a networked molecular tumor board in first-line advanced NSCLC: The COPE randomized phase II trial.

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Background: Circulating tumor DNA (ctDNA) complements tissue profiling and may provide early response information in advanced NSCLC, but prospective evidence is limited. **Methods:** COPE is an open-label, multicenter, randomized (2:1), two-arm non-comparative phase II trial in stage IIIB/IV NSCLC (NCT04258137). Arm A included FoundationOneLiquidCDx ctDNA profiling at baseline, week 3, each radiologic assessment, and progression with centralized molecular tumor board (MTB) review; Arm B used baseline tissue profiling and standard imaging. ctDNA-guided treatment changes were discretionary. The primary endpoint was18-month (mo) overall survival (OS) rate in Arm A vs a prespecified historical benchmark; secondary/exploratory endpoints included profiling success, objective response rate (ORR), ctDNA dynamics, and genomic evolution. **Results:** From 2020–2023, 176 patients (pts) were enrolled (Arm A n = 117; Arm B n = 59). At median follow-up 24.0 mo, 18-mo OS was 53.8% (95% CI 44.3–62.5) in Arm A (median OS 22.4 mo) and 65.7% (95% CI 52.0–76.3) in Arm B. Baseline plasma profiling rescued genotyping in 32/35 pts with tissue insufficiency, increasing genotyping success from 69% (tissue alone) to 97% (tissue + plasma). In Arm A, 90/117 had evaluable paired baseline and week-3 plasma samples. Among pts receiving first-line (1L) chemo-immunotherapy (chemo + ICI), early molecular response (MR), defined as ctDNA no longer detected at day 21 was strongly associated with more favorable outcomes, including higher ORR (81.8% vs 50.0%), longer progression-free survival (median PFS 22.9 vs 5.9 mo), and OS (18-mo OS 81.8% vs 57.1%). Similar results were observed in the overall study population. MR50, defined as ≥50% reduction at day 21, showed similar associations with more favorable outcomes. In pts on chemo + ICI with further ctDNA testing, those with durable MR50 through mo 5-9 had longer mPFS (23 mo vs 11 mo), similar to pts with early ctDNA clearance. Importantly, excluding pts who progressed at/before week 3, the median lead time in detecting progression on chemo + ICI with ctDNA prior to radiographic progression was 3.5 mo (N = 19pts). Among 59 responders with paired baseline and any on treatment plasma, 35 were treated with 1L chemo + ICI and 13 with 1L targeted therapy. Tumor-associated emergent alterations were detected in 37 pts (63%), with treatment-specific resistance patterns observed across therapeutic classes. **Conclusions:** COPE is, to our knowledge, the first randomized prospective study of sequential ctDNA profiling in 1L advanced NSCLC. Serial ctDNA analysis within a networked MTB model was feasible, improved baseline molecular profiling, and provided a strong exploratory early molecular response signal, supporting future ctDNA-guided interventional trials. Clinical trial information: NCT04258137. Research Sponsor: Foundation Medicine.

8552 Poster Session

Clinico-genomic landscape and prognostic impact of APC/CTNNB1 oncogenic alterations in non–small cell lung cancer.

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Background: Genomic activation of the WNT/β-catenin pathway via APC loss-of-function or activating CTNNB1 mutations is well established across multiple cancer types, but its prevalence and genomic context in non–small cell lung cancer (NSCLC) remain poorly characterized. We systematically characterized the prevalence of APC and CTNNB1 alterations in NSCLC, and defined their mutational landscape and prognostic impact. **Methods:** We conducted a multicenter cohort study including patients with NSCLC whose tumors underwent targeted exon sequencing at Dana-Farber Cancer Institute (DFCI) and Memorial Sloan Kettering Cancer Center (MSKCC). Tumors were classified as APC-mutated, CTNNB1-mutated, or WNT-mutated (APC and/or CTNNB1 mutated). Pathogenic alterations were defined as oncogenic or likely oncogenic per OncoKB, or as missense variants with a REVEL score > 0.5. Gene enrichment analyses used gene-wise logistic regression adjusted for tumor mutational burden (TMB), testing genes meeting a predefined prevalence threshold, with Bonferroni correction within each analysis. **Results:** In the DFCI cohort (N = 4,717), APC or CTNNB1 alterations were identified in 4.5% of NSCLC (212/4,717), including APC in 1.7% (79/4,717) and CTNNB1 in 2.8% (133/4,717), and were mutually exclusive. APC alterations were predominantly loss-of-function events (85.3% of qualifying APC variants) and splice-region/site variants (14.8%). CTNNB1 alterations were all missense mutations (100%), clustering in exon 3, consistent with β-catenin stabilization and gain-of-function. Relative to WNT–wild-type tumors, WNT-mutated NSCLC occurred more frequently in never-smokers (32% vs 24%, $p = 0.03$), patients of Asian race (11.8% vs 4.2%, $p < 0.001$), and non-squamous histology (99.5% vs 88.6%, $p < 0.001$). These tumors exhibited lower median PD-L1 expression ($p < 0.001$) and TMB ($p = 0.03$). Similarly, in the MSK cohort (N = 4710), the prevalence of APC and CTNNB1 alterations was 0.7% and 2.7%, respectively. Relative to WNT–wild-type tumors, WNT-altered NSCLC was significantly enriched for EGFR mutations (19.3% vs 10.5%; OR 2.18; $p < 0.01$) and SMAD4 mutations (7.1% vs 2.1%; OR 3.47; $p = 0.0026$), with relative depletion of KRAS alterations (20.8% vs 32.1%; OR 0.55; $p = 0.027$). External validation reproduced these findings, with WNT-altered tumors enriched for EGFR (42% vs 21.7%; OR 3.21: $p < 0.001$) alterations and depleted for KRAS (16.7% vs 29.4%; OR 0.47; $p = 0.011$). In the DFCI cohort, APC/CTNNB1 alterations were not associated with overall survival [HR 1.05 (0.88-1.25 95% CI; $p = 0.57$)]. **Conclusions:** Genomic activation of the WNT/β-catenin pathway is characterized by EGFR and SMAD4 co-alterations, relative KRAS depletion, and lower PD-L1 and TMB. These results suggest that WNT pathway alterations contribute to molecular heterogeneity in NSCLC with potential relevance for future biomarker and therapeutic studies. Research Sponsor: None.

8553 Poster Session

Use of LIF and LIFR expression to characterize survival and tumor microenvironment composition in lung adenocarcinoma.

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Background: In lung adenocarcinoma (LUAD), EGFR-directed therapy has transformed clinical practice, yet heterogeneity in treatment response persists. Novel biomarkers are needed to refine therapeutic selection and identify new treatment targets. Leukemia inhibitory factor (LIF) and its receptor (LIFR) have emerged as potential mediators of the tumor microenvironment (TME), but their clinical significance in LUAD remains poorly defined. This study sought to investigate LIF and LIFR expression in LUAD, especially *EGFR*-mutant (EGFRm), and their TME composition and impact on survival outcomes. **Methods:** 10,041 LUAD tumors underwent next-generation sequencing of DNA (592-gene panel or whole exome sequencing) and RNA (whole transcriptome) at Caris Life Sciences. Tumors were stratified by LIR and LIFR RNA expression quartiles (Q1, low; Q4, high). QuantiSEQ was used to profile TME. Statistical analyses were performed using chi-square and Mann–Whitney U tests. Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards models to calculate hazard ratios and log-rank tests to determine p-values. **Results:** In LUAD, LIF Q4 tumors demonstrated lower abundance of $CD8^+$ T cells (fold change (FC) 0.75, $p < 0.001$), but higher abundance of NK cells, M1 macrophages, neutrophils, Tregs and B cells vs LIF Q1 tumors (FC 1.1-1.4, $p < 0.001$). LIFR Q4 tumors exhibited higher abundance of dendritic cells, NK cells and M2 macrophages vs Q1 tumors (FC: 1.2-1.5, $p < 0.001$). For LIF, Q4 tumors had higher median MAPK activation (1.73 vs −0.93, $p < 0.001$) and T-cell–inflamed scores (94 vs −2, $p < 0.001$). LIFR Q4 tumors demonstrated higher MAPK activation (1.51 vs −0.83, $p < 0.001$), and higher T-cell–inflamed scores (105 vs −29, $p < 0.001$). IFN-γ signaling was modestly lower in LIF Q4 and LIFR Q4 tumors. Longer OS was observed in LIF Q1 vs Q4 (HR 0.79, 95% CI: 0.75-0.84, 25.1 vs 18.1 m, $p< 0.001$) but shorter OS in LIFR Q1 vs Q4 (HR 1.59 , 95% CI: 1.5-1.7, 14.0 vs 27.9 m, $p< 0.001$). *EGFR* mutations were significantly more frequent in LIF Q1 vs Q4 (21.2% vs 12.8%, $p< 0.001$) and LIFR Q4 vs Q1 (27.2% vs 7.6%, $p< 0.001$). In *EGFR*m tumors treated with osimertinib, OS differences based on LIF expression were accentuated:(LIF Q1 vs Q4, HR 0.681, 95% CI: 0.58-0.80, 35.7 vs 24.7 m, $p <0.00001$). **Conclusions:** Findings demonstrate distinct transcriptional immune activation profiles between LIF- and LIFR-driven states, with superior survival in low LIF and high LIFR expressors. Despite elevated T-cell–inflamed scores, differences in immune cell composition suggest qualitative differences in immune activation between LIF- and LIFR-driven states. These findings support their relevance as prognostic and biologically informative biomarkers, and identify the LIF–LIFR axis as a key stratifier of immune state and survival heterogeneity in LUAD, with additional survival differences observed in EGFRm LUAD treated with osimertinib. Research Sponsor: None.

8554 Poster Session

A randomized phase III study of pembrolizumab versus pembrolizumab with carboplatin plus pemetrexed for locally advanced or metastatic nonsquamous non–small cell lung cancer with PD-L1 TPS ≥ 50%: LAPLACE-50.

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Background: For patients with advanced non-squamous non-small cell lung cancer (NSCLC) and high PD-L1 expression (TPS ≥50%), both pembrolizumab monotherapy and immune checkpoint inhibitor with platinum and pemetrexed combination chemotherapy are recognized as standard first-line therapies. However, direct head-to-head comparisons to determine the optimal strategy in this specific population are limited. We conducted a randomized phase III trial to compare these approaches. **Methods:** In this open-label, randomized phase III trial, previously untreated patients with advanced/metastatic non-squamous NSCLC and PD-L1 TPS ≥50% were randomized (1:1) to receive either pembrolizumab monotherapy (Arm A) or pembrolizumab plus carboplatin and pemetrexed (Arm B). The primary endpoint was progression-free survival (PFS) with a predefined non-inferiority margin of 1.25 for the hazard ratio (HR). Secondary endpoints included overall response rate (ORR), overall survival (OS), and safety. Due to slow accrual, the trial was terminated prematurely, and a final analysis was performed on the available cohort. **Results:** A total of 70 patients were randomized (Arm A, n=35; Arm B, n=35), and 69 patients were included in the full analysis set. Median PFS was 8.1 months in Arm A and 9.2 months in Arm B (HR 1.25; 90% CI, 0.77–2.04), and non-inferiority of pembrolizumab monotherapy was not demonstrated. ORR was 57.1% in Arm A and 73.5% in Arm B (odds ratio 0.49, 95% CI, 0.18–1.36; p=0.172). Median OS was 55.1 months in Arm A and 23.5 months in Arm B (HR 0.83, 95% CI, 0.42–1.63; p=0.663). Grade ≥3 hematologic toxicities were more frequent in Arm B. Serious adverse events occurred in 20.0% of patients in Arm A and 26.5% in Arm B. **Conclusions:** Although this trial was limited by early termination and did not statistically demonstrate the non-inferiority of pembrolizumab monotherapy in terms of PFS, the numerical OS favored the monotherapy group despite a lower ORR. These findings suggest that for patients with PD-L1 TPS ≥50%, pembrolizumab monotherapy remains a robust treatment option with a favorable safety profile, though the addition of chemotherapy may offer higher initial response rates. Clinical trial information: jRCTs031200078. Research Sponsor: NHO Multi-Center Clinical Research for Evidence-Based Medicine.

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Combination of golidocitinib (a JAK1 inhibitor) with anti–PD-1 antibody to improve tumor response and patient quality of life: Preliminary results from an ongoing JACKPOT 33 study.

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Background: Chemo-immunotherapy remains the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) without driver mutations. Unfortunately, treatment resistance is inevitable. Janus kinase (JAK) inhibition may improve the efficacy of immunotherapy by pivoting T cell exhaustion dynamics, enhancing and extending patient response. Herein, we report the anti-tumor efficacy and safety data from an ongoing phase 2 study (NCT06198907, JACKPOT33) evaluating golidocitinib, a JAK1-specific inhibitor, combined with sintilimab, an anti-PD-1 antibody, as first-line treatment in patients with PD-L1 positive advanced NSCLC without driver mutations. **Methods:** Eligible patients with advanced NSCLC with PD-L1 TPS ≥ 1% were enrolled in the study. Patients received two cycles of chemo-immunotherapy only, followed by golidocitinib 150 mg orally once daily plus sintilimab 200 mg intravenous every 3 weeks until disease progression, intolerance, up to 2 years of treatment, or other discontinuation criteria were met. The primary objective was to evaluate the anti-tumor efficacy, and the secondary objectives included safety and tolerability. **Results:** As of December 23, 2025, a total of 47 patients were enrolled in the JACKPOT33 study. The median age of these patients was 63 years, with 87.2% males, 61.7% with non-squamous histology, 40.4% with PD-L1 high (TPS ≥50%) and 59.6% with PD-L1 low (TPS 1-49%) expression. Most (74.5%) of the patients had metastatic disease at baseline, with 8.5% having brain metastasis. Per investigator assessment, the overall response rate (ORR) after two cycles of chemo-immunotherapy was 42.6%. Following the addition of golidocitinib with sintilimab, deeper tumor shrinkage and additional responders were observed, resulting in an ORR of 63.8% (30/47). The improvement in ORR with golidocitinib was most profound in patients with high PD-L1 levels, with rates of 84.2% vs. 50% in the high and low expression cohorts, respectively. No difference in ORR was observed between patients with squamous or non-squamous carcinoma (61.1% vs 65.5%). As of the data cut-off date, 32 out of 47 patients remained on treatment and benefiting. The longest treatment duration reached 15.9 months. The combination of golidocitinib and sintilimab was well tolerated. The incidence of immune-related adverse effects was markedly decreased, and patients' self-reported quality of life significantly improved. No new safety signal was observed. **Conclusions:** In treatment-naïve patients with advanced NSCLC, golidocitinib plus sintilimab following chemo-immunotherapy demonstrated encouraging and durable anti-tumor efficacy, particularly in those with high PD-L1 expression. A profound decrease in immune-related adverse effects was observed. Updated data will be presented at the conference. Clinical trial information: NCT06198907. Research Sponsor: None.

A first-in-human (FIH), phase I/II open-label, dose-escalation and -expansion study of ILKN421H, an LNP mRNA encoding an IL2Rβγ selective IL-2v, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors.

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Background: ILKN421H is an LNP mRNA encoding an IL2Rβγ selective IL-2v derivative fused with Human Serum Album. Preclinically, the novel LNP mRNA platform allowed expression and therefore extended plasma half-life of IL2v in animal models, which is not achieved with other protein-based IL-2 drugs. ILKN421H stimulated significant and sustained expansion of CD8 T cells for more than three weeks, with minimal expansion of regulatory T cells. Moreover, ILKN421H demonstrated superior efficacy than IL-2 based drugs in multiple cancer models and has an excellent safety profile in rodents and non-human primates. Therefore, the novel design of ILKN421H has the potential to fully unleash the antitumor effects of the IL-2 pathway while mitigating unwanted toxicity. **Methods:** This first-in-human, open label phase 1 study evaluates the safety, tolerability, and initial efficacy of ILKN421H with or without pembrolizumab in patients with advanced solid tumors. The design includes two portions of the study: Parts A, ILKN421H monotherapy in which patients receive intravenous ILKN421H once every 3 weeks (Q3W) and Part B in which patients receive ILKN421H in combination with pembrolizumab (200 mg on day 1), both intravenous Q3W. Both portions of the study consist of 3+3 escalation cohorts to define maximum tolerated dose (MTD). If response signal is observed in a given dose cohort, additional 10 patients will be enrolled in the expansion portion of the study to further evaluate the safety and efficacy. The trial is ongoing and data as of 5/7/2024 is presented in this abstract. **Results:** A total of 47 participants were enrolled so far. In Part A, 9 patients in three dose cohorts received ILKN421H. All patients demonstrated high and prolonged plasma level of IL-2, and remarkable elevation of CD8 T cells (up to 5 folds) and NK cells (up to 25 folds). No dose-limiting toxicities (DLT) were observed. In Part B, 38 patients in three dose cohorts were enrolled, 24 of which are 1L advanced NSCLC. All patients showed robustly increased CD8 T cells and NK cells, and well tolerated safety profile (TESAE=26%). At the cut-off date (Nov 25th, 2025), of the 22 efficacy evaluable 1L NSCLC patients regardless of the PDL1 expression levels, 17 were evaluated to be PR (ORR=77.2%), and 50% PFS was not reached and was projected to be more than 14 month. In PDL1 negative patients (TPS $<$1%), 3 out of 6 patients achieved PR (ORR=50%). **Conclusions:** ILKN421H was generally well tolerated at the current dose level, which already demonstrated high and prolonged plasma level of IL-2, and robust immune stimulatory activity in promoting CD8 T cells and NK cells proliferation. Initial signs of antitumor efficacy were seen in combination with pembrolizumab. Clinical trial information: NCT05978102. Research Sponsor: iLeukon Therapeutics.

Race-associated clinicogenomic predictors in non-small cell lung cancer treated with immune checkpoint inhibitors.

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Background: PD-L1 low and STK11 mutation associate with immune checkpoint inhibitor (ICI) resistance in non-small cell lung cancer (NSCLC), but appear differentially expressed among racial ethnic groups. This has not been validated in large, diverse studies. **Methods:** We retrospectively studied NSCLC patients 18 or older, without targetable EGFR or ALK alterations, treated with frontline ICI between January 2014 and February 2020 at MD Anderson Cancer Center and University of Illinois Chicago. We analyzed clinicogenomic and survival characteristics by race/ethnicity. Differences in clinicogenomic predictors were assessed through log-rank and chi-squared comparison of proportions tests. Survival differences were estimated via Kaplan-Meier method. **Results:** 1694 patients met inclusion criteria, 383 (22.6%) were minorities. Poor performance status (PS 2-3) was most frequent in African American (AA) (32.5%) and Native Alaskan/Hawaiian or American Indian (NAHAI) (27.3%) patients (p=0.005) (Table). Heavy smoking was more frequent in White (50.3%) patients. PD-L1 <1% was most prevalent among Asian (31.3%) and least prevalent among Hispanic/Latino (HL) (15.8%) patients (p=0.001). STK11 mutation rate was most prevalent in AA (14.7%) and least prevalent in HL (6.9%) and Asian (2.5%) patients (p=0.056). Median overall survival (OS) was lower (21.3, 23.5, and 24.3 months) for HL, NAHAI, and AA patients, and higher (25.4 and 30.6 months) for White and Asian patients, respectively (p<0.01). **Conclusions:** Our dual center study with 22% minority patient representation shows self-reported race can result in biological differences, because of ancestry and/or environmental differences. AA, HL, and NAHAI patients had lower rates of heavy smoking and different clinicogenomic patterns than White patients. AA tended towards higher prevalence of STK11 mutation—while not statistically significant, it was overall not highly represented in the sample. In line with these poor prognostic factors, AA had statistically significant lower median overall survival (OS) than their White and Asian counterparts. Asians had the lowest rates of heavy smoking and STK11 mutation, highest rates of PD-L1<1%, and highest median OS. HL had the lowest OS, with low prevalence of PD-L1<1% and STK11 mutation – future studies should evaluate other clinicogenomic factors to determine potential culprits. Research Sponsor: The University of Texas MD Anderson Lung Moon Shot Program and the MD Anderson Cancer Center Support Grant P30 CA016672.

	White	Black or African American (AA)	Hispanic or Latino (HL)	Asian	Native Alaskan/ Hawaiian or American Indian (NAHAI)	p-value
Total cohort n=1694, No. (%)	1311 (77.4)	191 (11.3)	101 (6.1)	80 (4.7)	11 (0.5)	
ECOG PS 2-3 at ICI start	267 (20.4)	62 (32.5)	23 (22.8)	20 (25.0)	3 (27.3)	**0.005**
20+ Pack Years Smoking	659 (50.3)	77 (40.3)	26 (25.7)	19 (23.8)	5 (45.5)	**4.9×10^{-9}**
PD-L1 <1%	317 (24.2)	47 (24.6)	16 (15.8)	25 (31.3)	1 (9.1)	**0.001**
$STK11_{mut}$	129 (9.8)	22 (14.7)	7 (6.9)	2 (2.5)	1 (9.1)	0.056
Median OS (mo)	25.4	24.3	21.3	30.6	23.5	**< 0.01**

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Safety and efficacy of CS2009, a first-in-class PD-1/VEGF/CTLA-4 trispecific antibody, in patients with advanced non-small cell lung cancer: Results from a phase 1/2 study.

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Background: CS2009 is a novel PD-1/VEGF/CTLA-4 trispecific antibody. An ongoing phase 1/2 study is evaluating its safety, tolerability, PK, PD, and anti-tumor activity as a single agent and in combination with systemic treatment in patients (pts) with advanced solid tumors. This study comprises a phase 1 dose escalation and phase 2 dose expansion. Here, we report the initial efficacy and safety data from advanced non-small cell lung cancer (NSCLC) pts treated in first-line and later-line settings. **Methods:** The study enrolled both treatment-naïve (1L) and heavily pre-treated later-line (≥2L) NSCLC pts. The ≥2L group included previously treated pts without known actionable oncogenic alterations (AGA) who had progressed on at least one prior line containing an anti-PD-1/L1 antibody and platinum-based chemotherapy; these pts received CS2009 at 10, 20, 30, or 45 mg/kg, i.v., Q3W, until disease progression or intolerance. The 1L cohort enrolled treatment-naïve pts with PD-L1 TPS ≥1% NSCLC without known AGA; these pts were randomized 1:1 to receive CS2009 at 20 or 30 mg/kg, i.v., Q3W, until disease progression or intolerance. Safety was assessed in all treated pts. Efficacy was assessed in pts who had at least one post-baseline tumor assessment per RECIST v1.1. **Results:** As of Jan. 4, 2026, 40 pts with ≥2L NSCLC were treated with CS2009 across four dose levels (10 mg/kg, n=3; 20 mg/kg, n=12; 30 mg/kg, n=20; 45 mg/kg, n=5). Median age was 67 (range 37-78) years; 72.5% were Asian, 27.5% were White; 77.5% were male; 77.5% had ECOG PS 1 at baseline. Among 30 efficacy-evaluable pts, ORR was 20.0% (6 PRs); in 16 pts treated at 30 mg/kg, ORR was 25.0% (4 PRs). Any-grade and grade ≥3 treatment-related adverse events (TRAEs) occurred in 27 (67.5%) and 8 (20.0%) pts, respectively. The most common TRAEs were proteinuria (12.5%), hypertension (12.5%), bilirubin conjugated increased (10.0%), and fatigue (10.0%), which were mostly grade 1 or 2, except for grade ≥3 hypertension in two pts. No treatment-related deaths were reported. TRAEs led to discontinuation in 3 (7.5%) pts. More mature ≥2L efficacy data with additional evaluable pts will be presented at the conference. As of Jan. 4, 2026, 19 pts with 1L NSCLC (PD-L1 TPS ≥1%) were randomized to receive CS2009 at 20 mg/kg (n=10) or 30 mg/kg (n=9). Median age was 69 (range 52-82) years; 84.2% were male; 89.5% had ECOG PS 1 at baseline. Preliminary encouraging efficacy and favorable safety signals were observed. Updated efficacy and safety data in approximately 50 1L pts will be disclosed at the conference. **Conclusions:** CS2009, as a first-in-class trispecific antibody targeting PD-1, VEGF, and CTLA-4, demonstrated a favorable safety profile and clinically meaningful anti-tumor activity in advanced NSCLC pts without known AGA. These findings warrant further investigation of CS2009 in this population. Clinical trial information: NCT06741644. Research Sponsor: CStone Pharmaceuticals.

8559 Poster Session

A phase II study of ubenimex combined with pembrolizumab, nab-paclitaxel, and carboplatin for previously untreated advanced squamous non–small cell lung cancer: TORG2241(UBE-Q).

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Background: Pembrolizumab plus platinum-based chemotherapy is a standard first-line treatment for previously untreated advanced squamous non-small cell lung cancer (NSCLC) based on the KEYNOTE-407 trial. Ubenimex, an oral CD13/aminopeptidase inhibitor, has immunostimulatory and antitumor activity. We conducted a phase II trial to assess the safety and efficacy of ubenimex in combination with pembrolizumab, nab-paclitaxel, and carboplatin in patients with previously untreated advanced squamous NSCLC. **Methods:** This study was a prospective, multicenter, single-arm phase II trial. Eligible patients with previously untreated advanced squamous NSCLC received ubenimex orally plus 4 cycles of pembrolizumab, nab-paclitaxel, and carboplatin, followed by continuous administration of ubenimex and pembrolizumab for a maximum of 2 years. To confirm tolerability, the daily dose of ubenimex started at level 1 (30mg/day), which was increased to levels 2 (60 mg/day) and 3 (120 mg/day) according to the escalation criteria, with a standard 3 + 3 design for achieving the target dose-limiting toxicity (DLT) rate of 33%. The efficacy, safety, and tolerability of ubenimex at the determined dose level were analyzed. The primary efficacy endpoint was objective response rate (ORR) by independent central review, estimated descriptively with a 90% confidence interval; the ORR in the KEYNOTE-407 (62.6%) served as a reference value for study design. **Results:** No DLTs were observed across dose levels 1–3. Therefore, level 3 was selected as the recommended dose. From January 2024 to January 2025, 28 patients were enrolled from 18 institutions, and all patients were evaluable for efficacy and safety. Baseline characteristics were male/female 25/3; median age 72 (range, 40-86); ECOG PS 0/1 12/16. The ORR was 71.4% (90% CI, 54.3-84.9). With a median follow-up of 12.8 months, median progression-free survival (PFS) was 16.8 months (95% CI, 5.6-not reached); median overall survival (OS) was not reached. Grade 3/4 adverse events included pneumonitis (3.6%), anemia (46.4%), febrile neutropenia (10.7%). There was no treatment-related death. **Conclusions:** Ubenimex with 120 mg/day (60 mg twice daily) combined with pembrolizumab, nab-paclitaxel, and carboplatin was feasible and showed encouraging antitumor activity with manageable safety in previously untreated advanced squamous NSCLC, supporting further randomized evaluation. Clinical trial information: jRCT2031210707. Research Sponsor: Nippon Kayaku Co., Ltd.

FF-10832 liposomal gemcitabine monotherapy or combination with pembrolizumab in patients with advanced non–small cell lung cancer.

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Background: FF-10832, a stable liposomal formulation of gemcitabine with a prolonged half-life (mean $t_{1/2}$ of 26 hours compared to ~3 hours for gemcitabine HCl), has demonstrated single agent activity in patients (pts) with solid tumors. In pre-clinical models, FF-10832 has yielded superior anti-tumor activity compared to gemcitabine alone and in combination with PD-1 inhibitors. Following a safety run-in, we investigated the clinical activity of FF-10832 in an expansion study, administered alone or in combination with pembrolizumab (PEM), in pts with advanced/metastatic (m) NSCLC (NCT05318573). **Methods:** In the open-label single arm safety run-in, 40 mg/m^2 FF-10832 and 200 mg PEM every 3 weeks was established as safe and tolerable in 12 pts including 6 mNSCLC patients with unlimited prior therapies. The trial was expanded using this regimen. Pts were randomized to receive FF-10832 alone (mono) or FF-10832 +PEM (combo). Eligibility stipulated up to 3 prior therapies in the advanced/metastatic setting with prior disease progression (PD) on platinum and PD-(L)1-directed therapy. Pts receiving FF-10832 monotherapy could add PEM to FF-10832 upon PD determined by RECIST 1.1. To be evaluable for anti-tumor activity, pts must have had at least one RECIST assessment ≥6 weeks after baseline. All pts were evaluable for safety. **Results:** A total of 41 NSCLC pts were treated with FF-10832 (N=21) or FF-1032+PEM (N=20); median # of prior therapies was 2 for both arms. RECIST evaluability was achieved in 30 pts (14/16; mono/combo); 11 pts (7/4; mono/combo) came off study before evaluation for anti-tumor activity. No objective responses were observed. Stable disease (SD) was recorded in 9/14 pts in the mono arm and 13/16 in the combo arm; 4 pts (1 mono/3 combo) with >20% tumor shrinkage. Median time on study for the mono and combo arms was 9 (1 – 48.1) and 12.1 (1.1 – 44) weeks, respectively. Median (95% CI) PFS in months: mono arm, 2.7 (1.4 – 4.3); combo arm, 2.8 (1.9 – 5.5). Five mono pts began FF-10832+PEM treatment upon PD, two that remain on combination therapy with SD for 23 and 33 weeks after progressing on FF-10832 monotherapy. Related AEs were similar in mono vs combo arms; those in ≥15% of pts in each arm included nausea, vomiting, fatigue, rash, infusion-related reaction, and anemia. Related grade ≥3 AEs occurred in 33% (mono) and 45% (combo) of pts. The only attributable grade ≥3 events in >1 pt were in the combo arm (n): anemia (3), fatigue (2), dyspnea (2), and lymphopenia (2). FF-10832 PK showed a profile consistent with that previously reported (terminal $t_{1/2,}$ ~30 hours). Overall survival data are pending. **Conclusions:** FF-10832 alone or in combination with PEM in platinum-CPI refractory pts proved tolerable with a safety profile matching previous experience. There were no objective responses, but the majority of evaluable pts had SD at 1st assessment, some with tumor shrinkage. Aggregate mPFS was 2.7 mos. Clinical trial information: NCT05318573. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

Disease kinetics and practice patterns in ≥ 4-year long-term beneficiaries of immune checkpoint inhibitors for advanced non–small cell lung cancer.

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Background: Immune checkpoint inhibitors (ICIs) have transformed outcomes in advanced non-small cell lung cancer (NSCLC), enabling durable responses in a subset of patients (pts). However, detailed clinical trajectories and patterns of late disease progression among long-term survivors remain poorly characterized. **Methods:** This multicenter retrospective cohort study enrolled advanced NSCLC pts who initiated ICI-containing therapy between January 2015 and April 2020. Long-term beneficiaries (LTBs) were defined as pts achieving both overall survival (OS) and time to next cytotoxic chemotherapy (TTNC) ≥4 years (yrs). We performed 4-yr landmark analyses, characterized late progression (defined as the first radiographic progression ≥4 yrs from ICI initiation), and evaluated cause-specific mortality using competing risk analysis. **Results:** Of 3,144 pts, 537 (17%) survived ≥4 yrs; 295 (9.4%) were LTBs (median follow-up, 68.6 months; only 8.1% lost to follow-up). ICI was initiated as first-line therapy in 186 pts (63.1%) and as second-line or later in 109 pts (36.9%). The median age was 67 yrs, and PD-L1 Tumor Proportion Score ≥50% was observed in 57%. Among 235 LTBs without progression at 4 yrs, 156 (66%) had discontinued ICI. Among pts progression-free at 4 yrs, lung cancer-specific OS (LC-OS) rates from ICI initiation were 97.8% at 6 yrs and 88.0% at 8 yrs (Table). Late progression occurred in 26 of 235 progression-free LTBs (11.1%); all had progression involving ≤5 lesions. The median interval from the last non-progressive assessment to the first assessment meeting radiographic progression was 98 days (IQR, 56–189), with a median sum-of-diameters growth rate of 6.2 mm/month (IQR, 3.4–9.6). Local therapy was selected in 42% after progression. Among 22 deaths occurring ≥4 yrs after ICI initiation, only 7 (32%) were lung cancer–related, whereas 15 (68%) were due to other causes, including five secondary malignancies. Competing risk analysis showed that the cumulative incidence of other-cause death consistently exceeded that of lung cancer death throughout follow-up (lung cancer death: 0.5% at 5 yrs to 10.7% at 8 yrs; other-cause death: 2.3% to 14.8%). **Conclusions:** LTBs of ICIs achieved durable disease control, with LC-OS approaching 90% at 8 yrs. In these pts, late progression was uncommon, typically involving ≤5 lesions with modest growth kinetics, often treated with local therapy without requiring immediate systemic treatment. The predominance of non-lung cancer mortality suggests that survivorship care addressing second malignancies is increasingly important in this population. Research Sponsor: None.

Landmark survival analysis from 4 years after ICI initiation (n=235).

Timepoint	PFS	TTNC	OS	Other Cause OS	LC-OS
5-year	90.1%	96.4%	97.2%	97.7%	99.5%
6-year	82.4%	90.3%	91.8%	93.8%	97.8%
7-year	74.6%	81.3%	82.7%	87.3%	94.7%
8-year	69.9%	74.3%	74.5%	84.7%	88.0%

8562 Poster Session

Impact of immunotherapy era on survival in stage IV non–small cell lung cancer.

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Background: The introduction of immunotherapy (IO) has transformed treatment paradigms in Stage IV non-small cell lung cancer (NSCLC). However, large-scale population-based evidence quantifying its impact on survival remains limited. We evaluated overall survival trends before and after the IO era using SEER data. **Methods:** We identified patients diagnosed with Stage IV NSCLC from 2006 to 2020 in the SEER 17 database. Patients were grouped by era: pre-IO (2006–2014) and post-IO (2015–2020). Demographics, histology, and socioeconomic variables were included. Overall survival (OS) was assessed using Kaplan-Meier analysis. Multivariable Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs) adjusting for age, sex, race, and histology. **Results:** A total of 101,243 Stage IV NSCLC patients were included. The post-IO era was associated with a 19% reduction in mortality compared to the pre-IO era (HR 0.81; 95% CI 0.79–0.82; $p<0.001$). Older age (≥75 years) conferred increased mortality risk (HR 1.32; 95% CI 1.30–1.34; $p<0.001$), while younger patients (<65 years) had better outcomes (HR 0.91; 95% CI 0.89–0.93; $p<0.001$). Male sex (HR 1.16; 95% CI 1.14–1.17; $p<0.001$), non-adenocarcinoma histology (HR 1.30; 95% CI 1.28–1.32; $p<0.001$), and Black race (reference group) were independently associated with worse survival. White (HR 0.83; 95% CI 0.81–0.85; $p<0.001$) and Other races (HR 0.75; 95% CI 0.73–0.77; $p<0.001$) demonstrated survival advantages. Kaplan-Meier curves confirmed significantly improved OS in the post-IO era (median OS 8 vs 10 months, log-rank $p<0.001$). **Conclusions:** This large population-based study confirms a significant survival benefit in Stage IV NSCLC patients diagnosed in the immunotherapy era, alongside expected demographic and histologic disparities. These findings support the real-world impact of immunotherapy and underscore the need for continued efforts to address survival inequities. Research Sponsor: None.

8563 Poster Session

Ablation plus immunotherapy in advanced NSCLC patients who develop oligo-residual disease after anti–PD-1/L1 therapy: Updated results from the BOOSTER trial.

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Background: Local consolidative therapy (LCT) has been demonstrated to augment the survival benefits of immunotherapy in non-small cell lung cancer (NSCLC) patients with oligo-residual disease (ORD) in the phase2 BOOSTER Trial (ChiCTR2000032479) as previously reported (2024 WCLC OA05.03; *Signal Transduction and Targeted Therapy* 2025). Here we report updated data with longer follow-up. **Methods:** This randomized, phase 2 trial enrolled patients with advanced NSCLC who developed oligo-residual disease after anti-PD-1/L1 therapy, defined as partial response or stable disease as the best response with residual tumors confined to a maximum of three organs and five lesions. Participants were randomly assigned (2:1) to receive ablation (thermal ablation or cryoablation) plus immunotherapy or immunotherapy maintenance alone. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), safety, patterns of disease progression and immunogenic changes after ablation. **Results:** Among 65 patients enrolled, the full analysis set finally included 42 patients in ablation plus immunotherapy group and 20 patients in immunotherapy maintenance group. In this updated data cutoff (December 2025) compared to the prior data cutoff (March 2024), median duration of follow-up has increased from 17.8 months to 28.9 months. Patients receiving ablation were associated with significantly longer PFS than those without ablation (median 28.1 vs. 12.8 months, $p < 0.001$, HR = 0.310, 95%CI 0.169–0.596). The median OS was not reached in either group. The 48-months OS rate were 79.0% (95% CI, 59.5–90.0) in ablation group and 67.6% (95% CI, 41.3–84.1) in the without ablation group. Updated subgroup analysis further suggested a trend of superior efficacy of cryoablation (n=13) compared with thermal ablation (n=29), with a median PFS of 37.6 versus 22.4 months, respectively (p=0.028). The safety profile of ablation combining with immunotherapy was similar to previously reported, and most of the adverse events were well managed. **Conclusions:** With extended follow up, the updated data suggested that the addition of local consolidative ablation confers durable clinical benefit in patients with advanced NSCLC who develop ORD after anti-PD-1/L1 therapy. Cryoablation was associated with potentially superior survival outcomes compared with thermal ablation. Clinical trial information: ChiCTR2000032479. Research Sponsor: None.

Inhaled delivery of KB707, a novel HSV-based immunotherapy, in combination with pembrolizumab in advanced non–small cell lung cancer: A phase 1/2 study.

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Background: Though immune checkpoint inhibitors (ICIs) have significantly improved the treatment for lung cancers, resistance invariably develops and novel approaches are needed to overcome such resistance and enhance anti-tumor immunity. KB707 is a replication-defective herpes simplex virus type 1 (HSV-1)-based vector engineered to deliver human interleukin (IL)-12 and IL-2 to induce both innate and adaptive antitumor immunity. Inhaled KB707 monotherapy was previously shown to be well tolerated with encouraging efficacy in pts with advanced non-small cell lung cancer (aNSCLC): 4 of 11 pts achieved partial response (PR). Delivery of IL-12/IL-2 by inhaled KB707 may significantly increase the anti-tumor efficacy of ICI (pembro) in pts with aNSCLC who are relapsed or refractory to standard therapy. Extending from the monotherapy results, the safety and efficacy of adding inhaled KB707 to pembro in pts with aNSCLC is presented. **Methods:** KB707-02 is a Phase 1/2, open-label, multicenter study of inhaled KB707 (NCT06228326). Eligible pts with at least one measurable lung lesion at screening and histological confirmation of stage 3 or 4 NSCLC received nebulized KB707 (10^9 PFU) every 2 weeks and pembro (400 mg) every 6 weeks. Pts must have previously received one line of prior ICI, with or without platinum-based chemotherapy. The primary objective is to assess safety and tolerability per CTCAE v5.0, with a secondary objective to evaluate preliminary efficacy per RECIST 1.1. **Results:** As of 01 Jan 2026, a total of 21 pts (11 female) were enrolled and received at least one dose of inhaled KB707 plus pembro. The majority of treatment-related adverse events (TRAE) have been mild to moderate in severity and transient. Consistent with known adverse event profiles of IL-2 and IL-12, the most common TRAE were flu-like symptoms (fever, chills, vomiting, fatigue) and dyspnea. The efficacy population (n=16) received at least one treatment cycle and had at least one evaluation per RECIST 1.1. The 16 pts were of advanced age (median 72 [50-88] years old) and heavily treated (3 median lines of prior therapies). The ORR was 31.3% (5/16) and DCR was 75% (12/16) with 5 pts achieving confirmed PR and 7 with stable disease (SD). Median treatment duration was 24.1 weeks (6.1-71.9) with 5 out of 16 pts remaining on study. Median overall survival and progression free survival were not reached. **Conclusions:** Delivery of IL-12/IL-2 by inhaled KB707 in combination with pembro was well tolerated and encouraging antitumor effects were observed in heavily treated aNSCLC, as evidenced by 31.3% ORR and 75% DCR. The study is proceeding with enrollment of an additional cohort to further evaluate inhaled KB707 in combination with docetaxel in aNSCLC. Clinical trial information: NCT06228326. Research Sponsor: Krystal Biotech Inc.

Impact of *STK11/KEAP1/SMARCA4* co-mutations in RAS-activated *KRAS* wild-type metastatic NSCLC treated with immune checkpoint inhibitors.

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Background: RAS-activated *KRAS* wild-type (RASa/KRASwt) non-small cell lung cancer (NSCLC) shares key biological features with KRAS-mutant (KRASm) tumors, including MAPK pathway activation. In KRASm NSCLC, co-mutations in *STK11*, *KEAP1* and *SMARCA4* are associated with poor outcomes to immune checkpoint inhibitors (ICI). Whether these alterations similarly impact outcomes in RASa/KRASwt tumors is unknown. **Methods:** We analyzed patients with metastatic NSCLC treated with ICI at Dana-Farber Cancer Institute. RASa/KRASwt tumors were defined by pathogenic alterations in RAS–MAPK pathway genes (*NF1*, *NF2*, *BRAF*, *RAF1*, *MAP2K1/2*, *MAP3K1*, *MAPK1*, *PTPN11*, *SOS1*, *HRAS*, *NRAS*, *RIT1*, *RASA1*, *GNAS*). Co-mutations in *STK11*, *KEAP1* and *SMARCA4* were evaluated using targeted exome sequencing. Survival analyses were performed using log-rank test and survival risks estimated with Cox regression models. **Results:** Among 1,215 patients included, 492 (40%) had KRASm tumors and 264 (22%) were RASa/KRASwt. Compared with RASa/KRASwt tumors, KRASm tumors were more frequent in female patients (65% vs 50%, p<0.001), ever-smokers (93% vs 86%, p=0.004) and non-squamous histology (98% vs 88%, p<0.001). The frequency of *KEAP1* (21% vs 22%), *STK11* (26% vs 20%) and *SMARCA4* (10% vs 12%) mutations was similar between the groups. High tumor mutation burden (≥10 mut/Mb) was more frequent in RASa/KRASwt tumors (60% vs 46%, p<0.001), while PD-L1 expression, age and performance status were comparable. Within the RASa/KRASwt cohort, 103 patients (39%) had co-mutations in *STK11*/KEAP1/*SMARCA4* and were more frequently ever-smokers compared with non co-mutated RASa/KRASwt (95% vs 80%, p<0.001), with otherwise similar clinical characteristics. As expected, co-mutations were associated with shorter median progression free survival (mPFS) and median overall survival (OS) in KRASm group (mPFS: 4.4 vs 6.2 mo., HR:1.33 (1.1-1.62), p=0.004; mOS: 11.4 vs 21.7 months(mo), HR:1.43 (1.16-1.78), p<0.001). However, among RASa/KRASwt tumors, concurrent mutations in STK11/KEAP1/SMARCA4 had no impact on survival outcomes (mPFS: 5.9 vs 4.1 mo., HR:0.79 (0.6-1.02), p=0.07; mOS: 15.8 vs 14.8 mo, HR: 1.02 (0.77-1.35), p=0.89). This differential effect was confirmed by a significant interaction between RAS status and co-mutational status (aHR 1.71, p=0.004). For OS, interaction analysis did not show a differential effect of co-mutations according to RAS status (aHR 1.43; p=0.073). **Conclusions:** Known co-mutations that confer worse outcomes to ICI in KRASm NSCLC do not appear to have the same impact in KRASwt tumors with other RAS activating mutations. RASa/KRASwt tumors with co-mutations behave more similarly to KRAS wild-type NSCLCs, highlighting biological heterogeneity within RAS-driven tumors and potential implications for patient selection for treatment intensification or de-escalation strategies. Research Sponsor: None.

Effect of dual immune checkpoint inhibitors (ICI) by the time of infusion in advanced non–small cell lung cancer (NSCLC): A secondary analysis of CCTG BR34 trial.

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Background: There is increasing evidence suggesting the impact of circadian biology on ICI efficacy in solid tumours, though evidence for dual checkpoint blockade is limited. We conducted a secondary analysis of BR.34 to assess whether time of infusion (TOI) correlates with outcomes with durvalumab–tremelimumab ± platinum chemotherapy in advanced EGFR/ALK-negative NSCLC. **Methods:** Patients were classified into the AM group when ≥80% of the PD-1 inhibitor infusions were started before 13:00 (threshold based on prior literature); otherwise, they were placed into the PM group. OS and PFS were analyzed using Cox models adjusted for imbalanced baseline factors. Sensitivity analyses were performed to assess correlations with other TOI thresholds. **Results:** TOI was evaluable for 296/301 patients; 186 were AM and 110 PM. PM infusion was associated with longer median OS (19.1 vs 13.4 months (m); HR 0.58, 95% CI 0.41–0.82) and median PFS (8.3 vs 4.1 m; HR 0.67, 95% CI 0.51–0.88). The improvement in OS associated with the PM group was consistent across both arms. In the multivariable analyses, PM administration remained associated with improved OS (adjusted HR (aHR) 0.62, 95% CI 0.44–0.88) and PFS (aHR 0.73, 95% CI 0.55–0.96). Sensitivity analyses using an alternative threshold of ≥60% of the PD-1 inhibitor infusions started before 1300 yielded consistent trends. Using a median TOI of 11:00 AM as an additional threshold, later infusions were also associated with longer OS (HR 0.77, 95% CI 0.56–1.05), with similar trends across both treatment arms. There was no apparent difference in fatal adverse events (n = 4), with two in the AM and two in the PM group. Serious adverse effects that led to therapy discontinuation also did not significantly differ between AM vs. PM in the IO-alone group (3 vs. 5) or the IO-chemo group (6 vs. 4). **Conclusions:** Afternoon infusion of dual ICI ± chemotherapy was associated with improved survival in BR.34, in contrast to earlier reports with anti-PD-1 therapy. These findings highlight the potential for regimen- and disease-specific chronotherapeutic effects and support the need for prospective trials across tumour types and of different checkpoint inhibitor combinations. References: 1. Leighl NB, et al. *J Thorac Oncol.* 2022;17(3):434–445. 2. Karaboué A, et al. *Br J Cancer.* 2024;131:783–796. Research Sponsor: Grants to the Canadian Cancer Trials Group from the Canadian Cancer Society Research Institute and AstraZeneca.

Baseline factors.

Baseline Factors	IO-AM (n)	IO-PM (n)	IO-CHEMO-AM (n)	IO-CHEMO-PM (n)
Sex (F/M)	41/54	28/25	42/49	27/30
Age (<65/≥65)	48/47	84/64	36/55	32/25
ECOG (0/1)	22/73	23/30	26/65	20/37
Disease Stage (IVA/IVB)	26/69	22/31	34/57	19/38
Histological subtype (NSq/Sq)	77/18	44/9	73/18	48/9
Liver Metastases (N/Y)	78/17	42/11	68/23	50/7
Brain Metastases (N/Y)	76/19	45/8	82/9	44/13
PD-L1 Expression (<1/1-49/≥50%/ Unknown)	37/25/20/ 13	23/19/7/ 4	33/27/16/15	22/17/13/5
TMB (<20/≥20 mut/MB)	74/21	39/14	69/22	46/11

Nsq = non-squamous, Sq = squamous.

A phase 2 study of plinabulin (Plin)/docetaxel (Doc) plus pembrolizumab (Pemb) in metastatic NSCLC (mNSCLC) after acquired resistance (AR) to anti–PD-1/L1 alone or in chemotherapy combination: Efficacy and immunophenotyping.

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Background: PD-1/L1 inhibitors have become a part of 1L treatment for EGFR/ALK wild-type NSCLC. However, >60% patients (pts) develop AR associated with T cell exhaustion and defective antigen presentation. Doc remains a mainstay for pts who relapse after anti-PD-1/L1 therapy, while multiple late-stage clinical trials have failed in comparison. Plin is a first-in-class, brain-penetrating dendritic cell maturation agent with clinically validated potential to restore antigen presentation/T cell function after AR to PD-1/L1 inhibitors. Plin also reduces severe neutropenia and thereby increases Doc tolerability. In a global phase 3 study (Dublin-3, n=559), Plin/Doc outperformed Doc with significant OS/PFS/ORR benefits, doubling of 2-/3-year OS rates, and 80% reduction in G4 neutropenia ($p<0.0001$). The aim of this study was to assess the efficacy/safety of Plin/Doc plus Pemb in mNSCLC after anti-PD-1/L1 based therapy. **Methods:** This single-arm phase 2 trial (NCT05599789; Study 303) enrolled 47 pts after immediate progression on anti-PD-1/L1 alone or combined with platinum doublets. Pts received Plin 30mg/m2, Doc 75mg/m2 and Pemb 200mg, on Day 1 in 21-day cycles. The primary/secondary endpoints at the median follow-up of 20.6 months (mo) are tabulated. For immunophenotyping, whole blood from baseline and post treatment were analyzed by flow cytometry. **Results:** At the data cutoff date of 31-Dec-2025, cORR was 18.2% with 79.5% DCR. mPFS was 7.0 mo, and mDoR at 9.3 mo. While mOS was 34 mo, the 24-mo OS rates were 64.3% (ITT), 71.1% (NSQ), and 52.0% (SQ). In all endpoints assessed, prior Pemb exposure did not reduce the efficacy of this regimen. Whole blood analysis indicated that activated CD4+/CD8+ T cells and proliferating Ki67+CD8 T cells were significantly increased post two cycles of treatment. Also observed were concurrent elevations of Ki67+B cells and CD38+NK cells. **Conclusions:** Plin/doc plus Pemb shows promising efficacy in mNSCLC with AR to anti-PD-1/L1 confirmed by immune activation post-treatment. TRAEs were manageable. These findings along with DUBLIN-3 support a global confirmatory study in EGFR/ALK wild-type NSQ NSCLC following progression on anti-PD1/L1 based therapy. Clinical trial information: NCT05599789. Research Sponsor: BeyondSpring Pharmaceuticals, Inc.

Efficacy endpoints.

Endpoint*	ITT (N=47)	NSQ (N=30)	SQ (N=17)
Primary endpoint			
cORR (RECIST 1.1)	18.2%	13.8%	26.7%
Secondary endpoints			
mPFS (RECIST 1.1)	7.0 mo	7.7 mo	5.5 mo
mOS	34 mo	(not reached)	34 mo
mDoR (RECIST 1.1)	9.3 mo	(not reached)	9.1 mo
DCR (PR+SD > 4 mo)	79.5%	82.8%	73.3%
12-mo OS rate	78.2%	80.0%	74.8%
24-mo OS rate	64.3%	71.1%	52.0%

*cORR/DoR/DCR: 44 evaluable pts; PFS/OS & follow-up duration: ITT.

Efficacy, safety, and cytokine profiling with addition of the toll-like receptor (TLR) 7/8 dual agonist EIK1001 to standard of care (SOC) first-line (1L) therapy: The phase 2 TeLuRide-005 trial in stage 4 NSCLC.

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Background: EIK1001 a TLR 7/8 dual agonist activates dendritic cells via both innate and adaptive pathways. This mechanism of action (MOA) associated with cytokine (CK) release and T-cell differentiation is complementary to immune checkpoint inhibitors (ICIs) that enhance anti-tumor T-cell activity. It provides rationale to add EIK1001 to SOC chemotherapy (chemo) + ICI in Stage 4 NSCLC, a disease with unmet therapeutic needs. **Methods:** TeLuRide-005 (NCT#06246110) is an ongoing multicenter, open-label study of intravenous weekly (wk) EIK1001 combined with SOC q3-wk pembro + chemo in treatment-naïve patients (pts) with Stage 4 NSCLC. The nonsquamous (NSQ) and squamous (SQ) cohorts completed accrual in May '25 and Jan '26, respectively. CK were sampled pre- and post EIK1001 treatment (PT) on Day 1 of Cycle (C) 1 and C4. **Results:** 71 pts (median age: 68, male:73%) were treated. An ORR of 61% and DCR of 90% were observed for the pooled study population. Cytokine release syndrome (CRS) events were of low grade: 4 pts with Grade 1 and 3 pts with Grade 2. For safety, and efficacy by histology, see Table. 71% of NSQ remain progression free at 8 months and despite over 11 months of follow-up, median PFS is not yet accurately estimable. Type 1 and 2 interferons (IFN) and Interleukin 6/8 (IL6/8) increased PT on C1. By C4, baseline IP-10, an IFN inducible protein that is a T-cell chemotactant, was upregulated by a median of 1.6- fold increase from baseline C1D1. Conversely, CRS-associated IL6 and IL8 were reduced or less inducible on C4D1 than on C1D1, consistent with our observation of only one pt. experiencing CRS after C4. **Conclusions:** 1L EIK1001 + SOC demonstrates encouraging efficacy in Stage 4 NSCLC with evidence of durable effect. AEs were similar to SOC alone and CRS events were low-grade. Cytokine data support the MOA of the TLR 7/8 dual agonist, EIK1001, and reduced inducibility of IL6/IL8 PT by C4 may suggest CRS likelihood diminishes with time. Clinical trial information: NCT#06246110. Research Sponsor: None.

Safety Results		
At least 1 ≥ Grade 3 TEAE % (n/N)	76.1% (54/71)	
Serious adverse event (SAE) % (n/N)	46.5% (33/71)	
Efficacy Results	**NSQ (n=39)**	**SQ (n=32)**
Months of follow up (f/u), median (range)	11.2 (5.5-23.0)	6.5 (0.5-19.1)
Progression-Free Survival at 8 months* (95% CI)	70.7% (56.9-87.8%)	NA
Objective Response Rate (ORR), % (95% CI)**	55.6% (38.1-72.1%)	68.0% (46.5-85.1%)
Disease Control Rate (DCR), % (95% CI)	83.3% (67.2-93.6%)	100% (86.3-100%)
Duration of Response (DOR), Range in Months	2.1+ - 15.1+	1.0 - 13.2+

NA: Not Analyzed due to short duration of follow-up; *4 scan opportunities at 8 months; **Response evaluable.

8569 Poster Session

SHR-1701 combined with fuzuloparib and chemotherapy as first-line therapy for advanced lung squamous cell carcinoma: Efficacy and safety results from a phase II study.

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Background: Although immune checkpoint inhibitors are established in the treatment of advanced lung squamous cell carcinoma (LUSC), many patients derive limited or no durable benefit, underscoring the need for novel therapeutic strategies. However, poly (ADP-ribose) polymerase inhibitors (PARPi) can upregulate PD-L1 expression and promote immune-mediated response, which may increase the efficacy of anti-PD-(L)1 based therapy. Additionally, blocking TGF-b signaling has the potential to facilitate the recovery from chemo-induced myelosuppression. This phase II study evaluates the efficacy and safety for first-line approach combining SHR-1701, a bifunctional anti–PD-L1/TGF-β trap, with the PARP inhibitor fuzuloparib, combined with standard chemotherapy, which may potentiate anti-tumor immunity. To our knowledge, this is the first clinical investigation of this multi-pathway targeting strategy in advanced LUSC. **Methods:** Treatment-naïve patients with advanced LUSC received induction therapy with SHR-1701 (30 mg/kg IV q3w) plus platinum-based chemotherapy (investigator's choice) for 4 cycles. Patients with disease control proceeded to maintenance therapy with SHR-1701 (same dose) plus oral fuzuloparib (100 mg twice daily) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) by Blinded Independent Review Committee (BIRC) per RECIST v1.1. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Results:** Between February 2023 and June 2025, 71 treatment-naïve advanced LUSC patients were enrolled (median age 65 years; 96% male). As of data cutoff (December 1, 2025; median follow-up 17.4 months), 57 patients (80.3%) had started maintenance therapy (median 12 cycles). Disease progression or death had occurred in 27 of 71 patients (38.0%) by the cutoff date. Median PFS was 11.0 months (95% CI, 8.1 to not estimable). Among 69 response-evaluable patients, best overall response included 1 complete response (1.4%), 56 partial responses (81.2%, including 46 confirmed), and 11 stable disease (15.9%), yielding an unconfirmed ORR of 82.6% (57/69), a confirmed ORR of 68.1% (47/69), and a DCR of 98.6% (68/69). OS data were immature; the 12-month OS rate was 83.0% (95% CI 71.1–90.2). Treatment-related adverse events occurred in 94.4% (67/71) of patients, most commonly anemia (42.3%), increased blood creatinine (19.7%), and proteinuria (18.3%). No new safety signals were observed. **Conclusions:** SHR-1701 plus fuzuloparib and chemotherapy as first-line therapy demonstrated promising anti-tumor activity and a manageable safety profile in patients with advanced LUSC. Clinical trial information: NCT04937972. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

1L olomorasib plus pembrolizumab +/- chemotherapy in *KRAS* G12C-mutant NSCLC patients +/- a prior cycle of SOC: Results from LOXO-RAS 20001 and SUNRAY-01.

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Background: Real-world data suggests allowing 1 cycle of standard of care (SOC) prior to enrollment into first-line (1L) NSCLC trials of targeted therapies could expand the potential enrollable population by accommodating molecular testing turnaround time and enabling a more representative patient (pt) population. Here, we report results from 1L pts who did or did not receive 1 prior cycle of SOC in LOXO-RAS-20001 and the dose optimization/safety lead-in of SUNRAY-01, which investigated olomorasib, a KRAS G12C inhibitor, with pembrolizumab +/- chemotherapy. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC, PD-L1 0-100% and ECOG PS 0-1 were eligible to receive olomorasib (50 or 100 mg, orally BID) with either pembrolizumab (doublet) or pembrolizumab + chemotherapy (quad) at their physician's discretion. One cycle of SOC prior to enrollment was permitted when timely initiation of treatment was clinically indicated, this included pembrolizumab (doublet) and pemetrexed + platinum +/- pembrolizumab, or pembrolizumab alone (quad). ORR was assessed in the efficacy evaluable population, defined as pts with ≥1 post-baseline response assessment or who discontinued treatment before the first response assessment. Safety was assessed across all treated pts. **Results:** As of 6 June 2025, 85 pts received the doublet and 77 pts received the quad; 13 pts (15%) and 23 pts (30%) received 1 prior cycle of SOC, respectively. Baseline characteristics of pts who did and did not receive 1 prior cycle of SOC were comparable. Accounting for small sample sizes, efficacy and safety were broadly similar across both the doublet and the quad among those who did and did not receive a prior cycle of SOC (Table). **Conclusions:** Treatment with 1 cycle of SOC prior to enrollment appeared to have no detrimental effect on safety and efficacy outcomes of olomorasib in combination with pembrolizumab +/- chemotherapy in pts with *KRAS* G12C NSCLC. This is the first analysis of the clinical impact of 1 prior cycle of SOC in a NSCLC clinical trial, allowing early access to treatment if clinically indicated. Implementation of this strategy in SUNRAY-01 and other 1L NSCLC trials may expand enrollment and allow for a more representative pt population. Clinical trial information: NCT04956640, NCT06119581. Research Sponsor: Eli Lilly and Company.

1L treatment outcomes.

	Olomorasib + Pembrolizumab		Olomorasib + Pembrolizumab + Chemotherapy	
	1 prior cycle of SOC n=13	No prior SOC n=72	1 prior cycle of SOC n=23	No prior SOC n=54
ORR, (%)	76.9	71.8	73.9	55.6
(95 %, CI)	(46.2, 95.0)	(59.9, 81.9)	(51.6, 89.8)	(41.4, 69.1)
DCR, %	100	88.7	95.7	87.0
(95 %, CI)	(75.3, 100.0)	(79.0, 95.0)	(78.1, 99.9)	(75.1, 94.6)
TRAE All Grade / Grade 3+ (%)	100 / 30.8	87.5 / 41.7	95.7 / 26.1	96.3 / 59.3
Grade ≥3 Hepatic Events* (%)	15.4	22.2	0	22.2
Grade ≥3 Diarrhea (%)	7.7	6.9	4.3	5.6
Grade ≥3 Neutropenia (%)	0	0	4.3	16.7
Discontinuation of regimen	15.4	11.1	0	11.1
Median Duration of Treatment, mo (IQR)	10.3 (5.6-13.3)		7.9 (3.8-9.9)	

*Consolidated term.

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Phase II study of multidisciplinary therapy combined with pembrolizumab for patients with synchronous oligometastatic non-small cell lung cancer: TRAP-OLIGO study (WJOG11118L).

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Background: Several clinical trials have demonstrated that local ablative therapy (LAT) to all lesions, including primary site, may provide a survival benefit for patients with oligometastatic non-small cell lung cancer (NSCLC). However, few studies have evaluated the efficacy of integrating immune checkpoint inhibitors with chemotherapy and LAT. This study aimed to evaluate the efficacy of multimodal therapy combining platinum-doublet chemotherapy plus pembrolizumab followed by LAT to all sites of disease in patients with synchronous oligometastatic NSCLC. **Methods:** This multicenter, single-arm, phase II trial enrolled treatment-naive patients with stage IV NSCLC and three or fewer metastatic lesions. Patients received 4 cycles of induction therapy consisting of pembrolizumab plus platinum-doublet chemotherapy. Patients then received LAT to all residual lesions, followed by maintenance therapy with pembrolizumab. The primary endpoint was the 24-month progression-free survival (PFS) rate from the initiation of LAT. Secondary endpoints included safety, response to induction therapy, PFS, overall survival (OS), and the proportion of patients who underwent LAT. The threshold and expected 24-month PFS rates were set at 25% and 60%, respectively, with a one-sided alpha of 0.025 and 80% power. **Results:** Between October 30, 2020, and August 12, 2022, 30 patients were enrolled. At enrollment, seven patients had one metastasis (23.3%), 14 had two (46.7%), and 9 had three (30%). Twenty-three patients (76.7%) received LAT to all residual disease sites. The 24-month PFS rate from the initiation of LAT was 56.5% (95% CI, 34.3–79.8%). The median PFS from the initiation of LAT was 25.8 months (95% CI, 11.7–not reached). The OS rates at 24 and 36 months from the initiation of LAT were 78.0% (95% CI, 55.0–90.2%) and 61.6% (95% CI, 37.2–78.9%), respectively. During the LAT phase, grade 3/4 adverse events occurred in 3 patients (13.0%). No treatment-related deaths were observed. **Conclusions:** The TRAP-OLIGO study met its primary endpoint with the lower limit of the 95% CI exceeding the threshold, demonstrating that multimodal therapy combining platinum-based chemotherapy plus pembrolizumab and LAT provides favorable efficacy for patients with synchronous oligometastatic NSCLC. These findings suggest that this integrated approach is a promising treatment strategy for this population. Trial registration: Japan Registry of Clinical Trials, jRCTs041200046. Clinical trial information: jRCTs041200046. Research Sponsor: None.

Immune-related adverse event severity and clinical outcomes with immune checkpoint inhibitor immunotherapy in participants with non–small cell lung cancer: Analysis of the lung MAP sub-studies S1400A, S1400I, S1400F, and S1800A.

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Background: Immune checkpoint inhibitors (ICIs) have advanced the treatment paradigm for non-small cell lung cancer (NSCLC), but ICIs are associated with risk of immune-related adverse events (irAEs). There is an unmet need to better understand how the severity of irAE impacts the clinical outcome of NSCLC treated with ICIs. We hypothesized that participants (pts) with lower grade irAEs would have better outcomes than those with higher grade irAEs and those without irAEs. **Methods:** We evaluated outcomes in Lung-MAP pts with advanced NSCLC treated with ICIs in the 2L setting (S1400A [durvalumab vs docetaxel], S1400I [nivolumab +/- ipilimumab], S1400F [durvalumab + tremelimumab], and S1800A [pembrolizumab + ramucirumab vs standard-of-care]), using 6-, 12-, and 24-week landmark analyses of the relationship between irAE severity (Grade(G) 1 or 2 vs G3 or 4 and vs no irAE) and overall survival (OS) from the landmark timepoint. OS was compared between groups using Cox Proportional hazards model with separate analyses for ICI-naïve (S1400A and S1400I) and ICI-exposed (S1400F and S1800A). **Results:** Analyses included 315 ICI-naïve and 127 ICI-refractory pts. In the ICI- naïve cohort, no irAEs and G 3-4 irAEs were associated with inferior OS compared with G1-2 irAEs by 12 wks of treatment (no irAEs: HR 1.68, CI 1.28 – 2.22, $p < 0.0005$ G3-4: HR 2.28, CI 1.47 – 3.53; $p < 0.0005$). This difference in OS between the irAE groups was consistent at the 6 wk ($p = 0.006$) and 24 wk ($p = 0.03$) landmark timepoints. See table for outcomes in the ICI naïve cohort. In the ICI-exposed cohort, there was no difference in OS between the irAE groups at any landmark timepoint (6 weeks: $p = 0.39$; 24 weeks: $p = 0.98$). **Conclusions:** In the ICI-naïve cohort, G1-2 irAEs in were associated with better OS compared to no irAEs and G3-4 irAEs for all landmark times. This association was not observed in the ICI-exposed cohort. Additional analyses will incorporate molecular and immune features evaluating risk and severity of irAEs. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA18088; National Cancer Institute/U.S. National Institutes of Health; U10CA180819.

Outcomes for ICI naïve cohort.

Landmark Time	irAE Group	N	mOS (95% CI)
6 weeks	No irAE	160	9.0 (7.9-10.9)
	G 1-2	124	14.6 (10.1-19.0)
	G 3-4	20	5.9 (3.5-10.8)
12 weeks	No irAE	124	8.2 (6.5-9.8)
	G 1-2	130	15.4 (11.5-9.8)
	G 3-4	29	5.3 (2.9 - 8.0)
24 weeks	No irAE	77	7.0 (5.8-9.8)
	G 1-2	121	14.9 (10.9-18.5)
	G 3-4	34	5.9 (3.1-13.9)

Durable efficacy of first-line necitumumab plus pembrolizumab in PD-L1–high advanced NSCLC: Final results of the phase II K-TAIL-202 study.

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Background: Pembrolizumab is a standard 1st line treatment for advanced non–small cell lung cancer (NSCLC) with high PD-L1 expression (tumor proportion score [TPS] ≥50%); however, durable benefit is achieved in only a subset of patients. Prior pembrolizumab-based combination strategies (e.g., anti-TIGIT) have inconsistently improved outcomes over pembrolizumab monotherapy in this setting. Epidermal growth factor receptor (EGFR) signaling may promote immune evasion by stabilizing PD-L1 expression and shaping an immunosuppressive tumor microenvironment, providing a rationale for combining the anti-EGFR antibody necitumumab with pembrolizumab. We therefore evaluated the efficacy and safety of necitumumab plus pembrolizumab in treatment-naive patients with PD-L1–high advanced NSCLC. **Methods:** K-TAIL-202 (jRCT2031200248) was an open-label, multicenter, single-arm phase II study conducted in Japan. Eligible patients were aged ≥20 years with unresectable stage III/IV or recurrent NSCLC, PD-L1 TPS ≥50% (22C3), ECOG PS 0–1, and ≥1 measurable lesion. Patients received necitumumab 800 mg IV on days 1 and 8 plus pembrolizumab 200 mg IV on day 1 every 3 weeks for up to 35 cycles or until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1; secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. The study assumed an expected ORR of 54.8% and a threshold ORR of 39.0% (one-sided α = 0.10; 80% power), requiring enrollment of 50 patients. **Results:** Between December 2020 and March 2023, 50 patients were enrolled (median age, 72 years). The ORR was 68.0% (95% CI, 53.3–80.5) and the disease control rate was 78.0% (95% CI, 64.0–88.5). Complete response, partial response, stable disease, progressive disease, and not evaluable status were observed in 2.0%, 66.0%, 10.0%, 12.0%, and 10.0% of patients, respectively, meeting the primary endpoint. Median PFS was 16.0 months (95% CI, 9.0–24.0), with a 24-month PFS rate of 35.9%. Median OS was not attained (95% CI, 38.0 months–not estimable), and the 24-month OS rate was 71.3%. The most treatment-emergent adverse events included acneiform dermatitis (66.0%), hypomagnesemia (60.0%), and pneumonitis (12.0%). One grade 5 cardiac arrest occurred in 1 patient (2.0%), for which a causal relationship to study treatment could not be ruled out. **Conclusions:** At final analysis, first-line necitumumab plus pembrolizumab demonstrated durable antitumor activity and encouraging long-term survival as a chemotherapy-free regimen in patients with PD-L1–high advanced NSCLC. Toxicities were consistent with the known profiles of EGFR-targeted antibodies and PD-1 inhibitor therapy, underscoring the need for careful monitoring. These findings warrant further confirmation in a randomized phase III clinical trial. Clinical trial information: jRCT2031200248. Research Sponsor: Nippon Kayaku Co; READYFOR (Japan) crowdfunding (public donations).

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A phase II study of HB0025 (a PD-L1/VEGF bispecific antibody) in combination with chemotherapy as first-line treatment for non–small cell lung cancer (NSCLC).

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Background: HB0025, developed by Huaota, is a novel anti-PD-L1/VEGF bispecific antibody with VEGFR1D2 linked at the N-terminal of anti-PD-L1 antibody. This Phase II study assesses the efficacy and safety of HB0025 combined with chemotherapy in locally advanced unresectable, recurrent or metastatic non-small cell lung cancer (NSCLC). **Methods:** This open-label, multi-center, Phase II trial enrolled previously untreated patients with locally advanced unresectable, recurrent or metastatic NSCLC, without *EGFR* or *ALK* gene alterations. Participants were assigned to two cohorts: Cohort 1 (squamous NSCLC) received 20 mg/kg HB0025 plus carboplatin and paclitaxel every three weeks (Q3W) for 4-6 cycles, followed by HB0025 maintenance; Cohort 2 (non-squamous NSCLC) received 20 mg/kg HB0025 plus carboplatin and pemetrexed Q3W for 4-6 cycles, followed by maintenance with HB0025 and pemetrexed. Primary endpoint was objective response rate (ORR) per RECIST 1.1. **Results:** As of January 5, 2026, 125 patients were enrolled in the study (62 patients in Cohort 1 and 63 patients in Cohort 2). The median age was 65 years old (range: 34, 74). The median follow-up period was 10.55 months (range: 1.0, 17.4). A total of 119 patients had at least one post-baseline tumor assessment. In Cohort 1, ORR was 84.5% (49/58), with subgroup ORRs of 81.3%, 72.2%, and 100% for PD-L1 TPS $<$ 1%, 1–49%, and $\geq$50%, respectively; disease control rate (DCR) was 94.8% (55/58), median progression-free survival (mPFS) was 12.62 months, and median duration of response (mDOR) was immature. In Cohort 2, ORR was 65.6% (40/61), with ORRs uniformly 66.7% across all PD-L1 TPS subgroups; DCR was 96.7% (59/61), mPFS was 14.65 months, and mDOR was 12.06 months. Overall survival data remained immature. The most common immune-related adverse events (irAEs) were hypothyroidism (7.2%), hyperthyroidism (4.8%), increased alanine aminotransferase (4.0%), increased aspartate aminotransferase (3.2%), and increased blood thyroid stimulating hormone (3.2%). Anti-VEGF-related AEs of grade $\geq$3 were proteinuria (8.8%), hypertension (6.4%), hemorrhage (4.0%), and thromboembolism (4.0%). 6 (4.8%) patients discontinued HB0025 due to TRAE, and 2 (1.6%) patients died due to TRAE. **Conclusions:** The combination of HB0025 and chemotherapy has demonstrated promising efficacy and favorable safety as a first-line treatment for patients with locally advanced unresectable, recurrent or metastatic NSCLC. Multi-center, randomized, double-blind, controlled phase III trials in both squamous and non-squamous NSCLC have been initiated. Clinical trial information: NCT06758557. Research Sponsor: Shanghai Huaota Biopharmaceutical Co., Ltd.

Chronotherapy in metastatic non–small cell lung cancer: Clinical outcomes according to immune checkpoint inhibitor administration time during the day in patients treated with first-line chemoimmunotherapy.

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Background: Although circadian rhythms are known to modulate immune cell function, the effect of immune checkpoint inhibitor (ICI) infusion timing during the day on oncologic outcomes in metastatic non–small cell lung cancer (NSCLC) patients treated with first-line chemoimmunotherapy has not been fully elucidated. **Methods:** We retrospectively analyzed patients with de novo metastatic NSCLC without actionable oncogenic driver alterations who received first-line chemotherapy plus ICI between January 1, 2018, and October 31, 2025, at two centers. Patients receiving platinum-based doublet chemotherapy plus pembrolizumab and/or nivolumab were included, whereas those treated with dual ICIs (nivolumab plus ipilimumab with platinum-based chemotherapy) were excluded. Infusion times for the first four cycles were recorded, and patients were categorized as the early group if they received ≥2 of the first four ICI cycles before 11:00 a.m., and as the late group if they received ≤1 of the first four ICI cycles before 11:00 a.m. Endpoints were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** We identified 101 eligible patients who met the inclusion criteria, comprising 34 patients in the early group and 67 patients in the late group. Median follow-up was 18.4 months (95% CI 12.4 – 24.4). There were no differences between the early group and the late group in terms of age, gender, body mass index, smoking status, ECOG performance status, stage (IVA vs. IVB), histologic subtype (squamous vs. non-squamous), PD-L1 tumor proportion score (< 1% vs. 1-49% vs. ≥50%), central nervous system metastases, liver metastases, number of metastatic sites (≤2 vs. ≥3 organ systems), and ICI agent (pembrolizumab vs. nivolumab). The early group demonstrated significantly longer median PFS (14.6 vs. 7.1 months; HR = 0.54 [95% CI 0.31 – 0.93]; p = 0.027) and median OS (not reached vs. 27.3 months; HR = 0.28 [95% CI 0.11 – 0.71]; p = 0.008). Both the ORR (97.1% vs. 56.7%; p < 0.001) and the disease control rate (97.1% vs. 64.2%; p < 0.001) were significantly higher in the early group. The majority of patients who experienced primary progression after the first four cycles were in the late group (24 of 25 patients; 96%). In multivariate analysis, only disease stage (IVB vs. IVA; HR = 2.35 [95% CI 1.05 – 5.26]; p = 0.039) and timing-based group assignment according to the number of the first four ICI infusions administered before 11:00 a.m. (late vs. early; HR = 2.97 [95% CI 1.14 – 7.76]; p = 0.026) were independently associated with OS. **Conclusions:** Our findings demonstrated that receiving majority (≥2) of the first four ICI infusions before 11:00 a.m. might be associated with better response rates, improved PFS and OS in patients with de novo metastatic NSCLC treated with first-line chemotherapy plus ICI.
Research Sponsor: None.

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Multi-omic ctDNA-based MRD for predicting clinical outcomes in advanced NSCLC receiving chemoimmunotherapy.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized treatment for advanced non–small cell lung cancer (aNSCLC); however, many patients achieving radiographic partial or complete response (PR/CR) relapse early. This underscores the need for more precise risk stratification after an initial response. We investigated whether circulating tumor DNA -based minimal residual disease (ctDNA-MRD) assessment could stratify patients with durable benefit versus those at risk of early progression after chemoimmunotherapy (Chemo-IO). **Methods:** We analyzed 152 retrospective and 60 prospective aNSCLC patients who achieved PR/CR after first-line (1L) PD-1-based Chemo-IO. Plasma was collected at the first imaging-confirmed PR/CR (retrospective) or at baseline and Cycle 5 Day 1 (C5D1; prospective). ctDNA-MRD was assessed using a tumor-naïve, mutation-based panel and a fragmentomics model derived from low-pass whole-genome sequencing (LP-WGS). In the retrospective cohort, 89 patients were used for LP-WGS model training and 63 for validation. Risk stratification was evaluated using progression-free (PFS) and overall survival (OS). **Results:** In the retrospective validation cohort (n = 63), both the mutation- and fragmentomic-based assays stratified PFS and OS. For the mutation-based assay, median PFS (mPFS) was 27.0 vs. 10.1 months (negative vs. positive; Hazard ratios [HR] 0.414, 95% confidence intervals [CI] 0.211–0.814, p = 0.008) and median OS (mOS) was not reached (NR) vs. 17.5 months (HR 0.341, 95% CI 0.151–0.768, p = 0.007). For the LP-WGS-based model, mPFS was 27.0 vs. 13.8 months (HR 0.412, 95% CI 0.216–0.785, p = 0.005) and mOS was NR vs. 25.1 months (HR 0.355, 95% CI 0.158–0.795, p = 0.009). Integration using an either-assay-positive definition further improved prognostic discrimination, with mPFS NR vs. 13.8 months (HR 0.379, 95% CI 0.201–0.714, p = 0.002) and mOS NR vs. 25.1 months (HR 0.324, 95% CI 0.143–0.730, p = 0.004). In the prospective cohort (n = 60), both assays at C5D1 identified patients at higher risk of progression: mutation-based mPFS 18.3 vs. 6.1 months (HR 0.184, 95% CI 0.075–0.457, $p < 0.0001$); LP-WGS-based mPFS NR vs. 5.3 months (HR 0.178, 95% CI 0.070–0.456, $p < 0.0001$). Integration-based mPFS was NR vs. 6.5 months (HR 0.130, 95% CI 0.039–0.440, p = 0.0001). Multivariable analysis confirmed the independent and complementary prognostic value of both approaches across cohorts. **Conclusions:** Both mutation- and fragmentation-based ctDNA-MRD assays effectively stratified risk among aNSCLC patients with radiographic response to 1L Chemo-IO. Their integration further improved prognostic performance, refining risk beyond imaging-defined PR/CR and informing post-response management decisions. Research Sponsor: None.

8577 Poster Session

Real-world efficacy and safety of bispecific antibody ivonescimab-based regimens in EGFR-TKI–resistant advanced NSCLC.

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Background: Ivonescimab is a first-in-class bispecific monoclonal antibody targeting programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF)-A. In the phase III HARMONi-A trial, ivonescimab plus chemotherapy significantly improved progression-free survival (PFS) compared with chemotherapy alone in patients with epidermal growth factor receptor (EGFR)-mutant advanced non–small cell lung cancer (NSCLC) after resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, in real-world clinical practice, ivonescimab is administered across heterogeneous treatment lines after EGFR-TKI resistance, and evidence regarding its effectiveness in these settings remains limited. **Methods:** This real-world study included patients with advanced NSCLC who received ivonescimab plus chemotherapy following progression on EGFR-TKIs. The primary endpoints were median PFS (mPFS) and safety. **Results:** A total of 254 patients were included. At the data cutoff of November 30, 2025, the median follow-up was 8.9 months. The median age was 61 years; 54.3% were female, and 48.0% had brain metastases. The overall objective response rate (ORR) was 47.9%, with a mPFS of 6.9 months (95% CI, 6.2–7.5). A total of 124 patients were treated with ivonescimab plus chemotherapy immediately after EGFR-TKI resistance with HARMONi-A–like sequence and achieved an ORR of 52.9% with a mPFS of 7.0 months (95% CI, 4.5–9.4). The other 130 patients receiving ivonescimab plus chemotherapy after failure of prior immunotherapy-, anti-angiogenic therapy-, and/or chemotherapy-based regimens achieved an ORR of 43.1% with a mPFS of 6.7 months (95% CI, 6.0–7.4). No statistically significant difference in PFS was observed between the two groups (p= 0.269). Grade 3–4 adverse events occurred in 14.6% of patients, including leukopenia (n = 9), neutropenia (n = 7), immune-related pneumonia (n = 6), and checkpoint inhibitor–related myocarditis (n = 5). Given the relatively short follow-up, overall survival data were not mature. **Conclusions:** In this real-world cohort, ivonescimab plus chemotherapy demonstrated clinically meaningful efficacy and a manageable safety profile when administered both immediately after EGFR-TKI resistance and following multiple prior lines of therapy, supporting its use across diverse treatment sequences in patients with EGFR-mutant advanced NSCLC. Research Sponsor: None.

Baseline characteristics of NSCLC first-line immunotherapy super-responders in three European lung cancer centers: An ENDEAVOUR-IMIGO project.

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Background: Immune-checkpoint inhibitors (ICI) are part of first-line treatment concepts for most patients with metastatic non-small cell lung cancer (NSCLC) without targetable driver mutations. Still, long-term response is rare and data on predictive biomarkers limited. **Methods:** As part of the Daiichi Sankyo ENDEAVOUR programme supporting young LC researchers, the ENDEAVOUR-IMIGO working group aims to explore novel predictive biomarkers for ICI response with a focus on imaging data. We present the baseline characteristics of first-line ICI "super-responders" with PFS ≥24 months, derived from three independent cohorts from Austria, Italy and the Netherlands. Also, an exploratory single-center analysis compared ICI super- to non-responders (PFS<6M) matched for age, sex, histology, PD-L1 positivity, stage and ECOG performance status. **Results:** The Linz (Austria) cohort reported 50 (12.4%) super-responders out of a total of 402 patients, the Milan cohort (Italy) 45 out of 283 (15.9%), and the Groningen cohort (Netherlands) 46 (10.7%) out of 428. As shown in table 1, all cohorts had a high prevalence of adenocarcinomas, with KRAS mutations present in nearly half of patients and a mean PD-L1 expression of approximately 50%. In the Austrian cohort, matched baseline data showed a higher frequency of systemic steroids among non-responders, and lower absolute neutrophil count as well as neutrophil-to -lymphocyte ratio in super-responders. **Conclusions:** Baseline characteristics of ICI super-responders were similar in three European cohorts, with a majority of high-PD-L1 expressing adenocarcinomas. Exploratory matched analyses from one cohort showed implications of baseline systemic steroid treatment as well as of differential blood cell count. Research Sponsor: None.

	Linz			Milan	Groningen
	PFS < 6M n = 50 (matched)	**PFS ≥ 2Y** n = 50	**p value** < 6M vs. ≥ 2Y	**PFS ≥ 2Y** n = 45	**PFS ≥ 2Y** n = 46
Male sex, n (%)	24 (48)	25 (50)	0.841	34 (75.5)	22 (48)
Age <70, n (%)	14 (28)	15 (30)	0.826	15 (33.3)	34 (74)
ECOG, n (%)					
0	25 (50)	24 (48)	0.768	21 (47)	18 (39)
1	16 (32)	19 (38)		23 (51)	23 (50)
2+	9 (18)	7 (14)		1 (2)	5 (11)
Histological subtype, n (%)					
Adenocarcinoma	36 (72)	36 (72)	0.341	30 (67)	33 (72)
Squamous cell carcinoma	12 (24)	14 (28)		6 (13)	7 (15)
Other	2 (4)	0 (0)		9 (20)	6 (13)
PD-L1 expression %, mean (SD)	41.9 (36.8)	48.9 (38.8)	0.403	52.3 (35.4)	54.0 (39.0)
Brain metastases, n(%)	16 (32)	13 (26)	0.509	14 (31)	7 (15)
KRAS mutation, n (%)	12 (35)	18 (50)	0.214	19 (42)	23 (50)
Treatment, n (%)					
Chemo-ICI combination	29 (58)	38 (76)	0.056	18 (40)	19 (41)
ICI-monotherapy	21 (42)	12 (24)		27 (60)	27 (59)
Systemic steroid treatment, n(%)	17 (34)	6 (12)	0.009	12 (27)	8 (17)
Absolute neutrophil count (G/L), mean (SD)	11.5 (8.7)	7.7 (2.9)	0.015	6.8 (3.2)	7.3 (2.6)
Absolute lymphocyte count (G/L), mean (SD)	1.7 (3.7)	1.4 (0.7)	0.071	1.9 (0.7)	1.6 (0.7)
Neutrophil-to-lymphocyte ratio, mean (SD)	13.4 (11.0)	7.2 (5.2)	0.006	4.4 (3.6)	5.9 (4.0)

8579 Poster Session

Initial safety and efficacy of A2B694, a logic-gated mesothelin (MSLN)–targeted Tmod chimeric antigen receptor T-cell (CAR T) therapy in patients with advanced solid tumors with HLA-A*02 loss of heterozygosity (LOH).

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Background: LOH may provide a means to target tumor versus normal cells, to augment the efficacy and safety of MSLN-targeted programs (Hecht et al. *JCO*. 2022). A2B694 is an autologous, logic-gated, Tmod CAR T therapy designed to improve tumor selectivity and decrease toxicity by integrating an MSLN CAR activator with an HLA-A*02 blocker (Hamburger et al. *Mol Imm.* 2020). **Methods:** The first-in-human, open-label, phase 1/2 EVEREST-2 (NCT06051695) study of A2B694 in patients with recurrent/metastatic MSLN-expressing cancers with tumor-associated HLA-A*02 LOH. The prescreening study BASECAMP-1 (NCT04981119) identifies eligible patients and cryopreserves leukapheresis product. Upon progression, A2B694 is manufactured and administered after lymphodepletion. Phase 1 primary objective: evaluate the safety and tolerability of A2B694 and identify a recommended phase 2 dose. **Results:** As of 05 January 2026, 13 patients were enrolled: 8 women/5 men, median age 59 years, 11 non-Hispanic White/2 Hispanic with unknown race. Tumor types included colorectal (n = 4), ovarian (n = 3), pancreatic (n = 3), non–small cell lung adenocarcinoma (NSCLC), gastro-esophageal, and mesothelioma (n = 1 each). A2B694 dose level (DL) groups were: DL1: 1×10^8 cells (n = 3), DL2: 2×10^8 cells (n = 4), DL3: 4×10^8 cells (n = 5), and DL4: 6×10^8 cells plus low-dose IL-2 (n = 1). Lymphodepletion prior to administration of A2B694 was well-tolerated, with expected, transient cytopenias. The only adverse event reported in more than 1 patient was grade 3 neutropenia. One patient had grade 3 ICANS and 1 patient had grade 1 CRS. There were no dose-limiting toxicities or new safety signals after up to 17 months follow-up. All 13 patients received A2B694, were efficacy-evaluable, and had A2B694 detected post-infusion in peripheral blood. While A2B694 was not detected in tumor biopsies collected in patients treated at DL1 (0/2), all patients treated at DL2-DL4 with available biopsies (3/3) had detectable A2B694 in the tumor microenvironment. A patient with $KRAS^{G12V}$/STK11 co-mutated NSCLC who had progressed on carboplatin, pemetrexed, and pembrolizumab achieved a complete response (CR) at D90 post-infusion per RECIST 1.1 by central review and had a confirmed CR at D180. In addition, PET-CT scan and ctDNA on D190 demonstrated no evidence of disease. On D243, the patient had a CNS relapse, with an ongoing non-CNS CR per RANO-BM at D284. At M12, the patient's CT showed no new findings and persistence of A2B694 in the blood was confirmed by ddPCR. **Conclusions:** We report the first patient with NSCLC to have a CR after CAR T. Overall, A2B694 demonstrated manageable safety and tolerability in patients with advanced solid MSLN-expressing tumors with tumor-associated HLA-A*02 LOH. The maximum tolerated dose has not been reached; dose-escalation continues. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

8580 Poster Session

Phase I study of IMM2510, a PD-L1/ VEGF bispecific antibody, in participants with advanced IO-treated SQ-NSCLC.

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Background: Despite advancements in first-line treatments such as immunotherapy and targeted therapies, resistance to these treatments is common, especially those IO-treated and low PD-L1 TPS, creating a significant unmet need for effective second-line therapies. IMM2510 is a bispecific fusion protein targeting PD-L1 and VEGF which can modify tumor microenvironment to overcome resistance and improve sensibility to antitumor agents. The data of dose-escalation phase I was previously reported in ASCO2024. Here we summarize the updated efficacy and safety results of IMM2510 in advanced IO-treated SQ-NSCLC. Part of the data were previously reported in WCLC 2025. **Methods:** The phase I study was designed as a first-in-human, open-label, multi-center study to evaluate the safety, efficacy, PK and PD of IMM2510 in pts with advanced solid tumors. Eligible pts were enrolled to receive IMM2510 via intravenous infusion Q2W. **Results:** As of 31 Dec 2025, 32 pts with advanced IO-treated SQ-NSCLC received IMM2510. The median age was 61 years; 31.3% pts had PD-L1 TPS $<$ 1%; 75.0% pts had ECOG score of 1; the median prior lines of anti-tumor therapy were 2 (range: 1-5). All 32 pts experienced TEAEs. Grade $\geq$3 TEAEs were reported by 17 (53.1%) pts; Grade $\geq$3 TRAEs were reported by 12 (37.5%) pts; TRAEs leading to treatment discontinuation were reported by 1 (3.1%) participant. No participant experienced TRAE leading to death. 22 pts with advanced IO-treated SQ-NSCLC were evaluable for efficacy analysis. The ORR was 27.3% (6/22) and DCR was 81.8% (18/22). The median DoR was 11.1 months. The median PFS was 9.4 months at the median follow-up time of 8.3 months. The median overall survival was not reached. Exposure-response (ER) analysis within the 3 - 20 mg/kg dose range revealed a positive exposure-efficacy relationship in pts with SQ-NSCLC, with higher exposure corresponding to increased ORR or DCR, while a relatively flat ER was observed for Grade 3 or higher TRAE and most common AEs in NSCLC. Thus, 20 mg/kg Q2W was selected as the RP2D with well-balanced efficacy-safety profiles. **Conclusions:** In pts with advanced IO-treated SQ-NSCLC, IMM2510 provides clinical meaningful benefit and supports a favorable benefit-risk profile. The phase III clinical study is being planned. Clinical trial information: NCT05972460. Research Sponsor: None.

8581 Poster Session

First-line serplulimab for locally advanced or metastatic squamous non–small cell lung cancer: Updated survival from the ASTRUM-004R trial.

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Background: Although the ASTRUM-004 trial has confirmed that serplulimab plus platinum-based therapy improves survival in patients with locally advanced or metastatic squamous non-small cell lung cancer (sqNSCLC), evidence regarding its efficacy and safety in routine clinical practice remains limited. Previous results from the ASTRUM-004R trial have shown that a serplulimab plus platinum-based therapy exhibits promising antitumor activity in sqNSCLC. Here, we report the updated follow-up results from this study. **Methods:** The ASTRUM-004R trial is a retrospective, real-world study conducted across 14 centers in China. Patients with locally advanced or metastatic sqNSCLC received first-line serplulimab plus platinum-based therapy, followed by serplulimab maintenance treatment until disease progression, intolerable toxicity, or up to 2 years. This update presents the survival outcomes, including progression-free survival (PFS) and overall survival (OS). Additionally, PFS was assessed across various patient subgroups. **Results:** A total of 132 patients were enrolled in the analysis, with a median follow-up of 18 months as of October 31, 2025. The median patient age was 69 years. Overall, 92.4% (n = 122) were male, 71.2% (n = 94) were aged 65 or older, 19.7% (n = 26) had an ECOG performance status of 2, and 47.0% (n = 62) had stage IV disease. Maintenance therapy was administered to 50.8% (n = 67) of the patients. The median PFS for all patients was 14.8 months (95% CI: 11.9-19.6), with a 6-month PFS rate of 78.5% (95% CI: 71.5%-86.2%). The median PFS benefit was comparable between patients receiving nab-paclitaxel and those receiving paclitaxel (17.5 *vs.* 15.2 months, *P*= 0.677), suggesting no significant difference in efficacy between the two groups. Furthermore, a significantly longer median PFS was observed in patients with stage III disease compared to those with stage IV disease (20.4 *vs.* 11.9 months, *P*= 0.009). The median OS for all patients was 29.7 months (95% CI: 29.7-NR), with a 12-month OS rate of 90.1% (95% CI: 84.7%-95.9%). The updated findings confirm sustained antitumor activity, as evidenced by an objective response rate of 66.7% (95% CI: 57.9%-74.6%) and a disease control rate of 95.5% (95% CI: 90.4%-98.3%). Adverse events (AEs) of any grade occurred in 48 patients (36.4%), most of whom had hematological disorders. Immune-related AEs (irAEs) were reported in 35 patients (26.5%), including 9 (6.8%) who experienced grade ≥3 irAEs. **Conclusions:** Updated results from the ASTRUM-004R study show that first-line serplulimab platinum-based therapy provides a significant survival benefit with a manageable safety profile in locally advanced or metastatic sqNSCLC, consistent with findings from the ASTRUM-004 trial. The long-term survival benefit warrants further validation with extended follow-up. Research Sponsor: None.

8582 Poster Session

Impact of genomic HLA class I allelic imbalance on enduring immunotherapy response in advanced non–small cell lung cancer.

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Background: Human leukocyte antigen class I (HLA-I) molecules are essential for neoantigen presentation and T cell recognition, yet the clinical significance of allelic imbalance within HLA-I genes (HLA-AI) in immune checkpoint inhibitors (ICIs) therapy remains undefined. **Methods:** Here, we established haplotype-specific, coverage-based (cHLA-AI) compatible with routine biopsy-derived sequencing, based on 292 fully heterozygous non–small cell lung cancer (NSCLC) patients with paired tumor samples from the phase III CHOICE-01 trial and confirmed in RATIONALE-304 and real-world NCC cohorts, covering both first- and later-line immunochemotherapy as well as ICI monotherapy, and complemented by analyses in surgical, pan-cancer, and longitudinal datasets to assess immune correlates and evolutionary dynamics. **Results:** Patients with tumor mutational burden (TMB)–low and cHLA-AI derived no benefit from first-line immunochemotherapy, whereas all other patients achieved significant survival gains (TMB-low and cHLA-AI vs. others: immunochemotherapy arm: mOS 16.53 vs. 29.57 months, HR = 2.29, 95% CI 1.59–3.30, $p < 0.001$,interaction P = 0.019; mPFS 5.59 vs. 9.92 months, HR = 2.02, 95% CI 1.43–2.90, $p < 0.001$, interaction P = 0.016). These findings were validated in the RATIONALE-304 and RATIONALE-307 trials and independent real-world cohorts. Incorporating cHLA-AI with pathology, PD-L1 and TMB significantly improved 2-year OS prediction (DeLong's P = 0.003). Multi-omic profiling linked cHLA-AI to active DNA damage response signalings, high TMB -intratumor heterogeneity (ITH) -chromosomal instability (CIN) phenotype, immune-cold microenvironments, and failure of on-treatment TCR clone expansion, while longitudinal sampling revealed its late, branching emergence under immune pressure. Pan-cancer profiling (N = 5,989) demonstrated consistent associations with high TMB-ITH-CIN phenotype and proliferative activity (Ki-67 index). **Conclusions:** Collectively, these results establish cHLA-AI as a pivotal biomarker bridging genomic instability, immune evasion, and therapeutic outcomes, providing a framework for stratified immunotherapy response in non–small cell lung cancer and beyond. Research Sponsor: None.

8583 Poster Session

Concomitant radiotherapy, tremelimumab, and durvalumab for advanced NSCLC patients progressing on first-line immunotherapy: A phase 2 study (CORAL-Lung).

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Background: The optimal treatment for advanced NSCLC that developed resistance to immune checkpoint inhibitors (CPIs) remains undefined. We hypothesized that combining anti-PD-L1, anti-CTLA-4 (at an effective dose) and radiotherapy could be effective against CPI-resistant tumors. **Methods:** This open-label, single-arm, phase 2a trial evaluated two CPIs plus radiotherapy in patients with advanced/metastatic NSCLC who progressed on/after 1L CPI given alone or in combination with chemotherapy. Co-Primary endpoints were safety and response rate (RR; by RECIST 1.1). Secondary endpoints were to evaluate progression free survival (PFS) and overall survival (OS). The study included a safety run-in cohort and a Simon two-step design expansion. RR $\geq$ 20% in non-irradiated lesions was required to advance from the initial efficacy to expansion cohort. Patients with prior anti-CTLA-4 treatment were excluded. At least one measurable non-irradiated lesion was required. Treatment included tremelimumab at a fixed dose of 300 mg at D1 and 12 weeks later and 1500 mg Durvalumab q4w (starting from D1). This dosing was based on PK and pharmacodyamic data from study D4190C00006, suggesting tremelimumab of dose greater than 1 mg/kg with a higher peak exposure may be associated with a higher pharmacodynamic effect. On D21, patients began radiotherapy: 11 fractions of 3 Gy (total of 33 Gy), selected based on our real-world database analysis (Onn et al, Cancers 2021, 13(11), 2800). The study was sponsored by Sheba MC and funded by AstraZeneca Pharmaceuticals. NIH trials registry identifier: NCT05000710. **Results:** Ten patients were enrolled, median age was 71 (range 51-82); 50% males; all stage IV; 50% adenocarcinoma; 50% with PD-L1 $<$ 1%; 80% past/current smokers; none had actionable driver mutations. Previous treatment lines were 1/2 in 80%/20% respectively; all patients received prior pembrolizumab and platinum-based doublet. Median (range) durvalumab and tremelimumab cycles administered were 2 (1-7), 1(1-3). Median radiotherapy dose was 33 Gy, in 78% targeting lung lesions. Nine patients were included in the safety run-in, three experienced treatment-related toxicities leading to treatment discontinuation (all grade 3 diarrhea), remaining below the predefined 40% threshold and permitting continuation. All other treatment-related toxicities were grade 2 or lower. The initial efficacy cohort (n = 10) RR was 10%, leading to the study closure. Median PFS was 2.2 months, median OS was 13.9 months. The study was terminated on Dec 31, 2024. **Conclusions:** In unselected patients with advanced CPI-resistant NSCLC, the combination of anti-PD-L1, anti-CTLA4 at a high dose and radiotherapy did not demonstrate a meaningful response rate. Toxicity of a high dose of anti-CTLA-4 is not negligible. Better patient selection might lead to higher efficacy and lower toxicity. Clinical trial information: NCT05000710. Research Sponsor: AstraZeneca.

Final analysis of the biomarker-directed, randomized, phase 2 KEYNOTE-495/KeyImPaCT study of pembrolizumab (P)–based combination therapy for non–small cell lung cancer (NSCLC).

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Background: KEYNOTE-495/KeyImPaCT (NCT03516981) evaluated 3 P-based regimens in participants (pts) with advanced NSCLC across 4 prospectively defined biomarker subgroups based on T-cell–inflamed gene expression profile ($Tcell_{inf}GEP$) and tumor mutational burden (TMB). In interim analysis, ORR with P + lenvatinib (L) in the $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ subgroup met the prespecified efficacy threshold. We report final analysis results. **Methods:** Pts with previously untreated NSCLC were assessed for $Tcell_{inf}GEP$ (non-low, ≥ -0.16; low, < -0.16) and TMB (high, ≥ 5 mut/Mb; non-high, <5 mut/Mb; ≈ 175 mut/exome by WES and 10 mut/Mb on FoundationOne CDx). Pts were assigned to 1 of 4 subgroups ($Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$, $Tcell_{inf}GEP^{low}TMB^{high}$, $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$, and $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$) and adaptively randomized 1:1:1 to P (200 mg IV Q3W) + either L (20 mg PO QD), quavonlimab (Q; 25 mg IV Q6W), or favezelimab (F; 200 mg or 800 mg IV Q3W). The primary end point was ORR per RECIST v1.1 by investigator. Secondary end points included PFS, OS, and safety. Data cutoff: July 30, 2025. **Results:** 243 pts were treated (P + L, 80; P + Q, 82; P + F 200 mg, 30; P + F 800 mg, 51). Median follow-up was 66.5 mo (range, 43.0–81.2). The $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ subgroup treated with P + L met the prespecified efficacy threshold ($\geq$95% posterior probability of true ORR >20%); PFS and OS were generally consistent with anticipated results among biomarker-defined subgroups (Table). Safety profile of each combination was consistent with the known profiles of each therapy. **Conclusions:** With longer follow-up, OS benefit was comparable across the 4 biomarker subgroups for the 3 combination therapies, with no new safety signals. These data continue to show the feasibility of prospective biomarker assessment to evaluate P-based therapies in advanced NSCLC. Clinical trial information: NCT03516981. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	$Tcell_{inf}GEP^{low}$ $TMB^{non\text{-}high}$	$Tcell_{inf}GEP^{low}$ TMB^{high}	$Tcell_{inf}GEP^{non\text{-}low}$ $TMB^{non\text{-}high}$	$Tcell_{inf}GEP^{non\text{-}low}$ TMB^{high}
ORR, % (95% CI)				
P + L	12.0 (2.5-31.2)	33.3 (9.9-65.1)	40.9 (20.7-63.6)	57.1 (34.0-78.2)
P + Q	11.5 (2.4-30.2)	30.8 (9.1-61.4)	13.6 (2.9-34.9)	52.4 (29.8-74.3)
P + F 200 mg	0.0 (0.0-28.5)	33.3 (4.3-77.7)	25.0 (3.2-65.1)	60.0 (14.7-94.7)
P + F 800 mg	27.3 (6.0-61.0)	13.6 (2.9-34.9)	-	50.0 (26.0-74.0)
Median (95% CI) PFS, mo				
P + L	5.4 (2.3-8.8)	13.8 (1.5-19.4)	8.2 (4.2-19.7)	17.8 (6.0-20.7)
P + Q	2.8 (2.0-6.0)	3.9 (1.9-17.3)	6.1 (2.1-12.8)	17.0 (9.3-29.1)
P + F 200 mg	2.1 (1.9-2.1)	8.1 (1.7-NR)	2.1 (0.9-6.5)	6.3 (0.4-NR)
P+ F 800 mg	4.2 (1.8-12.2)	3.5 (2.0-8.2)	-	20.2 (6.1-NR)
Median (OS, mo				
P + L	16.0 (5.4-20.2)	16.9 (3.8-33.2)	22.5 (12.0-41.3)	22.7 (16.9-56.0)
P + Q	13.3 (8.4-20.0)	20.1 (7.7-NR)	23.7 (7.9-43.1)	51.6 (17.6-NR)
P + F 200 mg	8.6 (3.8-35.4)	20.8 (1.7-NR)	12.6 (0.9-25.4)	NR (13.5-NR)
P + F 800 mg	18.6 (3.4-41.2)	11.1 (5.2-19.6)	-	NR (13.0-NR)

-, no pts enrolled.
NR = not reached.

8585 Poster Session

Single-cell spatial analysis of the tumor immune microenvironment in NSCLC primary tumors and brain metastases.

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Background: Brain metastases (BrM) are associated with poor prognosis in non-small cell lung cancer (NSCLC). Although immune checkpoint inhibitors (ICIs) demonstrate intracranial activity, intracranial progression remains common, especially in patients with driver-negative NSCLC. To define mechanisms of intracranial immune resistance, we applied imaging mass cytometry to profile the tumor immune microenvironment (TIME) in BrM and primary lung tumors. **Methods:** Forty-four patients with advanced driver-negative NSCLC were included; 39 (89%) were treated with ICIs. A 40-marker antibody panel enabled site-specific immune phenotyping of primary lung tumors and BrM, with all samples obtained prior to initiation of systemic immunotherapy. Three regions of interest per sample (two intratumoral, one peritumoral) were analyzed using a Hyperion imaging mass cytometer. Single-cell segmentation was performed using Mesmer with immune phenotypes defined by marker expression. Spatial neighborhoods were identified using unsupervised k-means clustering of nearest-neighbor-derived local cellular compositions. **Results:** Compared with primary lung tumors, BrM demonstrated significantly reduced $CD4^+$ and $CD8^+$ T cells ($p < 0.001$), B cells ($p = 0.017$) and endothelial markers ($p < 0.001$). Despite reduced overall $CD4^+$ infiltration, BrM exhibited higher proportions of regulatory T cells (Tregs; $p = 0.017$), $Ki67^+CD4^+$ T cells ($p = 0.002$) and $Ki67^+$ Tregs ($p = 0.017$). BrM were enriched for CD206-high immunosuppressive macrophages, whereas primary tumors demonstrated predominance of CD11c-high inflammatory myeloid cells ($p = 0.006$). Spatial analysis demonstrated increased proximity of $CD8^+$ T cells ($p = 0.039$) and Tregs ($p = 0.020$) to M2-like macrophages in BrM. Neighborhood analysis revealed site-specific immune organization, with primary tumors enriched for adaptive immune-dominant niches containing mixed $CD4^+$, $CD8^+$ and B-cell populations. In contrast, BrM were characterized by myeloid-T-cell interface neighborhoods marked by close spatial coupling of T cells with macrophages and monocytes. In primary tumors, durable immunotherapy benefit (≥24-month PFS and OS) was associated with significantly higher $CD8^+$ and $CD4^+$ T cells, B cells, dendritic cells, monocytes and macrophages. In BrM, no consistent immune correlates of long-term benefit were observed. **Conclusions:** NSCLC BrM exhibit a distinct TIME characterized by depleted adaptive immune infiltration, CD206-high macrophage dominance and myeloid-T-cell spatial organization. While primary lung tumors display adaptive immune signatures predictive of durable ICI benefit, BrM lack consistent immune correlates of response. These site-specific compositional and spatial differences provide a mechanistic framework for the attenuated and less durable intracranial responses to immune checkpoint blockade. Research Sponsor: Western Sydney Local Heath District.

IBI363 (TAK-928) plus chemotherapy as first-line (1L) treatment for advanced non–small cell lung cancer (NSCLC).

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Background: IBI363 is a first-in-class, PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein with great potential for immune-cold and immunotherapy (IO)-resistant tumors. Previously, IBI363 monotherapy demonstrated encouraging and durable efficacy in patients (pts) with IO-treated advanced NSCLC (2025 ASCO #8509). Here, we report a phase 1 study evaluating IBI363 plus platinum-based doublet-chemotherapy (PDC, pemetrexed/paclitaxel plus platinum) in 1L NSCLC. **Methods:** Previously untreated pts with advanced NSCLC, without sensitizing EGFR, ALK, or ROS1 alterations were enrolled. The safety lead-in evaluated IBI363 at 1.5 or 3 mg/kg Q3W plus PDC. In dose optimization (PD-L1 TPS $<$ 50% required), pts were randomized 1:1:1 to 3 cohorts: 3-1.5 mg/kg (IBI363 3 mg/kg plus PDC in cycle 1, then 1.5 mg/kg Q3W plus PDC in subsequent cycles), 3 mg/kg (IBI363 3 mg/kg Q3W plus PDC) and 1.5 mg/kg (IBI363 1.5 mg/kg Q3W plus PDC). Stratification factors were squamous vs non-squamous, and PD-L1 TPS $<$ 1% vs 1-49%. Primary endpoints were safety and efficacy assessed by investigators per RECIST v1.1. Secondary endpoints included pharmacokinetics (PK) and immunogenicity. **Results:** As of December 22, 2025, 80 pts were enrolled in safety lead-in (N = 11) and dose optimization (N = 69) with median follow-up (mFU) of 5.8 months (range: 0.9-9.5). Baseline characteristics (median age: 64 years, male: 88.8%, ECOG PS 1: 81.3%, stage IV: 72.5%, sqNSCLC: 66.3%) were balanced among 3-1.5 mg/kg (N = 23), 1.5 mg/kg (N = 28) and 3 mg/kg (N = 29) cohorts. Median treatment duration of IBI363 was 25.0 weeks (range: 4.0-41.1) while 65.0% pts with ongoing treatment, and 88.9% pts having completed ≥4 cycles of PDC. Grade≥3 (G3+) treatment-emergent adverse events (TEAEs) occurred in 81.3% pts including 65.2% for 3-1.5 mg/kg, 82.1% for 1.5 mg/kg and 93.1% for 3 mg/kg cohorts. Common TEAEs were anemia (any grades 78.8%, G3+ 18.8%), neutrophil count decrease (75.0%, G3+ 42.5%), white blood cell count decrease (63.8%, G3+ 20.0%), arthralgia (51.3%, G3+ 2.5%), and platelet count decrease (45.0%, G3+ 17.5%). IBI363-related AEs led to corresponding treatment discontinuation and death in 6.3% and 1.3% pts. In dose optimization, 65.2% pts had PD-L1 TPS $<$ 1 and 34.8% had TPS 1-49%. Efficacy was evaluable in 62 pts with at least 1 tumor assessment. For 3-1.5 mg/kg cohort (N = 22), ORR was 86.4% (95% CI: 65.1-97.1, confirmed ORR [cORR]: 81.8%) and DCR was 100% (95% CI: 84.6-100). ORR was 85.7% for sqNSCLC (N = 14) and 87.5% for non-sqNSCLC (N = 8). For the 1.5 mg/kg (N = 19) and 3 mg/kg cohorts (N = 21), ORR was 57.9% (cORR: 42.1%) and 66.7% (cORR: 57.1%). PFS was immature (events 28.8%). Clinical PK data also supported an optimal benefit-risk profile based on efficacy and safety observed at 3-1.5 mg/kg. **Conclusions:** IBI363 plus PDC was well tolerated and showed encouraging efficacy in advanced NSCLC. Safety, efficacy, and PK data supported 3-1.5 mg/kg as the recommended dose. Clinical trial information: NCT06468098. Research Sponsor: None.

Immunonutrition intervention in driver gene–negative non–small cell lung cancer patients with sarcopenia: A randomized controlled trial.

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Background: Cancer-related sarcopenia impairs treatment tolerance and survival in advanced NSCLC. This Phase II trial evaluated IMPACT (arginine and omega-3 enriched formula) in driver gene-negative advanced NSCLC patients receiving chemoimmunotherapy. **Methods:** Single-center, open-label, randomized Phase II study. Eligible patients: driver gene-negative advanced NSCLC with sarcopenia (AWGS criteria). Randomization 1:1 to IMPACT plus chemoimmunotherapy (Arm A, n=59) versus chemoimmunotherapy alone (Arm B, n=49). IMPACT administered continuously during treatment. Primary endpoint: PFS. Secondary endpoints: body composition (BIA, CT-L3), inflammatory markers (NLR), nutritional status (PG-SGA), safety. Statistical design: 80% power, HR=0.60, alpha=0.05. Dropouts: 7 (11.9%) in Arm A, 5 (10.2%) in Arm B. Modified ITT: 96 patients (52 vs 44). **Results:** Baseline characteristics balanced. Median PFS: not reached (Arm A) versus 7.0 months (95% CI: 5.2-8.8, Arm B); HR=0.45 (95% CI: 0.23-0.88), P=0.018. Six-month PFS: 82.7% versus 54.5%; 12-month PFS: 59.6% versus 31.8%. NLR change: -1.28 versus +0.16 (P=0.0045). Lean mass change: +0.59 kg versus -1.00 kg (P<0.05). L3 skeletal muscle density: +1.93 HU versus +0.37 HU (P<0.05). PG-SGA improved in Arm A (9.1±5.6 to 6.4±5.1, P<0.001) but not Arm B (8.9±5.8 to 8.2±5.5, P=0.156). Elderly subgroup (≥65y) showed enhanced benefit: HR=0.23 (95% CI: 0.06-0.95), P=0.043. Grade 3-4 AEs: 38.5% versus 52.3% (P=0.156). No IMPACT-related SAEs. **Conclusions:** IMPACT immunonutrition with chemoimmunotherapy significantly improved PFS, preserved lean mass, reduced inflammation, and enhanced nutritional status in driver gene-negative advanced NSCLC with sarcopenia. Well-tolerated with favorable safety. Phase III evaluation warranted. Clinical trial information: ChiCTR2300078741. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-NESTLE2022ZD–0517.

Key efficacy outcomes.

Endpoint	Arm A (Sustagen, n=52)	Arm B (Control, n=44)	P value
edian PFS, months	NR	7.0 (5.2-8.8)	0.018
6-month PFS, %	82.7	54.5	-
12-month PFS, %	59.6	31.8	-
NLR change	-1.28	+0.16	0.0045
Lean mass change, kg	+0.59	-1.00	<0.05
L3 SMD change, HU	+1.93	+0.37	<0.05

Efficacy outcomes in first-line (1L) non–small cell lung cancer (NSCLC) with maintenance of immune competence: QUILT-2.023 randomized phase 3 study of IL-15R agonist nogapendekin alfa inbakicept (NAI) with checkpoint inhibitor (CPI) ± chemotherapy.

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Background: Baseline and treatment-induced lymphopenia are adverse prognostic factors in NSCLC and may limit CPI durability. CPI and chemo-IO can reduce peripheral absolute lymphocyte counts (ALC) over time. NAI expands NK and effector/memory T cells and increases ALC, a biological marker of immune competence. In QUILT-3.055 (≥2L NSCLC after CPI failure), sustained ALC increases were associated with prolonged overall survival (OS). QUILT-2.023 tests whether preserving immune competence with NAI improves response rate, progression-free survival (PFS), and OS when added to 1L standards of care (SOC). To inform the design of the ongoing registrational-intent QUILT-2.023 study, results from 98 enrolled subjects were unblinded for exploratory analysis. **Methods:** QUILT-2.023 (NCT03520686) is an ongoing randomized multicohort phase 3 trial in untreated advanced/metastatic NSCLC (ECOG 0–1; squamous or nonsquamous). Cohort A (PD-L1 TPS ≥1%) was randomized 1:1 to CPI+NAI vs CPI; ALC over time was analyzed using a mixed model for repeated measures. The primary efficacy endpoint was PFS with hierarchical testing (TPS ≥50% then TPS ≥1%). PFS was analyzed at 8 months to evaluate the temporal relationship of ALC through 27 weeks of CPI alone versus CPI+NAI. Cohorts B (squamous) and C (nonsquamous), with any PD-L1 TPS, were randomized 1:1 to SOC platinum chemo-IO ± NAI; pooled Cohort B+C efficacy (ORR, DCR, PFS, OS) was assessed per RECIST v1.1. **Results:** Cohort A (N = 63): baseline ALC was comparable between arms; CPI+NAI showed significant, sustained ALC increase vs CPI alone over 27 weeks (P = 0.0065), regardless of PD-L1 TPS. In TPS ≥50% (N = 45), ALC over time significantly improved with CPI+NAI vs CPI alone (P = 0.0420). Correlating with this increased ALC, PFS in the CPI+NAI arm demonstrated median PFS of 7.0 vs 2.2 months (HR 0.40; 95% CI 0.17–0.94; p = 0.0298). Grade ≥3 CPI-related TEAEs occurred in 16% of subjects in both arms. In pooled Cohorts B+C (ITT N = 36), ORR (CR+PR) was 56% with chemo-IO+NAI vs 33% chemo-IO alone; DCR was 83% vs 78%. Median PFS was 18.9 vs 10.6 months (HR 0.48; 95% CI 0.19–1.23; p = 0.1192) and median OS reached significance of 34.7 vs 20.2 months (HR 0.38; 95% CI 0.15–0.98; p = 0.0394). **Conclusions:** Adding NAI to CPI-based SOC increased ALC and improved PFS in PD-L1 TPS ≥50% 1L NSCLC, with manageable safety. In platinum chemo-IO cohorts, pooled efficacy shows improved response and a significant OS signal, consistent with immune-competence preservation as a modifiable determinant of CPI durability. Enrollment and follow-up are ongoing. These interim findings are consistent with the single-arm trial QUILT-3.055 and support continued accrual in QUILT-2.023 and ResQ201A (NCT06745908), randomized NAI+CPI studies across 1L and ≥2L advanced NSCLC. Clinical trial information: NCT03520686. Research Sponsor: ImmunityBio.

8589 Poster Session

Response to cancer immunotherapy for p53 antibody-positive non-small cell lung cancer according to treatment regimen.

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Background: Cancer immunotherapy has enabled long-term survival in advanced non-small cell lung cancer (NSCLC), but there are some patients with resistance to cancer immunotherapy. Mutations in the p53 gene have been reported to suppress immunity in the tumor immune microenvironment and influence resistance to cancer immunotherapy. Serum p53 antibody is an autoantibody produced in association with p53 gene mutations. However, it is unclear whether p53 antibody-positive NSCLC correlates with treatment response to cancer immunotherapy, particularly whether treatment response differs according to the treatment regimen. **Methods:** Participants were patients with advanced NSCLC who received immune checkpoint inhibitors (ICI) with or without chemotherapy at our hospital from November 2018 to June 2024. Blood samples were obtained before and after treatment with ICI and serum p53 antibody levels were measured. We compared the serum anti-p53 antibody and treatment response (early progressive disease, progression-free survival, and overall survival). Furthermore, we investigated whether treatment response of cancer immunotherapy in p53 antibody-positive NSCLC differs according to the treatment regimen. **Results:** A total of 173 patients were enrolled (mean age 69.4 years, 76.7% male, 58.4% adenocarcinoma). The regimen of ICI with chemotherapy was more common in 130 cases (75.1%) than ICI alone. There were 70 patients (40.4%) who were positive for serum p53 antibody before treatment. The p53-positive group had a significantly higher early progressive disease than the p53-negative group in the patients who received ICI with chemotherapy (28.6% vs 15.5%, p = 0.04). Multivariate analysis showed that serum p53 antibody was the only factor significantly associated with early progressive disease (HR 3.11, 95%CI 1.19-8.50, p = 0.02). PFS was significantly shorter in the p53-positive group than in the p53-negative group in patients with PD-L1 low expression (0-49%) (3.7m vs 7.2m, p = 0.01). Regarding the impact of treatment regimens on treatment response, there was no difference based on ICIs with or without chemotherapy. However, the group that combined anti-VEGF antibodies with ICIs had a significantly lower early progressive disease rate than the group that did not combine them (14.3% vs 30.2%, p = 0.03). **Conclusions:** Serum p53 antibody influenced the therapeutic efficacy of cancer immunotherapy in NSCLC. p53 antibody-positive NSCLC demonstrated differing treatment responses depending on therapeutic regimen. We believe that the combination of ICIs and anti-VEGF antibodies is a promising treatment option for p53 mutation-positive NSCLC. Research Sponsor: None.

Indefinite versus 2 years fixed duration of immune checkpoint inhibition in metastatic non–small cell lung cancer.

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Background: Clinical trials of immune checkpoint inhibitors (ICIs) in metastatic non-small cell lung cancer (mNSCLC) limited treatment duration to 2 years despite the absence of evidence defining the optimal time on therapy. In routine clinical practice, however, many patients receive ICIs for more than 2 years. We evaluated survival outcomes in patients treated with 2 years versus > 2 years of therapy. **Methods:** We conducted a global, retrospective cohort study of patients with mNSCLC treated with ICIs for at least 2 years. Patients were classified as receiving fixed-duration ICI (discontinued at 2 years) or indefinite ICI therapy. Outcomes included progression-free survival (PFS), and overall survival (OS) from ICI start. Multivariable Cox regression, propensity score matching, and 2-year landmark analyses with inverse probability weighting (IPW) were used to address time-dependent biases and adjust for relevant covariates. **Results:** Among 889 patients who received at least 24 months of ICI therapy, median age was 65.5 years; 45.6% were women; 92.8% had a smoking history; 80.2% had adenocarcinoma histology; 70% of patients received ICI as first-line therapy and median PD-L1 tumor proportion score was 60%. Overall, 58.8% received indefinite ICI and 41.2% discontinued at 2 years. Median PFS and OS for the overall cohort were 5.7 years and 8.1 years, respectively. Baseline clinicopathologic characteristics, including age, sex, histology, PD-L1 expression, ECOG performance status, and smoking history, were well balanced between groups. Indefinite ICI therapy was associated with significantly longer PFS (HR 0.75, $p < 0.01$) and OS (HR 0.62, $p < 0.001$) compared to 2 years of therapy. These findings were consistent in a propensity-matched analyses (PFS HR 0.62, $p < 0.01$; OS HR 0.60, $p < 0.001$) and multivariable models (adjusted PFS HR 0.75, $p = 0.02$; adjusted OS HR 0.57, $p < 0.001$). In 24-month landmark analyses with IPW, indefinite ICI remained associated with improved PFS (HR 0.74, $p = 0.02$) and OS (HR 0.56, $p < 0.001$). Benefit with indefinite therapy was observed across all predefined subgroups, including age, sex, histology, PD-L1 strata, ECOG performance status, smoking history. Among 98 patients who received ICI rechallenge at disease progression, the objective response rate was 45%, with a median PFS of 12.9 months and a median OS of 30.2 months. **Conclusions:** Continuation of ICI therapy beyond 2 years was consistently associated with superior PFS and OS compared with treatment limited to 2 years across subgroups and sensitivity analyses. These findings highlight the limitations of arbitrary treatment caps in clinical trial design, support individualized duration decisions, and underscore the need for prospective trials to define the optimal duration of ICI therapy in NSCLC. Research Sponsor: None.

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Comparison of a highly sensitive, tumor-informed Illumina whole genome sequencing research assay and a tumor-informed bespoke whole exome sequencing assay for molecular residual disease detection in CheckMate-77T (NCT 04025879).

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Background: In CheckMate 77T (NCT 04025879), nivolumab showed clinically meaningful improvements in event free survival and pathologic complete response *vs* placebo in 461 patients with resectable (stage IIA-IIIB) NSCLC. Previously, circulating tumor DNA (ctDNA) clearance rates of 66% in NIVO and 38% in PBO of the neoadjuvant period (C1D1 to definitive surgery) had been reported from 130 patients by Provencio et. al. (LBA50, ESMO 2024). In this study, we aim to extend on the previous exploratory study by using a highly sensitive whole genome sequencing (WGS) minimal residual disease (MRD) assay to detect ctDNA clearance rates and compare to those measured using a tumor-informed whole exome sequencing (WES) MRD assay. **Methods:** Residual samples (tumor FFPE tissue/isolated DNA, normal, cfDNA) from 61 of the 130 participants previously reported comprised this study. The Illumina WGS MRD assay employs WGS of tumor and matched normal to generate tumor fingerprints which were bioinformatically monitored in plasma using low-pass WGS (lp-WGS). All samples were prepared using Illumina's WGS Oncology Prep (research use only) and analyzed with DRAGEN MRD pipeline. A comparison of the operational complexity and turn-around-time (TAT) between tumor-informed WES MRD assays and the Illumina WGS MRD assay was performed. **Results:** Detection rates at C1D1 were greater in this study than previously reported, 91% for WGS *vs* 86% for WES, supporting the hypothesis that WGS MRD is more sensitive than WES MRD assays. Using the WES MRD results as reference, the Illumina WGS assay demonstrated a high concordance with positive percent agreement of 100%, negative percent agreement of 63% and overall percent agreement of 95%. Clearance rates of ctDNA in both study arms were calculated, summarized and compared to previous results by Provencio et. al. Compared to tumor-informed MRD assays, the Illumina WGS MRD assay significantly reduced operational complexity and TAT, as it eliminated the need for bespoke panel design, including analysis, manufacturing and assay validation. The Illumina Oncology WGS Prep uses a single streamlined workflow for all MRD sample types. The lpWGS testing of plasma cfDNA required only 2-5 ng cfDNA which can be obtained from a single tube of whole blood compared to 2 tubes of whole blood as required for many tumor-informed MRD assays. The total TAT of the WGS MRD workflow, including both tissue and plasma testing, was 1-2 weeks, substantially shorter than the 4-6 weeks required for most tumor-informed MRD assays. **Conclusions:** This study found the Illumina WGS MRD research assay to be highly concordant with previous tumor-informed WES MRD results for MRD positive results, with improved sensitivity, reduced TAT, lower cfDNA input requirements and decreased operational complexity. Clinical trial information: NCT04025879. Research Sponsor: Bristol Myers Squibb; Illumina.

Efficacy and safety of anamorelin in patients with non–small cell lung cancer and cancer cachexia undergoing chemoimmunotherapy: A real-world prospective cohort study (SPIRAL-ANA).

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Background: The efficacy and safety of combining anamorelin with chemoimmunotherapy for non–small cell lung cancer (NSCLC) complicated by cancer cachexia remain unclear. This study aims to clarify the potential clinical benefits of combining anamorelin with standard first-line treatment in this challenging patient subpopulation. **Methods:** We prospectively enrolled patients with advanced NSCLC who had cancer cachexia and were scheduled to initiate anamorelin together with chemoimmunotherapy. Cancer cachexia was defined according to the eligibility criteria for anamorelin administration in Japan. Anamorelin is indicated for patients with body weight loss of ≥5% within the previous 6 months and with anorexia, who meet at least two of the following criteria: 1) fatigue or malaise, 2) generalized muscle weakness, or 3) C-reactive protein level >0.5 mg/dL, or albumin level <3.2 g/dL, or hemoglobin level <12 g/dL. Progression-free survival (PFS) from start of chemoimmunotherapy was the primary endpoint. **Results:** Overall, 123 patients were enrolled, of whom 118 comprised the safety analysis set and 114 comprised the full analysis set. The median duration of anamorelin treatment was 13.15 weeks. Median age, body weight, and body mass index were 73 years (range: 42–89 years), 53.2 kg (range: 32.5–79.4 kg), and 20.2 kg/m^2 (range: 15.0–29.1 kg/m^2), respectively. Among these patients, 20 (17.5%) had an Eastern Cooperative Oncology Group performance status of 2. At week 12, 62 patients (54.4%) were still being treated with anamorelin. The median PFS and overall survival (OS) were 6.2 months and 18.5 months, respectively, and the study did not meet the prespecified PFS endpoint. In a 12-week landmark analysis stratified by cachexia status at week 12, OS was significantly longer in patients who had achieved cachexia improvement by week 12 than in those who remained cachectic (19.9 months versus 7.1 months, log-rank p = 0.0098; hazard ratio for death, 2.19; 95% confidence interval, 1.19–4.02). The safety profile was manageable, with grade ≥3 neutropenia and hyperglycemia occurring in 31.4% and 5.1% of patients, respectively, and no deaths were considered related to anamorelin. **Conclusions:** In this prospective real-world cohort of patients with NSCLC and cancer cachexia receiving first-line chemoimmunotherapy, anamorelin was associated with a manageable safety profile but did not achieve the primary endpoint of PFS prolongation. Cachexia improvement at week 12 was observed in a substantial proportion of patients and was associated with longer OS. These findings suggest that the clinical value of anamorelin in this setting may lie in facilitating cachexia improvement. Research Sponsor: Ono Pharmaceutical.

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Disaggregated lung cancer mortality trends in Asian American, Native Hawaiian, and Pacific Islander (AANHPI) patients by key sociodemographic features including sex, age, and smoking status.

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Background: Lung cancer is a leading cause of death in AANHPI populations, yet studies aggregate patients with diverse cultural backgrounds and immigration histories into an "Asian American" monolith, obscuring high-risk subgroups. Prior national disaggregation work has not captured key demographic variables important to understanding epidemiologic trends. **Methods:** This study analyzed the US Multiple Cause of Death database for deaths from lung cancer from 2018–2023, sociodemographic information included age at death, sex, race/ethnicity, smoking status, and education. Disaggregated AANHPI subgroup trends were evaluated using ACS 1-year estimates; other analyses used CDC WONDER bridged-race populations. Joinpoint estimated annual percent change in mortality(APC)/AdjustedAPC by race and sex. Pearson's Chi-squared test tested comparisons. **Results:** From 2018-2023, there were 430,703 deaths due to lung cancer in males, of which 2.7% (n=11,441) were in AANHPI males; there were 379,199 deaths in females, of which 2.5% (n=9397) were in AANHPI females. There were demographic differences in deaths within AANHPI subgroups and compared against white patients. For example, 0.5% of deaths in white male and females occurred in those aged 25-44, but this younger age group had 2.1% (male) and 4.3% (female) of Indian American deaths and 1.2% (male) and 1.7% (female) of Chinese American deaths. Deaths in white patients were associated with smoking in 48% (male) and 43% (female) of cases, but in far less of Chinese American (17% male, 4.4% female) and Filipino American (21% male, 9.7% female) lung cancer deaths ($p<0.001$ comparison). From 2018–2023, adjusted AANHPI male lung cancer mortality significantly declined −1.63% (95% CI −1.87 to −1.38; $p<0.0001$) but this was not seen AANHPI females (AAPC −1.20%; −2.86 to 0.79; p=0.22). The magnitude of AANHPI mortality decreases were smaller than in White (male -3.95, -4.43 to -3.24, female -2.35, -3.64 to -1.10; $p<0.0001$ both) and Black (male -4.35, -5.22 to -3.52, female -2.99, -3.99 to -2.96) adults during the same time period ($p<0.0001$ both). Disaggregation showed rising lung cancer mortality in Filipino women (AAPC +1.99%; 95% CI 0.59–3.54; p=0.006) and upward trends in Vietnamese women (AAPC +2.29%; 95% CI −1.05 to 5.81), whereas most AANHPI men had stable or modestly declining mortality. **Conclusions:** Despite large gains in lung cancer mortality over time, AANHPI populations —especially AANHPI women— show slower improvements despite high never-smoker prevalence, underscoring the need for disaggregated research. Rising lung cancer mortality in specific unique populations like Filipino women should motivate further research and guide targeted community outreach so that all populations benefit from improvements in early diagnosis and precision oncology. Research Sponsor: None.

A phase 2 study of docetaxel (D), ramucirumab (R), and pembrolizumab (P) for patients with metastatic or recurrent non–small cell lung cancer (NSCLC) who progressed on platinum-doublet and PD-1/PD-L1 blockade.

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Background: NSCLC treatment (trt) efficacy remains modest after progression on platinum and immune checkpoint inhibitors (ICI). Salvage trt with D + R has a 6-month progression-free survival (PFS) rate of 37%. **Methods:** We conducted a phase 2, single-arm study of D (75mg/m^2), R (10mg/kg), P (200mg) given intravenously in 21-day cycles until disease progression or unacceptable toxicity. Eligibility: metastatic or recurrent NSCLC, progression on concurrent or sequential platinum and ICI, no prior exposure to D or R, ECOG 0-1, measurable disease, adequate organ function. A safety run-in cohort was performed followed by efficacy evaluation using Simon's two-stage design. The null hypothesis (H_o) of 6-month PFS rate of 37% was tested against a one-sided alternative hypothesis with a rate >62% (α 0.1, power 80%). H_o will be rejected if ≥11 of 21 patients (pts) remain free of progression or death by 6 months (m) with planned sample size of 30 to accommodate early dropout. PFS and overall survival (OS) were estimated using Kaplan Meier method. **Results:** 30 pts were enrolled. Median (range) age = 66.5 (57-84) years. 20 (67%) were white, 11 (37%) female, 25 (83%) ever-smoker, 23 (77%) non-squamous, 23 (77%) PD-L1 <50%, 29 (97%) received platinum + ICI concurrently, 19 (63%) progressed after 6m on prior ICI, 10 (33%) had brain metastases (mets), and 7 (23%) had liver mets. 28 pts completed at least one cycle of trt: 22 were evaluable for 6-month PFS (primary endpoint), 6 early dropouts <6m on trt w/o progression (including 1 prior to first imaging). No dose limiting toxicities were observed in the first month on trt. 14 (64%) of 22 pts were free of progression by 6m. Median PFS = 7.3m (95CI, 5.6-9.9); median OS = 15m (95CI, 8.4-18.9); ORR = 37%; 10 partial responses; median duration of response = 5.9m (95CI, 1.6-7.2); disease control rate = 96%; clinical benefit = 67%. Nine (31%) pts had trt-related serious adverse event (trSAE) including 1 (3%) death (Table 1). Median (range) cycles for D, R, P were 6 (1-11), 8 (1-23), 8 (1-23), respectively. Two pts remain on trt. Number of D cycles was associated with improved OS (HR 0.73; p= 0.01) and PFS (HR 0.83; p= 0.01). Presence of brain or liver mets (HR 3.13; p= 0.03) and progression in <3m on prior ICI (HR 5.42; p= 0.02) were associated with shorter OS. **Conclusions:** The study met its primary endpoint and demonstrated a manageable safety profile and a promising efficacy of this regimen. Clinical trial information: NCT04340882. Research Sponsor: Merck; 58866.

Summary of trSAE (n= 29).	
Lethargy / weakness	3 (10%)
Pneumonia	3 (10%)
Atrial Fibrillation	2 (7%)
Dehydration / volume depletion	2 (7%)
Low K/Mag	2 (7%)
Neutropenia	2 (7%)
Death	1 (3%)
Diverticulitis	1 (3%)
Fever	1 (3%)
Interstitial nephritis	1 (3%)
Infusion reaction with cardiac arrest	1 (3%)
Neutropenic fever	1 (3%)
Pancreatic fistula	1 (3%)
Pancreatitis	1 (3%)
Port infection	1 (3%)
Pneumonitis	1 (3%)
Septic shock	1 (3%)

Trends in lung cancer mortality among U.S. adults aged ≥55 before and after the introduction of immunotherapy: A CDC WONDER Joinpoint-style analysis.

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Background: Lung cancer remains the leading cause of cancer-related mortality in the United States. Although sustained reductions in tobacco use have contributed to gradual declines in incidence and mortality, recent therapeutic advances have transformed the management of non–small cell lung cancer. The introduction of immune checkpoint inhibitors (ICIs) in the early 2010s led to substantial survival gains in clinical trials and shifted treatment paradigms toward frontline and perioperative settings. Whether these advances have translated into accelerated reductions in lung cancer mortality at the population level remains incompletely characterized. **Methods:** We conducted a nationwide population-based analysis using the CDC WONDER Underlying Cause of Death database from 1999 to 2020. Lung cancer deaths were identified using ICD-10 codes C34.0–C34.9. Annual age-adjusted mortality rates per 100,000 population standardized to the 2000 U.S. population were analyzed. Among adults aged ≥55 years, joinpoint-style segmented log-linear regression was used to identify inflection points and estimate annual percent changes (APC) before and after the identified breakpoint. **Results:** From 1999 to 2020, age-adjusted lung cancer mortality declined substantially. Among adults aged ≥55 years, segmented regression identified a significant inflection point in 2011. Prior to 2011, mortality declined at −1.52% per year, whereas after 2011 the decline accelerated to −3.88% per year ($p < 0.001$ for change in slope). In the overall population, mortality declined from 55.4 to 48.8 per 100,000 between 1999 and 2014 (APC −0.7%/year) and decreased more rapidly from 47.8 to 41.3 per 100,000 between 2015 and 2020 (APC −2.9%/year), representing more than a fourfold acceleration. **Conclusions:** In this nationwide age-adjusted analysis, lung cancer mortality demonstrated a sustained decline over two decades, with a marked acceleration beginning in the early 2010s. Although reductions in tobacco use remain an important contributor, the timing and magnitude of this acceleration, particularly among adults aged ≥55 years, are consistent with population-level benefits associated with advances in systemic therapy, including immune checkpoint inhibitors. These findings suggest that rapid clinical adoption of immunotherapy may have contributed to meaningful real-world improvements in lung cancer mortality. Research Sponsor: None.

Age-adjusted U.S. lung cancer mortality before and after immunotherapy integration, 1999–2020.

Era	Years	Start rate	End rate	Percent decline	APC (% per year)
Pre-immunotherapy	1999-2014	55.4	48.8	-10.5%	-0.7
Immunotherapy era	2015-2020	47.8	47.8	-13.6%	-2.9

APC = annual percent change. Rates are age-adjusted to the 2000 U.S. standard population.

Impact on overall survival after adjusting for treatment crossover in first-line metastatic NSCLC trials for pembrolizumab plus chemotherapy.

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Background: High crossover rates were observed in the chemotherapy alone arm in KEYNOTE(KN)-189 and KEYNOTE-407, attributable to protocol-permitted crossover to pembrolizumab monotherapy and subsequent anti-PD1/PD-L1 therapies per clinical practice. The objective was to assess the impact on overall survival (OS) by adjusting for treatment crossover. **Methods:** The analysis used pooled data from KN-189 global (NCT02578680; cut-off date: 08MAR2022) and Japan extension (NCT03950674; cut-off date: 07FEB2023), and pooled data from KN-407 global (NCT02775435; cut-off date: 23FEB2022) and China extension (NCT03875092; cut-off date: 10FEB2023). The survival time of participants (pts) in the chemotherapy alone arm who crossed over to pembrolizumab or subsequent anti-PD1/PD-L1 therapy was adjusted using a Two-Stage Estimation model (TSE) and Rank-Preserving Structural Failure Time model (RPSFT). Subsequently, a stratified Cox regression model was used to estimate the treatment effect of pembrolizumab+chemotherapy (P+C) relative to chemotherapy. **Results:** Overall, 646 and 669 patients were included in the analysis for KN-189 & KN-407 with a median follow-up of 64.6 months (range, 59.3-82.8) and 56.7 months (range, 50.1-69.3), respectively. In KN-189, adjusting OS for 56.3% pts who crossed over from the chemotherapy arm resulted in a larger treatment effect estimate for P+C relative to chemotherapy than observed in the unadjusted Intention-to-Treat (ITT) analysis. Similarly, for KN-407, after adjusting OS for 53.7% pts who crossed over, compared with chemotherapy alone, P+C showed more pronounced benefit than in the unadjusted ITT approach. The greater treatment effect for P+C was consistently demonstrated in both studies regardless of the PD-L1 TPS cutoff values. **Conclusions:** After adjusting for treatment crossover, pembrolizumab + chemotherapy demonstrated greater magnitude of OS benefit versus chemotherapy alone in both trials. TSE and RPSFT analyses support the robustness of these findings showing similar direction and magnitude of treatment effects across PD-L1 TPS cut-offs. Clinical trial information: NCT02578680; NCT03950674; NCT02775435; NCT03875092. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	KN-189				KN-407			
Population	N	Unadjusted ITT	TSE	RPSFT	N	Unadjusted ITT	TSE	RPSFT
All comers	431 vs 215	0.60 (0.50; 0.72)	0.44 (0.33, 0.58)	0.46 (0.35, 0.61)	332 vs 337	0.65 (0.55, 0.76)	0.47 (0.35, 0.63)	0.52 (0.40, 0.67)
TPS <1%	140 vs 66	0.51 (0.37, 0.70)	0.41 (0.27, 0.63)	0.42 (0.28, 0.63)	115 vs 121	0.75 (0.56, 0.99)	0.59 (0.35, 0.98)	0.64 (0.42, 0.98)
TPS ≥1%	267 vs 132	0.65 (0.52, 0.82)	0.48 (0.32, 0.71)	0.50 (0.34, 0.73)	207 vs 209	0.60 (0.48, 0.74)	0.40 (0.28, 0.59)	0.45 (0.32, 0.63)
TPS 1-49%	132 vs 61	0.66 (0.47, 0.92)	0.48 (0.27, 0.86)	0.54 (0.33, 0.88)	114 vs 124	0.59 (0.45, 0.79)	0.38 (0.22, 0.64)	0.45 (0.30, 0.70)
TPS ≥ 50%	135 vs 71	0.66 (0.47, 0.93)	0.48 (0.26, 0.87)	0.48 (0.26, 0.87)	93 vs 85	0.63 (0.45, 0.88)	0.44 (0.24, 0.79)	0.46 (0.26, 0.81)

Early lipid-lowering therapy initiation after lorlatinib and clinical outcomes in non–small cell lung cancer: A propensity-matched real-world analysis.

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Background: Lorlatinib improves outcomes in NSCLC but commonly causes marked hyperlipidemia, prompting initiation of lipid-lowering therapy (LLT). Beyond lipid control, LLT may be associated with vascular events; however, its association with thromboembolism, healthcare utilization, and mortality among lorlatinib-treated patients has not been characterized in real-world cohorts. **Methods:** Using TriNetX, we identified adults with NSCLC who received lorlatinib (index = first lorlatinib record). Patients were grouped by early LLT initiation within 30 days of index versus no LLT within 30 days. LLT included statins, ezetimibe, PCSK9 inhibitors, or fibrates. Cohorts were balanced 1:1 using propensity score matching on demographics and baseline comorbidities. Outcomes were assessed through 365 days; patients with prior outcome documentation were excluded. **Results:** After matching, 387 patients per cohort were analyzed. Early LLT was associated with lower all-cause mortality at 365 days (16.1% vs 26.4%; risk ratio [RR] 0.61, 95% CI 0.46-0.81; p=0.0004) and improved time to death (hazard ratio 0.60, 95% CI 0.44-0.82). Early LLT was also associated with lower venous thromboembolism (6.2% vs 12.1%; RR 0.51, 95% CI 0.30-0.86; p=0.0093) and fewer inpatient hospitalizations (14.6% vs 23.6%; RR 0.62, 95% CI 0.40-0.97; p=0.0320). Emergency department visits were numerically lower (8.3% vs 13.9%; RR 0.59, 95% CI 0.35-1.00; p=0.0467). No significant differences were observed for acute kidney injury or major adverse cardiovascular events. **Conclusions:** In a real-world propensity-matched cohort of lorlatinib-treated NSCLC patients, LLT initiated within 30 days was associated with lower 1-year mortality, venous thromboembolism, and hospitalization. Given the frequency of lorlatinib-associated dyslipidemia, these findings support early lipid monitoring and timely LLT initiation in practice. Prospective studies are warranted to confirm these associations. Research Sponsor: None.

365-day outcomes after matching.

Outcome	Early LLT (n=387)	No early LLT (n=387)	RR (95% CI)	HR (95% CI)	p
All-cause mortality	16.1%	26.4%	0.608 (0.458-0.806)	0.597 (0.435-0.818)	0.0004; log-rank 0.001
Venous thromboembolism	6.2%	12.1%	0.509 (0.302-0.857)	—	0.0093
Inpatient hospitalization	14.6%	23.6%	0.619 (0.396-0.967)	—	0.0320
ED visit	8.3%	13.9%	0.593 (0.352-1.001)	—	0.0467
Acute kidney injury	5.4%	7.1%	0.769 (0.429-1.378)	—	0.3758
MACE	4.6%	4.6%	1.006 (0.511-1.979)	—	0.9868

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Glucagon-like peptide-1 receptor agonist use in lung cancer patients receiving immune checkpoint inhibitors: A real-world study.

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Background: Immune checkpoint inhibitors (ICI) have become a cornerstone of treatment for lung cancer. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been associated with improved outcomes in cancer patients in prior studies; however, their impact on outcomes among lung cancer patients receiving immunotherapy remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX real-world data platform. Adult patients with lung cancer treated with ICIs, including PD-1, PD-L1, or CTLA-4 inhibitors, were included. Patients were stratified based on exposure to GLP-1 RA. Propensity score matching (1:1) was performed to balance baseline demographics and comorbidities, including type 2 diabetes mellitus and body mass index. Primary outcomes included all-cause mortality, intensive care unit (ICU) admission, and hospitalization. Secondary outcomes included immune-related pneumonitis, colitis/enteritis, cachexia, and major adverse cardiovascular events (MACE). **Results:** After matching, 2,013 patients were included in each group, with a median follow-up of 372 days in the GLP-1 RA group and 383 days in the non-GLP-1 RA group. Mean age was 66.8 and 67.2 years, respectively, and approximately 50% of patients were male. Most patients were White (77.2% vs 71.8%), followed by Black (14.1% vs 14.0%) and Asian (2.1% vs 1.8%). GLP-1 RA use was associated with a significantly lower all-cause mortality rate compared with non-use (35.7% vs. 53.4%; $p < 0.0001$), with a hazard ratio of 0.65 (95% CI, 0.59–0.71). Significant reductions were also observed in ICU admissions (22.8% vs 29.0%; $p = 0.0001$), hospitalizations (64.1% vs 71.8%; $p = 0.0001$), pneumonitis (5.2% vs 6.8%; $p = 0.0457$), and MACE (19.9% vs 25.3%; $p = 0.0026$). No significant differences were observed in colitis/enteritis (9.3% vs 9.4%; $p = 0.9704$) or cachexia (8.0% vs 9.8%; $p = 0.0650$). In a subgroup analysis of lung cancer patients not receiving ICI, GLP-1 RA use was similarly associated with lower mortality, ICU admission, hospitalization, and MACE, without differences in immune-related toxicities. **Conclusions:** GLP-1 RA use among lung cancer patients was associated with improved survival, reduced healthcare utilization, and fewer selected adverse events in patients receiving ICI therapy. These associations likely reflect established metabolic and cardiovascular benefits of GLP-1 RA and may also involve antitumor mechanisms suggested in prior studies. Residual confounding related to healthcare access and socioeconomic factors cannot be fully excluded and should be considered when interpreting these findings. Prospective studies are warranted to validate these observations and clarify underlying biological mechanisms. Research Sponsor: None.

8599 Poster Session

A comprehensive evaluation of the effectiveness of the Geriatric 8 screening tool in Japanese patients with non–small cell lung cancer: Results from the ENSURE-GA study, a cluster-randomized phase III clinical trial.

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Background: The Geriatric 8 (G8) is a widely utilized screening tool globally for assessing functional status in elderly cancer patients, with a score of 14 or lower indicating a positive result. Previous studies have reported that G8-positive patients are at a higher risk of mortality and experiencing Grade 3 or higher adverse events (AEs). At ASCO 2024, we reported that the G8 positivity rate exceeded 80% among Japanese patients aged 75 and older with non-small cell lung cancer (NSCLC), suggesting a potential issue with its sensitivity in this population. In the present study, we conducted a further detailed analysis of the scoring patterns for individual G8 items and their association with the incidence of AEs. **Methods:** The ENSURE-GA study was a cluster-randomized phase III clinical trial involving 1,021 patients aged 75 years and older with non-small cell lung cancer (NSCLC). Participating institutions were cluster-randomized into either the intervention group or the control group. All patients underwent a standardized Geriatric Assessment (GA) prior to the initiation of treatment. From this cohort, 1,001 patients who underwent G8 assessment were identified for analysis. We evaluated the association between the scoring patterns (loss of points) for each G8 item and the frequency and severity of adverse events. **Results:** The ROC curve for G8 regarding the occurrence of grade 3 or higher adverse events in cases receiving cytotoxic chemotherapy yielded an AUC of 0.525, indicating no discriminatory ability. Among the eight components of the G8 screening tool, self-rated health status (''In comparison with other people of the same age, how does the patient consider their health status?'') showed the highest rate of point loss at 72.0% (656/911), followed by polypharmacy at 67.5% (615/911) and Body Mass Index (BMI) at 61.9% (564/911).The G8 score did not correlate with the severity of adverse events. **Conclusions:** The G8 is a valuable screening instrument, but our findings suggest the need for optimization, including the establishment of cancer-specific and race-specific cut-offs, as well as the implementation of weighted scoring for its components. Clinical trial information: UMIN0000037590. Research Sponsor: None.

Five-year overall survival in lung adenocarcinoma: Real-world results from three French nationwide cohorts (2000–2010–2020).

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Background: Long-term (5-year) real-world overall survival (OS) in non–small cell lung cancer (NSCLC) remains poorly documented especially in prospective condition. The French nationwide KBP program comprises prospective cohorts conducted every 10 years since 2000 to evaluate lung cancer prognosis. In 2020, 8,941 patients were included across 81 non-academic public hospitals, with lung adenocarcinoma (LA) representing the most frequent histologic subtype. Building on previously reported 3-year survival results[1], we assessed temporal changes in 5-year OS and described the characteristics of long-term survivors with LC using the 2000, 2010, and 2020 cohorts. **Methods:** Patients with lung cancer, all stages, diagnosed in non-academic public hospitals in 2000, 2010, and 2020 were included in the French nationwide KBP cohorts, all conducted using the same prospective methodology. For the 2020 cohort, patient inclusion occurred between 1 January and 31 December 2020. Vital status was collected during follow-up. Five-year OS was estimated using the Kaplan–Meier method and compared across the 2000, 2010, and 2020 cohorts, overall and stratified by stage at diagnosis. In the 2020 cohort, a descriptive comparative analysis was performed between long-term survivors (≥5 years) and patients who died before this term. In the 2020 cohort, multivariable Cox proportional hazards models are ongoing to identify prognostic factors associated with OS. Prespecified covariates include age, sex, ECOG PS, smoking status, stage at diagnosis. These analyses remain preliminary and will be updated for the conference, as the 5-year vital status follow-up has recently been completed. **Results:** Among the 1,640, 3,199, and 5,009 patients with LA included in the 2000, 2010, and 2020 KBP cohorts, respectively, 5-year vital status was available for 99.3%, 96.2%, and 83.4% of patients. 5-year OS was 29.4% (95% CI, 28.1–30.7) in 2020, compared with 14.4% (95% CI, 13.3–15.7) in 2010 and 4.7% (95% CI, 3.0–7.2) in 2000, corresponding to an absolute improvement of 15.0% over the last decade. In the 2020 cohort, long-term survivors (≥5 years; n = 772) were 47.8% female, only six patients had an ECOG performance status ≥3, 48.2% were current smokers, 19.8% never-smokers and 32.0% former smokers. The distribution of stage at diagnosis among long-term survivors was 37.6% stage I, 9.9% stage II, 20.9% stage III, and 31.6% stage IV. **Conclusions:** 5-year real-world OS in LA has markedly improved over the last two decades with an increasing proportion of long-term survivors. Ongoing stage-stratified and multivariable analyses will further characterize long-term survival patterns. [1] https://evidence.nejm.org/doi/full/10.1056/EVIDoa2400443.
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8601 Poster Session

Long-term survival outcomes of consolidative local ablative therapy after response to first-line systemic treatment in oligometastatic NSCLC.

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Background: The role of consolidative local ablative therapy (LAT) for patients (pts) with oligometastatic non-small cell lung cancer (NSCLC) who have responded to first line (1L) systemic treatment remains controversial especially after negative results from the NRG LU002 phase II/III trial. Data on long-term survival outcomes remain limited. **Methods:** We retrospectively collected data from EMR records of pts with oligometastatic NSCLC treated with 1L systemic treatment at the University of Pennsylvania Health System (2015–2025). Oligometastasis was defined as ≤4 distant metastases. Eligible pts had either genuine synchronous or induced oligometastatic disease and had achieved partial response (PR) or stable disease (SD) after 1L systemic treatment. We hypothesized that LAT would be associated with improved PFS and OS using time-dependent Cox regression analysis. **Results:** We identified 187 eligible pts. 53% were female; median age was 67 yrs and 31% had PD-L1 expression > 50%. At diagnosis, 90% had genuine oligometastatic disease: 45% with one metastatic lesion, 24% with two, 15% with three, and 11% with four lesions. Median follow- up time was 81 mos. (Reverse Kaplan-Meier). Of 187 pts, 21 received consolidative LAT in addition to maintenance therapy (LAT+) while 166 received maintenance therapy alone (LAT-). The LAT+ group was less likely to have bone metastasis (4.8% vs 34%, P = 0.007) and more likely to have adrenal metastasis (38% vs 19%, P = 0.049). In the LAT+ group, 67% had received chemo-immunotherapy as 1L and 19% had received immunotherapy alone, compared with 58% and 17% in the LAT− group, respectively (P = 0.80, Chi-square). In the LAT+ group, 76% achieved PR and 24% had SD to 1L therapy, compared with 65% and 35% in the LAT− group, respectively (P = 0.30, Chi-square). Median time from diagnosis to LAT delivery was 6 mos. (range, 2 – 24 mos.). The most common LAT modality was radiation (82%). The most common site of LAT was lung (68%). Median PFS was 28 vs 12 mos. and median OS was 98 vs 24 mos. in the LAT+ and LAT− groups, respectively. In time-dependent Cox models treating LAT as time-varying exposure, LAT+ was associated with improved PFS (P = 0.045) and OS (P = 0.003). A multivariable model confirmed the benefit of LAT after adjusting for PD-L1 status, treatment response, brain metastasis, bone metastasis, and nodal status (PFS: HR = 0.38, P = 0.004; OS: HR = 0.27, P = 0.002). Adverse events grade ≥3 were similar in both groups. **Conclusions:** LAT was associated with significantly improved PFS and OS in pts with oligometastatic NSCLC with an objective response or stable disease following 1L systemic treatment. Prospective studies are warranted to define pt characteristics that predict the greatest benefit from and optimal timing of LAT. Research Sponsor: None.

Impact of time-of-day (ToD) of single-agent immune-checkpoint inhibitor (ICI) on survival in advanced non–small cell lung cancer (aNSCLC) with PD-L1 ≥ 50%: Analysis of the NOTCH collaborative REAL-SAIF study.

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Background: There is growing evidence and interest in the role of chrono-immunotherapy. Previous studies showing benefit of earlier ToD were limited by small cohorts with heterogenous groups and ToD cut-offs. Using one of the largest UK cohort, we explored this further. **Methods:** 896 patients treated with 3-weekly ICI monotherapy between 2017-2023 from 16 UK centres were included in this retrospective study. Early 30-day deaths were excluded. Multiple imputations were used for data missing at random (except ToD) with pooled estimates. The primary endpoint was overall survival (OS). A sinusoidal Cox model was used for multivariate analysis to represent the cyclical nature of ToD. **Results:** Median OS and progression-free survival (PFS) were 19.1 (95%CI 17.2-20.9) and 10.1 (95%CI 9.2-11.7) months. Baseline demographics were median age 70-years, 50% male, 77.3% non-squamous histology, and 91% pembrolizumab as ICI of choice. Mean C1 and C2 ToD was 13:18 and 13:12 respectively. 44.1% and 66.5% of patients received C2 within 1 and 4 hours from prior ToD. ToD was not correlated with age or socioeconomic deprivation. Age (HR 1.01; p=0.008), male sex (HR 1.25; p=0.005), performance status (PS) ≥2 (HR 1.22; p=0.038), squamous histology (HR 1.30; p=0.004), liver metastasis (HR 1.51; p=0.001), albumin (HR 0.98; $p<0.001$), and neutrophil-lymphocyte ratio (NLR) (HR 1.60; $p<0.031$) were associated with OS. PS ≥2 (HR 1.23; p=0.026), squamous histology (HR 1.26; p=0.010), albumin (HR 0.98; p=0.001), and PDL1% (HR 0.99; p=0.012) were associated with PFS. There was no correlation between C1 or C2 ToD with OS/PFS. There was a significant interaction between NLR and C1 ToD for both OS (HR 1.48; $p<0.001$) and PFS (HR 1.30; p=0.014), with a change in HR <1.0 for high NLR after 14:00 and 12:30 respectively. **Conclusions:** ToD alone was not associated with survival in aNSCLC ICI monotherapy. NLR has a strong interaction with ToD. A low NLR with early ToD and a high NLR with later ToD were correlated with improved OS/PFS. The relationship of ToD with survival is complex and further research is required before adoption into routine practice. Research Sponsor: None.

Multivariate Cox model for OS and PFS.

	PFS [HR (95%CI); *p*-value]		OS [HR (95%CI); *p*-value]	
Age	1.00 (1.00-1.01)	0.286	1.01 (1.00-1.02)	0.008
Male sex	1.14 (0.98-1.32)	0.093	1.25 (1.07-1.46)	0.005
Performance status ≥2	1.23 (1.03-1.48)	0.026	1.22 (1.01-1.48)	0.038
Squamous histology	1.26 (1.06-1.50)	0.010	1.30 (1.09-1.56)	0.004
Brain metastasis	1.24 (0.99-1.57)	0.062	1.24 (0.97-1.59)	0.091
Liver metastasis	1.32 (1.03-1.69)	0.029	1.51 (1.17-1.94)	0.001
Albumin	0.98 (0.97-0.99)	0.002	0.98 (0.96-0.99)	<0.001
NLR	1.16 (0.76-1.76)	0.498	1.60 (1.05-2.46)	0.031
PDL1%	0.99 (0.99-1.00)	0.012	1.00 (0.99-1.00)	0.091

8603 Poster Session

Lung cancer burden in AYAs: Global and U.S. trends.

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Background: Lung cancer remains a leading cause of cancer-related mortality and is increasingly observed among adolescents and young adults (AYA), with shifting tobacco use and rising air pollution implicated as potential risk factors. This study examines global and U.S. epidemiological and risk factor trends of tracheal, bronchial, and lung cancer (TBLC) in AYA population (20-54 years). **Methods:** We utilized Global Burden of Disease database (1990-2023) for TBLC, to extract Age Specific incidence (ASIR) and mortality rates (ASMR), as well as proportional and absolute ASMRs associated with all risk factors, tobacco use and ambient particulate matter (PM2.5). Joinpoint analysis assessed changes in trends and calculated EAPC (Estimated Annual Percentage Changes). All rates are reported per 100,000 population. **Results:** In 2023, the global ASIR of TBLC among AYAs was 8.69 (n = 167,524) in males and 4.70 (n = 88,569) in females, with absolute incidence increasing by 13% in males and 50% in females. Absolute mortality similarly increased by 9% in males and 39% in females, with ASMRs of 6.99 and 3.52, respectively in 2023. In US, while overall incidence and mortality declined, ASIR in 2023 for females (0.62) was found to be almost similar to males (0.64), whereas ASMR remained higher in males (0.49) than females (0.43). At global level, tobacco remained the leading ASMR contributor in 2023, with higher burden in males (males 4.8, 68.2%; females 1.1, 31%), followed by PM2.5 (males 1.1, 20.5%, females 0.5, 20.8%). No TBLC-related mortality was attributed to household air pollution in 2023. The most significant decline in tobacco- and PM2.5–associated TBLC mortality in males occurred from 2003 to 2020 (tobacco: EAPC −2.66; PM2.5: 2006-2017: EAPC −0.76), and in females between 2008 to 2021 (tobacco: EAPC −3.5, PM2.5: 2017-2020: EAPC -4.8). By 2023, 18.8% of male and 43.1% of female TBLC deaths had no identified risk factors. In the US, ASMR declined continuously across all risk factors in both sexes, and by 2023, 25.4% of male and 32.0% of female TBLC deaths had no identified associated risk factors. Despite overall reductions in ASIR and ASMR globally and in USA, Mortality to Incidence ratio remained largely stable, with only minimal decreases observed globally (males −3.6%, females −7.5%) and in the US (males −2.3%, females −5.8%). **Conclusions:** Our analysis demonstrated an absolute increase in TBLC incidence and mortality globally in both sexes, with males continuing to experience higher mortality. In the USA, the sex-based gap in ASIR has nearly disappeared. Although tobacco-related mortality declined, it remained the leading risk factor. By 2023, 20–25% of AYA males and 30–43% of AYA females TBLC deaths were attributable to non-modifiable risk factors, highlighting the need for screening guidelines that better address AYAs, particularly those without traditional risk factors. Research Sponsor: None.

Resistance mechanisms and efficacy of first-line alectinib and sequential treatments in advanced *ALK*+ NSCLC: Real-world outcomes from a multicenter, observational study in Japan (ALCURE).

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Background: First-line (1L) alectinib has shown superior progression-free survival (PFS) vs crizotinib in advanced *ALK*+ non-small cell lung cancer (NSCLC). We present final data from ALCURE (UMIN000038934), a real-world study exploring resistance mechanisms to 1L alectinib and treatment sequencing in Japanese patients (pts) with advanced *ALK*+ NSCLC. **Methods:** Eligible pts, aged ≥20 years with *ALK*+ NSCLC, were enrolled into 2 cohorts: pts already receiving 1L alectinib before enrollment (cohort A) or treatment-naïve pts starting alectinib (cohort B). Results were reported separately by cohort to address the potential immortal time bias introduced by cohort A (pooled analyses were reported for second-line [2L] treatment since the bias did not apply and the sample size was limited). Clinical samples were collected and analyzed using next-generation sequencing. **Results:** From Jan–Nov 2020, 249 pts were enrolled (cohort A/B, n=200/49). Demographics in cohort A/B were: age ≥75 years, 21%/18%; female, 60%/57%; never smokers, 65%/67%; brain metastases, 22%/31%; *TP53* mutations, 9%/41%. *EML4-ALK* variant 1 was the most common *ALK* variant (50% cohort A, 42% cohort B). Secondary *ALK* mutations at disease progression (PD) or end of 1L treatment were detected in 14/60 pts (23%) in cohort A and 3/25 pts (12%) in cohort B (primarily G1202R or I1171N). Median duration of 1L alectinib before enrolment in cohort A was 24 months (range 1–111). At data cutoff (Nov 6, 2024), median follow-up was 74.1 months (95% CI 11.8–163.3) in cohort A and 48.7 months (95% CI 0.6–56.7) in cohort B. Median PFS (mPFS) was not reached (NR) (95% CI 83.7–NR) in cohort A and 32.9 months (95% CI 11.8–38.5) in cohort B. In pts whose tumors were *TP53* wildtype vs mutant prior to alectinib, mPFS was NR vs NR (HR 0.47, 95% CI 0.15–1.50) in cohort A and 33.6 vs 14.1 months (HR 0.96, 95% CI 0.46–2.00) in cohort B. mPFS in pts with secondary *ALK* mutations detected vs not detected at PD or end of 1L treatment was 14.6 vs 37.1 months (HR 1.68, 95% CI 0.84–3.34) in cohort A and 9.0 vs 11.8 months (HR 1.56, 95% CI 0.35–6.95) in cohort B. Median OS was NR (95% CI NR–NR) in cohort A and 54.7 months (95% CI 54.7–NR) in cohort B. Of the 118/249 pts who discontinued 1L alectinib, 84 received 2L treatment (including 18 who received non-ALK TKIs); mPFS for 2L treatment was 9.9 months (95% CI 7.4–12.1) in the overall cohort. Among these pts, 40 received lorlatinib and had the longest mPFS of all pts receiving 2L treatment (17.2 months). **Conclusions:** The use of 1L alectinib in clinical practice demonstrated efficacy consistent with that seen in clinical trials in pts with *ALK*+ NSCLC and confirms the existence of long-term responders. Lorlatinib may be an effective treatment following 1L alectinib; further research is needed to identify factors that may predict response and inform optimal treatment sequencing strategies. Clinical trial information: UMIN000038934. Research Sponsor: The ALCURE study was sponsored by Chugai Pharmaceutical Co., Ltd; Third-party medical writing assistance, under the direction of the authors, was provided by Helen Cathro, PhD, of Ashfield MedComms, an Inizio company, and was funded by Chugai Pharmaceutical Co., Ltd.

Afatinib versus osimertinib for non–small cell lung cancer with uncommon epidermal growth factor receptor mutations: Real-world outcomes (HOT-Next001/HOT2501).

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Background: Non–small cell lung cancers (NSCLC) with uncommon epidermal growth factor receptor (EGFR) mutations exhibit considerable biological and clinical heterogeneity. Consequently, the optimal first-line EGFR tyrosine kinase inhibitor (EGFR-TKI) and the role of subsequent immune checkpoint inhibitor (ICI)–based regimens remain uncertain. **Methods:** This multicenter retrospective cohort study was conducted at 29 institutions in Japan and included patients with advanced or recurrent non-squamous NSCLC harboring uncommon EGFR mutations who received first-line afatinib or osimertinib between January 2015 and January 2024. Exon 20 insertions and de novo T790M mutations were excluded. Outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and the effectiveness of subsequent systemic therapies, including ICI plus platinum doublet chemotherapy (ICI-Chemo) and platinum doublet chemotherapy alone. To adjust for baseline imbalances, analyses used inverse probability of treatment weighting (IPTW) based on covariate-balancing propensity scores. **Results:** Among 162 patients, 95 received afatinib and 67 received osimertinib. After IPTW adjustment, no significant differences were observed in PFS (median, 11.3 vs 5.9 months; hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.60–1.80) or OS (28.0 vs 25.5 months; HR, 1.34; 95% CI, 0.73–2.44). Afatinib yielded a higher ORR (70.2% vs 47.2%) and DCR (93.7% vs 82.5%) than osimertinib, while adverse events requiring dose reduction were more frequent (76.8% vs 31.3%) but generally manageable. Subgroup analyses suggested greater benefit with osimertinib in L861X mutations and with afatinib in compound mutations. In patients with PD-L1 ≥50%, afatinib was associated with significantly longer PFS (15.5 vs 2.6 months; HR, 0.14; 95% CI, 0.04–0.46), whereas OS was numerically longer (30.5 vs 12.9 months; HR, 0.38; 95% CI, 0.07–1.93). Among 56 patients who received subsequent systemic therapy and were chemotherapy- and ICI-naïve, IPTW-adjusted analyses showed that ICI-Chemo did not improve outcomes compared with platinum doublet chemotherapy: median PFS, 6.7 vs 7.3 months (HR, 1.08; 95% CI, 0.53–2.19) and post–EGFR-TKI OS, 14.6 vs 19.7 months (HR, 1.30; 95% CI, 0.63–2.68). **Conclusions:** In one of the largest multicenter real-world cohorts, afatinib and osimertinib demonstrated comparable survival outcomes as first-line EGFR-TKIs in NSCLC with uncommon EGFR mutations, with treatment effects modulated by mutation subtype and PD-L1 expression. ICI-based regimens did not improve outcomes compared with platinum doublet chemotherapy and conferred no meaningful clinical benefit as post–EGFR-TKI therapy in this population. Research Sponsor: Sapporo Medical University Grants for Programs promoting Academic advancements; 246.

Brigatinib after lorlatinib and/or chemotherapy following first-line alectinib in ALK-rearranged NSCLC: Cohort B of the WJOG11919L/ABRAID study.

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Background: As survival improves in ALK-rearranged NSCLC, patients increasingly receive multiple lines of therapy; however, evidence to guide later-line ALK-TKI sequencing in the third line and beyond remains limited. Brigatinib has activity against multiple ALK resistance mutations, yet data on its effectiveness after progression on first-line alectinib and subsequent lorlatinib and/or chemotherapy—and on associated plasma ctDNA biomarkers—remain scarce. **Methods:** WJOG11919L/ABRAID Cohort B is a prospective, multicenter observational study enrolling patients with ALK-rearranged NSCLC who received brigatinib after lorlatinib and/or chemotherapy following first-line alectinib. Effectiveness and safety were summarized descriptively. Pretreatment plasma ctDNA was analyzed with the PGDx Elio Plasma Resolve panel. The data cutoff was September 26, 2024. **Results:** Twenty-five patients were analyzed (median age, 64 years; all adenocarcinoma); ECOG PS was 0-1/2-3 in 22 (88.0%)/3 (12.0%). Baseline CNS metastases were present in 10 patients. After alectinib, 13 patients received lorlatinib and 14 received platinum-based chemotherapy (overlap, n=2). Median follow-up was 12.7 months. Efficacy outcomes overall and by prior lorlatinib exposure are summarized in the Table. 23 patients had discontinued brigatinib, including 21 due to PD. Pretreatment ctDNA was evaluable in 24 patients: ALK mutations were detected in 4 (including 3 with prior lorlatinib), and compound ALK mutations (G1202R/I1171M/L1204V and D1203N/L1196M) were identified in 2, both after lorlatinib. In exploratory analyses, among the 3 patients with prior lorlatinib and detectable ALK mutations, all experienced early progression or death within 10 weeks of brigatinib initiation. Pneumonitis/ILD occurred in 1 patient (4%; grade 4). No new safety signals were observed. **Conclusions:** Brigatinib showed clinically meaningful activity with a manageable safety profile, providing durable disease control in a subset of patients previously treated with alectinib followed by lorlatinib and/or chemotherapy. Outcomes appeared less favorable after prior lorlatinib, although some patients derived benefit. In exploratory plasma ctDNA analyses among patients with prior lorlatinib, detectable ALK mutations were associated with less favorable outcomes and should be validated in larger cohorts. Clinical trial information: UMIN000042439. Research Sponsor: Takeda Pharmaceutical Company Limited.

Efficacy outcomes overall and by prior lorlatinib exposure.

Endpoint	Overall (n=25)	Prior lorlatinib (n=13)	No prior lorlatinib (n=12)
ORR, % (95% CI)	32.0 (14.9–53.5)	30.8 (12.7–57.6)	33.3 (13.8–60.9)
DCR, % (95% CI)	60.0 (38.7–78.9)	38.5 (17.7–64.5)	83.3 (55.2–95.3)
mPFS, mo (95% CI)	4.8 (2.2–12.7)	2.2 (1.2–18.8)	8.9 (2.3–15.6)
12-mo PFS, %	32.0	30.8	33.3
mOS, mo (95% CI)	13.7 (7.29–NR)	10.8 (3.7–NR)	16.2 (7.1–NR)
12-mo OS, %	56.0	38.5	75.0

8607 Poster Session

High-dose furmonertinib in *EGFR*-mutated advanced NSCLC with brain metastases after EGFR-TKI resistance: The iFORCE phase II trial.

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Background: Brain metastases (BM) are common in patients with EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) and are associated with poor prognosis. Furmonertinib is a pan-EGFR tyrosine kinase inhibitor (TKI) characterized by high central nervous system penetration and a wide therapeutic window. This study evaluated the efficacy and safety of high-dose furmonertinib (160 mg once daily) in previously EGFR-TKI-treated patients with EGFRm NSCLC and BM. **Methods:** iFORCE was a prospective, single-arm study conducted at a single center. Eligible patients had EGFR exon 19 deletion or L858R-mutant NSCLC with at least one measurable intracranial lesion (≥5 mm) and had received ≥1 prior EGFR-TKI therapy. Patients received furmonertinib 160 mg orally once daily. The primary endpoints were intracranial progression-free survival (iPFS). **Results:** Twenty-three patients were enrolled, with a median follow-up time of 19.7 months (95% confidence interval [CI], 14.5-25.3 months). Median iPFS was 14.6 months (95% CI, 4.2-not reached), with 12- and 24-month iPFS rates of 53.8% and 30.8%, respectively. The intracranial objective response rate (iORR) was 34.8% (95% CI, 16.4-57.3), and the intracranial disease control rate (iDCR) was 91.3% (95% CI, 72.0-98.9). Median systemic progression-free survival (PFS) was 10.7 months (95% CI, 3.9-not reached). Treatment-related adverse events occurred in 13 (56.5%) of patients and were predominantly grade 1; one patient (4.3%) experienced a grade 3 stomatitis. No treatment discontinuations or treatment-related deaths were observed. **Conclusions:** High-dose furmonertinib demonstrated encouraging intracranial efficacy with a manageable safety profile in previously EGFR-TKI-treated patients with EGFRm NSCLC and BM, supporting further investigation in randomized studies. Clinical trial information: NCT05465343. Research Sponsor: None.

Sotorasib vs adagrasib in the 2L+ setting: Outcomes in a large, multi-institutional, real-world database of KRAS-G12C mutated mNSCLC.

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Background: KRAS-G12C mutations are found in ~12% of mNSCLC. KRAS-G12C inhibitors sotorasib and adagrasib are approved treatments but have never been compared head-to-head. We report the first large, multi-institutional database analysis comparing efficacy and safety of sotarasib vs adagrasib. **Methods:** Flatiron Health's de-identified electronic health record US database was used to identify patients with KRAS G12C-mutated NSCLC who started treatment 12/2022-10/2025 with either sotorasib or adagrasib in 2L+. Baseline characteristics were abstracted and evaluated using chi-square tests, Wilcoxon rank-sum tests, and a multivariable logistic regression adjusting for practice type, sex, ECOG performance status, age, line of therapy, prior immunotherapy, and brain metastases. Overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) were estimated using Kaplan-Meier curves and compared using the log-rank test and Cox regression. Multivariable Cox regression model included sex, age, ECOG, line of therapy, prior immunotherapy, brain metastases, and PD-L1 expression to control for possible confounding. **Results:** Of the 1133 patients identified, 768 (69%) received sotorasib, and 345 (31%) received adagrasib. Sex, age, PD-L1 status and prior immunotherapy exposure did not affect choice of treatment (Table 1). In a multivariable logistic regression analysis, patients with brain metastases were more likely to be treated with adagrasib (HR =0.64; p=0.003), while patients with higher ECOG PS (2+) were more likely to be treated with sotorasib (HR =1.18; p=0.047). There was no difference in OS between sotorasib and adagrasib (HR = 1.01; p = 0.87), and there was no difference in OS on multivariable regression (adjusted HR = 0.96; p=0.02). There was no difference in PFS between sotorasib and adagrasib (HR = 0.91; p=0.15). Sotorasib had longer TTD than adagrasib (mTTD 3.8 vs 3.3m; HR = 0.82; p =0.005); this association persisted in the adjusted model (adjusted HR = 0.80; p=0.006). **Conclusions:** Sotorasib was associated with slightly longer TTD compared with adagrasib, which may suggest better tolerability, but no difference in PFS or OS. Sotorasib was more likely to be used in patients with poor PS while adagrasib was more likely to be used in patients with CNS metastases. Research Sponsor: None.

	Sotorasib (n = 768)	Adagrasib (n = 345)	p-value
2L (vs 3+)	68.6%	73.0%	0.15
ECOG PS 0-1 (vs 2-4)	64.6%	69.9%	0.13
PDL1	31.2%	38.3%	0.10
<1%			
1-49%	36.4%	32.4%	
>=50%	32.4%	29.3%	
Prior immunotherapy	85.9%	89.0%	0.18
Brain metastases	28.1%	35.1%	**0.02**
mPFS	3.5	3.3	0.15 *0.25
mTTD	3.8	3.3	**0.005** ***0.006**
mOS	9.6	8.7	0.87 *0.70

All survival data in months. Significant values in bold.

Reduction in circulating tumor DNA (ctDNA) in relation to radiographic response and tumor PD-L1 expression in a phase 1 study of PDL1V (PF-08046054) in patients with non-small cell lung cancer (NSCLC).

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Background: PDL1V (PF-08046054) is a novel, first-in-class, PD-L1–directed vedotin antibody-drug conjugate that consists of MMAE connected to an anti–PD-L1 antibody. Prior results from the phase 1 study (NCT05208762) showed promising antitumor activity and manageable safety in patients (pts) with refractory (2L+) NSCLC. We present ctDNA results from an exploratory analysis in this study. **Methods:** C5851001 is a phase 1 study in advanced solid tumors. Pts with NSCLC must have prior exposure to platinum and anti–PD-(L)1 agents, targeted therapies for tumors expressing AGAs, and measurable disease per RECIST 1.1. PD-L1 expression status by tumor proportion score (TPS) was reported by local sites. Paired baseline (T0) and on-treatment (T1; C2D15 to C3D1) ctDNA samples were used for ctDNA analyses using a methylation-based tissue-free assay (Guardant Infinity). Tumor fraction (TF) was quantified by methylation score. Changes in ctDNA from T0 to T1 were compared between subgroups using the Wilcoxon test. **Results:** As of Nov 22, 2025, 55 pts with 2L+ NSCLC received PDL1V: median age 63 yrs, 70.9% ECOG PS 1, 29.1% squamous (SQ) histology, 67.3% TPS ≥1%. The median number of prior lines of therapy was 2.0 (range, 1-8). The investigator-assessed confirmed objective response rate (ORR) was 32.4% (95% CI, 18.0-49.8) in pts with TPS ≥1% NSCLC (n=37) and 0% in TPS <1% (n=18). Grade 3-4 TRAEs occurred in 32.6%. Paired T0 and T1 samples were available in 47/55 pts. ctDNA analysis showed 46/47 pts (98%) had detectable ctDNA at baseline. At T1, ctDNA TF decreased in 36/46 pts (78%) and became nondetectable in 7/46 (15%). Pts with complete or partial responses (CR/PR) had a greater median ctDNA reduction from T0 to T1 than nonresponders (−99% vs −37%, p<0.001). Pts with TPS ≥1% NSCLC had a greater median ctDNA reduction than pts with TPS <1% NSCLC (−77% vs −4%, *P*=0.0023). For pts with TPS ≥1% NSCLC, there was no significant difference in median ctDNA reduction between nonsquamous (NSQ) and SQ histology (−73% vs −87%, p=0.48). **Conclusions:** PDL1V monotherapy showed promising antitumor activity with a manageable safety profile in pts with 2L+ TPS ≥1% NSCLC. Most pts had ctDNA reduction with PDL1V treatment, with greater ctDNA reduction in pts with radiographic response and TPS ≥1% NSCLC. These data further support evaluation of PDL1V in the ongoing phase 3 trial in 2L+ PD-L1+ NSCLC, SQ and NSQ (NCT07144280/PADL1NK-005) and the continued use of ctDNA for response monitoring and potential early prediction of clinical benefit. Clinical trial information: NCT05208762. Research Sponsor: Pfizer.

Subgroup		n	ctDNA reduction (%) from T0 to T1median (lower/upper quartile)
By ORR			
CR/PR		12	−99 [−100 to −93]
SD/PD		34	−37 [−72 to 5]
By PD-L1 status			
TPS <1%		14	−4 [−36 to 26]
TPS ≥1%		32	−77 [−98 to −39]
	TPS 1%-49%	17	−72 [−82 to −38]
	TPS ≥50%	15	−91 [−100 to −41]
By histology	TPS ≥1%		
	NSQ	24	-73 [-95 to -38]
	SQ	8	-87 [-98 to -70]

Firmonertinib combined with platinum-based chemotherapy in patients with *EGFR*-mutant advanced NSCLC following disease progression on first-line third-generation EGFR-TKI.

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Background: Patients (pts) who have progressed after first-line 3rd-generation EGFR-TKIs treatment exhibit limited therapeutic options. We report the preliminary antitumor activity and safety results of firmonertinib combined with platinum-based chemotherapy (Cohort C) in pts with EGFR-mutant advanced NSCLC who failed first-line 3rd-generation EGFR-TKIs from a prospective multi-cohort phase 2 trial (NCT06652048). **Methods:** Cohort C planned to include 20 pts with advanced NSCLC harboring EGFR-sensitizing mutations who progressed after first-line 3rd-generation EGFR-TKIs. Study treatment was firmonertinib (160 mg once daily) with chemotherapy (pemetrexed [500 mg/m^2] plus either cisplatin [75 mg/m^2] or carboplatin [AUC 5]). The primary endpoint was progression-free survival (PFS) assessed by investigators according to RECIST v1.1. **Results:** Cohort C completed accrual with 18 pts who received at least one dose of study treatment: median age was 64.5 years (range 43 to 80), ten (55.6%) were female, 16 (88.9%) were ECOG PS 1, nine (50%) were exon 21 L858R, six (33.3%) had CNS metastases at baseline. As of 30-Nov-2025, the median PFS was 8.4 months (95%CI 4.2-NR). The objective response rate (ORR) was 50.0% (95%CI 26.0-74.0). The disease control rate (DCR) was 88.9% (95%CI 65.3-98.6). The median duration of response (DOR) was not reached (95%CI 6.2-NR). The 9-month DOR rate was 75.0% (95%CI 12.8-96.1). The median overall survival (OS) was not reached (95%CI 9.1-NR). The 12-month OS rate was 70.0% (95%CI 16.2-93.3). Treatment-emergent adverse events (TEAEs) of any grade/grade≥3 occurred in 88.9%/44.4% of pts. The most common any-grade TEAEs were anemia (66.7%) and white blood cell count decreased (50%). The most common grade≥3 TEAEs were white blood cell count decreased (16.7%), neutrophil count decreased (11.1%) and anemia (11.1%). No TEAE with fatal outcome was reported. **Conclusions:** Firmonertinib combined with chemotherapy showed promising antitumor activity with a manageable safety profile in pts with EGFR-mutant advanced NSCLC following disease progression on first-line 3rd-generation EGFR-TKIs. Clinical trial information: NCT06652048. Research Sponsor: None.

8611 Poster Session

Spatial transcriptomic profiling to identify stroma-based prognostic groups in oncogene-addicted lung cancer.

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Background: Driver genomic aberrations determine prognosis and therapy in non-small cell lung cancer (NSCLC). In this context, some other genomic features such as *TP53* mutations confer poor outcomes. However, other mechanisms leading to worse prognosis in patients (pts) sharing the same genomic profile remain incompletely characterized. **Methods:** NSCLC pts from three cohorts based on their molecular profile (*EGFR*-mutated [EGFRm], *KRAS*-mutated [KRASm] and *ALK/ROS1/RET* fusions) were included. Baseline formalin-fixed paraffin-embedded (FFPE) tumor samples were analyzed using NanoString GeoMx Digital Spatial Profiling. Regions of interest (ROIs) were selected based on histopathological features and fluorescently labeled antibodies for tumor (Tm) and stromal (St) areas. RNA expression of >1,800 genes from selected ROIs was assessed using GeoMx Cancer Transcriptome Atlas. Leiden algorithm was used for clustering, and differential gene expression and other statistical analyses were performed using R software. **Results:** A total of 189 pts (100 EGFRm, 56 KRASm, 33 fusions [17 *ALK*, 7 *ROS1* and 9 *RET* rearrangements]) were identified. Separate analysis of Tm and St compartments revealed an association between genotype and transcriptome in the first, whereas the St transcriptome failed to correlate with the molecular profile. Unsupervised clustering of the Tm compartment identified four subgroups with distinct gene expression. Tm Cluster 4 (30 pts) was mainly composed of KRASm pts (86.7%) and presented the poorest prognosis, with a median overall survival (mOS) of 7.5 months (mo) ($p<0.0001$). Within St compartment, four prognostic clusters were also identified. St Cluster 1 (76 pts: 43.4% EGFRm, 40.8% KRASm, 15.8% fusions) and St Cluster 4 (23 pts: 21.7% EGFRm, 52.2% KRASm, 26.1% fusions) included pts from all three cohorts and showed significantly decreased OS (17.4 mo and 15.6 mo, respectively; $p<0.0001$). Genes involved in matrix remodeling and epithelial-mesenchymal transition signaling were overexpressed in St Cluster 1, while St Cluster 4 exhibited a highly immunogenic profile; no correlation with *TP53* mutation status was observed. **Conclusions:** Spatially resolved transcriptomic profiling suggests that stromal composition could identify oncogene-addicted NSCLC pts with poor prognosis regardless of molecular subtype, potentially guiding the development of novel therapeutic strategies. Further validation studies are warranted. Research Sponsor: None.

Profiling patients with *MET* exon 14 (*MET*ex14) skipping NSCLC with a sustained clinical benefit to tepotinib in VISION.

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Background: Tepotinib is a highly selective MET inhibitor with clinical activity in patients with *MET*ex14 skipping NSCLC. We previously reported long-term efficacy and safety outcomes of tepotinib from VISION in patients with ≥3-years follow-up (data cut-off: May 20, 2024; Mazieres et al. ELCC 2025 [Poster 81P]). Here, we provide a subset analysis of patients from VISION who achieved long-term responses to tepotinib to identify clinical characteristics associated with durable benefit. **Methods:** Patients with advanced *MET*ex14 skipping NSCLC detected by liquid (L+) and/or tissue (T+) biopsy received tepotinib 500 mg (450 mg active moiety) once daily. The primary endpoint was objective response by independent review using RECIST v1.1. Secondary endpoints included duration of response and safety. Exploratory analyses of baseline and on-treatment liquid biopsy biomarkers were carried out for potential prognostic, predictive, or pharmacodynamic relevance. For this subset analysis, patients with a long-term response were defined as those with a duration of response (DOR) to tepotinib of >36 months. **Results:** Of 313 patients enrolled, 26 patients had a DOR >36 months (range: 36.6–78.9). In these patients, median age was 67.7 years (range: 52–84), 53.8% were male, 50.0% were White and 34.6% were Asian, 92.3% had adenocarcinoma, 53.8% had a history of smoking, and 53.8% were L+ and 65.4% were T+. Median duration of treatment was 50.7 months (range: 15.9–83.1). Seventeen patients received tepotinib as first-line and nine as second-or-later line therapy. Twenty-four patients achieved >50% decrease, while six patients achieved >80% decrease in the sum of longest diameters from baseline. Eighteen patients' cancer had not progressed at the data cut-off of May 20, 2024, and 14 patients were still receiving treatment. In 12 patients who discontinued treatment, reasons for discontinuation were: adverse events (5 patients [peripheral edema in 2 patients]), disease progression per investigator (3 patients), non-compliance (1 patient), consent withdrawal (1 patient), and other reasons (2 patients). Among patients with long-term responses who stopped treatment early due to adverse events (prior to disease progression), continued responses were observed for up to 52 months after tepotinib discontinuation without any further subsequent anticancer treatment. Of nine patients who received treatment prior to tepotinib, four patients received immunotherapy alone, and eight patients received chemotherapy without immunotherapy. Baseline and on-treatment biomarker data will be presented. **Conclusions:** Patients who achieved long-term responses to tepotinib in VISION had similar clinical characteristics and safety outcomes to the overall population of patients from VISION (Mazieres et al. ELCC 2025 [Poster 81P]); ongoing biomarker analyses may help to further characterize these patients. Clinical trial information: NCT02864992. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

COPERNICUS, a pragmatic phase 2b study of first-line (1L) subcutaneous (SC) amivantamab (ami) + lazertinib (laz) with supportive care in *EGFR*-mutated advanced NSCLC: Early safety results.

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Background: In MARIPOSA, intravenous (IV) ami + laz significantly prolonged overall survival vs osimertinib (HR, 0.75; *P*=0.005) in 1L *EGFR*-mutated (exon 19 deletion [Ex19del]/L858R) advanced NSCLC. However, extended infusion times, infusion-related reactions (63%), venous thromboembolism (VTE; 36%), and dermatologic adverse events (AEs; paronychia [68%], rash [62%]) were observed, potentially leading to discontinuations of ami due to AEs (34%). Several studies have since identified ways to optimize ami + laz administration. In PALOMA-3/-2, SC ami coformulated with hyaluronidase (rHuPH20) enhanced patient (pt) experience by reducing administration-related reactions (ARRs) and time, as well as VTE with prophylactic anticoagulation, leading to FDA/EMA approval. In COCOON, an enhanced dermatologic regimen reduced grade ≥2 dermatologic AEs vs standard of care. **Methods:** COPERNICUS (NCT06667076) is the first study to combine SC ami, optimized supportive care and a pragmatic design to broaden the pt population and better resemble real-world usage. This is an early report from Cohort 1 on pt demographics and safety of SC ami every 4 weeks (Q4W) + laz daily in pts with 1L *EGFR* Ex19del/L858R advanced NSCLC receiving VTE/dermatologic AE prophylaxis. Pragmatic design included partnering with academic/community sites to enhance pt diversity, allowing 1 cycle of 1L chemotherapy while awaiting biomarker results and using SC ami Q4W to reduce visit frequency. Pts received prophylactic anticoagulation for the first 4 months of treatment. Dermatologic prophylaxis aligned with the regimen described in COCOON. Here we report safety (key secondary endpoint), including incidence/severity of VTE, ARRs and dermatologic AEs. All comparisons to MARIPOSA are descriptive. **Results:** As of data cutoff (02 Jan 2026), Cohort 1 had enrolled 190 pts in the US (target enrollment, 300; median [range] follow-up, 3.9 [0.1–11.7] mo); 92% were still ongoing in the study. Median age was 66 y, with 55% of pts ≥65 y and 21% ≥75 y; 28% were Asian and 9% African American, reflecting broad enrollment. 6 pts had received 1 chemotherapy cycle. AEs were mostly grade 1–2, with no new safety signals; 5% discontinued ami due to AEs. With dermatologic prophylaxis, paronychia and rash were 26% and 22%, respectively, showing numerical reductions vs MARIPOSA. ARRs and VTE (both grouped terms) were also numerically lower at 9% and 7%, respectively. **Conclusions:** Compared with MARIPOSA, SC ami and dermatologic/VTE prophylaxis in COPERNICUS substantially reduced ARRs, dermatologic AEs, VTE, and ami discontinuations, highlighting the impact of early supportive care interventions. Using a pragmatic design, these early safety data support wide use of SC ami Q4W + laz in a diverse population. Given limited follow up, pts will continue to be evaluated for safety and efficacy. Clinical trial information: NCT06667076. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

COPERNICUS, a pragmatic phase 2b study of subcutaneous (SC) amivantamab (ami) + chemotherapy (chemo) with enhanced dermatologic adverse event (AE) prophylaxis in *EGFR*-mutated advanced NSCLC: Interim results.

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Background: In MARIPOSA-2, intravenous ami + carboplatin-pemetrexed chemo significantly prolonged progression-free survival (PFS) vs chemo (HR, 0.48; $P<0.001$) in participants (pts) with *EGFR*-mutated (exon 19 deletion [Ex19del]/L858R) advanced NSCLC after progression on osimertinib. However, longer infusion times, infusion-related reactions (59%), and dermatologic AEs (paronychia [37%], rash [43%]) were observed, with frequent interruptions of ami due to AEs (60%) as a potential result. Numerous studies have since tested ways to optimize ami administration. PALOMA-3/-2 showed reductions in administration-related reactions (ARRs) and administration time with SC ami coformulated with hyaluronidase (rHuPH20), thus enhancing patient experience and leading to approval by the FDA/EMA. COCOON also showed fewer grade ≥2 dermatologic AEs vs standard of care with an enhanced prophylactic regimen. **Methods:** COPERNICUS (NCT06667076) is the first study to combine SC ami and optimized supportive care, using a pragmatic design to broaden the pt population and better resemble real-world usage. We report planned interim results of Cohort 2 for SC ami every 3 weeks (Q3W) + chemo on/after EGFR TKI progression in US pts with *EGFR* Ex19del/L858R NSCLC receiving dermatologic AE prophylaxis aligned with the regimen described in COCOON. Pragmatic design included partnering with academic/community sites and less stringent eligibility criteria to enhance pt diversity. Primary endpoint is PFS by investigator. Key secondary endpoints are overall response rate (ORR) and safety, including incidence/severity of dermatologic AEs and ARRs. All comparisons to MARIPOSA-2 are descriptive. **Results:** As of data cutoff (02 Jan 2026), 29 pts had enrolled in Cohort 2 (target enrollment, 30; median [range] follow-up: 7.6 [0.5+−10.2] mo); 76% were still ongoing in the study. Median age was 62 y, with 45% of pts ≥65 y and 21% ≥75 y; 38% were Asian and 7% African American. Median PFS was 7.4 mo (95% CI, 4.8−NE; Table). AEs were mostly grade 1−2, with no new safety signals; 31% of pts interrupted ami due to AEs. With dermatologic prophylaxis, paronychia and rash occurred in 24% and 14% of pts, respectively, showing numerical reductions vs MARIPOSA-2. ARRs (grouped term) were also numerically lower at 21%. **Conclusions:** Compared with MARIPOSA-2, SC ami and dermatologic prophylaxis in COPERNICUS led to substantial reductions in ARRs, dermatologic AEs, and ami interruptions, establishing the positive effect of early supportive care interventions. These interim data obtained using a pragmatic design support wide use of SC ami Q3W + chemo post-EGFR TKI progression in a diverse population. Clinical trial information: NCT06667076. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

Median PFS, mo (95% CI)	7.4 (4.8−NE)
ORR (95% CI)	24.1% (10.3−43.5)
Partial response	7 (24.1%)
Stable disease	15 (51.7%)
Progressive disease	2 (6.9%)

8615 Poster Session

RET fusion–positive lung adenocarcinoma: Partner-specific clinicopathological characteristics, co-mutation profiles, and implications for targeted and immunotherapy.

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Background: RET fusions represent actionable oncogenic drivers in lung adenocarcinoma (LUAD). However, the clinicopathological features, co-mutation landscape, and therapeutic outcomes across different RET fusion partners remain incompletely characterized. **Methods:** We retrospectively analyzed 268 patients with RET fusion–positive LUAD diagnosed between July 2017 and December 2024. Clinicopathological characteristics, metastatic patterns, and concomitant mutations were compared between KIF5B and non-KIF5B subgroups. Treatment outcomes of selective RET inhibitors, multikinase inhibitors (MKIs), and immunotherapy combined with chemotherapy were assessed, with subgroup analyses according to RET fusion partners. **Results:** The median age at diagnosis was 58 years, and most patients were female (57.0%) and never/light smokers (60.8%). Bone (12.3%), pleural (11.9%), and brain metastases (6.7%) were the most common metastatic sites. KIF5B-RET fusions were more frequently detected in earlier disease stages compared with non-KIF5B fusions (p = 0.0531). Among 274 RET fusion events, KIF5B-RET was predominant (65%), followed by CCDC6-RET (16%) and NCOA4-RET (1%). Concomitant mutations were identified in 28.7% of patients, most commonly TP53 (39.0%) and CDKN2A (13.0%), with CDKN2A more enriched in the non-KIF5B group (p = 0.0393). Nineteen patients received targeted therapy, including pralsetinib (n=12), selpercatinib (n=2), and cabozantinib (n=5), achieving an overall ORR of 57.9% and median PFS of 12.0 months. Notably, non-KIF5B patients demonstrated longer median PFS than KIF5B patients under pralsetinib (17.0 vs. 5.5 months, p = 0.0473). Fifteen patients received first-line immunochemotherapy, achieving a median PFS of 17.0 months, ORR of 40.0%, and DCR of 80.0%, comparable to targeted therapy (p = 0.3871). PD-L1 expression showed no correlation with outcomes. **Conclusions:** RET fusion–positive LUAD comprises biologically heterogeneous subsets defined by fusion partners. KIF5B-RET fusions tend to occur at earlier stages, whereas non-KIF5B fusions are more frequently associated with CDKN2A co-mutations and appear to derive greater benefit from selective RET inhibition. Immunochemotherapy demonstrates comparable efficacy regardless of fusion partner, highlighting the need for partner-specific therapeutic strategies in RET fusion–positive LUAD. Research Sponsor: None.

PRO results from the Beamion LUNG-1 trial in treatment-naïve patients with *HER2*-mutant advanced NSCLC.

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Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Here, we report patient-reported outcomes (PROs) on NSCLC-related symptoms, physical functioning, symptomatic adverse events (AEs) and their burden, from patients who were given 120 mg zongertinib QD as first-line in Cohort 2 of the Phase Ib Beamion LUNG-1 trial (NCT04886804). **Methods:** EORTC QLQ-C30 physical functioning scale, NSCLC-SAQ (domains: cough, dyspnea, pain, fatigue and poor appetite), EORTC IL46 (overall side effect burden) and nine PRO-CTCAE symptoms (mouth and/or throat sores, taste changes, nausea, vomiting, diarrhea, rash, skin dryness, itching, and numbness/tingling) were collected at cycle 1: days 1, 8 and 15, and day 1 of cycles 2, 3, 5, 7 and 9, each cycle being 21 days. Change from baseline (CFB) in EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score were analyzed using mixed model repeated measures. The proportion of patients regarded as responders was defined as patients meeting within-patient meaningful improvements in PRO score or maintaining low levels of baseline symptomatology/high functioning. EORTC IL46 (1 = 'Not at all', 4 = 'Very much') and PRO-CTCAE (for frequency/severity/interference items: 0 "Never"/ "None"/ "Not at all" to 4 "Almost Constantly"/ "Very Severe"/ "Very much") were analyzed descriptively. **Results:** The PRO analysis set included 71 patients. High completion rates were observed, over 85% up to cycle 7. Patients had low levels of symptomatology and high levels of physical functioning at baseline. Mean CFB analysis showed patients reported rapid within-patient improvements in EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score after the first week of treatment (from cycle 1, day 8), which were sustained over time. A high proportion of patients responded to treatment in terms of their PRO score; at cycle 5, 70% of patients were responders for physical functioning, and 47% of patients for NSCLC-SAQ total score. There was low side-effect burden; at any post-baseline timepoint a maximum of 8.4% of patients [n=6] reported being troubled with side-effects of treatment 'Quite a bit' or worse; supported by low proportions of patients reporting symptomatic adverse events via PRO-CTCAE. **Conclusions:** Patients treated with first-line zongertinib reported a rapid improvement followed by stability in physical functioning and NSCLC-SAQ total score, with high proportions of patients qualifying as PRO responders. Zongertinib was well tolerated, as reflected by the low overall side effect burden and the low incidence and mild nature of patient-reported symptomatic adverse events. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

8617 Poster Session

Safety and efficacy of APS03118, a next-generation RET inhibitor, in patients with non-small cell lung cancer (NSCLC): Results from a phase I clinical trial.

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Background: Acquired resistance to first-generation selective RET inhibitors (SRIs) remains a significant clinical challenge in the treatment of RET fusion-positive NSCLC. APS03118 is a next-generation, highly selective RET inhibitor also with additional potent inhibitory activity against YES1, a SRC family kinases. This Phase I study evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy of APS03118 treatment in patients with advanced RET fusion-positive NSCLC. **Methods:** This multicenter Phase I trial enrolled 108 patients, including 85 patients with NSCLC harboring RET aberrations. In the dose escalation stage (Ia), APS03118 was administered orally at doses ranging from 40 mg once daily to 120 mg twice daily (BID) 28 days a cycle in 29 patients with solid tumors. In the expansion stage (Ib), 79 patients received 80 mg BID and 100 mg BID, including 66 patients of NSCLC with RET fusions. Efficacy was assessed per RECIST v1.1 every 2 cycles (4 weeks/cycle). Safety was evaluated according to CTCAE v5. Molecular profiling was performed using next-generation sequencing on blood and, when available, tumor tissue. This report focuses mainly on the NSCLC cohorts, including treatment-naïve and previously treated patients with 1-4 lines of therapy, including six different SRIs, (e.g., pralsetinib and selpercatinib). **Results:** Out of 85 NSCLC patients (Ia+Ib), the Objective Response Rate (ORR) was 80% (confirmed) in 20 (20/22) evaluable treatment-naïve patients. The median Progression-Free Survival (mPFS) is not reached, with 10 patients up to or over the 16 cycles at the data cutoff date. In 22 (22/25) evaluable patients with prior systemic therapy not including the SRIs, the ORR was 55%. There were 38 patients in the cohort of prior SRIs treatment failure. Among 22 (22/26) evaluable patients without known bypass pathway mutations, ORR was 23% with 14 patients' PFS up to or over 6 cycles and 10 patients up to or over 8 cycles (data cutoff date). Promising anti-tumor action was observed in the two patients with G810S and G810C mutations, who experienced tumor shrinkage of up to 50%. Grade ≥3 TRAEs occurred in 50.9% of patients. The most common AEs were creatine phosphokinase, AST and ALT elevation, which were reversible and mostly observed within cycle 1-3 and rarely after cycle 5. Dose reductions in 22.2%, and permanent discontinuation in 4.6%. Overall, APS03118 demonstrated a manageable and predictable safety profile. **Conclusions:** APS03118 shows highly promising clinical activity in both treatment-naïve and SRI failed NSCLC patients harboring RET fusions. Its survival benefit may result from potent inhibition of RET and YES1. The safety profile is manageable, characterized primarily by reversible enzyme elevations. Further development in NSCLC patients harboring RET fusion is warranted. Clinical trial information: NCT05653869. Research Sponsor: None.

8618 Poster Session

Efficacy and safety of larotrectinib in patients with *TRK* fusion lung cancer: An updated analysis.

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Background: *NTRK* gene fusions are oncogenic drivers in various tumor types, including lung cancer. Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in patients with TRK fusion cancer based on a robust and durable objective response rate in patients with various cancers. Here, we report updated long-term efficacy and safety data in the subset of patients with TRK fusion lung cancer treated with larotrectinib after 1 additional year of follow-up. **Methods:** Patients with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02122913, NCT02576431 [NAVIGATE]) were included. Larotrectinib was administered at 100 mg twice daily. In NCT02122913, primary endpoints were safety and the minimum tolerated and recommended dose; secondary endpoints included pharmacokinetics, overall response rate (ORR), and duration of response (DoR). In NCT02576431, the primary endpoint was best overall response; secondary endpoints included DoR, survival, and safety. Responses were independent review committee-assessed per Response Evaluation Criteria in Solid Tumors version 1.1. The data cutoff was July 20, 2025. **Results:** A total of 32 patients with measurable disease were treated, including 12 with known CNS metastases at baseline. Median age was 56 years (range 25–81). One patient (3%) was systemic treatment-naïve in the metastatic/unresectable setting; 19 (59%) had received ≥2 prior therapies. All *NTRK* gene fusions were identified by next-generation sequencing (NGS). The ORR was 69% (95% confidence interval [CI] 50–84): 4 (13%) complete responses, 18 (56%) partial responses, 6 (19%) stable disease, 2 (6%) progressive disease, and 2 (6%) not evaluable or undefined. Median duration of treatment was 20 months (range 2–81); at data cutoff, no patients remained on treatment. Median time to response was 1.8 months (range 1.5–7.3). Median DoR, progression-free survival (PFS), and overall survival (OS) were 20 months (95% CI 13–67), 19 months (95% CI 10–36), and 41 months (95% CI 17–not estimable), respectively, with median follow-ups of 53, 49, and 58 months. The 4-year rates for DoR, PFS, and OS were 34% (95% CI 12–57), 26% (95% CI 8–44), and 49% (95% CI 30–69), respectively. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 10 (31%) patients. One patient (3%) discontinued treatment due to TRAEs (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase increased). **Conclusions:** Larotrectinib continues to demonstrate rapid and durable responses, extended clinical benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer. These results support the wider adoption of NGS panels that include *NTRK* gene fusions in patients with lung cancer to identify those who may benefit from TRK inhibitor therapy. Clinical trial information: NCT02122913, NCT02576431. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

8619 Poster Session

First-in-human dose-escalation study of the selective EGFR/HER2 exon 20 inhibitor PFL-721 in patients with locally advanced or metastatic NSCLC.

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Background: PFL-721 is a highly selective, orally bioavailable tyrosine kinase inhibitor (TKI) targeting activating EGFR & ERBB2 exon 20 (ex20) mutations while sparing wild-type (WT) EGFR. Preclinical studies demonstrate potent inhibition of diverse ex20 variants, >20-fold selectivity over WT EGFR, and robust antitumor activity in xenograft models. **Methods:** PFL-721 is investigated in an ongoing phase I study in patients (pts) with advanced NSCLC and EGFR/ERBB2 ex20 alterations (Clinical trial identifier: NCT06043817). PFL-721 is administered once daily (QD) in continuous 28-day cycles. Assessments included adverse events (AEs), dose-limiting toxicities (DLTs), PK, and antitumor activity by RECIST v1.1. Key eligibility criteria included locally documented EGFR/ERBB2 ex20 alterations on solid or liquid tumor biopsy, ECOG 0–1, and adequate organ function. Molecular responses were based on EGFR/ERBB2 ex20 alterations variant allele frequency decrease in ctDNA. **Results:** A total of 45 pts were dosed , with a median age of 63 years. Pts had received a median of 3 prior treatment lines. Thirty-one pts had EGFR ex20 alterations, 13 had ERBB2 ex20 insertion mutations, and one had both. Dose levels evaluated were 30, 60, 120, 240, 360, 480, and 600 mg QD. Dose escalation was completed with the identification of the maximum tolerated dose at 480 mg. AEs were reported in 43 pts (96%), including gastro-intestinal AEs in 39 pts (87%). Commonly observed grade ≥3 AEs included diarrhea (n=10/45, 22% of pts), hypokalemia (n=4/45 , 9%), and increased blood creatinine (n=3/45, 7%). One grade 3 rash was observed. Six DLT events occurred in 39 evaluable pts, including grade 3 diarrhea (at 360 mg QD, n=2; 480 mg QD, n=1, 600 mg QD, n=1), grade 3 fatigue (600 mg QD, n=1), and grade 4 hypokalemia (600 mg QD, n=1). PK analyses showed dose-proportional exposure and achievement of plasma concentrations predicted to be effective based on preclinical models, at doses of ≥240 mg QD. Among efficacy population (n=42), partial responses (PRs) were observed in 15 / 28 pts at doses of ≥360 mg QD . The overall response and disease control rates at doses ≥360 mg QD were 54% (95%CI [33. 9-72.5]) and 79% (95%CI [59.0-97.7]), respectively. Among 25 evaluable pts, molecular responses (ctDNA decrease >50%) were observed in 12 at doses ≥120 mg. **Conclusions:** In this dose escalation study, class-effect local gastrointestinal AEs were observed in nearly all pts while the frequency of systemic skin toxicity was low, in line with the selectivity of the molecule for mutant EGFR. Antitumor activity was reported in 54% of pts at doses ≥360 mg QD in a heavily pretreated population, including with prior EGFR/ERBB2 ex20 TKI. Consistent with tumor shrinkage, ctDNA clearance was observed in 48% of evaluable pts. The randomized dose-optimization part is ongoing, with three dose regimens: 360 mg QD, 480 mg QD, and 240 mg BID. Clinical trial information: NCT06043817. Research Sponsor: Pierre Fabre Medicament.

Safety and efficacy results of the phase 2 study of silevertinib (BDTX-1535) in previously treated patients with non-small cell lung cancer with non-classical and C797S EGFR mutations.

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Background: Despite significant benefit from FDA-approved EGFR tyrosine kinase inhibitors (TKIs), patients with classical EGFR mutation positive non-small cell lung cancer (NSCLC) ultimately develop progressive disease due to mechanisms of resistance, including alterations of the EGFR pathway. A broad group of non-classical EGFR mutations (NCM), including P-loop and αC-helix compressing (PACC) mutations, and acquired C797S are major mechanisms of EGFR resistance. Silevertinib (BDTX-1535) is a fourth-generation covalent EGFR TKI with high CNS penetrance that targets classical mutations, NCM, and C797S mutations. Antitumor activity and safety of silevertinib in advanced NSCLC were evaluated in an open-label Phase 2 trial (NCT05256290). **Methods:** Patients (pts) with recurrent NSCLC following ≤ 2 lines of therapy with only 1 prior EGFR TKI (osimertinib preferred) and tumors positive for NCM (NCM Cohort) or C797S mutation (C797S Cohort) were enrolled based on a local molecular test. Based on dose optimization of silevertinib at 100 mg and 200 mg orally once daily, all patients after May 2024 received 200 mg once daily. The primary endpoint was ORR by RECIST v1.1, and secondary endpoints included progression-free survival (PFS), duration of response (DOR), dose optimization, and safety. **Results:** From August 2023 to January 2025, 41 pts were treated in the NCM Cohort (100 mg, n=11; 200 mg, n=30; 80% female; 56% white; 49% with CNS metastases) and 42 pts were treated in the C797S Cohort (100mg, n=9; 200mg, n=33; 62% female; 48% white; 31% with CNS metastases). In both cohorts, 29% of pts had received 2 prior therapies. As of November 3, 2025, median follow-up was 9.5 months for pts treated with the 200 mg dose. ORR and median duration of treatment (DoT) are shown in the table. Alterations of other oncogenic pathways (e.g. MET, RET, RAS, and RAF) were observed at baseline in approximately 20% of pts in post hoc analyses. For the 200 mg dose, serious treatment-related adverse events (TRAEs) were reported in 7 (11%) pts, and 5 (8%) of pts discontinued treatment due to TRAEs. The most common TRAEs at 200 mg included rash (13%, grade 3), diarrhea (8%, grade 3), stomatitis (2%, grade 3), and paronychia (2%, grade 3). Available PFS, DOR, and dose optimization results will be presented. **Conclusions:** Silevertinib demonstrated antitumor activity at 200 mg orally once daily in patients with recurrent NSCLC, EGFR NCMs, and acquired resistance C797S mutation with a safety profile consistent with the EGFR TKI class. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

Cohort	Dose	n	ORR (%, 95% CI)	Median duration of treatment, mo (range)
NCM Cohort	200 mg	30	16.7% (5.6–34.7)	4.99 (0.99-11.47)
PACC mutations	200 mg	23	21.7% (7.5–43.7)	4.86 (1.28-11.47)
C797S Cohort	200 mg	33	36.4% (20.4–54.9)	4.76 (0.46-12.55)

Cost-effectiveness of amivantamab plus lazertinib versus osimertinib plus chemotherapy for first-line treatment of *EGFR*-mutated advanced non–small cell lung cancer.

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Background: Amivantamab plus lazertinib and osimertinib plus chemotherapy are guideline-recommended first-line treatment options for patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletion or exon 21 L858R mutations. Although both treatments are first-line options, their relative economic value has not been evaluated. This study evaluated the cost-effectiveness of amivantamab plus lazertinib versus osimertinib plus chemotherapy from a United States payer perspective. **Methods:** A partitioned survival model (PSM) and a three-state Markov model were developed to compare the two treatment strategies over a lifetime horizon. Clinical efficacy inputs were derived from the MARIPOSA and FLAURA2 trials. Direct medical costs and health state utilities were obtained from published sources. Outcomes included total costs, life years (LYs), and quality-adjusted life years (QALYs). One-way and probabilistic sensitivity analyses were conducted to assess model robustness using a willingness-to-pay threshold of $150,000 per QALY or LY gained. **Results:** Across both modeling approaches, osimertinib plus chemotherapy was associated with greater effectiveness and lower costs compared with amivantamab plus lazertinib. In the partitioned survival model, osimertinib plus chemotherapy resulted in 1.68 additional QALYs and 2.18 additional LYs with cost savings of $34,799, indicating dominance. Similar findings were observed in the Markov model, with gains of 2.05 QALYs and 2.74 LYs and cost savings of $46,620. Sensitivity analyses identified survival extrapolation parameters and the discount rate as the primary drivers of uncertainty. In probabilistic sensitivity analysis, osimertinib plus chemotherapy was favored in approximately 82% of simulations. **Conclusions:** From the United States perspective, osimertinib plus chemotherapy was dominant over amivantamab plus lazertinib as first-line treatment for EGFR-mutated advanced NSCLC in this model-based economic evaluation. These findings highlight the importance of integrating clinical efficacy and economic value in first-line treatment selection. Future studies should compare all recommended first-line strategies using mature survival data and incorporate real-world treatment patterns and patient-centered outcomes. Research Sponsor: None.

Base case results.

Regimen	Total Costs	Total QALYs	Total LYs	Δ Cost	Δ QALYs	Δ LYs	ICER (Cost/QALY)	ICER (Cost/LY)
Partitioned Survival Model								
Amivantamab + Lazertinib	$1,297,932	3.23	4.65	-	-	-	-	-
Osimertinib + Chemotherapy	$1,263,133	4.91	6.83	-$34,799	1.68	2.18	Dominant	Dominant
Markov Model								
Amivantamab + Lazertinib	$1,311,688	2.76	3.97	-	-	-	-	-
Osimertinib + Chemotherapy	$1,265,068	4.81	6.71	-$46,620	2.05	2.74	Dominant	Dominant

SOHO-01: Updated safety and efficacy of sevabertinib in patients with advanced *HER2*-mutant non-small cell lung cancer (NSCLC).

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Background: Sevabertinib, a potent, reversible, oral tyrosine kinase inhibitor, received FDA accelerated approval for pretreated patients with advanced NSCLC harboring *HER2* tyrosine kinase domain–activating mutations. Sevabertinib demonstrated significant antitumor activity and manageable safety in patients with *HER2*-mutant NSCLC who had previously received treatment (Cohort D) or were treatment-naïve (Cohort F) in the ongoing, open-label, multicenter, Phase I/II SOHO-01 trial (NCT05099172) (Le X et al. *N Engl J Med* 2025). Here, we report updated safety and efficacy data from Cohorts D and F. **Methods:** Patients with *HER2*-mutant NSCLC received sevabertinib 20 mg twice daily in both cohorts: patients previously treated with systemic therapy but naïve to HER2-targeted therapy (Cohort D) and treatment-naïve patients (Cohort F). The primary endpoint was objective response rate (ORR) assessed by blinded independent central review (BICR) per RECIST v1.1. Other key prespecified and secondary endpoints included duration of response (DoR) and progression-free survival (PFS) assessed by BICR per RECIST v1.1, and safety per MedDRA v28.0 and CTCAE v5.0. **Results:** In total, 154 patients (n=81, D; n=73, F) received sevabertinib in the two cohorts; median follow-up was 19.5 (D) and 15.0 (F) months. Median age was 60 (D) and 65 (F) years; 61.7% (D) and 63.0% (F) were female; 61.7% (D) and 78.1% (F) had never smoked. As of November 17, 2025, ORR (95% CI) was 66.7% (55.3, 76.8; D) and 75.3% (63.9, 84.7; F); disease control rate (confirmed response or stable disease for ≥12 weeks; 95% CI) was 81.5% (71.3, 89.2; D) and 89.0% (79.5, 95.1; F). Median (95% CI) DoR was 9.5 (6.3, 13.5; D) and 12.2 (8.8, not estimable; F) months; median (95% CI) PFS was 8.3 (6.9, 12.3; D) and 13.5 (10.0, not estimable; F) months. Treatment-related adverse events (TRAEs) in both cohorts were consistent with previous reports. Grade 3 or higher TRAEs occurred in 39.5% (D) and 24.7% (F) of patients. Diarrhea was reported in 86.4% (D) and 87.7% (F) of patients; grade 3 diarrhea occurred in 23.5% (D) and 5.5% (F) of patients. No cases of interstitial lung disease or grade 4 diarrhea, discontinuations due to diarrhea, or new safety signals were observed. **Conclusions:** Sevabertinib demonstrated sustained efficacy with a manageable safety profile in treatment-naïve and pretreated patients with advanced *HER2*-mutant NSCLC. These data further support the rapid and durable responses of sevabertinib for patients with *HER2*-mutant NSCLC. Clinical trial information: NCT05099172. Research Sponsor: Bayer AG.

8623 Poster Session

Safety and antitumor activity of VRN110755, a brain-penetrant, selective EGFR inhibitor, in patients with EGFR-driven non–small cell lung cancer.

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Background: Third-generation EGFR tyrosine kinase inhibitors (TKIs) have improved outcomes in EGFR-mutant non–small cell lung cancer (NSCLC); however, acquired resistance, including EGFR C797S mutations, and central nervous system (CNS) progression remain major unmet medical needs. VRN110755 is an orally available, highly selective EGFR inhibitor designed to target a broad spectrum of EGFR mutations, including C797S, and has demonstrated robust brain penetration in preclinical models. **Methods:** This ongoing, open-label, multicenter Phase I/II study evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of VRN110755 in patients with EGFR-mutant NSCLC who progressed on prior third-generation EGFR TKIs and had no remaining standard treatment options. A dose-escalation phase (10–480 mg once daily) followed by protocol-defined backfill cohorts (80–400 mg) was conducted. Patients with stable, asymptomatic brain metastases and/or leptomeningeal metastases were eligible. This abstract reports data available at the time of analysis to characterize emerging safety, PK, and antitumor activity and to inform ongoing dose optimization and cohort expansion under protocol-defined safety monitoring. Early reporting was undertaken due to emerging systemic and intracranial activity in a population with high unmet medical need; enrollment and follow-up are ongoing. **Results:** As of January 18, 2026, 63 patients were enrolled. VRN110755 demonstrated dose-proportional PK. At 320 mg, target engagement (C_{trough}/IC_{50}) against common EGFR mutations exceeded that of osimertinib 80 mg by approximately four-fold. Treatment-related adverse events were predominantly low grade (grade 1: 37%; grade 2: 20%; grade 3: 2%), with no dose-limiting toxicities observed; the most common event was grade 1 rash (16%). Low rates of diarrhea were reported, with no interstitial lung disease or clinically meaningful QTc prolongation observed to date. Among 38 response-evaluable patients treated at doses ≥160 mg following progression on prior EGFR TKIs, 7 (18.4%) achieved partial responses and 28 (73.7%) achieved stable disease, yielding a disease control rate of 92.1%; approximately half remained on treatment beyond 7.5 months, suggesting durable disease control. In patients with baseline EGFR C797S mutations (n=7), the overall response rate was 85.7% (6/7), with ctDNA clearance of C797S observed in 83.3% (5/6) of responders. Complete intracranial responses were observed in two patients, and a $K_{p,uu,CSF}$ of 2.0 was documented at the 160 mg dose. **Conclusions:** VRN110755 demonstrated favorable PK, a manageable safety profile, and encouraging systemic and CNS antitumor activity in heavily pretreated EGFR-mutant NSCLC, including C797S-positive disease, supporting continued clinical development. Clinical trial information: VRN110755_01. Research Sponsor: Voronoi, inc.

Wait or treat? managing asymptomatic brain metastases in oncogene-mutated NSCLC: Results of a phase-III randomized controlled trial.

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Background: The timing of brain radiation therapy (RT) in patients with oncogene-mutated NSCLC with asymptomatic brain metastases (ABM) has been a matter of debate. No level 1 evidence supports delayed brain RT in ABM. This phase III, open-label, RCT (NCT05236946) evaluates Upfront Cranial RT (U-CRT) versus Delayed CRT (D-CRT) in ABM of oncogene-mutated NSCLC. **Methods:** Eligible patients (≥18 years, ECOG ≤2), with EGFR mutation or ALK gene rearrangement and completely ABM, were randomized to U-CRT vs D-CRT at intracranial progression (ICP), stratified by GPA score (0-2 vs > 2) and BM presentation (Synchronous vs Metachronous). Key exclusions include symptomatic BM, brainstem metastases, and prior cranial RT. All pts received standard systemic therapy (TKI ± CT). The primary endpoint is intracranial PFS with death treated as a competing event. Secondary endpoints included OS, PFS, and treatment toxicity. All patients underwent MRI brain every 3 months for 1st year and 6 months thereafter, unless indicated clinically. Cumulative incidence functions were estimated, and subdistribution hazards were compared using the Fine and Gray model. With a planned enrollment of 208 patients and 139 target events, the study had 80% power to detect a hazard ratio of 0.62 at a two-sided alpha of 0.05. The icPFS was analyzed in intention-to-treat populations using Kaplan-Meier estimates and log-rank tests. **Results:** A total of 208 patients were randomized (105-U-CRT; 103-D-CRT). Baseline characteristics were well-balanced in both arms. The median age was 53 years (range, 26-83). EGFR and ALK mutations were seen in 87.6% and 12.4% in U-CRT and 79.6% & 20.4% in D-CRT arm. 1st/2nd generation TKIs ± CT were received by 58% & 72% pts, respectively and rest received 3rd generation TKI. In U-CRT, 44.8% received SRS/SRT, 52.4% received WBRT± boost, and 3 pts did not receive RT. The median follow-up was 27.4 months (95%CI 26.2 -33). The cumulative incidence of ICP at 1 yr were 8.7% (95%CI 2.9%, 14.5%) & 25.7% (95%CI 16.8%, 34.7%), and at 2-yrs were 21.7% (95% CI 12.6%, 30.8%) & 50% (95%CI 39.2%, 60.9%) with sub-HR = 0.35 (95%CI 0.21, 0.59), p < 0.001. The median icPFS were 18 mo (95%CI 15.8, 23.5) and 14.3 mo (95%CI 12.6, 19.6) with HR-0.84 (95%CI 0.59, 1.20), p = 0.35. There was no difference in median PFS of 11.7 mo (95%CI 9.2, 14.1) & 12.0 mo (95% CI 9.8, 14.9), p = 0.37 and in median OS of 23.3 mo (95% CI 17.7-28.8) & 28.7 mo (95%CI 17.7, 39.7), p = 0.06, respectively. In the D-CRT arm, 39/47 who had ICP received salvage CRT. The incidence of grade ≤2 radiation necrosis was 25.4% and grade > 3 in 5.8% in upfront RT arm. **Conclusions:** In asymptomatic BM of oncogene-mutated NSCLC pts, upfront cranial RT significantly reduced the incidence of ICP; however, it did not improve the survival outcomes. The difference in survival may become more apparent as the OS data matures. Data on QOL, neurocognition, and molecular analysis will be reported later. Clinical trial information: NCT05236946. Research Sponsor: Tata Memorial Centre - Research Administrative Council (TRAC); Neuro-Oncology Research Fund of Brain Tumor Foundation (BTF) of India.

Osimertinib combined with bevacizumab and chemotherapy as 1L treatment in EGFR-mutated metastatic non-squamous non-small cell lung cancer (nsq NSCLC) with concurrent mutations.

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Background: Concurrent mutations in EGFR sensitive mutations (19 del/21 L858R) are associated with poor prognosis. Previous studies have shown that EGFR-TKI combined with chemotherapy or anti-angiogenic drugs confers heterogeneous degrees of benefit in this population. However, the efficacy of concurrent EGFR-TKI, anti-angiogenic agent, and chemotherapy has not been reported. **Methods:** This is a single-center, open-label, phase I clinical trial designed to evaluate the efficacy and safety of osimertinib combined with bevacizumab and chemotherapy as first-line treatment for EGFRm metastatic nsq NSCLC with concurrent mutations (NCT05507606). 4 induction cycles will be administered (Osimertinib, 80 mg/d, d8–21; bevacizumab, 7.5 mg/kg, d1; pemetrexed 500 mg/m^2, d1; and carboplatin AUC 5, d1; 3 week/cycle), after which carboplatin will be discontinued. Osimertinib combined with bevacizumab and pemetrexed will be continued as maintenance (Osimertinib, 80 mg/d, d1–21; all other remained unchanged). Bevacizumab and pemetrexed will be stopped at 2 years; osimertinib will be continued until disease progression. EGFRm include exon 19 del, L858R, T790M, G719X, L861Q, S768I, exon 20 A763–Y764 insertion, and concurrent mutations are defined as the presence of at least one destructive TP53 mutation in exons 5 to 8. The primary endpoints are safety and objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Exploratory endpoints comprise NGS comparative analysis pre-/post-treatment, 19 del/L858R subgroup analysis, ctDNA clearance, and the correlation between efficacy and prognosis. **Results:** 34 patients were enrolled. Males accounted for 29.41%, and the median age was 58.5 years (25-75). Patients with ECOG PS 1 and 2 comprised 97.1% and 2.9%, respectively. The EGFRm profile consisted of 19 del (50.0%), L858R (44.1%), and other mutations (5.9%, including 20 ins and L861Q). All patients have finished the 4 induction cycles. The median follow-up was 36.8 months (95% CI, 24.2–47.4). The ORR was 94.12% (95% CI, 80.32%–99.28%), the DCR was 100% (95% CI, 89.72%–100%). The median PFS and OS were 35.9 m (95% CI, 26.0–NR) with 44.1% maturity and NR with 26.5% maturity, respectively. 19 del: ORR 100%, PFS/OS NR. L858R: ORR 86.7%, mPFS 26.5m (95%CI:16.3-NR), mOS 47.8m (95%CI:22.1-NR). Others: ORR 100%, mPFS 10.8m (95%CI:7.9-NR), mOS 21.1m (95%CI:18.2-NR). Grade $\geq$ 3 AE occurred in 31.25% of patients during the induction phase. No deaths related to toxicity were observed. The discontinuation rate was 9.4%; no patient discontinued treatment because of AE. **Conclusions:** These results demonstrate that the four-drug regimen anchored by osimertinib is well tolerated and active in patients with EGFRm metastatic nsq NSCLC harboring concurrent mutations. Clinical trial information: NCT05507606. Research Sponsor: None.

Clinical utility of repeat next-generation sequencing in patients with driver-negative non-small cell lung cancer: A report from the LC-SCRUM-TRY screening platform.

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Background: While precision medicine targeting driver oncogenes has improved clinical outcome of non-small cell lung cancer (NSCLC), the clinical utility of repeat or late-line multiplex genomic profiling remains unclear for patients whose tumors were initially identified as driver-negative. We evaluated the clinical impact of genomic screening for treatment-resistant NSCLC within the nationwide framework (LC-SCRUM-TRY). **Methods:** Between September 2020 and November 2025, a total of 2,088 patients with NSCLC were enrolled into LC-SCRUM-TRY. Of these, this analysis focused on 840 patients who were diagnosed as driver-negative at the time of enrollment. Genomic profiling was performed using Oncomine Precision Assay (Thermo-Fisher Scientific) for tumor tissue sample, or liquid biopsy (Guardant360 [Guardant Health] or liquid OPA). We compared overall survival (OS) among three groups: (A) Driver-negative, (B) Driver-positive without targeted therapy, and (C) Driver-positive with subsequent corresponding targeted therapy. **Results:** Among the 840 patients, median age at enrollment was 68 years (range 34-86); the majority were male (70%), ever-smokers (79%), and had adenocarcinoma (74%), with good ECOG-PS of 0-1 (91%). Of these, 89% underwent tissue-based NGS using OPA, while 11% underwent liquid biopsy. Actionable driver alterations were identified in 186 patients (22%), without significant difference between tissue- and liquid-based NGS. The detected drivers included EGFR mutation (mut) (n = 60), HER2 mut (n = 33), $KRAS^{G12C}$ mut (n = 31), $BRAF^{V600E}$ mut (n = 7), MET exon 14 skipping (n = 17), RET fusion (fus) (n = 17), ALK fus (n = 9), ROS1 fus (n = 7), and NRG1 fus (n = 5). Of the 186 patients with detected drivers, 74 patients (40%) received subsequent matched targeted therapies (Group C), including 13 patients enrolled in clinical trials. The median OS was 36.2 months in Group A, 34.1 months in Group B, and 70.2 months in Group C, respectively. Patients who received matched targeted therapies (Group C) had significantly longer OS compared to Groups A and B ($p < 0.0001$). **Conclusions:** Multiplex genomic profiling effectively identified actionable driver oncogenes in 22% of NSCLC patients previously considered driver-negative. Access to matched targeted therapies based on these results more than doubled the median OS (70.2 vs. 34.1 months), highlighting the critical importance of a multiplex genomic re-screening approach in this population. Clinical trial information: UMIN000041957. Research Sponsor: Amgen Inc, Nippon Boehringer Ingelheim Company, Takeda Pharmaceutical Company, Haihe Biopharma, AstraZeneca, Eli Lilly Japan, Janssen Pharmaceutical, Novartis Pharma, Turning Point Therapeutics, Spectrum Pharmaceuticals, and Ono pharmaceutical Company.

First-line (1L) olomorasib + pembrolizumab in patients with *KRAS* G12C–mutant advanced NSCLC, and PD-L1 expression 0-49%, from the dose optimization cohorts of LOXO-RAS-20001 and SUNRAY-01.

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Background: For patients (pts) with 1L *KRAS* G12C-mutant advanced NSCLC and PD-L1 expression <50%, the current SOC is pembrolizumab + platinum-based chemotherapy. Combining olomorasib, a KRAS G12C inhibitor, with pembrolizumab may overcome the limited efficacy of single-agent pembrolizumab in this population, while offering a chemotherapy-sparing targeted approach. Here we report an integrated analysis of 1L pts with PD-L1 expression 0-49% (<1% and 1-49%) who received olomorasib + pembrolizumab from the dose optimization cohorts of LOXO-RAS-20001 and SUNRAY-01. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC, known PD-L1 expression and ECOG PS 0-1 were randomized to olomorasib (50 or 100 mg, orally BID) with pembrolizumab (200 mg Q3W). One cycle of SOC pembrolizumab prior to enrollment was permitted. Objective response rate (ORR) was assessed in the efficacy evaluable population, with PD-L1 0-49% Other efficacy endpoints included best overall response (BOR) and disease control rate (DCR). Safety was assessed across all treated pts (PD-L1 0-100%). **Results:** As of 6 June 2025, 85 pts received olomorasib + pembrolizumab, of which 31 pts had tumors with PD-L1 expression 0-49% (<1%: n=13; 1-49%: n=18). In pts with PD-L1 expression <1%, no pts received a prior cycle of SOC, 23% of pts had baseline brain metastases, and 38% had an ECOG score of 1. For the pts with PD-L1 expression of 1-49%, 17% received 1 prior cycle of SOC, 17% had baseline brain metastases, and 56% had an ECOG score of 1. The ORR was 58% in pts with PD-L1 <1%, 67% in pts with PD-L1 1-49% (Table). Across all treated pts the most common any grade treatment-related adverse events (TRAEs) were diarrhea (31%) and ALT/AST increased (26/24%). TRAEs led to permanent discontinuation of study treatment in 12% of pts (n=10). **Conclusions:** Olomorasib + pembrolizumab demonstrated promising efficacy in pts with 1L *KRAS* G12C-mutant advanced NSCLC, and PD-L1 expression <1% and 1-49% with ORRs that compare favorably with historical outcomes for pembrolizumab and chemo-immunotherapy in unselected advanced NSCLC. Olomorasib + pembrolizumab is under evaluation in pts with 1L *KRAS* G12C-mutant metastatic NSCLC (SUNRAY-01, NCT06119581) and early-stage NSCLC (SUNRAY-02, NCT06890598). Clinical trial information: NCT04956640, NCT06119581. Research Sponsor: Eli Lilly and Company.

Response and time-to-event endpoints in the Efficacy evaluable population with PD-L1 0-49% (N=30*).

Endpoint	Pts with PD-L1 <1% n=12	Pts with PD-L1 1-49% n=18
ORR[†], % (n/N)	58.3 (7/12)	66.7 (12/18)
BOR, n (%)		
CR[†]	1 (8.3)	1 (5.6)
PR[†]	6 (50.0)	11 (61.1)
SD	4 (33.3)	4 (22.2)
PD	1 (8.3)	1 (5.6)
NE	0 (0.0)	1 (5.6)
DCR, % (n/N)	91.7 (11/12)	88.9 (16/18)

[†]Includes responses confirmed and pending.
*Data for 1 patient are not shown in the table due to incomplete target lesion assessment.
CR, confirmed response; NE, not evaluable, PD, progressive disease; PR, partial response; SD, stable disease.

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Patient-reported outcomes (PROs) and health-related quality of life (HRQoL) with taletrectinib in advanced ROS1+ non-small cell lung cancer (NSCLC) from the TRUST-II study.

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Background: Taletrectinib is a next-generation, CNS-active, selective ROS1 tyrosine kinase inhibitor (TKI) approved by the US FDA for the treatment of patients with locally advanced or metastatic ROS1+ NSCLC based on results from two Phase 2 studies, TRUST-I (NCT04395677) and TRUST-II (NCT04919811). Here we report PROs with taletrectinib from TRUST-II. **Methods:** Patients with locally advanced or metastatic ROS1+ NSCLC were treated with taletrectinib 600 mg once daily in 21-day cycles. HRQoL and PROs for cancer-specific symptoms were evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item core module (QLQ-C30) and 13-item lung cancer module (QLQ-LC13). Questionnaires were only distributed to patients from North America and Europe. Data were collected at screening, then subsequently on Day (D)1 of every cycle (C) until C9D1, on D1 of every three cycles until C27D1, and every four cycles thereafter until the end of treatment (within 7 days of last dose). Changes from baseline over time were summarized using descriptive statistics. A change in score of $\geq$10 points from baseline was considered clinically meaningful. Time to first improvement (TFI) was assessed using Kaplan–Meier methods. **Results:** At data cutoff (August 31, 2025), the analysis set included 69 patients (23 TKI-naïve and 46 TKI-pretreated). Mean changes from baseline improved or remained stable for most domains across both questionnaires. For global health status/quality of life, the majority of patients showed clinically meaningful improvement or remained stable at multiple timepoints assessed (e.g. 74% of patients at C7). Mean cognitive function score improved or remained stable throughout treatment, with the majority (63–77%) of patients showing improvement or stability and only 9–23% of patients showing worsening at various assessment times. Common disease-related symptoms, including pain and fatigue (QLQ-C30), and dyspnea and coughing (QLQ-LC13), showed consistent clinically meaningful improvement throughout treatment, with a median TFI of 1–3 months across all patients. Coughing was particularly improved in TKI-naïve patients, with a median TFI of $<$ 1 month. **Conclusions:** Taletrectinib was associated with improved or stable HRQoL in the majority of patients and with rapid relief of disease-related symptoms. In contrast to other ROS1 TKIs, taletrectinib demonstrated preservation of cognitive function over time. Together with the efficacy and safety results, these data further support the use of taletrectinib for patients with ROS1+ NSCLC. Clinical trial information: NCT04919811. Research Sponsor: This study was sponsored by Nuvation Bio Inc. Medical writing support was provided by Flaminia Fenoaltea, MSc, of Ashfield MedComms, an Inizio company, and was funded by Nuvation Bio Inc.

Hi-C sequencing to identify clinically actionable fusions in non–small cell lung cancer missed by other sequencing technologies.

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Background: For a patient with non-small lung cancer (NSCLC) to benefit from targeted therapy, an actionable driver alteration needs to be identified. DNA-based next-generation sequencing (NGS) is the standard across many clinical laboratories, however, there are known limitations in the detection of structural rearrangements. RNA-based NGS is now being increasingly utilized in cases with negative DNA NGS testing, but it is currently unknown how many driver alterations are missed with RNA NGS. Hi-C, high-throughput chromosome conformation capture, is a newer NGS method that can be performed on formalin-fixed paraffin-embedded (FFPE) tissue to detect pairwise interactions between DNA regions and may have increased sensitivity for fusion detection. **Methods:** We collected FFPE tissue from NSCLC cases that were previously deemed to be negative for driver mutations through standard DNA and/or RNA based NGS. We performed Hi-C sequencing on these samples with the Arima Aventa FusionPlus test. This involves digestion of DNA in situ followed by religating to nearby DNA regions and sequencing pairs of DNA tags that reveal proximal DNA sequences. RNA-Sequencing was performed via multiple commercial testing labs using either panel based or whole transcriptome sequencing. **Results:** In 118 NSCLC specimens that were negative on prior NGS testing, 6 samples (5%) tested positive on Hi-C sequencing for a clinically actionable alteration, including 5 samples that were negative with both DNA and RNA-based NGS. Among these 6 samples were 5 cases of NRG1 fusions and one case of an NTRK2 fusion. All cases with NRG1 fusions have breakpoints proximal to exon 2 and therefore are expected to have expression of the full EGF-like domain. RNA-Sequencing of several of these cases confirmed high expression of NRG1. As an example, one patient had prior negative sequencing with tissue-based panel DNA NGS, ctDNA NGS, an RNA fusion panel, and whole transcriptome RNA-Seq. This patient's Hi-C sequencing identified a non-canonical NRG1 fusion with an intergenic region fused upstream of exon 2 of NRG1. After progression on chemo-immunotherapy, the patient was treated with zenocutuzumab, a recently approved bispecific antibody that blocks NRG1 from activating HER2/HER3 signaling. A CT Chest scan 6 weeks after initiation showed near complete resolution of the diffuse miliary metastases. **Conclusions:** Hi-C can identify clinically actionable driver alterations in NSCLC cases that were negative on other sequencing tests, highlighting the potential value of incorporating this technology into clinical practice. Research Sponsor: None.

Prognostic impact of actionable driver alterations and efficacy of targeted therapy in lung squamous cell carcinoma: A large-scale nationwide genomic screening (LC-SCRUM-Asia).

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Background: Precision medicine based on multi-gene analysis improves prognosis and has established multigene analysis as the standard of care in lung adenocarcinoma.However, the clinical utility of multi-gene analysis in lung squamous cell carcinoma (LUSC) remains controversial due to the rarity of actionable driver alterations and the uncertain therapeutic benefits of targeted therapy. This study aimed to elucidate the prognostic value of driver alterations and the efficacy of targeted therapy in LUSC. **Methods:** We have prospectively analyzed patients with non-small cell lung cancer (NSCLC) enrolled in a nationwide genomic screening project in Japan (LC-SCRUM-Asia) using NGS (Oncomine Comprehensive/Precision Assay). We evaluated clinical outcomes in patients with LUSC, comparing overall survival (OS) according to the presence of actionable driver alterations and receipt of targeted therapy. **Results:** From March 2015 to October 2025, 19,357 patients were enrolled, of whom 2,917 had LUSC. Among these LUSC patients, actionable driver alterations were identified in 180 patients (6.2%) cases, including *EGFR* mutations (n = 78), *KRAS* G12C (n = 33), *MET* exon 14 skipping (n = 28), *ALK* fusions (n = 18), *EGFR* exon 20 insertions (n = 7), *RET* fusions (n = 6), *ROS1* fusions (n = 5), *BRAF* V600E (n = 4), and *HER2* exon 20 insertions (n = 1).In the survival analysis of 2,017 patients with advanced/recurrent disease, median OS was significantly longer in patients with actionable driver alterations compared to those without (18.2 vs. 15.0 months; HR 0.79, p = 0.02). However, among patients with actionable driver alterations, there was no significant difference in median OS between patients who received targeted therapies (n = 97) and those who did not (n = 45) (18.3 vs. 17.0 months, p = 0.94). The efficacy of targeted therapies was notably limited; median progression-free survival was 12.4 months for ALK tyrosine kinase inhibitors (TKIs) (n = 17), 8.4 months for EGFR TKIs (n = 46), 4.5 months for KRAS G12C inhibitors (n = 10), 3.6 months for MET TKIs (n = 15), and 3.4 months for ROS1 TKIs (n = 5). Collectively, these outcomes were consistently inferior to those reported in pivotal clinical trials. **Conclusions:** Although actionable driver alterations were identified in approximately 6% of LUSC and were associated with a favorable prognosis, targeted therapy demonstrated limited efficacy and failed to extend overall survival compared to non-targeted approaches. These findings indicate that the clinical utility of multi-gene analysis in LUSC is currently limited, highlighting the need for the development of novel therapeutic strategies specific to this histology. Research Sponsor: Japan Agency for Medical Research and Development (AMED) and the National Cancer Center Research and Development Fund; Eisai Co., Ltd.; Janssen Pharmaceutical K.K.; Kyowa Kirin Co., Ltd.; Merck Biopharma Co., Ltd.; MEDICAL & BIOLOGICAL LABORATORIES CO., LTD.; MSD K. K.; Nippon Kayaku Co., Ltd; Novartis Pharma K.K.; ONO PHARMACEUTICAL CO., LTD.; Pfizer Japan Inc.; AbbVie GK; Sumitomo Pharma Co., Ltd.; TAIHO PHARMACEUTICAL CO., LTD.; Eli Lilly Japan K.K.; Bayer Yakuhin, Ltd.; Merus N.V.; Takeda Pharmaceutical Co., Ltd.; Amgen K.K.; Astellas Pharma Inc.; AstraZeneca K.K.; Nippon Boehringer Ingelheim Co., Ltd.; Bristol-Myers Squibb K.K.; CHUGAI PHARMACEUTICAL CO., LTD.; DAIICHI SANKYO COMPANY.

Actionable genomic alterations and outcomes in lung squamous and adenosquamous cell carcinoma.

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Background: Actionable genomic alterations (AGA) are uncommon in lung squamous/adenosquamous carcinoma (LUSC/LUASC) and may contribute to poorer survival than lung adenocarcinoma (LUAD). Though a subset of LUSC patients harbor AGA and may benefit from targeted therapy, outcomes are poorly characterized. We hypothesized that AGA-LUSC patients treated with first-line (1L) targeted therapy have superior survival to those receiving chemotherapy and that AGA-LUSC has a distinct immune tumor microenvironment (TME) compared to non-AGA-LUSC. **Methods:** We identified and analyzed LUSC (6,970) and LUASC (227) patients from the Tempus Lens database with DNA (xT, 648-gene) and whole-transcriptome RNA (xR) NGS using the Lens Platform. AGA were defined as *ALK*, *ROS1*, *RET*, *NTRK1/2/3* fusions, *EGFR*, *KRAS*, *BRAF* p.V600E, *MET* exon 14 skipping, or *ERBB2* alterations. *KRAS*, *BRAF* p.V600E, and *MET* exon 14 skipping were classified as immune-associated AGA. RNA data were quantified as transcripts per million (TPM) and reported as log2(TPM+1). We assessed tumor mutational burden (TMB), *TTF1* and *TP63* gene expression, and TME (via quanTIseq). OS and PFS were measured from 1L treatment initiation to death, progression/death or last follow up, respectively. **Results:** AGA incidence was 7.5% in LUSC and 45% in LUASC. Non-immune AGA had significantly lower median TMB than immune-AGA and non-AGA in both LUSC (5.3 vs 7.4 vs 7.9) and LUASC (3.7 vs 5.5 vs 8.4) (both $p < 0.001$) and had numerically lower CD8 T-cell infiltration in LUSC. *TTF1* expression did not differ among AGA and non-AGA groups; but *TP63* expression was significantly higher in LUSC than LUASC (8.70 vs 6.23, $p < 0.001$) and in non-AGA compared to AGA in both LUSC ($p < 0.001$) and LUASC ($p = 0.027$). In AGA-LUSC, 1L targeted therapy (n = 15) was associated with numerically longer PFS (27.7 mo vs 8.1 mo, $p = 0.17$) and OS (19.2 mo vs 15.7 mo, $p = 0.78$) compared with chemoimmunotherapy/chemotherapy. No difference in outcomes was observed between non-AGA and AGA LUSC patients treated with chemoimmunotherapy/chemotherapy. **Conclusions:** Given the observed rates of AGA in both LUSC and LUASC and numerically improved outcomes in AGA-LUSC patients receiving 1L targeted therapy, routine NGS testing is warranted. TME differs between non-immune and immune-AGA, and *TP63* expression is inversely associated with AGA in both tumor types. Research Sponsor: National Cancer Institute; T32CA009515.

	LUSC				LUASC			
	Overall N = 6,970	Non-AGA N = 6,449	Non-immune AGA N = 142	Immune-AGA N = 379	Overall N = 227	Non-AGA N = 124	Non-immune AGA N = 37	Immune-AGA N = 66
Classic *EGFR* alteration (exon 19 deletion or L858R)	51 (0.7%)	0 (0%)	51 (36%)	0 (0%)	21 (9.3%)	0 (0%)	21 (57%)	0 (0%)
Other *EGFR* short variant	31 (0.4%)	0 (0%)	30 (21%)	1 (0.3%)	8 (3.5%)	0 (0%)	7 (19%)	1 (1.5%)
ALK fusion	25 (0.4%)	0 (0%)	24 (17%)	1 (0.3%)	5 (2.2%)	0 (0%)	5 (14%)	0 (0%)
KRAS G12C	117 (1.7%)	0 (0%)	0 (0%)	117 (31%)	21 (9.3%)	0 (0%)	0 (0%)	21 (32%)
Other *KRAS* short variant	192 (2.8%)	0 (0%)	0 (0%)	192 (51%)	32 (14%)	0 (0%)	0 (0%)	32 (48%)

Ablation of oligo-residual disease to prolong progression-free survival in *EGFR*-mutant advanced NSCLC patients treated with third-generation EGFR-TKIs.

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Background: Combination of EGFR-TKIs with chemotherapy or amivantamab have become the standard of care for EGFR-mutant NSCLC. This study further evaluated the efficacy of ablation in advanced NSCLC patients who develop oligo-residual disease (ORD) after EGFR-TKI. **Methods:** We retrospectively enrolled patients with advanced NSCLC who achieved ORD after first-line third-generation EGFR TKIs therapy in Shanghai Pulmonary Hospital, Tongji University. Ablation, including radiofrequency ablation (RFA) and cryoablation, were administered for residual lung lesions. Using propensity score matching, patients with ORD who received TKIs monotherapy alone were set as the control group. The primary endpoint was progression-free survival (PFS). **Results:** From Jan 2019 to Dec 2023, a total of 292 patients (100 for TKIs plus ablation group and 192 for TKIs group) were included. With a median follow-up of 26.4 months, disease progression or death had occurred in 41 patients (41%) in the TKIs plus ablation group versus 159 patients (83%) in the TKIs group. The addition of ablation significantly improved PFS compared to TKIs alone (median 31.6 vs. 17.9 months; HR 0.36, 95% CI 0.26-0.51; $p < 0.001$). The 2-year PFS rate were 66.1% and 32.5%, respectively. A consistent trend was observed for overall survival (OS) (median OS: not reached; HR 0.36, 95% CI 0.20-0.65; $p < 0.001$). A total of 81 patients (22 for ablation group and 59 for TKIs group) underwent biopsies and NGS testing after resistance. The ablation group showed an increased incidence of MET amplification (17% vs. 7%) and HER2 amplification (8% vs. 4%), while on-target EGFR resistance mutations (C797S mutation or EGFR amplification) were similar. The side effects were similar in the two groups. **Conclusions:** Front-line third-generation EGFR-TKI combined with ablation for ORD led to significantly longer PFS than EGFR-TKIs alone in patients with advanced NSCLC, which provide an alternative strategy as the front line setting and warranting further prospective validation. Research Sponsor: National Natural Science Foundation of China; 82505082; China Postdoctoral Science Foundation; 2025M773920.

Clinicogenomic determinants of early progression on first-line osimertinib in *EGFR*-mutant NSCLC.

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Background: With the recent approvals of the FLAURA2 and MARIPOSA regimens in *EGFR*-mutant non-small cell lung cancer (NSCLC), identifying clinicogenomic features predictive of suboptimal outcomes with first-line osimertinib monotherapy is critical in guiding upfront treatment selections. **Methods:** This is a multicenter retrospective study enrolling patients (pts) with advanced NSCLC harboring common *EGFR* mutations (exon 19 deletions [ex19del], L858R) treated with first-line osimertinib monotherapy across 13 centers (Clinical cohort). Comprehensive baseline genomic data on tumor tissue were available for DFCI and MSKCC (Genomic cohort). The association of clinicogenomic features with real-world progression-free survival (rwPFS) was investigated. Time-dependent discrimination for very-early progression (rwPFS $<$ 6 months) was evaluated using Receiver Operating Characteristic (ROC) curve-based Area Under the Curve (AUC). Variable importance was assessed by delta (Δ) AUC after covariate exclusion. Moreover, very-early progression was analyzed with a Cox model censored at 6 months, reporting adjusted hazard ratios (aHR). **Results:** A total of 1488 pts were enrolled in the clinical cohort; at median follow-up of 43.3 months, median rwPFS was 16.3 months (95%CI 15.3-17.4), median overall survival was 36.7 months (95%CI 34.8-39.4). The strongest predictor of very-early rwPFS in a multivariable model, including, age, sex, *EGFR* mutations, PD-L1 tumor proportion score (TPS), concurrent *TP53* mutations, metastatic sites (brain, bone, liver), performance status, was PD-L1 TPS (aHR 2.75 for $\geq$50% versus 0%, $p < 0.0001$), with the largest decrease in the AUC when excluded from the model (ΔAUC = 0.17). Looking at genomic features in the genomic cohort, at median follow up of 38.2 months, loss-of-function mutations in *KMT2D* (HR 7.1, $p < 0.001$), *TP53* (HR 1.4, p = 0.01), *RB1* (HR 1.7, p = 0.01), *RBM10* (HR 1.6, p = 0.01), *CREBBP* (HR 2.7, p = 0.02), *ATM* (HR 2.1, p = 0.04), predicted shorter rwPFS. Next, we investigated the role of concurrent tumor suppressor gene (*TSG*) alterations beyond *TP53*, including in this cathegory those with a $p < 0.1$ for rwPFS and mutated in at least 5 cases *(RBM10, CREBBP, ATM, RB1, KMT2D, TSC2, PTEN). TSG^{MUT}* had shorter rwPFS compared to TSG^{WT} (aHR 1.5, p = 0.01), specifically in L858R subgroup (aHR 1.7, p = 0.02), while $TP53^{MUT}$ had shorter rwPFS compared to $TP53^{WT}$ in ex19del only (aHR 1.7, p = 0.01). Combining *TP53* with *TSG*, pts with $TP53^{MUT}$ plus at least one TSG^{MUT} and pts with $TP53^{WT}$-TSG^{MUT} had shorter rwPFS compared to $TP53^{WT}$-TSG^{WT} and $TP53^{MUT}$-TSG^{WT} (10.8, 13.1, 21.9, 18.1 months, respectively, p = 0.004). In the genomic cohort, PD-L1 TPS was the strongest predictor of very-early rwPFS (ΔAUC = 0.16), followed by *TP53* combined with *TSG* (ΔAUC = 0.08). **Conclusions:** In this multicenter real-world cohort, baseline PD-L1 and *TP53* combined with *TSG* predict very-early progression to first-line Osimertinib. Research Sponsor: None.

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EGFR-mutated lung cancer: A comparative analysis of common and uncommon variants.

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Background: Uncommon EGFR mutations represent a heterogeneous subset of EGFR-positive NSCLC with limited characterization. This study compares clinical, molecular, and survival outcomes between common and uncommon EGFR variants in a large real-world cohort. **Methods:** A retrospective analysis of 1,501 EGFR-positive NSCLC cases from MSK-CHORD was performed. Patients were classified as having common (Ex19del, L858R) or uncommon mutations (G719X, L861Q, S768I). Clinical and genomic variables were analysed using Wilcoxon and chi-square tests (significance $p < 0.05$). **Results:** The study included 1,501 EGFR-mutated NSCLC patients, with 195 (13.0%) harboring uncommon and 1,306 (87.0%) harboring common EGFR mutations. Patients with uncommon mutations were older at diagnosis (median 73 vs 69 years; $p = 0.003$), while sex distribution remained similar ($p = 0.868$). Race distribution differed ($p = 0.005$), with more White patients in the uncommon EGFR group (80.3% vs. 69.5%) and fewer Asian patients (11.8% vs. 25.5%), while Black patient proportions were similar (7.9% vs. 5.0%). Smoking history also varied ($p < 0.005$), with substantially fewer never-smokers among patients with uncommon mutations (25.6% vs 59.6%). Uncommon mutations were associated with higher genomic burden, including elevated TMB (median 4.92 vs 3.46 mut/Mb; $p < 0.001$) and mutation count (median 6 vs 4; $p < 0.001$). Stage at diagnosis did not differ ($p = 0.3$), nor did metastatic site distributions ($p = 0.477$). Median OS was significantly shorter for patients with uncommon EGFR mutations (36.69 vs 56.52 months), with HR 1.425 ($p < 0.005$). In Stage IV patients receiving osimertinib, OS was numerically shorter for uncommon mutations but not statistically significant (29.98 vs 34.32 months; HR 1.351; $p = 0.08$). Among Stage IV patients with uncommon mutations, OS was comparable between afatinib and osimertinib (25.48 vs 26.70 months; $p = 0.88$). *KRAS* co-mutations were significantly more frequent in the uncommon group (4.62% vs 1.15%; $p = 1.985 \times 10^{-3}$). **Conclusions:** Uncommon EGFR mutations exhibit distinct clinical and genomic features and poorer survival compared with common variants, highlighting their heterogeneity and the need for tailored therapeutic strategies. Research Sponsor: None.

The effect of glucagon-like peptide-1 (GLP-1) receptor agonists on outcomes in metastatic non-small cell lung cancer (mNSCLC) patients treated with tyrosine kinase inhibitors (TKIs): Real-world retrospective analysis.

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Background: The therapeutic landscape of mNSCLC has rapidly evolved, with multiple oncogenic alterations now targetable by approved TKIs used in first-line settings, leading to substantial survival gains. However, several TKIs are associated with metabolic toxicities, including weight gain and hyperlipidemia, particularly with ALK inhibitors (e.g., lorlatinib) and selective RET inhibitors. As use of GLP-1 has increased among patients with cancer, their impact on outcomes in oncogene-driven mNSCLC treated with TKIs remains unknown. We evaluated the association between GLP-1 use and survival outcomes in TKI-treated mNSCLC using real-world data. **Methods:** We conducted a retrospective analysis using TriNetX, a Global Collaborative electronic health record with $>$ 190 million patients and $>$ 170 healthcare organizations, from 2010-2025. Adults ($\geq$18 years) with mNSCLC, metabolic comorbidities (T2DM, obesity, or hyperlipidemia), and treatment with first line-approved TKIs (EGFR, ALK, ROS1, RET, NTRK, BRAF, MET) were included. Patients were stratified by concomitant GLP-1 use and matched 1:1 using propensity scores based on demographics, ECOG performance status, cardiometabolic comorbidities, tobacco and alcohol use, and outpatient healthcare utilization. 5 year overall survival (OS) was assessed. **Results:** A total of 25,008 patients met inclusion criteria, including 24,459 (97.8%) non-GLP1 users and 549 (2.2%) in GLP-1 users. After 1:1 propensity score matching (PSM), 546 patients were included per group. Amongst both cohorts average age was 64, 61% were female, 60% were White, 13% were Asian. In the overall mNSCLC TKI-treated patients, GLP-1 use was associated with significantly improved 5-year OS compared with non-use (63% vs 40%; HR 0.45, 95% CI 0.36-0.57; $p < 0.001$). In subgroup analyses, patients treated with ALK TKIs (lorlatinib or alectinib; n = 128/group) demonstrated improved 5 year OS with GLP-1 use 85% vs 48% in non-users (HR, 0.18; 95% CI, 0.09 - 0.36; $p < 0.0001$). Furthermore, GLP-1 use was also associated with improved 5-year OS among EGFR TKI-treated patients (54% vs 44%; HR 0.60, 95% CI 0.44-0.82; p = 0.001) and BRAF TKI-treated patients (41% vs 35%; HR 0.52, 95% CI 0.30-0.91; p = 0.02). Other TKI groups comprised relatively small numbers of patients and therefore were not analyzed separately. **Conclusions:** In this large real-world analysis, GLP-1 use was associated with significantly improved survival in patients with oncogene-driven mNSCLC treated with TKIs, with consistent benefit across ALK, EGFR, and BRAF-driven mNSCLC. To our knowledge, this is the first study to link the impact of the GLP-1 agonists on the outcomes of TKI treated mNSCLC. Further prospective studies are needed to validate these findings and to identify underlying mechanisms. Research Sponsor: None.

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Plasma epigenomic profiling for identification of mechanisms of sensitivity, primary and acquired resistance to tepotinib in METex14 skipping metastatic NSCLC.

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Background: *MET* exon 14 skipping mutations (METex14) are an actionable biomarker in a subset (3-4%) of advanced/metastatic NSCLC patients, with an approved oral and highly selective MET TKI, tepotinib. However, heterogenous clinical responses in patients warrant additional biomarkers of response and resistance. We applied Precede's epigenomic liquid biopsy platform to explore the feasibility of identifying transcriptional programs associated with sensitivity and resistance to tepotinib in patients with METex14 NSCLC. **Methods:** A total of 144 baseline, on-treatment (OT), and end-of-treatment (EOT) samples from patients with METex14 NSCLC from the VISION study (NCT02864992) were profiled using Precede's assay using 1mL of plasma. ctDNA fraction was independently estimated. Genome-wide differential epigenomic activity and pathway analyses compared PFS-stratified responders (top tertile PFS) vs. non-responders at baseline (bottom tertile PFS), and paired baseline vs. EOT samples to identify acquired resistance programs. SCLC/neuroendocrine transformation was assessed in all samples using an independent Precede lineage classifier. Plasma-inferred gene expression models, based on Precede's proprietary algorithms identified additional therapeutic targets. **Results:** At baseline, responders showed higher epigenomic activity in pathways underlying addiction to METex14 signaling, including the FAK-integrin axis, ECM remodeling and EMT/invasion. Non-responders displayed increased translational/intrinsic proliferative programs, altered metabolic fitness, and inflammatory/immune signaling, implicating these programs in intrinsic resistance to tepotinib. These METex14 signaling-associated pathway scores stratified clinical outcomes, highlighting their potential in patient selection. Paired analyses revealed EOT samples had increased activity of regulators of lineage plasticity and neuroendocrine differentiation, relative to baseline. Correspondingly, SCLC scores were elevated in OT and EOT samples, with a subset of baseline samples already harboring neuroendocrine features. Epigenomic activity of GD2 synthase (*B4GALNT1*) significantly increased with treatment, underscoring a potential rationale for combination therapies using anti-GD2 ADCs. **Conclusions:** Precede's comprehensive epigenomic liquid biopsy platform resolved METex14 skipping NSCLC biology associated with response and identified programs associated with intrinsic and acquired resistance to tepotinib, including emergence of neuroendocrine differentiation and induction of GD2 synthase. These findings support the use of plasma-based epigenomic profiling to inform therapy selection for patients at baseline and progression and non-invasively monitor resistance mechanisms in METex14 NSCLC. Research Sponsor: Merck KGaA, Darmstadt, Germany; CrossRef Funder ID: 10.13039/100009945.

8638 Poster Session

Efficacy and safety of deulorlatinib (TGRX-326) in patients with locally advanced or metastatic ALK+ non–small cell lung cancer: A multicenter, open-label, pivotal phase 2 trial.

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Background: Treatment options are limited for anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC) patients (pts) who have developed resistance to second-generation ALK inhibitors. Deulorlatinib is a highly potent third-generation ALK inhibitor. The Previous phase 1 study (NCT05441956) found that deulorlatinib had a high overall and intracranial response rate in pts who had progressed on second-generation inhibitors, with encouraging activity against the G1202R mutation and favorable tolerability. **Methods:** This is a multicenter, open-label pivotal phase 2 study. Pts with locally advanced or metastatic ALK+ NSCLC who had progressed on second-generation inhibitors received deulorlatinib 60 mg orally once daily. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by independent review committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. The ORR in patients harboring the G1202R mutation was also assessed. **Results:** Between Jan 18, 2023 and Dec 29, 2023, a total of 163 patients were enrolled and 158 were evaluable for efficacy. Of these pts, the median age was 53.5 years old, 53.2% were female, 95.6% had adenocarcinoma, and 56.2% had baseline brain metastasis; 56.3% of these pts had progressed on alectinib. As of December 16, 2025, the median follow-up was 28.7 months and 44 pts were still on deulorlatinib. The IRC assessed confirmed ORR was 43.7% (95%CI 35.8, 51.8). The median DoR and PFS was 20.7 months (95%CI 15.4, NR) and 13.8 months (95%CI 8.3, 16.5), respectively; median OS was not reached. Of the 43 pts with measurable baseline CNS lesions, confirmed ORR was 55.8% (95%CI 39.9, 70.9). In pts with the G1202R mutation, the ORR was 62.5% (95%CI 24.5, 91.5). Treatment-related adverse events (TRAEs) were reported in 96.3% of pts. The most common TRAEs were hypercholesterolaemia (77.9%), hypertriglyceridaemia (71.2%), and weight gain (52.8%). Grade ≥3 TRAEs were reported in 51.5% of pts. Of note, only 1.2% of pts had Grade ≥3 CNS TRAEs. **Conclusions:** Deulorlatinib produced robust and durable responses in locally advanced or metastatic ALK+ NSCLC pts with progression on second-generation inhibitors, including those with the G1202R mutation, with low incidence of Grade ≥3 CNS TRAEs. Although across trials comparisons must be interpreted cautiously, deulorlatinib might have a better safety profile than lorlatinib. Altogether these findings suggest that deulorlatinib has a favourable risk benefit ratio and support its further development, particularly in the first-line setting. Clinical trial information: NCT05955391. Research Sponsor: Shenzhen TargetRx, Inc.

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Clinical efficacy and tolerability of the selective RET inhibitor soxataltinib (SY-5007) in advanced *RET* fusion–positive non–small cell lung cancer (NSCLC): Primary findings from a confirmatory phase III trial.

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Background: Oncogenic RET gene fusions represent a clinically validated molecular driver occurring in approximately 1–2% of all NSCLC cases, establishing a critical need for targeted therapeutic strategies. Soxataltinib is a novel, orally bioavailable, and highly selective small-molecule inhibitor of RET kinase. Its anti-tumor potency and safety have been previously reported in a phase I/II study. Here we confirmed its clinical value in a pivotal phase III study. **Methods:** This multicenter, single-arm Phase III clinical trial was designed to evaluate the efficacy and safety of Soxataltinib in patients with RET fusion–positive NSCLC who were previously untreated for advanced disease. The primary endpoint was the confirmed Objective Response Rate (ORR), as determined by Blinded Independent Central Review (BICR) per RECIST v1.1. The secondary endpoints included investigator-assessed ORR, Disease Control Rate (DCR), Duration of Response (DOR), Progression-Free Survival (PFS), Overall Survival (OS), and safety. **Results:** At the data cutoff (April 10, 2025), the Per-Protocol Population (PPP) comprised 95 patients, 61 of whom were Key efficacy population (KEP) for statistical hypothesis. Soxataltinib demonstrated profound anti-tumor efficacy. The primary endpoint was met. The BICR-confirmed ORR was 90.0% (95%CI: 79.5, 96.2) for KEP and 87.4% (95%CI: 79.0, 93.3) for PPP. The overall DCR was 96.7% (95%CI: 88.5, 99.6) for KEP and 93.7% (95%CI: 86.8, 97.6) for PPP. The median PFS and DOR had not yet been reached, with an estimated 15-month PFS rate of 68.9% (95%CI: 54.3, 79.7) and 65.0% (95%CI: 51.5, 75.6) and 12-month DOR rate of 73.8% (95%CI: 58.2, 84.4) and 69.1% (95%CI: 53.8, 80.1), respectively for KEP and PPP. The OS data remained immature. The safety analysis population comprised 96 patients who received at least one dose of Soxataltinib. The most common Grade ≥3 treatment-emergent adverse events (TEAEs) were hypertension (22.9%), diarrhea (16.7%), Aspartate aminotransferase increased (6.3%), Alanine aminotransferase increased (5.2%), and hyponatraemia (5.2%). These events were predominantly manageable. None of the patients permanently discontinued treatment due to a treatment-related adverse event. No patient died due to TEAE that was definitely related, probably related, or possibly related to Soxataltinib. **Conclusions:** The primary analysis of this Phase III trial confirmed Soxataltinib as a highly effective and well-tolerated therapeutic agent for patients with RET fusion–positive NSCLC in the first-line setting. This observed high response rates and durable disease control benefit underscored its potential as a best-in-class RET inhibitor. The adverse event profile was predictable and manageable, supporting its feasibility for long-term administration. Clinical trial information: NCT06031558. Research Sponsor: Shouyao Holdings (Beijing) Co. Ltd.

Results from OCEAN II: A phase II study of encorafenib + binimetinib combination in Chinese patients with *BRAF*^{V600E} mutated metastatic non-small cell lung cancer.

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Background: Lung cancer is the most common cause of cancer and cancer death in China. Patients (pts) with *BRAF*^{V600E} mutant metastatic non-small cell lung cancer (mNSCLC) can benefit from targeted treatments such as encorafenib + binimetinib (E+B). E+B is approved in Western countries (PHAROS: NCT03915951); however, evidence of efficacy and safety in Chinese pts is lacking. OCEAN II (NCT05195632) is the 1st study to specifically evaluate the efficacy, safety and pharmacokinetic of this targeted combination in Chinese pts with *BRAF*^{V600E} mutant mNSCLC. **Methods:** OCEAN II is an ongoing multicenter, open-label, phase 2 (P2) study with a Safety Lead-in (SLI). Eligible pts had unresectable stage IV *BRAF*^{V600E} mutant NSCLC, were treatment-naive or had received systemic therapy, excluding BRAF/MEK inhibitors. Pts received E 450 mg once daily + B 45 mg twice daily. Primary endpoints were dose-limiting toxicities (DLT) during the 1st 28 days (SLI) and confirmed objective response rate (cORR) by independent central review (ICR) (P2). Secondary endpoints (P2) were disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between June 2022 and October 2023, 63 pts were enrolled (SLI = 15, P2 = 48): median age 65 yrs (range 52–82), 49% female, 75% with ECOG score = 1. There was only 1 DLT (non-serious grade 3 lipase increased) during SLI, supporting P2 initiation. At the primary analysis cut-off date (27 May 2024), the primary endpoint was met; cORR by ICR was 59.3% (95% confidence interval [CI] 45.0–72.4) in the Efficacy set, with pre-defined statistical significance criteria met. An *ad hoc* analysis (cut-off 27 March 2025) was conducted when all pts had ≥12 months (mo) follow up. cORR by ICR was 61.1% (95% CI 46.9–74.1), with 6 (11%) complete and 27 (50%) partial responses, and DCR of 87.0% (95% CI 75.1–94.6). Median time to response was 1.8 mo (range 1.7–13.7), median DoR 17.5 mo (95% CI 12.9–NR), median PFS 13.8 mo (95% CI 7.5–NR) and median OS 27.9 mo (95% CI 14.7–30.0). DoR and OS are not yet mature (median follow-up for OS: 21 months). Median treatment duration was 32.3 weeks, with 7 (11%) pts receiving treatment for > 2 years, and 10 (15.9%) remaining on treatment. Treatment-emergent adverse events (TEAEs) ≥ grade 3 occurred in 56% of pts. Related TEAEs in ≥25% were anemia (36%), increased aspartate aminotransferase (33%), increased alanine aminotransferase (30%), increased creatine kinase (29%), vomiting (27%), increased creatinine (25%). Nine (14%) pts discontinued any drug due to AEs. **Conclusions:** The data confirm the clinical benefit of E+B in Chinese pts with *BRAF*^{V600E} mutant mNSCLC, a population with distinct genomic and disease characteristics. No new safety concern was identified in the Chinese population. These data can support regulatory decisions and clinical practice guidelines in China. Clinical trial information: NCT03915951. Research Sponsor: Pierre Fabre Medicament.

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A phase 2 multicenter, open-label, parallel cohort study to evaluate the efficacy, safety, and pharmacokinetic profile of ABN401 in patients with advanced solid tumors harboring c-MET dysregulation.

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Background: Vabametkib is a small-molecule, tyrosine kinase inhibitor (TKI) that is a highly selective type I inhibitor of c-MET kinase, for the treatment of solid tumors harboring c-MET gene dysregulation. **Methods:** Phase 2 trial is an open-label, global study designed to evaluate the safety and efficacy of vabametkib in patients with NSCLC harboring MET exon 14 skipping mutations confirmed by NGS. Patients received oral vabametkib at a dose of 800 mg once daily (QD) until disease progression or unacceptable toxicity. The primary endpoint was ORR as assessed by blinded independent central review. Secondary endpoints included pharmacokinetics, DoR, DCR, PFS and OS. Exposure–response relationships of vabametkib were evaluated in enrolled patients to explore the optimal dose and dosing regimen to support further clinical development. **Results:** Forty-two (42) efficacy patients enrolled and median age were 76 years; 78 years in treatment naive and 75 years in the prior treated patients. Median follow-up duration was 14.1 months overall; 14.6 months for treatment naive and 13.5 months for prior treated patients. BICR confirmed ORR was 55% overall, with comparable response rate in both treatment-naive patients (52%) and prior-treated patients (57%). The median DoR assessed by BICR was 14.5 months with 19.9 months in treatment naive patients and 11.7 months in prior treated patients. Median PFS by BICR was 8.8 months overall, with 10.2 months in treatment naive patients and 7.3 months in prior treated patients. TRAE were experienced in 89% patients, 11% patients experienced Grade ≥3 TRAEs and no Grade 4 TRAE was reported. The most common TRAEs included nausea (75%), diarrhea (34%), hypoalbuminemia (25%), rash (18%), vomiting (18%), peripheral edema (16%), fatigue (14%), and elevated ALT and AST (14%). The most common Grade ≥3 TRAE was pneumonitis (4.5%). TRAEs led to dose reductions in 22.7% of patients, most commonly due to rash (6.8%), nausea (4.5%) and stomatitis (4.5%). TRAEs resulted in dose interruptions in 36.4% of patients most frequently due to nausea (9.1%), vomiting (9.1%), rash (6.8%), and fatigue (4.5%). Median AUC_{inf} values were highest in the PR group (2,946 ng·h/mL) compared to the SD (2,021ng·h/mL) and PD groups (988 ng·h/mL) with a statistically significant difference (p = 0.0347 by Kruskal-Wallis). PK simulation demonstrated BID dosing more effectively maintained EC_{90} coverage than QD dosing; sustaining drug conc above EC_{90} for 93% of the dosing interval and increasing AUC_{0-24hr} by 35.3% thereby increasing likelihood of achieving exposure observed in the PR patients. **Conclusions:** Alternative 350mg BID of Vabametkib had been selected to continue the clinical development. Clinical trial information: NCT05541822. Research Sponsor: AbionBio; Korean Drug Development Fund.

8642 Poster Session

Comprehensive epigenomic profiling of plasma for non-invasive detection of MET activation to uncover MET-associated biology in patients with *EGFR*-mutated advanced NSCLC and progression on osimertinib.

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Background: Genomic overexpression or amplification of *MET* is an established bypass resistance mechanism in EGFR-mutated (EGFRm) NSCLC, observed in up to 34% of patients whose tumors progress on osimertinib. Savolitinib, an oral, highly selective MET TKI, demonstrates clinical activity in tumors classified as MET-high by tissue-based IHC or FISH. However, tissue at progression is often inaccessible or insufficient for repeated assessment, constraining dynamic characterization of MET pathway dependence and emerging resistance mechanisms. To overcome these limitations, we applied an epigenomic liquid biopsy platform to a subset of patients enrolled in the Phase II SAVANNAH trial that combined osimertinib and savolitinib after progression on 1L osimertinib (NCT03778229), where we evaluated the feasibility of capturing MET activity and additional resistance markers from plasma. **Methods:** Baseline samples from 40 patients enrolled in the SAVANNAH trial with progression on 1L osimertinib, were profiled using an epigenomic assay (Precede Biosciences, Boston MA) on 1mL of plasma. Tissue-based analysis from the SAVANNAH cohort scored 15/40 tumors as MET-high/+ (FISH 10+, IHC 3+ $\geq$90%+) and 25 samples as MET-low/- (FISH $<$ 10, IHC 3+ $<$ 90%). A plasma-based MET classifier integrating comprehensive epigenomic features was applied to these samples and its performance evaluated against tissue MET status. ctDNA fraction was independently estimated. Pathway analyses on genome-wide differential epigenomic activity were performed to define MET-associated biology and infer tumor gene expression from plasma. **Results:** The plasma-based MET classifier demonstrated strong agreement with tissue-based MET status (AUC 0.97; balanced accuracy 88%), with an estimated limit of quantification (LoQ) of ~0.8% ctDNA. MET+ samples displayed enrichment of epigenomic signatures consistent with MET-dependence, including MYC targets, metabolic signatures, and invasive and developmental programs. In contrast, MET-negative (MET-) samples were enriched for IFN-driven immune pathways and apoptotic priming. Gene expression models across multiple ADC targets applied to patient plasma samples from SAVANNAH also identified elevated EGFR and HER2 expression in select cases. **Conclusions:** Comprehensive epigenomic profiling of plasma demonstrated high concordance with tissue-based approaches, identifying MET pathway activation and additional putative resistance-associated targets, from 1 mL of plasma in EGFRm NSCLC patients. This provides an accessible and scalable blood-based test to increase identification of patients post-EGFR inhibitor treatment, who may benefit from MET-targeted therapy, resistance monitoring, and informing future combination or sequential MET-directed strategies. Research Sponsor: AstraZeneca, Boston, USA.

Clinical significance of *EGFR* amplification in patients with *EGFR*-mutated metastatic non–small cell lung cancer receiving first-line osimertinib.

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Background: With rapidly expanding first-line options for patients (pts) with *EGFR*-mutated non-small cell lung cancer (NSCLC), identifying biomarkers that may assist treatment selection is critical. The impact of *EGFR* amplification ($EGFR^{AMP}$) on osimertinib outcomes is unclear. **Methods:** Pts with stage IV NSCLC and *EGFR* exon 19 deletions (ex19del) or the L858R mutation who received first-line osimertinib monotherapy at 5 centres across Italy and the United States and had undergone baseline next-generation sequencing (NGS) that included $EGFR^{AMP}$ assessment were included in this analysis. $EGFR^{AMP}$ was defined as an *EGFR* copy number (CN) $\geq$6. The predominantly amplified allele was inferred by INCOMMON, a biostatistical classifier, as previously described. **Results:** Among 473 pts, 81 (17.1%) had $EGFR^{AMP}$. Compared to pts with non-amplified *EGFR* ($EGFR^{Non-AMP}$, n = 392), pts with $EGFR^{AMP}$ more frequently had *TP53* co-mutations (80% vs 55%, $p < 0.001$) and baseline brain (51% vs 34%, p = 0.008), liver (26% vs 13%, p = 0.009), and bone metastasis (65% vs 51%, p = 0.03). When treated with osimertinib, pts with $EGFR^{AMP}$ achieved similar objective response rate (ORR) (88% vs 83%, p = 0.23), but shorter median progression-free survival (mPFS) (11.6 vs 19.0 months, HR 1.77, $p < 0.0001$) and overall survival (mOS) (34.0 vs 40.1 months, HR 1.40; p = 0.040). In a multivariable Cox-regression model, $EGFR^{AMP}$ retained its association with worse PFS (HR 1.36, p = 0.04), but not OS. $EGFR^{AMP}$ correlated with shorter PFS in both *TP53* co-mutated (n = 269) (11.7 vs 15.0 months, HR 1.43, p = 0.02) and *TP53* wild-type (n = 181) (10.4 vs 21.9 months, HR 2.38, $p < 0.001$) cases, despite similar ORR and mOS. Among pts with ex19del, $EGFR^{AMP}$ (n = 44) showed similar ORR compared to $EGFR^{Non-AMP}$ (n = 241), but shorter mPFS (14.2 vs 20.2 months, HR 2.01, $p < 0.001$) and mOS (35.4 vs 44.9 months, HR 1.62, p = 0.04). In contrast, no difference was observed in the L858R-mutated subgroup between $EGFR^{AMP}$ (n = 39) and $EGFR^{Non-AMP}$ (n = 150) cases (ORR 86% vs 75%, p = 0.14; mPFS 11.4 vs 14.3 months, HR 1.47, p = 0.06; mOS 33.2 vs 36.0 months, HR 1.19, p = 0.5). Within $EGFR^{AMP}$ cases, increasing *EGFR* CN ($EGFR^{Non-AMP}$ vs CN$\geq$6 $<$ 15 vs CN 15-30 vs CN $>$ 30) correlated with a stepwise reduction of mPFS (19.0, 16.7, 10.3, and 8.7 months, respectively; log-rank $p < 0.001$) and mOS (40.1, 37.5, 38.8, and 15.3 months, respectively; log-rank p = 0.02). Moreover, amplification of the mutant allele, as opposed to wild-type amplification, correlated with inferior mPFS (8.3 vs 12.1 months, HR 2.72, p = 0.002) and mOS (17.3 vs 39.7 months, HR 2.08, p = 0.046). Among pts with paired NGS before and after acquired osimertinib resistance (n = 113), those with baseline $EGFR^{AMP}$ more frequently showed acquired *MET* alterations (29% vs 12%, p = 0.04). **Conclusions:** $EGFR^{AMP}$ is associated with distinctive characteristics and worse outcomes to osimertinib among pts with stage IV *EGFR*-mutated NSCLC. Research Sponsor: None.

Leptomeningeal disease in ALK-positive NSCLC: Survival impact of third-generation ALK inhibitors.

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Background: As survival outcomes for patients with ALK-positive non-small cell lung cancer (NSCLC) continue to improve with successive generations of ALK tyrosine kinase inhibitors (TKIs), leptomeningeal disease (LMD) has emerged as a growing and critical area of unmet need. While next-generation ALK TKIs were developed to enhance central nervous system (CNS) penetration and improve control of parenchymal brain metastases, their role in the treatment of LMD remains less well defined. **Methods:** We performed a global multi-center retrospective analysis of 141 patients with a diagnosis of ALK-positive NSCLC and radiographically or cytologically confirmed LMD at 5 academic centers across the United States and China (MD Anderson Cancer Center, Zhejiang University, Guandong Lung Cancer Institute, National Cancer Centre Singapore, and Union Hospital at Tongji Medical College) between 2007-2024. Baseline clinical characteristics, treatment history, and outcomes were collected, and subgroup analyses were performed to identify clinical and treatment-related factors associated with leptomeningeal overall survival (LMOS). **Results:** Of the 141 patients with ALK+ NSCLC, most patients had radiographic LMD (79.4%), while 41.1% had positive CSF cytology and 59.6% were neurologically symptomatic. The median time from metastatic lung cancer to LMD diagnosis was 40.6 months among patients who were previously treated with a 3rd generation (3G) ALK TKI (lorlatinib), compared to 23.7 months among those without prior lorlatinib treatment ($p < 0.001$). The median overall survival following LMD diagnosis (LMOS) was 22.5 months. Use of a 3G ALK TKI following LMD diagnosis was associated with improved LMOS in both treatment-naïve patients and those previously treated with earlier-generation TKIs. Among TKI-naïve patients, LMOS was 42.4 months with second-generation (2G) TKI alone, 49.6 months with escalation from 2G to 3G TKI, and not reached with 3G TKI alone ($p < 0.001$). Among patients previously treated with a 2G TKI, LMOS was significantly improved with 3G TKI (32.6 months) compared with an alternative 2G TKI (7.0 months) or no ALK TKI (6.8 months; $p = 0.01$). Whole-brain radiotherapy, intrathecal therapy, and VEGF inhibition were not associated with improved LMOS. On multivariable analysis, ECOG performance status < 2 and female sex were associated with prolonged LMOS. **Conclusions:** This study represents the largest multi-institutional analysis of LMD in patients with ALK+ NSCLC. Highly CNS-penetrant 3G ALK TKIs are associated with delayed LMD development and significantly improved survival following LMD diagnosis, whereas WBRT and intrathecal therapies confer limited benefit. These findings support the need for potent CNS-active ALK TKIs and prospective studies including patients with LMD in ALK-driven NSCLC. Research Sponsor: None.

8645 Poster Session

Real-world effectiveness of MET inhibitors versus immunotherapy ± chemotherapy in 1L for patients with MET exon 14 skipping mutations in non-small cell lung cancer.

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Background: Metastatic non-small cell lung cancer (mNSCLC) remains a leading cause of cancer-related deaths, with MET exon 14 skipping mutations (METex14) identified as a key oncogenic driver in 1%–4% of cases. MET tyrosine kinase inhibitors (TKI) such as capmatinib and tepotinib have demonstrated efficacy in clinical trials, leading to FDA approval in any treatment line. This study aims to compare first-line (1L) survival outcomes with MET TKI versus immune checkpoint inhibitors ± chemotherapy (IO ± Chemo). **Methods:** Patient characteristics and survival outcomes were retrospectively analyzed for METex14 mNSCLC patients who received 1L therapy with either (1) MET TKI (tepotinib and capmatinib) or (2) IO ± Chemo. Patients were excluded if they had EGFR alterations. Data were sourced from ConcertAI's Patient360 and RWD360, datasets sourced from oncology EHR in the US. **Results:** Among a total of 344 patients, 174 (50.6%) were > 80 years of age, 94 (87.9%) had non-squamous mNSCLC, 176 (51.2%) were female, and 71 (20.6%) had ECOG PS ≥2. As 1L, 202 received MET TKI, 61 received IO + Chemo, and 81 received IO only. Baseline clinicopathologic features were balanced except for a slightly higher proportion of patients with TPS PD-L1 ≥50 in the IO ± Chemo group ($p< 0.05$). At a median follow up of 40.7 months (mo), in the overall group median progression-free survival (mPFS) was 6.6 mo (95% CI: 5.8–8.8) and median overall survival (mOS) was 15.5 mo (95% CI: 14.4–18.3). MET TKI yielded a mPFS of 7.8 mo (95% CI: 6.2–9.1) and a mOS of 13.8 mo (95% CI: 11.4–17.6). IO ± Chemo resulted in a mPFS of 5.1 mo (95% CI: 3.7–8.2) and a mOS of 21.9 months (95% CI: 15.5–25.8). The mPFS did not differ significantly between groups (p =0.38), while mOS favored IO ± chemotherapy (p= 0.03). Objective response rate was 61.0% with MET TKI and 50.7% with IO ± Chemo (p= 0.74); disease control rate was significantly higher with MET TKI (77.0% vs 64.8%; p= 0.03). In subgroup analysis, among patients with PD-L1 ≥50, OS was significantly longer with 1L IO ± Chemo compared with MET TKI (22.0 mo, 95% CI: 7.5–34.3 vs. 8.5 mo, 95% CI: 6.6–16.5; $p< 0.02$). In contrast, among patients with PD-L1 < 50, MET TKI was associated with longer PFS (9.2 mo, 95% CI: 4.2–11.7 vs. 4.9 mo, 95% CI: 2.1–11.0; p= 0.07) although OS was similar (17.6 mo, 95% CI: 9.6–29.6 vs. 14.5 mo, 95% CI: 4.0–23.2; p= 0.57). **Conclusions:** Among patients with METex14 mNSCLC, those treated with 1L IO ± Chemo had a better OS compared to those treated with MET TKI. This seems especially valid for patients with PD-L1 ≥50, for whom IO ± Chemo significantly improved OS. However, patients with PD-L1 < 50 showed prolonged PFS when treated with MET TKI. This highlights the need for personalized treatment patterns in this patient population. Research Sponsor: ConcertAI, LLC.

ALFA score as a predictor of long-term benefit with frontline brigatinib in *ALK*+ advanced NSCLC: A ctDNA-based composite biomarker from ALTA-1L.

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Background: Optimal sequencing of ALK-TKI in 1st-line *ALK*+ NSCLC remains controversial. Although 3rd-generation (G) TKI are increasingly used upfront, a subset of patients (pts) may achieve prolonged outcomes with 2ndG TKI. However, baseline (B) biomarkers to identify these pts are lacking. We evaluated whether a composite clinical-molecular score integrating (B) ctDNA and biological parameters could predict systemic and intracranial outcomes with upfront brigatinib. **Methods:** Post hoc analysis of pts with *ALK*+ NSCLC from the ALTA-1L trial with available (B) ctDNA NGS. *ALK* variants, co-occurring genomic alterations (co-GAs), and clinical/biological variables (PS, albumin, derived neutrophil-to-lymphocyte ratio [dNLR], and metastatic sites) were analyzed. Independent prognostic factors for progression-free survival (PFS) and intracranial PFS (IC-PFS) were identified by multivariable Cox models. A composite score (ALFA), based on the Cox models' coefficients was developed. **Results:** Among 124 pts, ctDNA detected *ALK* variant in 53% (n = 66), mostly *EML4::ALK* (V1 n = 25, V3 n = 24, V2 n = 7, V5 n = 4). co-GAs were present in 46%, including suppressor gene alt. in 35%. High dNLR was observed in 34% and hypoalbuminemia in 21%. In multivariable analysis, high dNLR (HR 1.67, 95% CI 1.02–2.73; p = 0.04), low albumin (HR 0.34, CI 0.20-0.57; p < 0.001) and suppressor co-GAs (HR 2.24, CI 1.32-3.79; p = 0.003) were independently associated with shorter PFS. Non-V1 variants showed a trend toward inferior PFS (HR 1.73; p = 0.05). For IC-PFS, high dNLR (HR 1.52; p = 0.03), brain metastases (HR 2.98; p < 0.001), and suppressor co-GAs (HR 2.41; p = 0.002) remained independently prognostic. The ALFA score stratified pts into low- (59%), intermediate- (27%), and high-risk (14%) groups, with median PFS of 35.5, 11.1, and 5.5 months (mo.), respectively (p < 0.0001; c-index 0.72). A similar separation was observed for intracranial PFS (IC-PFS; p < 0.0001), with median IC-PFS not reached in the low-risk group, 21.1 mo in the intermediate-risk group, and 5.5 mo. in the high-risk group (c-index 0.72). Overall survival (OS) showed consistent and significant discrimination across ALFA risk groups (log-rank p < 0.0001) with a median OS NR in low-risk, 44.3 mo. in intermediate-risk, and 19.3 mo. in high-risk pts. **Conclusions:** The ALFA score integrates baseline ctDNA-derived molecular features with routine blood-based parameters to robustly stratify clinical outcomes in *ALK*+ pts treated with frontline brigatinib. This composite score identifies a subset of patients with durable systemic and intracranial benefit from second-generation ALK inhibitors, supporting its potential role as a practical risk stratification tool in routine clinical practice. Research Sponsor: None.

Genomic determinants of resistance to BRAF/MEK inhibitors in *BRAF*^{V600E}–mutant non–small cell lung cancer.

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Background: *BRAF* V600E mutations occur in approximately 2–3% of non–small cell lung cancer (NSCLC). BRAF/MEK inhibition (BRAFi+MEKi) yields high response rates and durable clinical benefit but acquired resistance is inevitable. BRAFi+MEKi therapy may select for resistant tumor clones, induce secondary genomic alterations, and drive changes in the tumor immunophenotype. However, the landscape of resistance mechanisms to BRAFi+MEKi in NSCLC remains largely unknown. **Methods:** We conducted a global, multicenter analysis of patients with advanced *BRAF* V600E–mutant NSCLC treated with BRAFi±MEKi across multiple academic centers and available public datasets. Eligible patients had matched pre- and post-treatment next-generation sequencing (NGS). Analyses were restricted to oncogenic or likely oncogenic alterations per OncoKB and/or ClinVar. **Results:** Among 33 patients with matched pre- and post– BRAFi±MEKi samples, median age was 66 years; 39.4% were women, 67.7% had a history of tobacco use, and 97.0% had adenocarcinoma at diagnosis. Objective response to BRAFi±MEKi in this cohort was 81.8%, while median progression-free survival was 8 months; only 3 patients (9.1%) had primary resistance. Acquired resistance mechanisms were diverse, encompassing reactivation of the RAS/RAF/ERK signaling pathway (via *BRAF*-dependent and *BRAF*-independent mechanisms), activation of alternative bypass pathways (e.g. PI3K/AKT and HIPPO), and alterations associated with cell-cycle dysregulation. Concurrent resistance mechanisms were identified in 12.1% of cases, and one patient developed histologic transformation to small-cell lung cancer (SCLC). No identifiable resistance mechanism was detected in 11 patients (33.3%). The most common acquired genomic alterations were *RAS* mutations, observed in 21.2% of cases (*NRAS* Q61K, n = 1; *NRAS* Q61R, n = 1; *KRAS* G12D, n = 1; *KRAS* G12V, n = 1; *KRAS* Q61R, n = 1; *NRAS* Q61R + *KRAS* 61H, n = 1; *KRAS* G12V + *KRAS* Q61H, n = 1), followed by *MET* amplifications (12.1%, n = 4). Additional acquired events included *BRAF* kinase-domain duplication, *MAP2K1* and *NF2* mutations, and *FGFR4* amplification. Putative resistance alterations involving DNA damage repair genes (e.g., CHEK2, BRIP1) were also identified. Clinically, one patient with acquired *MET* amplification showed loss of the *MET*-amplified clone on liquid biopsy after adding crizotinib to BRAFi+MEKi, without grade≥3 adverse events, suggesting a potentially targetable resistance mechanism with therapeutic implications. **Conclusions:** Our findings define the genomic landscape of acquired resistance to BRAFi+MEKi in *BRAF* V600E–mutant NSCLC and highlight the emergence of diverse resistance mechanisms, including SCLC transformation, *MET* amplification, and *RAS* mutations, several of which are potentially actionable and may inform rational post-BRAFi/MEKi therapeutic strategies. Research Sponsor: None.

8648 Poster Session

A phase Ib study of osimertinib and tegavivint as first-line therapy in patients with metastatic *EGFR*-mutated non–small cell lung cancer (NSCLC).

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Background: EGFR TKIs improve clinical outcomes for patients with EGFR-mutated NSCLC. However, they are not curative even when combined with chemotherapy or antibody-based therapies because of slow-cycling, drug-tolerant cells that persist due to transcriptional reprogramming. This inevitably leads to tumor resistance and disease progression. Our pre-clinical studies showed that EGFR-mutated NSCLC cells enter a persistent state in response to TKIs due to increased transcriptional activity of β-catenin. Treatment of mice bearing EGFR-mutated NSCLC xenografts with an EGFR TKI and a β-catenin inhibitor caused a greater depth and duration of response than treatment with an EGFR TKI alone, which improved overall survival (OS). We also observed that patients with EGFR-mutated NSCLC who had the greatest increase in serum levels of the secreted β-catenin transcriptional target PAI-1 following treatment with a TKI had significantly worse progression free survival (PFS). These data led us to conduct a single-arm phase Ib clinical trial (NCT04780568) that investigated osimertinib in combination with tegavivint, an inhibitor of β-catenin transcriptional activity. **Methods:** Patients with metastatic EGFR-mutated (exon 19 deletion or L858R) NSCLC who had not received prior treatment with an EGFR TKI were eligible. All participants received osimertinib 80mg daily and were enrolled to escalating dose levels of tegavivint, which was administered weekly IV for 16 weeks. The primary objectives were to assess the safety and tolerability of the combination and to determine the recommended phase 2 dose (RP2D) of tegavivint. Secondary objectives measured the objective response rate (ORR), median PFS, and OS. **Results:** Fifteen evaluable patients received treatment on the dose escalation portion of this study, including six patients at the highest dose level of tegavivint (8 mg/kg), which was determined to be the RP2D. No dose limiting toxicities nor drug-related serious adverse events occurred. The adverse events that were observed included hematologic, skin, and GI toxicities, consistent with the known osimertinib toxicity profile. Pharmacokinetic analysis showed a dose-dependent increase in the C_{max} and AUC of tegavivint, and plasma levels of osimertinib were comparable to those seen historically when administered as a single agent. The ORR was 73% with 2 of 15 patients (13%) achieving a complete response. Median PFS was 20.6 months (95% CI: 7-32 months). OS data is still maturing. **Conclusions:** NCT04780568 showed that the combination of osimertinib and tegavivint was safe and tolerable as first-line therapy in patients with metastatic EGFR-mutated NSCLC. This novel combination has the potential to improve the depth and durability of response to EGFR TKIs, without significantly increasing toxicity, by targeting drug-tolerant persistence. Clinical trial information: NCT04780568. Research Sponsor: V Foundation; The Ohio State University Comprehensive Cancer Center Internal Research Program.

8649 Poster Session

Five-year outcomes of osimertinib-based treatment in a phase III study comparing EGFR tyrosine kinase inhibitor (EGFR-TKI) monotherapy and EGFR-TKI with inserted cisplatin plus pemetrexed as a first-line treatment for advanced non-squamous non–small-cell lung cancer harboring *EGFR* mutation (JCOG1404/WJOG8214L).

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Background: JCOG1404/WJOG8214L was an open label, multicenter, randomized phase III study comparing EGFR-TKI monotherapy (gefitinib [Gef] or osimertinib [Osi]) and EGFR-TKI with inserted cisplatin plus pemetrexed as a first-line treatment for advanced non-squamous non–small-cell lung cancer harboring *EGFR* mutation (*EGFR*-NSqNSCLC). In the primary analysis, the insertion of platinum-doublet chemotherapy after the initial response to EGFR-TKI could improve progression-free survival (PFS), but not overall survival (OS) compared with EGFR-TKI monotherapy (Clin Cancer Res 2025;31:2317-26). This study was commenced using Gef in December 2015 and was switched to Osi in October 2018. 501 patients (pts) (308 in the Gef cohort, 193 in the Osi cohort) were enrolled to October 2020, but it resulted in later accrual and shorter follow-up for the Osi cohort at the time of the primary analysis (data cutoff November 2022; median follow-up of all randomized patients 36.0 months). Therefore, we conducted the five-year (5y) follow-up analysis of the Osi cohort. **Methods:** The key eligibility criteria were pts with advanced or recurrent *EGFR*-NSqNSCLC (exon 19 deletion or exon21 L858R), age 20 to 74 years, and PS 0 or 1. In the standard arm (SA), Gef or Osi was administrated until disease progression. In the experimental arm (EA), Gef or Osi was administered on days 1-56. Then, after a two-week drug-free period, three cycles of cisplatin and pemetrexed were administered on days 71, 92, and 113. Thereafter, Gef or Osi was reinitiated on day 134 and continued until disease progression. **Results:** From October 2018 to October 2020, 193 pts were enrolled in the Osi cohort (97 pts in SA and 96 pts in EA). Median follow-up was 64.8 months. Advanced stage and recurrent disease were 79% and 21%, female and male were 63% and 37%, exon 19 deletion and exon 21 L858R were 54% and 46%, PS 0 and 1 were 50% and 50%, $\geq$ 65 year and $<$ 65 year were 57% and 43%, central nerve metastasis (+) and (-) were 27% and 73%, respectively. Median OS were 54.0 months (95% confidence interval [CI] 44.4 to 66.0) in SA and 50.4 months (95% CI 43.2 to 69.6) in the EA (HR, 0.984; 95% CI, 0.684-1.415; p = 0.9279). 5y OS were 43.9% and 40.4%, respectively. Median PFS were 20.4 months (95% CI 14.4 to 28.8) in SA and 25.2 months (95% CI 18.0 to 33.6) in EA (HR, 0.902; 95% CI, 0.663-1.227; p = 0.5147). 5y PFS were 14.3% and 16.3%, respectively. **Conclusions:** The insertion of platinum-doublet chemotherapy after the initial response to Osi could not improve PFS and OS of pts with advanced *EGFR*-NSqNSCLC. On the other hand, JCOG1404/WJOG8214L demonstrated that Osi-based first-line treatment achieved 5y PFS in approximately 15% of this population, providing a benchmark for emerging Osi-based strategies. Clinical trial information: UMIN000020242. Research Sponsor: National Cancer Center Research and Development Funds; 26-A-4, 29-A-3, 2020-J-3, and 2023-J-03; Japan Agency for Medical Research and Development Grants; JP18ck0106221 and JP22ck0106492.

Comprehensive profiling of EGFR PACC mutations and their co-mutation landscape in Chinese patients with non–small cell lung cancer: A large-scale NGS study of 2,360 cases.

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Background: EGFR PACC (P-loop and αC-helix compressing) mutations represent a group of noncanonical alterations located in critical structural regions of the EGFR kinase domain and have recently been implicated in reduced sensitivity to EGFR TKIs and treatment resistance. However, the prevalence, mutational spectrum, and co-mutation landscape of EGFR PACC mutations in Chinese patients with non–small cell lung cancer (NSCLC) remain poorly characterized. This study aimed to systematically delineate the molecular features of EGFR PACC mutations to inform molecular testing strategies and clinical decision-making. **Methods:** A total of 2,360 patients with NSCLC were enrolled. All tumor samples underwent NGS covering 733 cancer-related genes. The overall prevalence of EGFR PACC mutations, the distribution of individual PACC variants, and their co-occurrence with other EGFR alterations and non-EGFR driver mutations were comprehensively analyzed. **Results:** Among the 2,360 NSCLC patients, 112 harbored EGFR PACC mutations, yielding an overall prevalence of 4.74%. EGFR PACC mutations exhibited marked site heterogeneity. The most frequent variants were S768I (18/112), G719A (15/112), G719S (12/112), and G719C (8/112), followed by C797S (6/112), E709A (6/112), E709V (5/112), and E709K (5/112). The remaining PACC variants—including I740_K745dup, R776H, S752_I759del, V774M, E709_T710delinsD, G779F, K757R, L747P, L718V, R776C, A647T, K757M, L718Q, T751_I759delinsN, V769L, and V769M—were low-frequency events, underscoring substantial molecular diversity. In total, 61 PACC-associated co-mutation events were identified. Co-mutation analysis revealed that classic EGFR-sensitizing mutations predominated, with L858R as the most common co-occurring alteration (n = 10), followed by exon 19 deletion E746_A750del (n = 4) and L861Q (n = 3). Notably, T790M (n = 2) co-occurred with C797S PACC mutations, suggesting a potential role of PACC variants in the evolution of EGFR-TKI resistance. Beyond EGFR-intrinsic co-mutations, cross-driver co-mutations were also observed, including ROS1 (V1002A, I1685L), MET (V145A), and NRG1 (V516M) (each n = 2), indicating that a subset of EGFR PACC–mutant tumors may harbor more complex oncogenic signaling. **Conclusions:** EGFR PACC mutations occur at a non-negligible frequency in Chinese patients with NSCLC and display pronounced site heterogeneity. These mutations frequently co-exist with classic EGFR-sensitizing or resistance-associated alterations and, in some cases, with additional non-EGFR driver mutations, highlighting their potential biological and clinical relevance. Our findings underscore the importance of comprehensive NGS-based profiling for accurate detection of EGFR PACC mutations and their co-mutation landscape, thereby supporting precision treatment strategies. Research Sponsor: None.

8651 Poster Session

Efficacy and safety analysis of furmonertinib in the treatment of *EGFR*-mutated lung adenocarcinoma: A single-center real-world study based on high-risk stratification.

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Background: Real-world data on furmonertinib, a third-generation EGFR-TKI, for high-risk EGFR-mutant NSCLC patients (e.g., with brain metastasis, high tumor burden) are limited. This study evaluated its efficacy and safety via risk stratification. **Methods:** This retrospective study included 98 patients with locally advanced/metastatic EGFR-mutant NSCLC treated with furmonertinib (first-or later-line) from Sep 2021 to Dec 2024. Patients were stratified into high-risk (n = 73) and non-high-risk (n = 25) groups based on predefined criteria (brain/leptomeningeal metastases, high tumor burden, key co-mutations like TP53, or acquired T790M). Primary endpoint was investigator-assessed PFS. Secondary endpoints included ORR, DCR, iORR, iPFS, and OS. Safety assessed TRAEs (CTCAE v5.0). **Results:** Median follow-up was 17.7 months. In first-line group (n = 43), ORR was 69.8%, DCR 83.72%; in later-line group (n = 55), ORR was 64%, DCR 72.73%. PFS did not differ significantly between lines (P = 0.22). Median PFS was not reached overall. High-risk stratification analysis showed median PFS of 26.41 months in non-high-risk group vs not reached in high-risk group, with significant difference (P = 0.009). However, PFS rates showed a time-dependent effect: non-high-risk group had higher early PFS (96.0% vs 76.0% at 6 months), but high-risk group showed higher late PFS (98.6% vs 52.9% at 24 months). A time-dependent model confirmed high-risk features were detrimental early (HR = 33.03, P = 0.016) but protective after 6 months (interaction HR = 0.01, P = 0.001). In patients with measurable brain metastases (n = 39), iORR was 79.5%; median iPFS was not reached. TP53 co-mutation within high-risk group did not affect PFS (P = 0.731). TRAEs occurred in 15.3% (all grade 1-2, most common rash [5.1%] and diarrhea [4.1%]). Grade ≥3 events occurred in 6.1%, primarily elevated transaminases. No dose adjustments/discontinuations or fatal toxicities occurred. **Conclusions:** Furmonertinib showed durable efficacy in EGFR-mutant NSCLC, unaffected by line of therapy. Risk stratification had time-dependent prognostic value, with high-risk features transforming into a protective factor for PFS after 6 months. Furmonertinib demonstrated strong intracranial activity (iORR 79.5%). TP53 co-mutation did not confer additional prognostic value in the high-risk subgroup. Furmonertinib was well-tolerated with a favorable safety profile. Research Sponsor: Tianshan Talents Program for the Cultivation of High-Level Talents in Medical and Health Field; TSYC202301A068.

Circulating tumor DNA dynamics following molecularly targeted therapy for non–small cell lung cancer.

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Background: Biomarkers to guide treatment escalation following suboptimal response to molecular targeted therapy are urgently needed for patients (pts) with non-small cell lung cancer (NSCLC). Circulating tumor DNA (ctDNA) has shown promise for monitoring residual disease following definitive treatment, but ctDNA dynamics following targeted therapy response remain understudied. **Methods:** We examined a real-world, multi-institution cohort of pts with NSCLC undergoing personalized, tumor-informed ctDNA testing (Signatera, Natera, Inc.) and clinical annotations from a deidentified commercial claims dataset (Forian's Hybrid data ecosystem, CHRONOS). Longitudinal ctDNA results were evaluated before and after targeted therapy initiation and summarized by treatment line, clinical context, and demographic and clinicopathologic features as available. **Results:** We identified 839 pts (14.0%, 11.1%, 19.4%, and 55.5% with stages I, II, III, and IV) across 395 US institutions, who had ctDNA profiling and were treated with molecularly targeted agents. Median age was 71 years (range 25-93), 67.0% were female, and 85.3% had tumors with adenocarcinoma histology. Pts underwent a median of 4 ctDNA tests/pt (range: 1–58) over a median follow-up of 9 months (range: 0-75). Amongst ctDNA positive tests (n=1705 tests for 408 pts), median ctDNA levels were 1.20 mean tumor molecules/mL (range 0.01–36,599). Pts received osimertinib (58.5%), alectinib (10.7%), sotorasib (5.6%), adagrasib (3.7%), afatinib (3.7%), and capmatinib (3.0%). ctDNA tests prior to targeted therapy (baseline) were available for 336 patients, of which 49.7% (167/336) had detectable ctDNA ("ctDNA(+)"). Among these ctDNA(+) cases, 123 pts had longitudinal ctDNA assessment. ctDNA clearance observed in 38.2% (47/123); 52.1% (25/48) in stage I-III and 29.3% (22/75) in stage IV. Among the 169 pts with baseline ctDNA(-), 115 pts had ctDNA assessed longitudinally. Of these, 89.6% (103/115) remained serially negative, while 10.4% (12/115) had any time ctDNA(+). Among commonly used targeted therapies, ctDNA clearance was observed across multiple agents, and is summarized in table 1. We further analyzed associations between ctDNA dynamics, during different treatment lines, and clinical outcomes. **Conclusions:** In a multi-institution cohort, ctDNA clearance was observed in pts with NSCLC treated with molecularly targeted therapies. Clearance rates varied by treatment type. The use of ctDNA monitoring to guide treatment escalation in this population warrants further study. Research Sponsor: None.

Targeted Therapy	Pts with ctDNA available pre and post-therapy N	Pts with baseline ctDNA(+) N	Pts with ctDNA clearance N (%)
osimertinib	128	54	26 (48.1)
alectinib	22	7	3 (42.9)
sotorasib	15	14	4 (28.6)
adagrasib	12	10	2 (20.0)

Includes only therapies with more than 10 pts who had pre- and post-treatment ctDNA availability.

Molecular and immune profiling of *BRAF*-mutated (*BRAF*^{MUT}) non-small cell lung cancer (NSCLC).

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Background: *BRAF*^{MUT} occur in 6-7% of NSCLC and comprise of biologically distinct classes showing variable therapeutic responses. While Class 1 benefits from targeted therapy, molecular and immune determinants distinguishing *BRAF* classes remain incompletely characterized. We performed comprehensive profiling to identify class-specific biomarkers. **Methods:** 51,692 (BRAF wild-type [*BRAF*^{WT}]: n=48,288; *BRAF*^{MUT}: n=3404) NSCLC specimens underwent DNA (592-gene panel/whole-exome) and/or RNA (whole-transcriptome) sequencing at Caris Life Sciences. *BRAF*^{MUT} tumors were classified into 3 Classes, other pathogenic variants (O^{PV}), and unknown/unclassified variants (VUS). The tumor microenvironment (TME) was estimated using the QuanTIseq method. Overall survival (OS) and IO-associated survival (IO-OS) were derived from insurance claims and calculated from the date of tumor biopsy (OS) or IO initiation (IO-OS) to last contact using Kaplan-Meier estimates. Statistical significance was determined by Fisher's Exact, chi-square, and Mann-Whitney U test with adjustments for multiple comparisons ($P<0.05$). **Results:** Class 1 was significantly enriched for SETD2 mutations (mut) and more frequently PDL1+ (22c3, TPS>=1) while showing a lower prevalence of TMB-high (>=10 mut/Mb), TP53, STK11 and KEAP1 mut (Table). Class 2/3 tumors were moderately PDL1+ and TMB-high and enriched for STK11 and KEAP1 muts (Table). While both OPV and VUS were enriched for TMB-high and not PDL1, OPV was enriched in STK11, and VUS was enriched in TP53 mut (Table). Among BRAFMUT, Class 1 exhibited the highest infiltration of M1 macrophages (1.1-1.3-fold), neutrophils (1.2-1.3-fold) and the lowest infiltration of dendritic cells (0.4-0.8-fold). Class 2 and 3 had largely overlapping immune profiles. In metastatic NSCLC, only Class 1 and VUS demonstrated improved OS and IO-OS (vs BRAFWT, both p<0.05, Table). OPV had the poorest outcomes, exhibiting the shortest OS and shorter IO-OS relative to Class 1 and Class 2 (all p<0.05, Table). **Conclusions:** *BRAF*^{MUT} classes represent distinct molecular, immune and clinical phenotypes. Improved OS and IO-OS in Class 1 and VUS (vs WT) appears to arise from divergent molecular and immune interactions. These findings underscore the importance of evaluating of *BRAF*^{MUT} NSCLC beyond class 1-3, suggesting the expanded classification may have therapeutic and prognostic consequences. Research Sponsor: None.

Molecular features (odds ratio) and survival outcomes (median months [95% CI]) among *BRAF*^{MUT} classes.

Genes	Class 1 (n=695)	Class 2 (n=741)	Class 3 (n=701)	O^{PV} (n=123)	VUS (n=936)	WT
SETD2	21.5^{s}	1.2	1.0	0.6	1.4	0.2^{s}
TP53	0.4^{s}	1.0	1.0	0.8	1.6^{s}	1.1^{s}
STK11	0.1^{s}	1.7^{s}	2.3^{s}	2.1^{s}	0.8	0.9^{s}
KEAP1	0.1^{s}	1.5^{s}	1.7^{s}	1.5	1.1	1
TMB-high	0.3^{s}	1.8^{s}	2.3^{s}	2.3^{s}	3.3^{s}	0.6^{s}
PDL1+	3.4^{s}	1.3^{s}	1.1	0.9	1.0	0.7^{s}
med OS	18(14-21)	14(12-18)	13(11-16)	8(4-11)	16(12-20)	12(12-12)
med IO-OS	27(19-40)	20(15-24)	18(12-24)	8(2-15)	24(19-32)	17(17-18)

$P<0.05$ denoted by ^{s}.

8655 Poster Session

Correlation of CT changes, PET response, and histopathologic tumor regression in treated advanced *EGFR*-mutant NSCLC before disease progression.

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Background: Previous studies have examined the correlation between radiologic and pathologic responses using PET, CT, and histopathologic regression in patients receiving chemotherapy or immunotherapy. However, data on the relationship among these modalities after EGFR-TKI treatment remain limited, particularly in the context of emerging induction EGFR-TKI strategies. **Methods:** We conducted a two-arm, phase II clinical trial (PTR-1) enrolling patients with advanced EGFR-mutant NSCLC. After 12 weeks of EGFR-TKI therapy, participants were randomized (1:1) to either continue TKI treatment or undergo primary tumor resection. Surgery aimed to achieve locoregional control with negative margins, and lymph node dissection was not mandatory. All resected specimens were evaluated for pathologic response according to IASLC recommendations. Radiologic response was assessed by RECIST 1.1, and major pathologic response (MPR) and PET metabolic response were evaluated. **Results:** A total of 91 patients were enrolled, with 72 randomized into two treatment arms; 2 patients declined surgery. The median interval from treatment initiation to surgery was 3.7 months, and 18% of patients underwent resection beyond 4.5 months. Among the 34 resected cases, MPR was achieved in 29.4% (10/34) and pathologic complete response (pCR) in 5.9% (2/34). Patients harboring EGFR exon 19 deletions demonstrated higher rates of pathologic response than those with L858R mutations. The correlation between CT-based tumor regression and histopathologic response was weak (r = 0.30). Pathologic response rates were 24.5% in patients with partial response (PR) and 43.8% in those with stable disease (SD) by RECIST. The correlation coefficients between PR or SD status of the primary tumor and pathologic response were 0.15 and −0.29, respectively. Complete metabolic resolution on FDG-PET corresponded to MPR in 66% of cases. A preoperative SUVmax < 2.5 was associated with a mean pathology residual viable tumor of 20.7% and a 42.8% MPR rate, while patients with ≥90% regression in PET signal achieved MPR in 66.6% of cases. **Conclusions:** CT-based tumor regression modestly reflects histopathologic response after EGFR-TKI induction but with poor correlation, particularly in radiologic SD cases. This represents the first trial-based dataset analyzing imaging–pathology correspondence in advanced EGFR-mutant NSCLC prior to disease progression. PET metabolic response demonstrated relatively better discrimination of major pathologic responders, though its predictive accuracy remains limited. These findings underscore the need for refined imaging biomarkers or other NGS data to identify optimal candidates for local consolidation therapy in late stage and future neoadjuvant setting in early stage strategies in EGFR-mutant NSCLC. Clinical trial information: NCT05215548. Research Sponsor: None.

8657 Poster Session

Efbemalenograstim alfa for prophylaxis in non–small cell lung cancer patients patients with chemotherapy-induced febrile neutropenia: A randomized, multi-center, exploratory clinical trial.

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Background: Neutropenia is a common dose-limiting chemotherapy toxicity, with its severity and duration impairing therapeutic efficacy. In NSCLC management, chemotherapy regimens with high risk febrile neutropenia (FN) are relatively uncommon. However, real-world data show suboptimal prophylactic granulocyte colony-stimulating factor (G-CSF) use in intermediate risk FN patients with additional risk factors. This study evaluated efbemalenograstim alfa's efficacy and safety in maintaining absolute neutrophil count (ANC) during chemotherapy cycles in such NSCLC patients. **Methods:** This was a randomized, multicenter, exploratory clinical trial (NCT06143735) enrolling NSCLC patients receiving intermediate risk FN chemotherapy with additional risk factors. Eligible patients were randomized 2:1 into two groups: primary prophylaxis group (Group A) received subcutaneous efbemalenograstim alfa (20 mg) 48±4 h post-each chemo cycle starting from Cycle 1; secondary prophylaxis group (Group B) initiated treatment only upon grade ≥3 neutropenia (per CTCAE v5.0) in the prior cycle. All patients completed at least four cycles of platinum-based chemotherapy. The primary endpoint was the incidence of grade ≥3 neutropenia in Cycle 1 between the two strategies. Secondary endpoints included FN incidence, grade ≥3 neutropenia in subsequent cycles, and the occurrence of adverse events (AEs) or serious adverse events (SAEs). **Results:** As of Dec 31, 2025, 99 patients were enrolled; 93 (median age: 69 years; 61.3% with ECOG 0–1; 90.3% male) received ≥1 platinum-based chemo cycle; 83 received ≥1 efbemalenograstim alfa dose. Specifically, 61 patients were assigned to Group A and 32 to Group B (n = 93). In the first treatment cycle, the incidence of grade ≥3 neutropenia was 19.7% (12/61) in Group A vs. 50.0% (16/32) in Group B, representing a relative risk reduction (RRR) of 60.6% (absolute risk reduction: 30.3%; p = 0.002). Across all treatment cycles, the cycle-specific cumulative incidence of grade ≥3 neutropenia was 16.2% (32/198) in Group A vs. 25.6% (32/125) in Group B (p = 0.0382). FN occurred in 2 patients in both groups. Regarding safety, the most common adverse events (AEs) were hematological toxicities in both groups, with a numerically lower incidence of anemia, leukopenia, neutropenia, and thrombocytopenia in Group A than in Group B. Grade ≥3 AEs (52.5% vs. 43.8%, p = 0.514) and efbemalenograstim alfa-related treatment-emergent adverse events (TRAEs, 31.1% vs. 22.7%, p = 0.587) did not differ significantly. Pain-related TRAEs (mainly ankle pain and neuropathic pain) were reported in only 6 patients (7.2%) overall, with most being grade 1–2 per CTCAE v5.0 criteria. **Conclusions:** Efbemalenograstim alfa effectively reduces the incidence of chemotherapy-induced neutropenia and presents a favorable safety profile. Clinical trial information: NCT06143735. Research Sponsor: None.

Genomic clonality analysis of patients with metastatic lung-limited non–small cell lung carcinoma (NSCLC) who underwent double lung transplantation (DLT) across timepoints and tumor region.

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Background: Double lung transplantation (DLT) registry aimed for lung-limited malignancies (DREAM) study (NCT05671887) cohort A evaluates DLT as a therapeutic strategy for patients with advanced bilateral lung-limited NSCLC. This is the first translational report of the genomic clonality analysis of the DREAM study across timepoints and tumor regions. **Methods:** Patients with advanced bilateral lung-limited NSCLC who underwent DLT at Northwestern Memorial Hospital between September 2021 and December 2025 were included in the DREAM study cohort A. Patients with extrapulmonary disease were excluded. The primary indications for DLT were disease refractory to systemic therapies, with or without respiratory failure. Tissue next generation sequencing (tNGS) data was collected from diagnosis, bilateral explant and recurrence samples. Commercial tNGS panels utilized include Altera, Caris, Foundation Medicine, Tempus xT, and PGDx. Truncal genetic mutations were identified from genes that were common to all tNGS panels. **Results:** Among 18 patients enrolled in DREAM study cohort A, 11 patients with bilateral tissue NGS were analyzed. The median age was 55.5 years (range 37-74), 9 (81%) were female, and 5 (45%) had a history of smoking. 6 patients (54%) had invasive mucinous adenocarcinoma histology. All 11 patients harbored common gene mutations in bilateral tumors and had common oncogenic genomic clones indicating a truncal mutation. Details are outlined in Table 1. **Conclusions:** All patients harbored common oncogenic driver mutations across all available specimens, providing definitive genomic evidence of a monoclonal origin. These findings not only distinguish intrapulmonary metastasis from multiple primary tumors but also support a common ancestral tumor clone that has progressed over time and space. Further characterization of tumor evolution in advanced bilateral lung-limited NSCLC is warranted. Clinical trial information: NCT05671887. Research Sponsor: None.

Case	Tissue NGS by timepoints and region (Dx/Explant/Recur)	Shared variants
1	RML / Bilateral Exp / RUL	*PIK3CA E110del, *SETD2 D2112fs, GRM3 R331C
2	LUL / Bilateral Exp / Pelvic bone	*EGFR G719A
3	LLL / Bilateral Exp / T9 vertebra	*KRAS G12D
4	Bilateral Exp / Pelvic bone	*ETV6 splice, KMT2D L1443Q
5	Bilateral Exp	*KRAS G12V, STK11 (*A200fs, *314fs)
6	LUL / Bilateral Exp	*BAP1 Q595*, *GNAS R201C
7	Bilateral Exp	*EGFR Ex19del
8	Bilateral Exp / LLL	*KRAS G12V
9	Bilateral Exp	EGFR (*Ex19del, C797S), LRP1B R531H, PTPRT I320N, SF3B1 A368V

Additional Cases:
Case 10 (Bilateral Exp): *KRAS G12C, *ARID1A Q507*, *ATM c.1A>T, *ATRX W1572*, *STK11 W332*, CHD2, MALT1, PHLPP1, PTPRT, RICTOR, SEMA3C, TAF1 (W457L, D169Y).
Case 11 (RLL, Bilateral Exp): *MET Ex14 skip, *TP53 V143M, ERBB3, NF2.
Asterisk (*) indicates oncogenic/likely oncogenic variants defined by *OncoKB*.
Abbrev: Dx, diagnosis; Exp, explant; Recur, recurrence.

TPS8660 Poster Session

SigVie-003: Phase 3 trial of frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab alone in non-small cell lung cancer (NSCLC) with PD-L1 TPS ≥50%.

Martin Reck, Shun Lu, Kenneth John O'Byrne, Carlos H. Barrios, Fabian Tay, Wyatt Chafin, Dmitri Pavlov, Marcelo Vailati Negrao; Airway Research Center North, Center for Lung Research, LungenClinic, Grosshansdorf, Germany; Shanghai Jiao Tong University, Shanghai, China; Queensland University of Technology, Princess Alexandra Hospital, Brisbane, Australia; Latin American Cooperative Oncology Group, LACOG, Porto Alegre, Brazil; Pfizer, Zug, Switzerland; Pfizer, Ponchatoula, LA; Pfizer, San Diego, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Integrin beta-6 (IB6) is a tumor-associated membrane protein linked to poor outcomes in solid tumors, including NSCLC, where it is expressed in >90% of cases. Sigvotatug vedotin (SV), a novel, IB6-directed, vedotin-based, antibody-drug conjugate, has shown manageable safety and encouraging antitumor activity as monotherapy in advanced NSCLC in the phase 1 SGNB6A-001 study (Peters, ASCO 2024). Based on preclinical studies, SV may induce immunogenic cell death and enhance antitumor activity when used in conjunction with pembrolizumab, a PD-1 inhibitor. Therefore, SV plus pembrolizumab is also being evaluated in the SGNB6A-001 study. Initial results of the combination demonstrated promising antitumor activity with a manageable safety profile in advanced NSCLC (Sehgal, ASCO 2025). Based on these results, SV plus pembrolizumab is being investigated in the phase 3 SigVie-003 study.
Methods: SigVie-003 (NCT06758401) is an open-label, randomized, controlled study evaluating the efficacy of SV plus pembrolizumab vs pembrolizumab monotherapy as first-line treatment in adults with locally advanced, unresectable, or metastatic NSCLC with high PD-L1 expression (tumor proportion score ≥50%). Patients (pts) with nonsquamous histology must have negative documentation for *EGFR*, *ALK*, and *ROS1* mutations and no known actionable genomic alterations with approved first-line treatments per local standard of care. Pts must have an ECOG PS of 0 or 1 and have adequate organ function. Pts with stable, definitively treated, or inactive brain metastases <0.5 cm are eligible. Approximately 714 pts will be randomized at a 1:1 ratio to receive either SV 1.8 mg/kg AiBW (adjusted ideal body weight) intravenously on days 1, 15, and 29 plus pembrolizumab 400 mg intravenously on day 1 of a 42-day cycle (Q6W) or pembrolizumab 400 mg monotherapy Q6W. Randomization will be stratified by histology (nonsquamous vs squamous), ECOG PS (0 vs 1), region (East Asia vs rest of world), and presence or absence of brain metastases. Dual primary endpoints are overall survival and progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. Secondary endpoints include PFS by investigator per RECIST 1.1, confirmed objective response rate and duration of response by both BICR and investigator per RECIST 1.1, safety, and pharmacokinetics and immunogenicity of SV when combined with pembrolizumab. Enrollment began Jul 23, 2025. A genAI tool (2/27/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab for non-small cell lung cancer with PD-L1 tumor proportion score ≥50%: phase III study design, Reck M, et al., *Future Oncol*, Dec 13, 2025, Taylor & Francis, reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd. Clinical trial information: NCT06758401. Research Sponsor: Pfizer.

TPS8661 **Poster Session**

AndroMETa-Lung-713: A phase 2/3 study of telisotuzumab adizutecan (ABBV-400, Temab-A) vs standard of care (SOC) in patients with epidermal growth factor receptor (*EGFR*)–mutated non–small cell lung cancer (NSCLC).

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Background: Patients with advanced *EGFR*-mutated NSCLC routinely receive third-generation EGFR TKIs in first-line therapy, such as osimertinib or lazertinib, either as monotherapy or in combination with other agents. Following progression, available options primarily include platinum-doublet chemotherapy or amivantamab + chemotherapy, with country-specific approvals for additional agents including antibody-drug conjugates (ADCs). *MET* gene amplification and c-Met protein (also known as MET protein) overexpression are established mechanisms of acquired resistance to osimertinib. Temab-A is a c-Met–directed ADC composed of the telisotuzumab antibody linked to a potent topoisomerase 1 inhibitor payload and is designed to selectively target c-Met–expressing tumors. In the first-in-human study (NCT05029882), Temab-A demonstrated manageable safety and encouraging efficacy in heavily pretreated *EGFR*-mutated NSCLC (confirmed objective response rate [ORR] 63%; median duration of response 9.8 months; median progression-free survival [PFS] 10.9 months) (Camidge. JCO 2025;43: abstract 8512). **Methods:** AndroMETa-Lung-713 (NCT07155187) is a global, open-label, randomized phase 2/3 study enrolling adults with locally advanced or metastatic non-squamous *EGFR*-mutated NSCLC after progression on 1 prior third-generation EGFR TKI administered in the adjuvant, locally advanced, or metastatic setting, as monotherapy or in combination with other agents. Key eligibility criteria include ECOG PS 0–1, measurable disease per RECIST v1.1, exon 19 deletion or exon 21 L858R mutation, and provision of tumor tissue for c-Met protein immunohistochemistry. In phase 2, approximately 80 patients will be randomized 1:1 to Temab-A dose 1 or dose 2 IV every 3 weeks (Q3W) to select the recommended phase 3 dose (RP3D) on the basis of safety, efficacy, pharmacokinetics (PK), and available biomarker data. In phase 3, approximately 350 patients will be randomized 1:1 to Temab-A RP3D or investigator's-choice SOC (platinum-doublet chemotherapy or amivantamab + chemotherapy). Treatment continues until disease progression, intolerable toxicity, or other protocol-defined discontinuation criteria are met. The primary endpoints are ORR in phase 2 and PFS in phase 3, assessed by blinded independent central review. Tumor assessments are performed Q6W for 2 years, then Q12W. Assessment of PK, immunogenicity, and exploratory biomarker analyses, including c-Met protein expression levels and ctDNA dynamics, will be conducted. Clinical trial information: NCT07155187. Research Sponsor: None.

TPS8662 **Poster Session**

Petosemtamab plus pembrolizumab as first-line (1L) treatment of PD-L1 high metastatic non-small cell lung cancer (NSCLC): Global phase 2 trial.

Paul K. Paik, Koichi Goto, Alexander I. Spira, Wade Thomas Iams, Kees-Jan Koeman, Ernesto Wasserman, Fabian Zohren, Luis G. Paz-Ares; Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY; National Cancer Center Hospital East, Kashiwa, Japan; Virginia Cancer Specialists, PC, Fairfax, VA; Tennessee Oncology, Nashville, TN; Merus N.V., Utrecht, Netherlands; Merus NV, Utrecht, Netherlands; Department of Medical Oncology, Hospital 12 de Octubre, Madrid, Spain

Background: NSCLC has a heterogeneous biology frequently including high mutational burden, high EGFR expression and upregulated EGFR signaling that is associated with poor prognosis. In the first-line metastatic setting, combination regimens pairing platinum-based chemotherapy with immune checkpoint blockade are standard of care; however, most patients experience disease progression within the first year. Petosemtamab is a low-fucose human common light chain, IgG1 bispecific antibody targeting EGFR and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5). Petosemtamab mechanism of action includes inhibition of EGFR ligand binding and downstream signaling, degradation of EGFR via LGR5 internalization in EGFR/LGR5-expressing cells, and immune system activation via enhanced ADCC (Herpers et al. Nat Cancer 2022; Lundberg et al. Cancers 2025). Petosemtamab plus pembrolizumab has previously demonstrated clinically meaningful efficacy and a manageable safety profile in 1L PD-L1-positive recurrent/metastatic head and neck squamous cell carcinoma (van Herpen et al. ASCO 2025). **Methods:** MCLA-158-CL04 (NCT07353957) is an open-label, multicenter, phase 2 trial to investigate petosemtamab in combination with pembrolizumab in squamous (Sq) and non-SqNSCLC. Two cohorts will be evaluated in patients with PD-L1 high (TPS $\geq$50%) metastatic sqNSCLC and non-sqNSCLC, respectively, with no prior systemic treatment for metastatic disease. Patients will be treated with petosemtamab 1500 mg IV Q2W in combination with pembrolizumab 400 mg IV Q6W. The primary objective is investigator-assessed objective response rate. Enrollment of approximately 80 patients in North America, EU, and Asia-Pacific is planned. Clinical trial information: NCT07353957. Research Sponsor: Merus.

TPS8663 **Poster Session**

Telisotuzumab adizutecan (Temab-A) plus osimertinib (osi) as 1L treatment for unresectable/metastatic NSCLC.

Yasushi Goto, Christina S. Baik, Federico Cappuzzo, David Ross Camidge, Santosh Nair, Jair Bar, Mor Moskovitz, Luis G. Paz-Ares, Alona Zer, James Chih Hsin Yang, Chen Qian, Tony Navas, Gladys Morrison Thiele, Nivedita Aanur, Almudena Rodriguez-Gutierrez, Kailash Mosalpuria, Xiuning Le; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; University of Washington School of Medicine, Seattle, WA; IRCCS Istituti Fisioterapici Ospitalieri-Istituto Nazionale Tumori Regina Elena, Rome, Italy; University of Colorado Cancer Center, Aurora, CO; Mid Florida Cancer Centers, Orange City, FL; Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; The Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; Davidoff Cancer Center, Petah Tikva, Israel; Department of Medical Oncology, Hospital 12 de Octubre, Madrid, Spain; Rambam Health, Haifa, Israel; National Taiwan University Cancer Center, Taipei, Taiwan; AbbVie, Inc., North Chicago, IL; AbbVie Spain, Madrid, Spain; NHO Revive Research Institute, Lincoln, NE; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Most patients (pts) with EGFR-mutated (Mut) NSCLC and 1L osi treatment will eventually develop resistance. Although 1L combination strategies (osi+chemo or amivantamab+lazertinib) show potential long-term benefits, associated toxicities can impact quality of life. Temab-A, an antibody-drug conjugate with a topoisomerase 1 inhibitor payload, targets c-Met protein. *MET* gene amplification and c-Met protein expression are associated with poor survival outcomes in NSCLC. A Ph1 study of Temab-A in pts with refractory EGFR Mut NSCLC reported encouraging activity and a manageable safety profile (NCT05029882). Herein, we describe a Ph2/3 study of Temab-A+osi as 1L in pts with previously untreated, locally advanced or metastatic NSCLC harboring common EGFR Mut. **Methods:** Planned enrollment is ~194 pts in Ph2 and ~500 in Ph3 across ~200 sites in 22 countries. Adults (≥18 years) must have histologically/cytologically confirmed metastatic/locally advanced nonsquamous NSCLC with documented EGFR Mut and measurable disease by RECISTv1.1. Pts with prior EGFR tyrosine kinase inhibitor treatment in the metastatic setting are excluded. During dose escalation (Ph2), pts will receive Temab-A (1.6 or 2.4mg/kg) every 3 weeks (Q3W, 1 cycle) intravenously (IV) + 80mg osi daily. During dose expansion (Ph2), after 1 cycle of osi, pts will be randomized to receive Temab-A (1.6, 2.0, or 2.4mg/kg) Q3W IV + 80mg osi daily, or osi monotherapy, and stratified based on c-Met expression levels and history of CNS involvement. Ph2 primary objectives are safety/tolerability, efficacy as measured by objective response rate of Temab-A+osi, and determination of the recommended Ph3 dose (RP3D). Ph2 primary efficacy endpoint is objective response based on blinded independent central review assessment per RECIST v1.1. In Ph3, randomized pts will receive Temab-A+osi at RP3D or standard of care. Additional details for Ph3 will be confirmed after completion of Ph2. Clinical trial information: NCT05029882. Research Sponsor: None.

TPS8664 **Poster Session**

Combination of tulmimetostat and PD-1 blockade for patients with advanced non–small cell lung cancer who progressed from first or second line of treatments.

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Background: Immune checkpoint inhibitors (ICIs) have transformed advanced non–small cell lung cancer (NSCLC) treatment, yet many patients exhibit primary ICI resistance or progression after initial response. Epigenetic dysregulation, including aberrant EZH2-mediated trimethylation of histone H3 (H3K27me3), has been implicated in tumor immune evasion and reduced responsiveness to ICIs. Preclinical studies suggest that EZH2 inhibition may enhance antitumor immunity and potentiate PD-1 blockade. Tulmimetostat, a potent dual EZH2/EZH1 inhibitor, demonstrates favorable tolerability and antitumor activity across multiple solid tumors. We hypothesize that the addition of tulmimetostat to pembrolizumab may reverse the resistance to pembrolizumab in patients with ICI-refractory NSCLC. **Methods:** The primary objective of this open-label, single-arm, phase Ib/II study is to evaluate the safety, tolerability, and preliminary efficacy of combining tulmimetostat with pembrolizumab in Veterans with advanced NSCLC who have progressed after first- or second-line therapy, one of which must have included ICI. Key eligibility criteria include measurable disease per RECIST v1.1 and provision of adequate tumor tissue (archive or new). Tulmimetostat (200 mg or 300 mg) is administered orally once daily, beginning with a 7-day run-in period during cycle 1, followed by pembrolizumab 200 mg IV every 3 weeks. Treatment continues until confirmed disease progression, unacceptable toxicity, or withdrawal. Safety assessments include clinical exams, laboratory evaluations, ECGs, and CTCAE v5.0 grading of adverse events. Imaging is performed at baseline and every 9 weeks. Secondary endpoints include disease control rate, progression-free survival, and duration of response. Up to 18 patients will be enrolled in Phase Ib using a BOIN method to determine the dose-limiting toxicities (DLTs) and the recommended phase II dose (RP2D) of tulmimetostat. Phase II is a Simon optimal two-stage design to assess objective response rate (ORR) per RECIST v1.1. Subjects treated at the RP2D during phase Ib will be included in the efficacy analysis. In total, up to 66 patients will be enrolled across multiple VA sites. Optional on-treatment biopsies will be obtained at select timepoints. Biomarker analyses will include an assessment of H3K27me3 (Methyl Mark) and PD-L1 expression in tumor biopsy samples to explore epigenetic and immunologic correlates of treatment response. Correlative biomarker analyses, including H3K27me3 and PD-L1 expression in tumor biopsies, will offer insight into epigenetic and immunologic determinants of treatment response. Findings from this trial may support the development of a novel therapeutic approach for patients with NSCLC who have progressed after on standard immunotherapy or chemo-immunotherapy. Enrollment was initiated in January 2026. Clinical trial information: NCT05467748. Research Sponsor: VA ORD; CX002499-01.

TPS8665 Poster Session

Phase 2b randomized, blinded, placebo-controlled trial to investigate the efficacy and safety of visugromab added to pembrolizumab, pemetrexed, and carboplatin in first-line metastatic non-squamous NSCLC: GDFATHER-NSCLC-01.

Martin Reck, Konstantinos Ferentinos, Markus Joerger, Manuel Cobo, Benjamin Thiele, Manolo D'Arcangelo, Miguel F. Sanmamed, Mariam Alexander, Aakash Desai, Jhanelle E. Gray, Roy S. Herbst, Jorge J. Nieva, Rajwanth Veluswamy, Kathrin Klar, Marlene Fox, Vanja Radulovic, Lena Lemke, Eugen Leo, Sujata Rao, Felix Sebastian Lichtenegger; Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany; Clinics Essen-Mitte, Essen, Germany; Department of Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; Medical Oncology Section, Hospital Regional Universitario Carlos Haya, Málaga, Spain; Division of Medical Oncology, University Hospital Basel, Basel, Switzerland; Onco-Hematology Department, Santa Maria delle Croci Hospital, Ravenna, Italy; Department of Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain; Medical University of South Carolina, Charleston, SC; O'Neal Comprehensive Cancer Center at The University of Alabama in Birmingham, Birmingham, AL; Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; NYU Langone Health, New York, NY; CatalYm GmbH, Planegg-Martinsried, Germany

Background: Immune checkpoint inhibitors (ICIs) have improved outcomes in NSCLC, yet primary and secondary resistance remain common, limiting durable benefit. Growth differentiation factor 15 (GDF-15) has been implicated in ICI resistance. Clinical data for the anti–GDF-15 antibody visugromab in combination with nivolumab have been presented, demonstrating reinvigoration with deep and durable responses in relapsed/refractory solid tumors and increased efficacy in an ICI-naïve neoadjuvant setting, strongly supporting further evaluation in ICI-naïve NSCLC. This trial estimates the added clinical activity and safety of visugromab with standard chemo-immunotherapy and addresses primary immune resistance in first-line metastatic non-squamous NSCLC. **Methods:** GDFATHER-NSCLC-01 is a phase 2b, multicenter trial with an initial safety-run-in (SRI) followed by a randomized, double-blind, placebo-controlled part, conducted at >40 sites in seven countries across the US and Europe. The SRI employs a 3+3 dose escalation (two predefined visugromab dose levels; DLT window of 21 days) to determine the recommended dose for expansion; an independent data monitoring committee oversees escalation and the selection of the expansion dose. In the randomized part, participants with untreated metastatic non-squamous NSCLC (no actionable driver mutations), ECOG 0–1, are assigned 2:1 to receive visugromab or placebo in combination with pembrolizumab, pemetrexed, and carboplatin (21-day cycles). Brain metastases are allowed if untreated, asymptomatic and clinically stable, or if previously treated and stable per protocol. Patients are stratified according to PD-L1 tumor proportion score (<1% vs 1–49% vs ≥50%). The primary endpoint of the trial is objective response rate (RECIST v1.1). Key secondary endpoints include duration of response, progression-free survival, overall survival, safety, pharmacokinetics, and patient-reported outcomes; exploratory biomarker analyses are planned. The randomized part is not powered for statistical significance; the planned sample size is 90 participants, enabling descriptive estimation of effect sizes to inform future pivotal development. Enrollment status: The SRI has been completed. The randomized part is open to accrual; first patient pending. Clinical trial information: NCT07098988. Research Sponsor: CatalYm GmbH.

TPS8666 Poster Session

FUEL-IT Lung: Fasting to unleash and enhance lung cancer immunotherapy—A VA Lung Precision Oncology Program trial.

Razan Aljaras, Bharathi Muthusamy, Michael Wininger, Mahshid Shelechi, Pankaj Gupta, Theodore Seth Thomas, Lawrence Eric Feldman, Nisha Anjali Mohindra, Valter Longo, Shadia Ibrahim Jalal; Indiana University School of Medicine, Indianapolis, IN; Richard L. Roudebush VA Medical Center, Indiana University Melvin and Bren Comprehensive Cancer Center, Indianapolis, IN; West Haven CSPCC Coordinating Center, West Haven, CT; University of Southern California, Los Angeles, CA; Tibor Rubin VA Medical Center, Long Beach, CA; Saint Louis VA Medical Center John Cochran Division, St. Louis, MO; University of Illinois Hospital & Health Sciences System, Jesse Brown VA Medical Center, Chicago, IL; Jesse Brown VA Medical Center, Chicago, IL; USC School of Gerontology, Los Angeles, CA

Background: Single-agent PD-(L)1 inhibitors are standard first-line therapy for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50%, yielding objective response rates of approximately 45% and median overall survival of 20-26 months. However, immune-related adverse events (irAEs) occur in up to 20% of patients. Fasting-mimicking diets (FMD) induce metabolic reprogramming by reducing insulin-like growth factor 1 (IGF-1) and glucose while increasing IGF-binding protein 1. Preclinical data demonstrate that FMD enhances anti-tumor immunity by increasing T-cell mediated tumor cytotoxicity, reducing myeloid-derived suppressor cells, and suppressing T-regulatory cell function. Recent murine models show that FMD combined with anti-PD-L1 therapy prevents or reverses immune-mediated myocardial infiltration, reduces systemic inflammation, and is more effective than anti-PD-L1 alone in delaying tumor growth while reshaping the tumor microenvironment. Our prior feasibility study (IUSCCC-0662) in 10 advanced lung cancer patients demonstrated 80% compliance with FMD, with minimal toxicities. These findings suggest FMD may enhance checkpoint inhibitor efficacy while potentially reducing irAEs. **Methods:** This is an open-label, randomized pilot study evaluating the feasibility and safety of FMD combined with pembrolizumab in Veterans with newly diagnosed stage IV NSCLC and PD-L1 expression ≥50%. Eligible patients must have ECOG performance status 0-2 and adequate organ function. Patients receive pembrolizumab 200 mg IV every 3 weeks. The study employs a partial crossover design: Arm 1 receives regular diet with pembrolizumab for cycles 1-3, then crosses over to FMD with pembrolizumab for cycles 4-6; Arm 2 receives FMD with pembrolizumab for cycles 1-3, followed by regular diet thereafter. FMD consists of a 4-day cycle with calorie restriction (fats:carbs:protein ratio of 50:40:10) administered starting on the day of pembrolizumab infusion, followed by transitional diet on day 5, for 3 consecutive cycles. Primary endpoints include feasibility (proportion completing 3 FMD cycles, target ≥70%) and safety. Secondary endpoints include immune-mediated toxicity rates, objective response rate, disease control rate, and 12-month progression-free survival. Exploratory objectives assess FMD impact on metabolic markers (glucose, ketones, IGF-1, IGFBP-1), immune cell populations, body composition via CT imaging, physical function (Short Physical Performance Battery), and quality of life (FACT-L, EORTC QLQ-C30). Enrollment of 33 patients per arm is planned for total of 66 patients. Accrual began in October 2025. Clinical trial information: NCT06671613, Funded by VA ORD. Research Sponsor: This work is supported by a VA Merit, from the VA Clinical Science Research & Development Program.

TPS8667 Poster Session

Phase III study of multidisciplinary therapy combining local ablative therapy with immune-checkpoint inhibitors for patients with synchronous oligometastatic NSCLC (J-OLIGO: WJOG20924L).

Taichi Miyawaki, Yasuhisa Ohde, Hiroshi Doi, Masaki Oshima, Kentaro Sakamaki, Yuki Shinno, Ken Masuda, Kentaro Ito, Kyoichi Kaira, Kyoichi Okishio, Naoki Furuya, Kiichiro Ninomiya, Yu Tanaka, Masaru Takenaka, Ichidai Tanaka, Megumi Furuta, Hideyuki Harada, Nobuyuki Yamamoto, Hirotsugu Kenmotsu; Department of Respiratory Medicine, Juntendo University Hospital, Tokyo, Japan; Division of Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan; Department of Radiology, Wakayama Medical University, Wakayama, Japan; Department of Radiation Oncology, Juntendo University, Graduate School of Medicine, Tokyo, Japan; Faculty of Health Data Science, Juntendo University, Tokyo, Japan; Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Division of Respirology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan; Matsusaka Municipal Hospital, Matsusaka, Mie, Japan; Department of Respiratory Medicine, International Medical Center, Saitama Medical University, Saitama, Japan; Department of Thoracic Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan; St. Marianna University School of Medicine, Kawasaki, Japan; Center for Comprehensive Genomic Medicine, Okayama University Graduate School of Medicine Dentistry Pharmaceutical Science, Okayama-Shi, Japan; Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Second Department of Surgery (Chest Surgery), University of Occupational and Environmental Health, Fukuoka, Japan; Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya-Shi, Japan; Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University, Sapporo, Japan; Division of Radiation and Proton Therapy Center, Shizuoka Cancer Center, Nagaizumi, Japan; Internal Medicine III, Wakayama Medical University, Wakayama, Japan; Shizuoka Cancer Center, Shizuoka, Japan

Background: The standard of care for stage IV non-small cell lung cancer (NSCLC) patients without actionable driver mutations is immune-checkpoint inhibitors (ICIs) with or without platinum-based chemotherapy. For patients with synchronous oligometastatic disease, local ablative therapy (LAT) to all lesions, including primary sites, may improve survival based on several randomized phase II trials. Furthermore, combining LAT with ICIs may enhance anti-tumor immune responses by reducing tumor burden. However, a recent large phase II/III study failed to demonstrate a survival benefit for adding LAT to systemic therapy in patients with synchronous or induced oligometastatic NSCLC. Consequently, it remains unclear whether LAT provides a survival benefit in synchronous oligometastatic NSCLC. Based on the promising results from our preceding phase II trial (TRAP-OLIGO; WJOG11118L), we initiated this phase III trial to definitively evaluate the benefit of adding LAT to pembrolizumab plus platinum-based chemotherapy specifically for synchronous oligometastatic NSCLC. **Methods:** J-OLIGO is a multicenter, open-label, randomized phase III intergroup trial. Eligible patients have untreated stage IV NSCLC, ECOG PS 0-1, 1–3 metastases, and no actionable driver mutations. During the induction phase, patients receive 4 cycles of pembrolizumab plus platinum-based chemotherapy. Patients who achieve disease control with induction therapy and remain eligible for LAT to all residual lesions are randomized (1:1) to either the LAT group (Intervention) or the standard group (Control). The feasibility and appropriateness of LAT for each patient are evaluated by a multidisciplinary tumor board, consisting of medical oncologists, radiation oncologists, and thoracic surgeons, to ensure definitive treatment of all viable lesions. The LAT group receives definitive surgery and/or definitive radiotherapy to all sites, followed by maintenance pembrolizumab (±pemetrexed). Stratification factors include number of metastases, PD-L1 TPS, histology, and induction response. The primary endpoint is overall survival (OS), defined as the time from randomization. Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), and the safety. Based on results from previous studies, the study has 80% power to detect a hazard ratio of 0.55 for OS (median OS: 20 vs. 36 months) with a one-sided alpha of 0.05. The target sample size is 150 patients for primary registration and 100 for secondary registration. Accrual began in October 2025 and is planned for 4 years, followed by a 4-year follow-up period. This trial is supported by the Japan Agency for Medical Research and Development (AMED) under the Project for Innovative Cancer Research. Clinical trial information: jRCTs041250114. Research Sponsor: Japan Agency for Medical Research and Development.

TPS8668 **Poster Session**

A phase 2/3 study of EIK1001 in combination with pembrolizumab and chemotherapy in participants with stage 4 non–small cell lung cancer (NSCLC) (TeLuRide-008).

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Background: Immune checkpoint inhibitors (ICIs) reverse tumor-induced immune suppression and promote effective anti-tumor T-cell responses. Current standard of care (SOC) for Stage 4 NSCLC combining ICIs (e.g. pembrolizumab [pembro]) plus histology-appropriate chemotherapy (chemo) confers significant clinical benefit over chemo alone, yet many patients progress nonetheless, highlighting a large unmet medical need in this disease. EIK1001, a Toll-like receptor (TLR) 7/8 dual agonist, activates myeloid and plasmacytoid dendritic cells stimulating innate and adaptive immunity. In completed Phase 1 and ongoing Phase 2 studies, EIK1001 exhibits a manageable safety profile and encouraging anti-tumor activity both as monotherapy and in combination with ICIs. **Methods:** TeLuRide-008 (NCT#07365319) is a global, multicenter, randomized, double-blind, placebo-controlled, adaptive Phase 2/3 study of EIK1001 or placebo, in combination with pembro and histology-appropriate chemo in systemic-therapy-naïve pts with stage 4 NSCLC. In Phase 2, pts are randomized 1:1:1 to receive 1 of 2 doses of EIK1001 or placebo, + pembro and chemo (Part 1:Dose optimization; n~120), followed by additional enrollment with 1:1 randomization of new pts (n~160), at the EIK1001 selected dose or placebo (Part 2: Dose Expansion; n~280). If the study proceeds to Phase 3 (Part 3: Confirmatory), ongoing Phase 2 pts to continue treatment, and n~440 new pts will be randomized 1:1 to receive the selected dose of EIK1001 or placebo, + pembro and chemo (n = up to 750). Key eligibility criteria: pts ≥ 18 years of age, life expectancy ≥ 3 months, stage 4 NSCLC (NSQ or SQ), no actionable mutations requiring targeted therapy, ≥ 1 measurable lesion per RECIST v1.1, and no history of symptomatic pneumonitis. Primary objectives: evaluate efficacy and safety of 2 doses of EIK1001 + pembro and chemo for dose optimization and compare PFS (RECIST v1.1 by BICR) and OS between the selected EIK1001 dose and placebo, + pembro and chemo. Secondary objectives: safety and tolerability, ORR and DOR per RECIST v1.1 by BICR. Exploratory objectives: time to response, EIK1001 exposure-response relationships, and health-related quality of life. Clinical trial information: NCT#07365319. Research Sponsor: None.

TPS8669 **Poster Session**

Lung-MAP S1800E: A randomized phase II/III study of docetaxel and ramucirumab with or without cemiplimab for patients previously treated with platinum-based chemotherapy and immunotherapy for stage IV or recurrent non-small cell lung cancer (NSCLC).

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Background: Integration of immunotherapy into first line systemic therapy for patients with metastatic NSCLC has led to improvement in survival, but most patients experience disease progression. Blockade of PD-1 and VEGFR2 synergistically inhibits tumor growth by reducing tumor neovascularization and leads to upregulation of proinflammatory cytokines. We hypothesize that continuing second line anti-PD-1 therapy using cemiplimab in combination with docetaxel and ramucirumab may reverse immunotherapy resistance, and lead to improved overall survival (OS) compared to docetaxel and ramucirumab. **Methods:** Lung-MAP is a master protocol for patients with previously treated advanced NSCLC. S1800E is a phase II/III non-match Lung-MAP substudy, in which patients are randomized 1:1 to receive either standard of care treatment with intravenous docetaxel and ramucirumab (arm A) or investigational treatment with intravenous docetaxel and ramucirumab in combination with cemiplimab (arm B). The primary objective is to compare OS between patients assigned to arm A and arm B who have acquired resistance to platinum-based chemotherapy and immunotherapy for Stage IV or recurrent NSCLC. The total enrollment goal is 378 patients based on a design with 90% power to rule out an HR = 1 at the 1-sided 2.5% level, if the true HR = 0.66. The design includes 3 interim analyses, with a safety run-in for the first 10 patients on arm B. The main inclusion criteria are patients who experienced disease progression 84 days or more following initiation of anti-PD-(L)1 immunotherapy, with complete response, partial response or stable disease as their best response, in addition to progression on or following platinum-based chemotherapy. If a known sensitizing molecular alteration for which an FDA-approved targeted therapy for NSCLC exists (e.g., *EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS, HER2*, and *MET* sensitizing mutations), patients must have previously received at least one line of targeted therapy. Prior docetaxel is not permitted, and there is a washout of 14 days from palliative radiation (shortened to 7 days for bone radiation) and 28 days from major surgery, with no plans for concurrent systemic therapy while on the clinical trial. Patients must have adequate organ and marrow function and ECOG performance status of 0-1. S1800E was activated on 4/28/2025, with first patient registered on 5/22/2025. As of 1/6/2026, 49 of the planned 378 patients have been enrolled. Clinical trial information: NCT06616584. Research Sponsor: NIH/NCI grants; U10CA18088, U10CA180819; Regeneron Pharmaceuticals.

TPS8670 Poster Session

INTerpath-013: A phase 2, randomized, double-blind study of intismeran autogene plus pembrolizumab and chemotherapy as first-line treatment for metastatic squamous non–small cell lung cancer.

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Background: Non–small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. The anti-PD-1 pembrolizumab plus platinum-based chemotherapy is a recommended treatment for metastatic squamous NSCLC. Despite the inclusion of anti-PD-(L)1 therapies into treatment guidelines, there remains an unmet medical need for further improving patient outcomes. Intismeran autogene (intismeran; formerly V940, mRNA-4157) is an investigational mRNA-based individualized neoantigen therapy (INT) encoding up to 34 neoantigens unique to each patient's tumor and is designed to promote antitumor immune response. INTerpath-013 is a phase 2 study evaluating the addition of intismeran to pembrolizumab plus chemotherapy for previously untreated metastatic squamous NSCLC. **Methods:** This phase 2, randomized, double-blind, placebo-controlled study is enrolling patients aged ≥18 years with previously untreated histologically or cytologically confirmed stage IV squamous NSCLC (M1a, M1b, M1c1, or M1c2 per AJCC version 9) and measurable disease per RECIST v1.1 by investigator. Participants are also required to have ECOG PS 0 or 1 and provide a tumor sample for next-generation sequencing. Exclusion criteria include known active CNS metastases and/or carcinomatous meningitis, or untreated or symptomatic brain metastases. Approximately 180 participants will be randomized 2:1 to receive 1 treatment cycle comprising intravenous pembrolizumab 400 mg Q6W (1 dose) plus carboplatin AUC 6 mg/mL/min Q3W (2 doses), with either paclitaxel 200 mg/m^2 Q3W (2 doses) or nab-paclitaxel 100 mg/m^2 QW (6 doses). At week 6 (after cycle 1), tumor imaging will be performed and participants with complete response, partial response, or stable disease per RECIST v1.1 by BICR will continue 1 more treatment cycle and also receive up to 2 cycles of intismeran intramuscularly 1 mg (study arm A) or placebo (arm B) Q3W. All participants who complete the first 2 cycles of treatment will then receive up to 7 additional doses of intismeran or placebo (9 total) plus pembrolizumab up to 15 additional doses (17 total). Any participant with PD at the 6-week scan will have treatment unblinded and those in arm A may receive exploratory treatment with up to 9 doses of intismeran plus docetaxel 75 mg/m^2 Q3W until PD, unacceptable toxicity, or participant/physician decision; those in arm B will not receive further investigational treatment. Randomization will be stratified by PD-L1 tumor proportion score ($<$ 1% vs ≥1% to ≤49% vs ≥50%), ECOG PS (0 vs 1), and the number of metastatic sites (1 vs $>$ 1). Primary endpoints are PFS per RECIST v1.1 by BICR and OS. Secondary endpoints include ORR and duration of response per RECIST v1.1 by BICR and safety. Enrollment began in December 2025 and is ongoing across 55 global sites. Clinical trial information: NCT07221474. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.; N/A

TPS8671 Poster Session

Phase 3 trial ResQ201A of nogapendekin alfa inbakicept (NAI) plus tislelizumab and docetaxel vs. docetaxel monotherapy for advanced or metastatic NSCLC resistant to ICI therapy.

Andreas Nicholas Saltos, Edgardo S. Santos, Eric S. Schaefer, Wade Thomas Iams, Daniel Morgensztern, Amol Rajeev Rao, Jennifer W. Carlisle, Courtney Lewis, Leylah Drusbosky, Sandeep Bobby Reddy, Patrick Soon-Shiong; Moffitt Cancer Center, Tampa, FL; The Oncology Institute of Hope and Innovation, Fort Lauderdale, FL; Highlands Oncology Group, Fayetteville, AR; Tennessee Oncology, Nashville, TN; Division of Oncology, Washington University School of Medicine, St. Louis, MO; MemorialCare Cancer Institute, Fountain Valley, CA; Winship Cancer Institute of Emory University, Atlanta, GA; ImmunityBio, Inc., Culver City, CA

Background: Immune checkpoint inhibitors (ICIs) are approved as monotherapy and in combination with chemotherapy in advanced NSCLC. Most patients experience progression with limited treatment options other than chemotherapy. NAI is a first-in-class IL-15 receptor agonist that induces proliferation and activation of natural killer cells, CD8+ T cells and memory T cells without activating regulatory T cells, enhancing both the innate and adaptive immune system to maximize immunogenic cell death. Phase 2 data demonstrated evidence of NAI prolonging OS when used in combination with an ICI. The rationale for ResQ201A (NCT06745908) is based on the prior QUILT-3.055 study, wherein median OS was prolonged at 14.3 months overall and 21.1 months when ALC≥1.2x10^3 was maintained with NAI as a lymphocyte stimulating agent. Randomized clinical trials have demonstrated that the standard of care docetaxel in the 2L+ NSCLC setting results in a mOS of approximately 9 months. **Methods:** ResQ201A is a randomized, open-label phase 3 global, registrational intent trial where 462 adult participants will be enrolled 2:1 in the experimental arm, consisting of two 3-week induction cycles of NAI [SC 1.2 mg], tislelizumab [IV 200 mg] and docetaxel [IV 75 mg/m^2] followed by maintenance NAI and tislelizumab, or a docetaxel monotherapy control arm [IV 75 mg/m^2] until disease progression or unacceptable toxicity. Participants are stratified based on histology, presence of actionable genomic alterations (AGA), and geographical region. Key inclusion criteria are pathologically confirmed stage IV NSCLC with acquired resistance to an ICI (PD after an initial response OR stable disease ≥ 6 mo. duration) to a single line of ICI with or without chemotherapy, ECOG 0 to 2, and measurable tumor lesions per RECIST v1.1. Key exclusion criteria are systemic autoimmune disease, history of organ transplant, and AGA of ALK. The primary endpoint is OS by KM with treatment arm comparison based on the stratified log-rank test and OS hazard ratio summarized based on the stratified Cox proportional hazard model, both stratified by the randomization strata. Secondary efficacy endpoints include iDCR per iRECIST; PFS, ORR and duration of response. Safety is graded using the NCI CTCAE v5.0. Exploratory analyses will be performed to meet objectives. This trial has enrolled and treated participants. Clinical trial information: NCT06745908. Research Sponsor: None.

TPS8672 Poster Session

A phase 3 study of ateganosine (THIO; 6-thio-2'-deoxyguanosine) sequenced with immune checkpoint inhibitor (ICI) versus standard-of-care chemotherapy in ICI-resistant advanced NSCLC: THIO-104 trial in progress.

Tomasz Jankowski, Ahmet Sezer, Mariola Kowal-Rosinska, Veronika Muller, Tibor Csoszi, Tünde Nagy, Rodryg Ramlau, Szabolcs Soter, Constantin D. Volovat, Florin Amurariti, Daniela E. Sirbu, Razvan Bobora, Ilgen Mender, Romina Girotti, Marcel Mitsunaga, Oleg Tudos, Matthew Failor, Vlad Vitoc, Sergei Gryaznov, Victor Zaporojan; Medical University in Lublin, Lublin, Poland; Baskent University, Adana, Turkey; University Hospital No 4, Lublin, Poland; Semmelweis Egyetem Pulmonologiai Klinika, Budapest, Hungary; Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary; Országos Onkológiai Intézet, Budapest, Hungary; Department of Oncology, Poznań University of Medical Sciences, Poznań, Poland; Koranyi National Institute of Pulmonology, Budapest, Hungary; Department of Medical Oncology, Victoria Hospital (Euroclinic Oncology Center) and Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania; Department of Medical Oncology, Victoria Hospital (Euroclinic Oncology Center), Iasi, Romania; Department of Medical Oncology, OncoHelp - Oncology Center Timisoara, Timişoara, Romania; Department of Oncology, Municipal Clinical Emergency Hospital of Timisoara, Timisoara, Romania; Maia Biotechnology, Chicago, IL; UADE - Universidad Argentina de la Empresa Buenos Aires, Ciudad De Buenos Aires, Argentina; Maia Biotechnology, Inc., Chicago, IL

Background: Despite progress in the treatment of advanced non-small cell lung cancer (NSCLC), therapeutic options remain scarce for patients who have developed resistance to immune checkpoint inhibitors (ICIs). Ateganosine (THIO; 6-thio-2'-deoxyguanosine), a telomere-targeting agent, is selectively recognized by telomerase and integrated into the telomeres of cancer cells. Once incorporated, Ateganosine compromises the telomere structure and function, leading to 'uncapping' of the chromosome ends and thus resulting in rapid tumor cell apoptosis. **Methods:** THIO-104 is a multicenter, open-label, randomized Phase 3 study enrolling approximately 300 subjects with histologically confirmed advanced/metastatic NSCLC. Eligible participants must have received two prior lines of systemic treatment, including at least one line of ICIs and platinum-based chemotherapy. Participants will be randomized 1:1 to receive either THIO 180 mg per cycle (60 mg IV on Days 1-3 of a 3-week cycle) followed by cemiplimab 350 mg IV on Day 5, or single-agent chemotherapy (vinorelbine, gemcitabine, or docetaxel). The primary endpoint is overall survival (OS). Secondary endpoints include objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR). Current Status: Enrollment is ongoing , preliminary safety data and efficacy outcomes will be assessed through scheduled interim analyses. **Conclusion:** THIO-104 will provide critical insights into the potential role of telomere-targeting agents in restoring tumor sensitivity to ICIs in NSCLC. The study will also explore key biomarkers to further characterize Ateganosine's mechanism of action and its potential to predict patient response to therapy. Clinical trial information: 2024-520164-33-00. Research Sponsor: None.

TPS8673 **Poster Session**

Randomized phase 3 study (MarsLight-11) evaluating IBI363 (TAK-928) versus docetaxel in patients (pts) with squamous non-small cell lung cancer (sqNSCLC) after prior chemotherapy (chemo) and immunotherapy (IO).

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Background: In most series, sqNSCLC has worse clinical outcomes compared with non-squamous NSCLC with IO combinations. After chemo and IO failure, docetaxel±ramucirumab remains the standard of care for advanced sqNSCLC, but offers only short-lived disease control (median progression-free survival [PFS] of approximately 3–4 months), and high rates of severe toxicities. Thus, effective post-chemo and IO options for advanced sqNSCLC remain a significant unmet clinical need. IBI363 is a first-in-class, PD-1/IL-$2^{\alpha\text{-bias}}$ bispecific antibody fusion protein designed to block the PD-1/PD-L1 pathway and simultaneously activate the IL-2 pathway. It selectively expands and rejuvenates exhausted tumor-specific T cells by cis-activating IL-2 receptors. The IL-2 arm of IBI363 is engineered to retain its affinity for IL-2Rα while reducing binding to IL-2Rβ and IL-2Rγ thereby minimizing off-target toxicity. This dual mechanism has shown potential to address the unmet clinical needs of pts with IO-resistant and immune-cold tumors. In prior phase 1/2 studies, IBI363 monotherapy at 3 mg/kg every 3 weeks (Q3W) was well-tolerated and showed encouraging, durable efficacy in pts with advanced, IO-treated NSCLC and other solid tumors (2025 ASCO [8509, 2502 and 104]). Here, we present the trial in progress for MarsLight-11 (NCT07217301), a randomized, open-label, multi-regional Phase 3 study evaluating IBI363 versus docetaxel in pts with sqNSCLC after prior chemo and IO. **Methods:** This study is enrolling eligible pts with unresectable, locally advanced or metastatic sqNSCLC who have progressed on or after platinum-based chemo and anti-PD-1/PD-L1 treatments (defined as radiographic progression per RECIST v1.1 during or within 6 months after discontinuation of IO). Pts with known actionable genomic alterations, active or symptomatic brain metastases are excluded. Pts are randomized 1:1 to IBI363 or docetaxel (control). Stratification factors include the type of IO resistance (primary vs. acquired), the sequence of prior IO and chemo (concurrent vs. sequential), and region (Asia vs. non-Asia). Pts in the experimental arm will receive a priming dose of IBI363 (0.1 mg/kg) seven days prior to the first full dose (3 mg/kg Q3W). The control arm will receive docetaxel (75 mg/m² Q3W). The primary endpoint is overall survival (OS). Secondary endpoints include investigator-assessed PFS, objective response rate, disease control rate, duration of response, and time to response per RECIST v1.1, as well as safety, pharmacokinetics, and immunogenicity. One interim analysis (IA1) and one final analysis are planned for OS. The study plans to enroll approximately 600 pts globally, including sites in China, the United States, Canada, the European Union, the United Kingdom, Japan and South Korea. Clinical trial information: NCT07217301. Research Sponsor: None.

TPS8674 Poster Session

A randomized phase III trial of chemo-immunotherapy vs immunotherapy alone for the vulnerable older adult with advanced non–small cell lung cancer: The ACHIEVE study—ECOG-ACRIN EA5221.

Megan Ann Baumgart, Yating Wang, Balazs Halmos, Carolyn J. Presley, Efrat Dotan, Apar Kishor Ganti, Mohammed Al-Jumayli, Melissa A. Simon, Kim Sandler, Julie R. Brahmer, ECOG-ACRIN Cancer Research Group; University of Rochester, Rochester, NY; ECOG-ACRIN, Boston, MA; Montefiore Einstein Comprehensive Center for Cancer Care, Bronx, NY; The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University, Columbus, OH; Ann B. Barshinger Cancer Institute, Penn Medicine Lancaster General Health, Lancaster, PA; University of Nebraska Medical Center, Omaha, NE; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Northwestern University Feinberg School of Medicine, Chicago, IL; Vanderbilt University Medical Center, Nashville, TN; The Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD

Background: Lung cancer disproportionately affects older adults, with 70% of cases diagnosed in patients ≥65 years old, though older adults are often underrepresented in clinical trials.[1,2] KEYNOTE-189[3] and KEYNOTE-407[4] studies established superiority of chemotherapy-immunotherapy (chemo-IO) compared to chemotherapy irrespective of PD-L1 tumor proportion score (TPS) in patients with ECOG PS 0-1. Single-agent pembrolizumab was also shown to be superior to chemotherapy based on KEYNOTE-024[5] and KEYNOTE-042[6] studies. KEYNOTE-189[3]/407[4] studies highlighted synergistic benefit from chemo-IO across TPS subsets while single-agent IO benefit is mostly in the TPS ≥50% population. It is unknown if single-agent IO versus chemo-IO is superior for patients with PD-L1 TPS 1-49%, especially in older adults. There is increased risk for toxicity for adults with co-morbidities and impaired function that is enriched along the age continuum. Use of single-agent IO may limit benefit from synergy. Alternatively, chemo may increase toxicity and adversely impact quality of life (QOL) and survival in older adults. The goal of this study is to evaluate overall survival (OS) in older adults with metastatic NSCLC, PD-L1 TPS 1-49% treated with first-line single-agent IO versus chemo-IO. **Methods:** This phase 3 study randomizes (1:1) patients age ≥70 years old with metastatic NSCLC, PD-L1 TPS 1-49% to treatment with pembrolizumab versus pembrolizumab plus chemotherapy with primary endpoint of OS. Patients undergo an abbreviated baseline geriatric assessment (GA) of function, nutrition, cognition, and QOL with opportunity for modification of chemotherapy regimen and dosing based on results. Patients are treated with 4 cycles of induction pembrolizumab 200 mg IV every 3 weeks (Arm A) or 4 cycles of induction pembrolizumab 200 mg IV every 3 weeks in combination with chemotherapy (Arm B). Chemotherapy is investigator-selected from platinum doublet (carboplatin/pemetrexed, carboplatin/paclitaxel, carboplatin/*nab*-paclitaxel) or single-agent options (pemetrexed, paclitaxel, *nab*-paclitaxel) with dose attenuation per investigator discretion. Induction is followed by up to two years of maintenance pembrolizumab (200 mg IV every 3 weeks or 400 mg IV every 6 weeks) with option for continuing maintenance pemetrexed. Modified GA is repeated at specified time points. Optional stool studies are collected at baseline and after four cycles of therapy. Secondary endpoints include progression-free survival, objective response rate, tolerability and QOL. Exploratory aims evaluate GA metrics as predictors of clinical outcomes and relate gut microbe diversity and abundance to treatment outcomes. Efficacy analyses are conducted on an intention-to-treat basis. Enrollment is ongoing, and current accrual (as of January 6, 2026) is 22 of 304. Clinical trial information: NCT06096844. Research Sponsor: National Cancer Institute.

TPS8675 **Poster Session**

ALPACCA: Phase 3 trial of firmonertinib vs investigator's choice of EGFR inhibitor as first-line treatment for locally advanced or metastatic NSCLC with EGFR P-loop and alpha c-helix compressing (PACC) uncommon mutations (FURMO-006).

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Background: Despite advances in treatment of NSCLC with EGFR classical mutations, no universally accepted standard-of-care treatment exists for patients with EGFR uncommon mutations including PACC mutations. Treatment options include EGFR tyrosine kinase inhibitors (TKIs) (osimertinib, afatinib), chemotherapy, or other targeted therapies (amivantamab for exon 20 insertion mutations). EGFR PACC mutations comprise approximately 12.5% of all NSCLC EGFR mutations (Robichaux et al 2021, Nilsson et al 2024). Firmonertinib is a once daily oral, highly brain penetrant, broadly active mutant-selective EGFR inhibitor that targets classical and uncommon mutations (Musib et al., NACLC 2022). In the phase 1b FURMO-002 study (FURTHER), first-line locally advanced or metastatic EGFR PACC mutation NSCLC patients treated with firmonertinib 240 mg daily achieved a confirmed ORR of 68.2%, best ORR of 81.8%, disease control rate (DCR) of 100%, and median progression-free survival (mPFS) of 16.5 months by blinded independent central review (BICR) (Le et al., WCLC 2025). Firmonertinib was generally well-tolerated with manageable EGFR TKI-associated adverse events. **Methods:** ALPACCA (FURMO-006; NCT07185997) is a global, phase 3, randomized, open-label study investigating firmonertinib vs investigator's choice of osimertinib or afatinib. Eligible patients have locally advanced or metastatic NSCLC with EGFR PACC mutations. Key inclusion criteria include documented presence of EGFR PACC mutation and measurable disease per RECIST v1.1. Patients with asymptomatic CNS metastases are allowed. Key exclusion criteria include prior systemic anticancer therapy in the locally advanced or metastatic setting or any prior EGFR TKI therapy. Approximately 480 patients will be randomized 1:1 to receive firmonertinib 240 mg daily or investigator's choice of osimertinib 80 mg daily or afatinib 40 mg daily. Primary endpoints are PFS and ORR per RECIST v1.1 by BICR. Key secondary endpoints include OS, investigator assessed PFS and ORR, and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT07185997. Research Sponsor: ArriVent BioPharma Inc.

TPS8676 **Poster Session**

Randomized phase II study of amivantamab + lazertinib versus afatinib in patients with uncommon/compound *EGFR*-mutated non-small cell lung cancer (WJOG17323L: AGEHA study).

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Background: While EGFR tyrosine kinase inhibitors (TKIs) such as afatinib are standard treatments for patients with advanced non-small cell lung cancer (NSCLC) harboring uncommon or compound *EGFR* mutations (excluding exon 20 insertions and T790M), the duration of response is often limited, with a median progression-free survival (PFS) of approximately 8 to 10 months. Amivantamab is an EGFR mesenchymal–epithelial transition factor (MET) bispecific antibody with immune cell–directing activity that has multiple mechanisms of action as defined in preclinical models. For common *EGFR* mutated NSCLC, combination therapy with lazertinib has been approved in several countries based on its superiority in Phase III trial. Although a phase I study of amivantamab plus lazertinib combination therapy showed promising efficacy with a median PFS of 19.5 months in treatment-naïve patients with uncommon or compound *EGFR* mutations, this was a small-scale non-comparative study where efficacy was not the primary endpoint. The AGEHA study (WJOG17323L) is designed to prospectively evaluate whether amivantamab + lazertinib provides superior efficacy and acceptable safety compared to afatinib in patients with treatment-naïve, uncommon or compound *EGFR* mutated NSCLC. **Methods:** This multicenter, randomized, open-label, phase II trial is conducted by the West Japan Oncology Group (WJOG). Eligible patients are randomized in a 1:1 ratio to receive either combination therapy with amivantamab plus lazertinib in Arm A, or afatinib monotherapy in Arm B. The primary objective is to compare PFS between the two treatment arms. Secondary objectives include safety, overall response rate, and overall survival. Additionally, mandatory blood samples are collected at baseline and at the time of disease progression for comprehensive biomarker analysis using the Guardant Health platform to identify molecular predictors of response and resistance mechanisms, including approximately 740 gene alterations and methylation abnormalities. The target sample size is 70 patients (35 per arm). This study is designed with a one-sided alpha of 0.1 and a power of 80% to detect the superiority of amivantamab plus lazertinib over afatinib monotherapy. The primary analysis will compare PFS using a stratified log-rank test, and hazard ratios will be estimated using a Cox proportional hazards model. Key Eligibility Criteria: Patients must be histologically confirmed advanced or recurrent non-squamous NSCLC harboring uncommon or compound *EGFR* mutations, excluding exon 20 insertions and T790M. Participants must be treatment-naïve for advanced disease with an ECOG performance status of 0–1. Patient enrollment began in January 2026, with a recruitment period of two years and a total study duration of five years. Clinical trial information: jRCTs031250560. Research Sponsor: Janssen Pharmaceutical K.K.

TPS8677 **Poster Session**

A randomized phase II study of capmatinib plus osimertinib with or without ramucirumab in patients with *EGFR*-mutant, *MET*-amplified stage IV or recurrent no–small cell lung cancer (Lung-MAP Sub-Study S1900G).

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Background: Patients (pts) with advanced *EGFR*-mutant non-small cell lung cancer (NSCLC) typically respond well to first-line tyrosine kinase inhibitor (TKI) therapy, however disease progression is inevitable. A common mechanism of resistance to third-generation EGFR TKIs is *MET* amplification in up to 15% of patients. Prior trials have demonstrated efficacy of combined EGFR and MET TKI for patients with acquired *MET* amplification, however treatment can be limited by toxicity due to peripheral edema. Preclinical evidence demonstrates the benefit of VEGF inhibition combined with an EGFR TKI and MET TKI, both in efficacy and reduced edema. Lung MAP S1900G is a randomized phase II trial of osimertinib and capmatinib plus or minus the VEGFR2 inhibitor ramucirumab in patients with *EGFR*-mutant NSCLC and *MET* amplification after progression on osimertinib. **Methods:** Pts have stage IV or recurrent NSCLC with a sensitizing *EGFR* mutation and have disease progression on osimertinib alone or in combination with other agents. Documentation of *MET* amplification must be determined by tissue- or blood-based assay; testing for *MET* amplification can be done locally or centrally through the LUNGMAP screening process and any level of amplification is allowed. Measurable disease is not required. Patients with asymptomatic treated or untreated brain metastases are eligible. Prior VEGF inhibitor or MET antibody (such as amivantamab) are allowed. Pts are randomly assigned to receive osimertinib 80mg by mouth daily, capmatinib 400mg by mouth twice daily, and ramucirumab 10m/kg intravenously on days 1 and 15 of a 28 day cycle, or osimertinib plus capmatinib alone. Treatment continues until disease progression, symptomatic deterioration, unacceptable toxicity or treatment delay greater than 28 days. Disease assessment per RECIST 1.1 is performed every 8 weeks for the first year and every 12 weeks thereafter. The primary endpoint is investigator-assessed progression-free survival (PFS) and secondary endpoints include toxicity, ORR, duration of response, overall survival, rates of edema, and change in weight. A safety run-in of the first 10 pts in each arm evaluable for dose-limiting toxicity is included due to limited safety data on both the doublet and triplet combinations. The target sample size is 40 eligible pts (20 per arm) which will provide 85% power to rule out no difference at a 1-sided 15% level if the true hazard ratio is 0.5. A hazard ratio of 0.71 or less, equivalent to a 2.4 month difference in median PFS, will be consistent with rejecting the null hypothesis. Accrual is ongoing, with 24 of 40 patients enrolled. S1900G is the first Lung-MAP sub-study that focuses on *EGFR*-mutant lung cancer, representing a new era for this platform trial. Clinical trial information: NCT05642572. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA18088; National Cancer Institute/U.S. National Institutes of Health; U10CA180819; Novartis; Eli Lilly.

TPS8678 **Poster Session**

First-in-human phase I, open-label, multicenter study of HJ-004, a novel EGFR-PROTAC degrader, in patients with advanced *EGFR*-mutated non–small cell lung cancer.

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Background: Despite remarkable progress with 1st- to 3rd-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), nearly all patients with EGFR-mutated non-small cell lung cancer (NSCLC) eventually develop acquired resistance through secondary EGFR mutations, bypass pathway activation, or histologic transformation. Targeted options that specifically address EGFR-dependent (on-target) resistance after progression on 3rd-generation EGFR-TKIs remain limited. HJ-004 is an orally bioavailable, highly selective proteolysis-targeting chimera (PROTAC) that degrades mutant EGFR by recruiting the cereblon (CRBN) E3 ubiquitin ligase. Preclinically, HJ-004 showed broad activity against classical, uncommon, and osimertinib-resistant EGFR variants with favorable pharmacokinetics (PK) and safety profiles. **Methods:** This first-in-human, phase I, multicenter, open-label study evaluates the safety, tolerability, PK, and preliminary antitumor activity of HJ-004 in patients with recurrent or metastatic EGFR-mutant non-squamous NSCLC. The study comprises two parts: dose escalation and dose expansion. In the dose-escalation phase, oral HJ-004 is administered once daily in 28-day cycles using accelerated titration followed by a conventional 3 + 3 design (planned doses: 12.5, 25, 50, 87.5, 125, and 162.5 mg). Dose-limiting toxicities (DLTs) are assessed during the single-dose (C0D1-C0D3) and first multiple-dose cycle (C1D1-C1D28) periods. The expansion phase will enroll approximately 20-40 participants in two dose cohorts to further evaluate safety, PK, and preliminary efficacy. Key eligibility criteria include measurable disease per RECIST v1.1 and adequate organ function. The trial is currently ongoing and is expected to enroll up to 76 patients. The phase I study initiated in 2025, and site activation and patient screening are currently underway. No safety or efficacy data are yet available. Enrollment is projected to be completed in 2027, and updated enrollment and PK data will be presented at a future meeting. Clinical trial information: NCT07361237. Research Sponsor: None.

TPS8679 **Poster Session**

KEYMAKER-U01J: Calderasib plus pembrolizumab with or without cetuximab as first-line treatment for advanced or metastatic nonsquamous non–small-cell lung cancer (NSCLC) with *KRAS* G12C mutations.

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Background: The anti–PD-1 pembrolizumab (pembro) + chemotherapy (chemo) is a standard of care first-line therapy for metastatic NSCLC with no *EGFR* or *ALK* alterations. Despite these advances, here remains an unmet need for patients with tumors that have certain mutations, including those in the *KRAS* gene. *KRAS* mutations are associated with poor OS in NSCLC. Calderasib (MK-1084), a next-generation, selective *KRAS* G12C-GDP covalent inhibitor, has previously demonstrated preliminary antitumor activity in combination with pembro ± chemo in *KRAS* G12C–mutant metastatic NSCLC in the phase 1 KANDLELIT-001 study. The anti-EGFR cetuximab has shown promising efficacy in combination therapies in NSCLC with *KRAS* G12C mutations. The phase 2 KEYMAKER-U01J study (NCT07252739) is evaluating the addition of investigational agents to pembro in advanced or metastatic nonsquamous NSCLC with *KRAS* G12C mutations; the treatment arms presented here include pembro + calderasib ± cetuximab.
Methods: This phase 2, randomized, open-label study is enrolling participants (pts) aged ≥18 years with previously untreated histologically or cytologically confirmed stage IIIB, IIIC, or IV (M1a, M1b, or M1c) nonsquamous NSCLC (AJCC v9), with a *KRAS* G12C mutation that is ineligible for curative resection or chemoradiation. Pts must also have measurable disease per RECIST v1.1, an ECOG PS of 0 or 1, and provide a tumor sample for biomarker analysis. Following a safety lead-in of ~10 pts in arm 3, 1:1:1 randomization of ~120 pts will occur. In arm 1 (control arm), pts will receive up to 18 cycles of pembro 400 mg Q6W intravenously (IV) plus carboplatin AUC 5 mg/mL/min up to 2 cycles and pemetrexed 500 mg/m^2 Q3W until discontinuation criteria are met. Pts in arm 2 (reference arm) will receive up to 18 cycles of pembro 400 mg IV Q6W plus calderasib orally until discontinuation criteria are met. Pts in arm 3 will receive up to 18 cycles of pembro 400 mg IV Q6W plus calderasib with cetuximab 500 mg/m^2 IV Q2W until discontinuation criteria are met. Discontinuation criteria include unacceptable AEs, PD, occurrence/progression of another malignancy, or pt/physician withdrawal. Randomization will be stratified by PD-L1 tumor proportion score (< 50% vs ≥50%). Dual primary endpoints are safety (dose-limiting toxicities, AEs, and AEs leading to study discontinuations) and objective response (CR or PR) per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are duration of response and PFS per RECIST v1.1 by BICR, OS, and pharmacokinetic characterization. On-study tumor imaging will occur Q6W until week 24, Q9W until week 51, then Q12W, or more frequently if clinically indicated. AEs will be graded per NCI CTCAE v5.0. Enrollment began in December 2025, with 80–105 sites scheduled to enroll globally. Clinical trial information: NCT07252739. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8680 **Poster Session**

A phase II study of amivantamab hyaluronidase in *MET* amplification–positive stage IV or recurrent non–small cell lung cancer (Lung-MAP Sub-Study).

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Background: *MET* amplification is a known oncogenic driver in non-small cell lung cancer (NSCLC), estimated to occur in approximately 3-4% of non-squamous (nsq) and squamous (sq) cases. While targeted therapies such as tyrosine kinase inhibitors (TKIs) have demonstrated activity in this population, with objective response rates (ORR) approximating 30%, there is a need for novel therapeutic approaches, particularly for patients who have progressed on standard systemic therapies. Amivantamab hyaluronidase is a fully human bispecific antibody targeting *EGFR* and *MET* co-formulated with recombinant human hyaluronidase (rHuPH20) for subcutaneous administration. The mechanism of action involves the inhibition of *EGFR* and *MET* signaling, receptor degradation, and the induction of antibody-dependent cellular cytotoxicity. S1900J is evaluating the efficacy of this subcutaneous formulation in specific histological cohorts. **Methods:** S1900J is a 2-stage, single arm phase II biomarker-driven Lung-MAP sub-study. The study includes 2 cohorts of Stage IV or recurrent NSCLC, based on histology (non-squamous and squamous NSCLC). Biomarker eligibility requires documentation of *MET* amplification as primary driver via tissue or ctDNA NGS. Participants must have received at least one prior line of systemic therapy; notably, patients who have received prior *MET* TKI therapy (e.g., crizotinib, capmatinib) or harboring other actionable alterations are excluded. Participants receive amivantamab hyaluronidase via subcutaneous injection weekly during Cycle 1 (Days 1, 8, 15, 22) and every 2 weeks thereafter (Days 1, 15). Dosing is weight-based: 1,600 mg amivantamab/20,000 units hyaluronidase for participants $<$ 80 kg, and 2,240 mg amivantamab/28,000 units hyaluronidase for patients $\geq$80 kg. The primary endpoint is response. with a goal of 40 evaluable participants per cohort. The study design has 90% power to rule out a 15% ORR at the 1-sided 5% level, if the true ORR is 35%. Secondary objectives include progression-free survival, duration of response, and response rates in the subset with MET amplification by FoundationOne CDx assays. Correlative studies of interest include the evaluation of concordance between tissue-based and liquid biopsy (ctDNA) next-generation sequencing for the detection of *MET* amplification. S1900J opened to accrual on 9/27/2024 and is actively enrolling patients. Clinical trial information: NCT06116682. Research Sponsor: NIH/NCI grants; U10CA18088, U10CA180819.

TPS8681 Poster Session

An ongoing phase 1–2a study of EO1001, an oral brain-penetrant pan-ErbB inhibitor, in patients with advanced ErbB-driven solid tumors including CNS disease.

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Background: Central nervous system (CNS) metastases and primary brain tumors remain a major cause of morbidity and mortality in patients with ErbB-driven malignancies, particularly as improved systemic therapies prolong survival. Aberrations in the ErbB family of receptor tyrosine kinases—including EGFR, HER2, and HER4—are frequently associated with CNS progression, therapeutic resistance, and poor outcomes across multiple tumor types. In glioblastoma and other CNS malignancies, specific EGFR extracellular domain (ECD) alterations, including EGFRvIII and recurrent ECD missense variants, have been previously reported to promote ligand-independent signaling, invasive tumor biology, and resistance to currently available EGFR-targeted therapies. EO1001 is a novel, oral, irreversible pan-ErbB inhibitor designed to achieve sustained CNS exposure and broad ErbB pathway inhibition. This ongoing Phase 1–2a study is evaluating the safety, pharmacokinetics, and preliminary antitumor activity of EO1001 in patients with advanced ErbB-driven solid tumors, including those with CNS involvement. **Methods:** This is a first-in-human, multicenter, open-label Phase 1–2a study of once-daily oral EO1001. The Phase 1 dose-escalation component uses an accelerated titration design transitioning to a standard 3+3 schema following the occurrence of ≥Grade 2 treatment-related toxicity. A Phase 2 expansion component is enrolling patients at or below the recommended Phase 2 dose (RP2D). Eligible patients are adults with advanced or metastatic ErbB-expressing solid tumors that have progressed following standard therapy; patients with treated or untreated CNS disease are eligible. EO1001 is administered once daily in 28-day cycles following an initial single-dose pharmacokinetic assessment. The primary objectives are to evaluate safety and tolerability and to determine the RP2D. Secondary objectives include characterization of the pharmacokinetic profile and assessment of preliminary antitumor activity using RECIST v1.1 and/or RANO criteria, as appropriate. Exploratory objectives include evaluation of pharmacodynamic and molecular biomarkers in available tissue and optional cerebrospinal fluid sampling to further assess CNS exposure and pathway modulation. Current Status: Dose escalation has been completed across multiple dose levels, and enrollment is ongoing in Phase 2 expansion cohorts designed to further characterize safety, pharmacokinetics, and CNS-directed antitumor activity at biologically active dose levels. Clinical trial information: ACTRN12620000583943. Research Sponsor: Edison Oncology Holding Corp.