First-line adagrasib (ADA) with pembrolizumab (PEMBRO) in patients (pts) with advanced/metastatic KRAS^{G12C}-mutated non-small cell lung cancer (NSCLC) from the phase 2 portion of the KRYSTAL-7 study.

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Background: In the phase 2 KRYSTAL-7 study (NCT04613596), first-line ADA, a KRAS^{G12C} inhibitor, plus PEMBRO demonstrated clinical activity and a manageable safety profile in pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC and PD-L1 ≥50% (Garassino et al. *Ann Oncol* 2023). Here we report efficacy and safety data, including the first disclosure of survival data, for pts across all PD-L1 tumor expression levels. **Methods:** Pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC and known PD-L1 tumor proportion score received first-line ADA (400 mg orally BID) plus PEMBRO (200 mg IV Q3W). The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included duration of response (DOR) and progression-free survival (PFS) assessed by investigator, overall survival (OS), and safety. **Results:** As of August 23, 2024, 149 pts had received ADA plus PEMBRO (median OS follow-up 22.8 mo): median age was 67 years, 48% were female, and 62% had ECOG PS 1. ORR was 44.3% (95% CI 36.2–52.7); median DOR was 26.3 mo (95% CI 14.9–not estimable [NE]); median PFS was 11.0 mo (95% CI 5.8–14.0) with an 18-mo PFS rate of 37.6% (95% CI 29.0–46.1); and median OS was 18.3 mo (95% CI 14.3–NE) with an 18-mo OS rate of 51.8% (95% CI 43.0–59.8). Efficacy outcomes per PD-L1 status are shown in the Table. Treatment-related adverse events (TRAEs) of any grade (G) were reported in 94.6% of pts (G3/4 in 68.4%); three G5 TRAEs were reported (pneumonia [n=2]; pneumonitis [n=1]). The most common hepatic TRAEs (any G) were increases in alanine aminotransferase (39.6%; G3/4 in 11.4%), aspartate aminotransferase (35.6%; G3/4 in 14.1%), and alkaline phosphatase (19.5%; G3/4 in 6.7%). The discontinuation rate due to hepatic TRAEs was 2.0% for ADA, 6.7% for PEMBRO, and 0.7% for both ADA and PEMBRO. **Conclusions:** In pts with advanced/metastatic *KRAS*^{G12C}-mutated NSCLC, first-line ADA plus PEMBRO demonstrated promising clinical efficacy and a manageable safety profile, regardless of PD-L1 status. These data represent the largest dataset evaluating a first-line KRAS^{G12C} inhibitor plus PD-(L)1 inhibitor in this population presented to date. The phase 3 portion of KRYSTAL-7, comparing first-line ADA plus PEMBRO vs PEMBRO monotherapy in pts with *KRAS*^{G12C}-mutated NSCLC and PD-L1 ≥50%, is ongoing and recruiting. Clinical trial information: NCT04613596. Research Sponsor: Mirati Therapeutics, a Bristol Myers Squibb company.

	PD-L1 <50%(n=95)	PD-L1 ≥50% (n=54)
ORR, n (%)	34 (35.8)	32 (59.3)
95% CI	26.2–46.3	45.0–72.4
Median DOR, mo (95% CI)	(n=34)	(n=32)
	18.2 (11.1–NE)	26.3 (26.3–NE)
Median PFS[a], mo (95% CI)	6.9 (3.9–12.4)	27.7 (8.1–NE)
18-mo rate, % (95% CI)	29.8 (19.8–40.4)	50.7 (35.5–64.0)
Median OS[b], mo (95% CI)	15.5 (11.1–21.0)	NE (15.4–NE)
18-mo rate, % (95% CI)	45.2 (34.3–55.6)	62.4 (47.5–74.1)

[a]Median PFS follow-up 17.5 mo (PD-L1 <50%) and 22.6 mo (PD-L1 ≥50%); [b]Median OS follow-up 21.4 mo (PD-L1 <50%) and 24.9 mo (PD-L1 ≥50%).

8501 Oral Abstract Session

TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) as first-line (1L) therapy for advanced non-small cell lung cancer (aNSCLC).

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Background: TROPION-Lung02 (NCT04526691) evaluated the TROP2-directed antibody-drug conjugate (ADC) Dato-DXd plus pembro combination with or without Pt-CT in aNSCLC. Here we report primary analyses of pts receiving combination therapy in the 1L setting. **Methods:** Pts across 6 cohorts were dosed with Dato-DXd (4 or 6 mg/kg) plus pembro 200 mg alone (doublet) or with pembro plus Pt-CT (triplet; cisplatin 75 mg/m^2 or carboplatin AUC 5) Q3W. PD-L1 expression (tumor proportion score) was assessed locally by immunohistochemistry (22C3 assay). Primary objectives were safety and tolerability; efficacy was a secondary objective. **Results:** As of Apr 29, 2024, 96 pts received either the doublet (n=42) or triplet (n=54) combination as 1L therapy; 29% and 15% of pts were ongoing, respectively. Median ages were 65 (doublet) and 64 years (triplet). Median treatment durations were 9.7 and 5.8 months, respectively. Stomatitis (doublet, 57%; triplet, 33%) and nausea (doublet, 42%; triplet, 48%), primarily Gr 1–2, were the most common adverse events (AEs) across both regimens. Treatment related serious AEs occurred in 5 (12%) and 12 (22%) pts in each cohort and no deaths related to study drug were seen. Efficacy outcomes, including by histology, are summarized in the Table. Biomarker analyses, including efficacy by PD-L1 status, will be presented. **Conclusions:** In this largest data set to date evaluating an ADC combined with an anti-PD-1/L1 agent in the 1L setting, the combination of Dato-DXd plus pembro treatment both with and without Pt-CT elicited durable antitumor activity in pts with aNSCLC. Tolerability of the combinations was as expected, based on known profiles of the individual agents. Clinical trial information: NCT04526691. Research Sponsor: Daiichi Sankyo, Inc.

	All 1L (n=96)		1L, Nonsquamous (n=75)		1L, Squamous (n=21)	
Response, n (%)	Doublet (n=42)	Triplet (n=54)	Doublet (n=33)	Triplet (n=42)	Doublet (n=9)	Triplet (n=12)
Confirmed objective response rate	23 (55)	30 (56)	17 (52)	24 (57)	6 (67)	6 (50)
Complete response	1 (2)	2 (4)	1 (3)	2 (5)	0	0
Partial response	22 (52)	28 (52)	16 (49)	22 (52)	6 (67)	6 (50)
Stable disease	14 (33)	18 (33)	12 (36)	14 (33)	2 (22)	4 (33)
Progressive disease	3 (7)	2 (4)	3 (9)	1 (2)	0	1 (8)
Disease control rate[a]	37 (88)	48 (89)	29 (88)	38 (91)	8 (89)	10 (83)
Median duration of response, mo (95% CI)	20.1 (9.7–NE)	13.7 (5.7–NE)	24.9 (9.7–NE)	18.0 (8.0–NE)	12.0 (5.5–NE)	5.5 (4.1–NE)
Median PFS, mo (95% CI)	11.2[b] (8.2–21.3)	6.8[c] (5.5–11.1)	11.2 (6.1–21.3)	10.8 (5.5–17.3)	10.2 (0.4–NE)	6.7 (1.0–8.2)

[a]Proportion of pts with confirmed CR + PR + SD at 12 wks. [b,c]Median (95% CI) PFS follow-up, mo: [b]17.3 (11.3−26.8); [c]23.5 (17.3−27.9).
mo, months; NE, not evaluable.

LBA8502 **Oral Abstract Session**

CAMPASS: Benmelstobart in combination with anlotinib vs pembrolizumab in the first-line treatment of advanced non-small cell lung cancer (aNSCLC)—A randomized, single-blind, multicenter phase 3 study.

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8503 Oral Abstract Session

Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab.

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Background: Despite the approval of amivantamab (ami) for EGFR exon 20 insertion (ex20ins) mutant NSCLC, an unmet need remains for well-tolerated oral targeted therapies with durable clinical benefit. Zipalertinib (zipa, CLN-081, TAS6417) is a novel EGFR TKI which showed promising clinical activity and manageable safety in a phase 1/2a study in pts with ex20ins NSCLC that progressed on platinum-based chemotherapy (plt-chemo). Here we report the primary data from the pivotal phase 2b REZILIENT1 study of zipa in patients (pts) with advanced or metastatic EGFR ex20ins mutant NSCLC that progressed after prior plt-chemo with or without prior ami. **Methods:** Pts were enrolled in two parallel cohorts (prior plt-chemo, prior plt-chemo and ami) and treated with zipa 100 mg BID. Tumor response was assessed by blinded independent central review (BICR) per RECIST v1.1. Pts with stable, asymptomatic, or treated brain metastases (mets) were allowed. **Results:** As of 10 December 2024 data cut off, 176 pts (51 with prior ami and 125 with plt-chemo) were enrolled with median follow-up of 9.3 months: median age: 65 (33-85), median lines of prior therapy: 2 (1-7), prior PD1/L1: 100 (56.8%), history of brain mets: 68 (38.6%). Among all pts treated, zipa demonstrated a confirmed ORR (cORR) of 35.2%, mDoR of 8.8 months, and mPFS of 9.5 months (table 1). In pts with plt-chemo without ami, the cORR was 40.0%. Of the 51 pts with prior ami, 30 had no other ex20ins-directed therapy, while 21 had also received other ex20ins drugs (such as mobocertinib, sunvozertinib, BLU-451, or poziotinib), the cORR was 30.0% and 14.3%, respectively. Among all pts with brain mets, systemic cORR was 30.9%. The most common treatment-emergent AEs (TEAEs, all-grade) were paronychia, rash, anemia, diarrhea, dry skin, nausea, and stomatitis and the majority of the TEAEs were CTCAE grade 1 or 2. **Conclusions:** Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in pts with exon20ins NSCLC who have received prior platinum-based chemotherapy and for those who received prior amivantamab, a significant and growing unmet need. Clinical trial information: NCT04036682. Research Sponsor: None.

BICR assessed tumor responses per RECIST v1.1.

	N	CR(%)	PR(%)	SD(%)	cORR(%, 95%CI)	mDOR(m, 95%CI)	mPFS(m, 95%CI)
Plt-chemo	125	0	50 (40.0)	55(44.0)	40.0(31.3, 49.1)	8.8(8.3, 11.4)	9.5(7.7,11.5)
Prior Ami ± other ex20ins drug	51	1 (2.0)	11 (21.6)	33(64.7)	23.5(12.8, 37.5)	8.5(4.2, 14.8)	7.3(5.3,9.7)
Total	176	1 (0.6)	61 (34.7)	88(50.0)	35.2(28.2, 42.8)	8.8(8.3, 11.4)	9.5(7.4, 10.0)

CR=complete response, PR=partial response, SD=stable disease.

SOHO-01: Safety and efficacy of BAY 2927088 in patients with advanced *HER2*-mutant non-small cell lung cancer (NSCLC) who were pretreated but naïve to HER2-targeted therapy or had not received any treatment for advanced disease.

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Background: The potent, reversible HER2 tyrosine kinase inhibitor BAY 2927088 has demonstrated manageable safety and anti-tumor activity in patients with advanced NSCLC with *HER2*-activating mutations. Here we report safety and efficacy data from 2 cohorts of the ongoing, open-label, multicenter Phase I/II SOHO-01 trial. **Methods:** Patients with advanced NSCLC with *HER2*-activating mutations were enrolled and received oral BAY 2927088 20 mg twice daily. Patients in expansion/extension Cohort D had disease progression following ≥1 systemic therapies and were naïve to HER2-targeted therapy; patients in expansion Cohort F had not received any systemic therapy for locally advanced or metastatic disease. Safety (MedDRA v27.1 and CTCAE v5.0) was the primary endpoint; anti-tumor activity (RECIST v1.1) was a key secondary endpoint. **Results:** As of October 14, 2024, 81 (D) and 39 (F) patients were treated. Median age was 60 years (D) and 65 years (F), 61.7% (D) and 64.1% (F) were female, 61.7% (D) and 79.5% (F) had never smoked, and 43.2% (D) had received ≥2 systemic therapies. All patients were analyzed for safety and efficacy; response was based on the full analysis set. Treatment-related adverse events (TRAEs) were observed in 96.7% of patients; diarrhea was the most common TRAE leading to dose reduction in 8.3% of patients (Table). No patients discontinued BAY 2927088 treatment because of diarrhea, and no cases of interstitial lung disease were reported. Investigator-assessed objective response rates were 59.3% (95% CI 47.8, 70.1; D) and 59.0% (95% CI 42.1, 74.4; F). Disease control rates (confirmed response or stable disease for ≥12 weeks) were 84.0% (95% CI 74.1, 91.2; D) and 84.6% (95% CI 69.5, 94.1; F). One patient in Cohort D achieved a complete response. **Conclusions:** BAY 2927088 demonstrated manageable safety in both cohorts, consistent with previous reports. Diarrhea was the most common TRAE, but it was manageable and did not lead to treatment discontinuation. Similar response rates were observed in patients with advanced *HER2*-mutant NSCLC who were pretreated but naïve to HER2-targeted therapy and in those treated in the first-line setting. Clinical trial information: NCT05099172. Research Sponsor: Bayer AG.

	Cohort D (n=81)		Cohort F (n=39)	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Any TRAE	78 (96.3)	31 (38.3)	38 (97.4)	8 (20.5)
Most common TRAEs occurring in ≥20% of all patients				
Diarrhea	68 (84.0)	19 (23.5)	32 (82.1)	1 (2.6)
Rash	40 (49.4)	0	22 (56.4)	0
Paronychia	20 (24.7)	0	7 (17.9)	0
Stomatitis	15 (18.5)	1 (1.2)	9 (23.1)	0
Most common TRAE leading to dose reduction				
Diarrhea	9 (11.1)	3 (3.7)	1 (2.6)	1 (2.6)

LBA8505 **Oral Abstract Session**

Savolitinib (Savo) combined with osimertinib (osi) versus chemotherapy (chemo) in EGFR-mutant (EGFRm) and *MET*-amplification (*MET*amp) advanced NSCLC after disease progression (PD) on EGFR tyrosine kinase inhibitor (TKI): Results from a randomized phase 3 SACHI study.

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Patritumab deruxtecan (HER3-DXd) in resistant *EGFR*-mutated (*EGFR*m) advanced non-small cell lung cancer (NSCLC) after a third-generation EGFR TKI: The phase 3 HERTHENA-Lung02 study.

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Background: After disease progression on a 3rd-gen (3G) EGFR TKI for advanced *EGFR*m NSCLC, available therapies provide limited efficacy. HER3-DXd, an antibody-drug conjugate consisting of a fully human mAb to HER3 attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker, showed promising efficacy in HERTHENA-Lung01. **Methods:** HERTHENA-Lung02 (NCT05338970) is a phase 3, randomized, open-label study of HER3-DXd vs platinum-based chemotherapy (PBC) in patients (pts) with advanced *EGFR*m (Ex19del or L858R) NSCLC following disease progression on a 3G EGFR TKI. The primary endpoint is PFS by BICR, tested using a stratified log-rank test. The key secondary endpoint is OS. **Results:** 586 pts were randomized to HER3-DXd or PBC (median age, 64 y; 61% female; 60% Asian). At the 31 May 2024 data cutoff for primary analysis of PFS, median (range) study duration was 10.7 (5.2-21.9) mo, and treatment duration was 5.5 (0.7-16.8) mo and 4.6 (0.7-16.5) mo with HER3-DXd and PBC, respectively. HER3-DXd provided a significant improvement in PFS vs PBC (HR, 0.77; 95% CI, 0.63-0.94; *P*=.011). Median PFS (95% CI) with HER3-DXd vs PBC was 5.8 (5.5-6.8) mo vs 5.4 (5.0-5.6) mo. The PFS rate (95% CI) with HER3-DXd vs PBC was 0.50 (0.44-0.56) vs 0.38 (0.32-0.44) at 6 mo; 0.29 (0.23-0.35) vs 0.19 (0.14-0.25) at 9 mo; and 0.18 (0.12-0.25) vs 0.05 (0.01-0.13) at 12 mo. ORR (95% CI) was 35.2% (29.7%-40.9%) with HER3-DXd vs 25.3% (20.4%-30.6%) with PBC. Median DOR (95% CI) was 5.7 (5.1-7.3) mo with HER3-DXd vs 5.4 (4.1-5.6) mo with PBC. OS data were immature at this protocol-specified interim data cut. In pts with brain metastases at baseline (per CNS BICR), median (95% CI) intracranial PFS was 5.4 (4.0-5.9) mo with HER3-DXd (n=105) vs 4.2 (2.8-5.0) mo with PBC (n=95) (HR, 0.75; 95% CI, 0.53-1.06). TEAEs occurred in 100% of pts in the HER3-DXd arm and 99% in the PBC arm. TEAEs were associated with treatment discontinuation in 33 pts (11%) in the HER3-DXd arm and 27 (10%) in the PBC arm. The most common TEAEs (n [%]) in the HER3-DXd/PBC arms were nausea (168 [57.9]/118 [42.1], thrombocytopenia (151 [52.1]/76 [27.1]), and fatigue (146 [50.3]/118 [42.1]). Grade [G] ≥3 TEAEs occurred in 73% (HER3-DXd) and 57% (PBC) of pts; the difference was driven by a higher rate of G≥3 thrombocytopenia with HER3-DXd (30% vs 7.9%). Each arm had 1 G≥3 bleeding event associated with G≥3 platelet count decreased. Adjudicated drug-related ILD occurred in 14 pts (5%; 11 G1/2, 1 G3, 2 G5) in the HER3-DXd arm. **Conclusions:** HER3-DXd demonstrated statistically significant improvement in PFS vs PBC in pts with *EGFR*m NSCLC post EGFR TKI therapy. The safety profile was manageable, consistent with prior reports. Most common TEAEs were hematologic and gastrointestinal. Follow-up is ongoing, along with further exploration of secondary/exploratory/biomarker endpoints from this data cut. Clinical trial information: NCT05338970. Research Sponsor: Daiichi Sankyo Company, Limited; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

8507 Oral Abstract Session

Sacituzumab tirumotecan (sac-TMT) in patients (pts) with previously treated advanced EGFR-mutated non-small cell lung cancer (NSCLC): Results from the randomized OptiTROP-Lung03 study.

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Background: Sac-TMT (MK-2870/SKB264), a novel TROP2 ADC developed to conjugate a belotecan-derivative topoisomerase I inhibitor, has shown encouraging antitumor activity in EGFRm NSCLC pts in phase I trial (Fang *et al*. AACR 2024). Here, we report the results from a multicenter, randomized, controlled study comparing sac-TMT with docetaxel in previously treated EGFRm NSCLC pts (OptiTROP-Lung03, NCT05631262). **Methods:** Pts with advanced EGFRm NSCLC who had progressed after EGFR TKI and platinum-based chemotherapy were randomized (2:1) to receive sac-TMT 5 mg/kg Q2W or docetaxel 75 mg/m^2. Pts with verified progression on docetaxel could be crossed over to receive sac-TMT if eligible. Hierarchical fixed-sequence testing was employed for efficacy endpoints, including ORR (primary) and PFS, assessed by blinded independent review committee (BIRC), followed by OS. Pre-specified OS interim analysis was conducted alongside final PFS analysis, with the level at one-sided alpha of 1.23% determined by alpha spending function. The crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model. **Results:** A total of 137 pts (median age 56 yrs; 43.8% male; 82.5% ECOG PS 1; 93.4% prior 3rd EGFR TKI) were randomized to receive sac-TMT (n=91) or docetaxel (n=46). At a median follow-up of 12.2 mo (data cutoff: Dec 31, 2024), 25.3% of pts (sac-TMT) vs 4.3% (docetaxel) remained on treatment. The study met its primary and key secondary endpoints. Sac-TMT achieved statistically significant clinical outcomes compared to docetaxel: confirmed ORR (BIRC: 45.1% vs 15.6%, 1-sided p=0.0004; investigator [INV]: 34.1% vs 8.7%), PFS (BIRC: median 6.9 vs 2.8 mo, HR 0.30 [95% CI: 0.20, 0.46], 1-sided p<0.0001; INV: median 7.9 vs 2.8 mo, HR 0.23 [95% CI: 0.15, 0.36]), and OS (median not reached [NR] for both groups, HR 0.49 [95% CI: 0.27, 0.88], 1-sided p=0.007), with 36.4% of pts in docetaxel group crossed over to receive sac-TMT. The RPSFT model adjusted median OS was 9.3 mo for docetaxel and NR for sac-TMT (HR for OS 0.36 [95% CI: 0.20, 0.66]). Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 56.0% of pts in sac-TMT group vs 71.7% in docetaxel group, and treatment-related SAEs were 16.5% vs 41.3%. Most common (≥ 10%) grade ≥ 3 TRAEs (sac-TMT vs docetaxel) were neutrophil count decreased (42.9% vs 58.7%), WBC count decreased (25.3% vs 52.2%), stomatitis (16.5% vs 2.2%), anemia (12.1% vs 4.3%) and febrile neutropenia (0% vs 19.6%). No cases of ILD were reported in sac-TMT group. **Conclusions:** Sac-TMT demonstrated improved ORR, PFS and OS compared to docetaxel, with manageable safety profile in pts with previously treated advanced EGFRm NSCLC. These results highlight significant survival benefits and suggest that sac-TMT could emerge as a new standard of care for this population. Clinical trial information: NCT05631262. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

8509 Clinical Science Symposium

First-in-class PD-1/IL-2 bispecific antibody IBI363 in patients (Pts) with advanced immunotherapy-treated 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 to block PD-1 checkpoint and rejuvenate exhausted tumor-specific T cells by cis-activating α-bias IL-2. It has potential to address the unmet clinical need of patients (pts) with immunotherapy-resistant and cold tumors. Here, we report safety and efficacy results from a phase I, multi-center, first-in-human study (NCT05460767) of IBI363 in pts with advanced NSCLC. **Methods:** Eligible pts with advanced NSCLC who failed or were intolerant of standard therapy were enrolled and received IBI363 intravenously at dose levels of 2/10/300/600 ug/kg every week (QW), 0.3/0.6/1 mg/kg every two weeks (Q2W) or 1.5/2/3/4 mg/kg every three weeks (Q3W). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS) by investigator per RECIST v1.1. **Results:** As of December 6, 2024, 136 NSCLC pts were enrolled (median age: 61 years; prior treatment lines ≥2: 72%). Most patients were treated with IBI363 at 0.6/1 mg/kg Q2W (n=56), 1.5 mg/kg Q3W (n=11) or 3 mg/kg Q3W (n=57). Treatment-emergent adverse events (TEAEs) occurred in 135/136 pts (≥G3: 42.6%). TEAEs led to treatment discontinuation in 9 (6.6%) pts and TEAEs led to death in 4 (2.9%) pts with only 1 (0.7%) event considered treatment-related (unexplained death). Most common TEAEs were arthralgia (51.5%; 3.7% ≥G3), anemia (43.4%; 3.7% ≥G3), and rash (38.2%; 4.4% ≥G3). In pts with squamous cell carcinoma who had at least 1 post-baseline tumor assessment, 30 (including 1 pt who had not received PD-(L)1 before enrolled) and 27 pts had been treated with IBI363 3 mg/kg and 1/1.5 mg/kg, respectively; more encouraging efficacy signals were observed in the 3 mg/kg group: ORR 43.3% vs 25.9%, confirmed ORR 36.7% vs 25.9%, DCR 90.0% vs 66.7%, median PFS 7.3 (95% CI: 6.0-11.7) vs 5.5 (95% CI: 1.5-8.3) months, with a median follow up time of 7.3 vs 11.1 months. In the PD-(L)1 treated adenocarcinoma pts with no actionable genomic alterations who had at least 1 post-baseline tumor assessment, 25 and 30 pts had been treated with IBI363 3 mg/kg and 0.6/1/1.5 mg/kg, respectively, similarly, 3 mg/kg group showed higher ORR (28.0% vs 16.7%), confirmed ORR (24.0% vs 13.3%), DCR (76.0% vs 63.3%) and median PFS (4.2 [95% CI: 3.0-not estimable] vs 2.8 [95% CI: 1.4-5.1] months, with a median follow up of 5.9 vs 16.5 months). A higher ORR of 29% versus 4% and a longer PFS of 5.3 months compared to 2.7 months were observed in smokers (N=31, 56.4%). Notably, in patients at all dose levels with a tumor cell proportion score (TPS) under 1%, the ORR was 45.5% for squamous cell carcinoma (N=22) and 29.4% for adenocarcinoma (N=17). **Conclusions:** IBI363 was well tolerated with encouraging and durable efficacy observed in pts with advanced NSCLC who progressed to PD-(L)1, especially in the squamous subtype. Clinical trial information: NCT05460767. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Efficacy and safety of MHB088C, a novel B7-H3-targeted ADC, in patients with relapsed extensive-stage small cell lung cancer (ES-SCLC): Subgroup analysis from a phase 1/2 multicenter study.

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Background: MHB088C is a novel B7-H3-targeted antibody-drug conjugate (ADC) containing the potent SuperTopoi payload that is 5 to 10 times more potent than Dxd. Initial findings from an ongoing phase 1/2 study indicated that MHB088C was generally well tolerated, with early signs of clinical activity (ASCO 2024, abstract #3012). This analysis presents efficacy and safety results for the subset of pts with ES-SCLC. **Methods:** This study consisted of 2 parts: dose-escalation (part 1) and expansion (part 2). Part 1 evaluated the safety and tolerability of MHB088C at doses ranging from 0.8 to 4.0 mg/kg, administered intravenously every 2 (Q2W) or 3 weeks (Q3W). Doses of 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W were selected for part 2. Part 2 focused on assessing safety and prospective efficacy of MHB088C in selected tumor types, including SCLC. **Results:** At data cutoff (January 3, 2025), a total of 91 pts with relapsed ES-SCLC had received ≥ 1 dose of MHB088C (1.6 mg/kg Q2W, n=28; 2.0 mg/kg Q2W, n=33; 2.4 mg/kg Q3W, n=30). MHB088C showed encouraging efficacy in relapsed ES-SCLC (Table). The objective response rates were 42.9%, 57.6%, and 46.7% in the 1.6, 2.0, and 2.4 mg/kg cohorts, respectively, with median progression-free survival (PFS) of 5.5, 5.9, 5.5 months. Safety data were consistent with previous reports. The most common grade≥3 treatment-related adverse events were neutropenia, platelet count decreased and anemia. The 1.6 and 2.0 mg/kg cohorts exhibited favorable safety profiles, with only single-digit rates of the aforementioned hematologic adverse events. One case (1.0%) of mild interstitial lung disease (ILD) was reported. **Conclusions:** MHB088C demonstrated promising anti-tumor activity and favorable safety in previously treated pts with ES-SCLC. A Phase 3 study is planned to compare the efficacy and safety of MHB088C with standard-of-care chemotherapy in relapsed ES-SCLC. Clinical trial information: CTR20231298. Research Sponsor: None.

	1.6 mg/kg Q2W (n=28)	2.0 mg/kg Q2W (n=33)	2.4 mg/kg Q3W (n=30)
Unconfirmed ORR, (%)	42.9	57.6	46.7
Confirmed ORR, (%)	21.4	42.4	43.3
DCR, n (%)	89.3	87.9	93.3
Median PFS, month	5.5	5.9	5.5

8511 Clinical Science Symposium

First report of efficacy and safety results from a phase 2 trial evaluating BNT327/PM8002 plus chemotherapy (chemo) as first-line treatment (1L) in unresectable malignant mesothelioma.

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Background: Malignant mesothelioma is a rare neoplasm with a high unmet medical need. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. BNT327 has shown encouraging preliminary activity in thoracic malignancies incl. SCLC (ESMO 2023) and NSCLC (ASCO & ESMO 2024). **Methods:** After a safety run-in (n=6), this ongoing, multicenter, single-arm phase 2 clinical trial recruited chemo naive pts (pts) aged ≥18 yrs with unresectable malignant mesothelioma (pleural (MPM) or peritoneal (MPeM)) to evaluate BNT327 30 mg/kg Q3W IV combined with 4-6 cycles pemetrexed and platinum, followed by BNT327 maintenance. Primary endpoints were efficacy (ORR per RECIST 1.1 for MPeM, mRECIST 1.1 for MPM) and safety (CTCAE V5.0). **Results:** As of 25 Oct 2023, 31 pts, median age 58 yrs (range 43-71), 80.6% ECOG PS 1 and 83.9% with metastatic disease had been enrolled, of which 23 had MPM and 8 MPeM. At the cutoff date of 20 Dec 2024, the median exposure duration was 16.0 mo (95% CI 8.1, 19.5) and median follow-up time 19.3 mo (95% CI 17.3, 20.9). In 23 pts with MPM, 1 pt had a CR and 9 had PRs as BOR, resulting in a confirmed ORR (cORR) of 43.5%. 10 pts had SD and 1 non-CR/non-PD, giving a DCR of 87.0%. Median PFS (mPFS) was 11.8 mo, and median DOR was 11.8 mo. The 12 mo OS rate was 82.6% (95% CI 60.1, 93.1), with median OS not yet reached. Among 13 pts with MPM of epithelioid histology, cORR was 30.8%, DCR was 84.6% and mPFS was 16.6 mo. Among 8 pts with MPeM, 6 had PR as BOR, leading to a cORR of 75.0%. 2 pts had SD, resulting in a DCR of 100%; median DOR was 16.3 mo. Median PFS and OS were not yet reached, with an OS rate of 62.5% (95% CI 22.9, 86.1) at 12 mo. 6 pts with MPeM of epithelioid histology displayed a cORR of 83.3%, DCR of 100% and mPFS of 19.5 mo. All pts experienced TRAEs, 93.5% of pts (29/31) of Grade (G) 3-4. 5 pts (16.1%) had G 3-4 treatment-related SAEs. 5 pts (16.1%) experienced an irAE, 1 (3.2%) of G 3-4. The most common TRAEs were decreased neutrophil count (27 pts, 87.1%), decreased white blood cell count (26 pts, 83.9%), proteinuria (24 pts, 77.4%), anemia (23 pts, 74.2%), decreased platelet count (19 pts, 61.3%), and nausea (16 pts, 51.6%). 6 pts discontinued treatment due to TRAEs; no treatment-related deaths occurred. 9 pts remain on treatment. **Conclusions:** BNT327 plus chemo as a 1L regimen for mesothelioma showed encouraging efficacy, including in tumors of epithelioid histology. AEs were consistent with those expected for the treatment regimen. Clinical trial information: NCT05918107. Research Sponsor: Biotheus Inc.

8512 Rapid Oral Abstract Session

Telisotuzumab adizutecan (ABBV-400; Temab-A), a c-Met protein–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced *EGFR*-mutated (MT) non-squamous (NSQ) non-small cell lung cancer (NSCLC): Results from a phase 1 study.

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Background: c-Met protein (also known as MET protein) expression is increased in NSCLC and is a negative prognostic indicator. Temab-A is an ADC comprising the c-Met protein–targeting mAb telisotuzumab conjugated to a novel topoisomerase 1 inhibitor payload. A phase 1 study (NCT05029882) of Temab-A in advanced solid tumors is ongoing. In dose expansion, Temab-A had manageable safety and promising efficacy in pts with NSQ *EGFR* wildtype NSCLC (*Ann Oncol*. 2024;35:1257MO). Herein, we present the results for pts with advanced *EGFR* MT NSQ NSCLC. **Methods:** Pts (≥18 yr) whose disease had progressed after platinum-based chemotherapy doublet and tyrosine kinase inhibitor(s) (TKIs) were enrolled. Pts received Temab-A at 2.4 (n=36) or 3.0 (n=5) mg/kg Q3W. Primary objectives were evaluating safety, tolerability, PK, and preliminary efficacy of Temab-A. Tumor tissue c-Met protein expression was assessed centrally by IHC. **Results:** Forty-one pts were enrolled in the *EGFR* MT cohort. Median age was 64 yr (43–88), 63% were female, and 32% had baseline brain metastases. Median prior therapies was 3 (1–8); 93% had prior anti-EGFR treatment. Median treatment duration was 9.2 months; median follow-up was 9.7 months. TEAEs of any grade/grade ≥3 occurred in 100%/73% of pts. The most common any-grade TEAEs were hematologic (83%) and gastrointestinal (81%); any-grade TEAEs in ≥30% of pts were anemia (63%), nausea (61%), vomiting (37%), decreased appetite (34%), and neutropenia (34%). Grade ≥3 TEAEs were mostly hematologic (42%), and most common were anemia (27%) and neutropenia (22%). The any-grade adjudicated interstitial lung disease/pneumonitis rate was 7% (grade ≥3: 2%). TEAEs leading to discontinuation occurred in 20% of pts. Four deaths occurred; 1 (pneumonitis) was considered related to study drug. All pts with post-baseline data had some decrease in tumor burden. ORR was 63% (Table); similarly high ORR was observed regardless of c-Met protein expression. Responses occurred irrespective of *EGFR* L858R alterations, exon 19 deletions, or TKI resistance mutations including T790M and C797S. As of the data cut (Sep 2024), 19 (46%) pts remain on treatment. Time-to-event endpoints are immature; to date, 54% of responders have a DOR of ≥6 months. Exploratory biomarker analysis is ongoing. **Conclusions:** Temab-A has a manageable safety profile with promising clinical activity in pts with 3L+ NSQ *EGFR* MT NSCLC, meriting further investigation. Clinical trial information: NCT05029882. Research Sponsor: AbbVie Inc.; n/a

Efficacy	NSQ *EGFR* MT NSCLC (n=41)
Best overall response,[a] n (%)	
PR	26 (63)
SD	12 (29)
NE/Not assessed	3 (7)
ORR,[a] n (%)	26 (63)
CBR12,[a] n (%)	34 (83)
P[PFS at 6 mo], % (95% CI)	80 (63, 89)
P[OS at 6 mo], % (95% CI)	93 (79, 98)

[a]Confirmed responses. P, probability.

8513 Rapid Oral Abstract Session

Efficacy and CNS results from a randomized subset of the phase 2 SAVANNAH study comparing savolitinib (savo) + osimertinib (osi) combination with savo + placebo (PBO).

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Background: The MET pathway is a known mediator of EGFR-TKI resistance and represents a therapeutic vulnerability to select MET-TKIs. Savo is an oral, highly selective MET-TKI that, when combined with osi, has the potential to overcome MET-driven resistance after progressive disease (PD) on osi. The Phase 2 SAVANNAH study has demonstrated clinically meaningful activity with the combination of savo + osi in patients (pts) with EGFR-mutated (EGFRm) advanced NSCLC and MET overexpression/amplification (NCT03778229). Isolating the efficacy of savo in the use of savo + osi is a key question for this combination. **Methods:** A subset of SAVANNAH included eligible pts who had EGFRm advanced NSCLC with MET overexpression (IHC 3+ intensity in ≥90% of tumor cells [IHC3+/≥90%]) and/or amplification (≥10 MET gene copies by FISH [FISH10+]) after PD on first-line (1L) osi; asymptomatic stable brain metastases (treated/untreated) were allowed. Pts were randomized 2:1 (double-blind) to savo 300 mg BID + osi 80 mg QD, or savo 300 mg BID + PBO (stratified by investigator [INV] assessed baseline [BL] brain metastases [yes/no]), until INV-assessed PD per RECIST 1.1. Brain imaging occurred at BL and PD; pts with brain metastases were re-imaged at each tumor assessment to PD. Endpoints included objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS) by BICR and INV; CNS PFS, and presence/absence of CNS lesions at PD by BICR. **Results:** Overall, 73 pts were randomized (savo + osi n=48; savo + PBO n=25). At BL, median age: 67 vs 65 years, female: 73% vs 64%, White: 73% vs 52% in the savo + osi and savo + PBO arms, respectively. Efficacy outcomes (ORR, DoR, and PFS) were higher with savo + osi than savo + PBO (Table). CNS PFS events by CNS BICR occurred in 5/14 (36% savo + osi) and 2/4 pts (50% savo + PBO). In pts without BL brain metastases, none of the 13 pts (savo + osi) with RECIST PD by BICR had a new CNS lesion; 6/11 pts in the savo + PBO arm developed a new CNS lesion. **Conclusions:** In EGFRm advanced NSCLC with MET IHC3+/≥90% and/or FISH10+ status after PD on 1L osi, efficacy of savo 300 mg BID + osi was numerically greater than savo + PBO and showed promising CNS activity. To date, this is one of the largest randomized data sets presented evaluating an oral MET-TKI in EGFRm NSCLC. Efficacy findings from SAVANNAH suggest that targeting both EGFR and MET is key and support further investigation of savo + osi and CNS activity in the Phase 3 SAFFRON study. Clinical trial information: NCT03778229. Research Sponsor: AstraZeneca.

	Assessment	Savo + osi (n=48)	Savo + placebo (n=25)
ORR, % (95% CI)	BICR	58 (43, 72)	16 (5, 36)
	INV	54 (39, 69)	24 (9, 45)
DoR, mo, median (95% CI)	BICR	11.8 (6.0, NC)	4.5 (2.6, NC)
	INV	8.0 (4.9, 11.7)	4.2 (2.6, NC)
PFS, mo, median (95% CI)	BICR	8.3 (5.8, 15.1)	3.6 (1.4, 5.7)
	INV	7.6 (5.6, 11.0)	2.7 (1.4, 4.1)

BICR, blinded independent central review; CI, confidence interval; mo, months; NC, not calculable.

8514 Rapid Oral Abstract Session

Phase 3 study of benmelstobart in combination with chemotherapy followed by sequential combination with anlotinib for the first-line treatment of locally advanced or metastatic squamous non-small cell lung cancer (sq-NSCLC).

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Background: PD-1/ PD-L1 inhibitors plus platinum-based chemotherapy is the standard first-line therapy for locally advanced or metastatic sq-NSCLC. Improvements in clinical benefits of sq-NSCLC receiving antiangiogenic agents and immune-checkpoint inhibitors have remained elusive, highlighting an urgent need to develop new therapeutic strategies. TQB2450-III-12 is a multicenter, randomized, double-blind, parallel-controlled phase III study of benmelstobart (PD-L1 inhibitor) in combination with chemotherapy followed by sequential combination with anlotinib (multi-targeted angiogenesis inhibitor) versus tislelizumab plus chemotherapy as first-line therapy for locally advanced or metastatic sq-NSCLC. **Methods:** Patients with unresectable locally advanced or metastatic sq-NSCLC without prior systematic therapy were randomized 1:1 to receive benmelstobart (1200 mg, Q3W) plus chemotherapy for 4 cycles followed with benmelstobart plus anlotinib (10mg, P.O., D1-D14, Q3W) (group A) or tislelizumab (200mg, Q3W) plus chemotherapy for 4 cycles followed with tislelizumab (group B). Paclitaxel (175 mg/m^2, day 1) and carboplatin (area under the concentration [AUC] of 5, day 1) were given every 3 weeks. The primary endpoint was PFS per RECIST 1.1 by independent review committee and the key secondary endpoint was OS. Here we present the primary interim analysis for PFS per prespecified analysis plan. **Results:** As of March 1, 2024, 565 patients were randomized 1:1 to group A and group B. Baseline characteristics were well balanced. Median PFS was significantly improved in group A (10.12 months, 95% CI, 8.54–NE) versus group B (7.79 months, 95% CI, 6.87–9.69), HR=0.64 (98.35% CI, 0.45–0.93; P =0.0038). The subgroup analysis showed that PFS benefit favored group A in almost all subgroups, particularly in patients with ECOG PS 0 (HR 0.44, 0.23-0.84), PD-L1 expression (tumor proportion scoring) of 1-49% (HR 0.47, 0.30-0.73), and age <65 years (HR 0.59, 0.39-0.90). The ORR of group A and group B were 71.9% and 65.1%, respectively. The median DoR was longer in group A (9.69 months, 95% CI, 8.44, NE) than Group B (8.34 months; 95% CI, 5.78-NE) HR=0.58 (95% CI, 0.38, 0.88; P=0.0091). OS was immature. ≥Grade 3 benmelstobart/tislelizumab or anlotinib/ placebo-related adverse events was 61.57% in group A and 51.06% in group B. There was no difference of the grade 5 treatment-emergent adverse events (TEAE) between the treatment groups (group A: 5.69%, group B: 5.63%). The discontinuation of any treatment components by TEAE was 4.27% in group A and 5.28% in group B. **Conclusions:** Benmelstobart in combination with chemotherapy followed by sequential combination with anlotinib significantly improved PFS, with a manageable safety profile. It might be a new first-line treatment for sq-NSCLC. Clinical trial information: NCT05718167. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

8515 Rapid Oral Abstract Session

Plasma-guided adaptive first-line chemoimmunotherapy for non-small cell lung cancer (NSCLC).

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Background: There is clinical uncertainty as to which patients with advanced/metastatic NSCLC require first-line treatment with chemoimmunotherapy (ChemoIO) versus treatment with immune checkpoint inhibitor (ICI) monotherapy. While PD-L1 expression can predict for ICI response, it is an imperfect biomarker. Cell-free DNA (cfDNA) clearance is a dynamic biomarker that predicts for benefit to immunotherapy in metastatic NSCLC. Here we evaluate the use of cfDNA clearance after initial cycles of first-line ICI monotherapy to guide early treatment intensification via addition of platinum-based chemotherapy. **Methods:** In this prospective clinical trial patients with advanced/metastatic PD-L1 positive (TPS $\geq$ 1%) NSCLC were treated with two cycles of pembrolizumab monotherapy and then assessed for plasma and radiographic response. Plasma response was defined as $\geq$50% reduction in the maximum variant allele fraction and/or persistent low-shedding status at cycle two day one compared to pretreatment using an amplicon-based plasma NGS assay. Patients with radiographic response or with radiographic stable disease with plasma response continued pembrolizumab monotherapy. Patients with RECIST stable disease without plasma response were intensified to carboplatin doublet (paclitaxel squamous/pemetrexed nonsquamous) plus pembrolizumab. Those with radiographic progression ended study treatment. **Results:** Forty patients were enrolled across six sites. 56.8% (n=21) had nonsquamous histology and 37.5% (n=15) were PD-L1 low (TPS 1-49%). 36 patients (90%) completed a C2D1 plasma response assessment, with plasma response to ICI monotherapy in 58.3% (n=21) patients (57.1% in PD-L1 low, 59.1% in PD-L1 high [TPS $\geq$ 50%]). At cycle 3, 52.8% (n = 19) continued pembrolizumab monotherapy (7 with PR, 12 with SD and plasma response). 19.4% (n=7) had radiographic SD and plasma non-response and received intensification to ChemoIO (pemetrexed in 6, paclitaxel in 1). 27.8% (n=10) went off study treatment for PD (n=4), death (n=1), adverse event (n=3), or patient/physician decision (n=2). 20% (n=3) of PD-L1 low patients and 16% (n=4) of PD-L1 high patients received treatment intensification to ChemoIO. The ORR to this adaptive treatment strategy was 50%, the median PFS was 11 months (95% CI 3.4-15.9 months), and the median OS was 14.9 months (95% CI 8.2-27.2 months). Median PFS was higher in patients with plasma response (16.4 vs 4.8 months; HR 0.34; 95% CI 0.12-0.92). Fewer patients were treated with platinum doublet chemotherapy than would have been predicted by PD-L1 status alone (17.5% vs 37.5%). **Conclusions:** The use of a cfDNA-guided adaptive treatment design resulted in a median progression-free survival which compared favorably to historical controls with less upfront exposure to platinum doublet chemotherapy. Further study within a randomized prospective trial design is needed to validate this treatment strategy. Clinical trial information: NCT04166487. Research Sponsor: Dunkin Donuts Breakthrough Grant; Dana-Farber Cancer Institute; ASCO CDA.

8516 Rapid Oral Abstract Session

Randomized trial of relevance of time-of-day of immunochemotherapy for progression-free and overall survival in patients with non-small cell lung cancer.

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Background: Recent retrospective studies across 10 cancer types suggest increased efficacy of Early rather than Late Time-of-Day (ToD) infusions of immune checkpoint inhibitors (ICIs). This first randomized controlled phase III trial aimed to determine the relevance of ToD of immunochemotherapy for efficacy in patients (pts) with non-small cell lung cancer (NSCLC). **Methods:** Eligible pts received ICI pembrolizumab or sintilimab combined with chemotherapy, as 1st line treatment for stage IIIC-IV NSCLC without driver mutation. Pts were randomly assigned in a 1:1 ratio to receive the initial four immunochemotherapy cycles either before 15:00 in the Early ToD group, or after 15:01 in the Late ToD group. We hypothesized an increase in median progression-free survival (PFS) from 6 months in the Late ToD group up to 10 months in the Early ToD group. A total of 210 pts was required to validate PFS differences, using a two-sided significance level (α, 0.05; β, 0.80). Secondary endpoints were overall survival (OS) and objective response rate (ORR). **Results:** From 09/2022 to 05/2024, 210 pts (median age, 61 y.o.; male sex, 90.5%; Stage IV, 80.5%) were randomized. The pts in each group had similar characteristics. After a median follow-up of 18.9 months (mo.), median PFS was 13.2 mo. [95% CI, 10.1-16.3] in the early ToD group and 6.5 mo. [5.9-7.1] in the late ToD group, with a hazard ratio (HR) of an earlier progression of 0.43 [0.31-0.60] ($P < 0.0001$). Median OS was not reached in the early ToD group, whereas it was 17.8 mo. [14.2-21.5] in the late ToD group (HR of an earlier death, 0.43 [0.27-0.69]; $P = 0.0003$). ORR was 75.2% [66.8%-83.6%] for early ToD and 56.2% [46.5%-56.8%] for Late ToD ($P = 0.007$). PFS, OS, and ORR were consistently improved in the early ToD group regardless of age, sex, performance status, tumor stage, histology, PD-L1 status, and ICI agent. **Conclusions:** In this randomized trial, all three efficacy endpoints of immunochemotherapy were significantly improved through Early vs Late ToD dosing in pts with previously untreated stage IIIC-IV NSCLC. The near doubling in PFS and OS in our trial support the need for further randomized trials to determine the relevance of ToD for ICI efficacy and their underlying circadian mechanisms in pts with various cancer types. Clinical trial information: NCT05549037. Research Sponsor: National Natural Science Foundation of China.

8517 Rapid Oral Abstract Session

Hypoxia-responsive CEA CAR-T cells therapy for relapsed or refractory non-small cell lung cancer: A single-arm, open-label, phase I trial.

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Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide. Chimeric antigen receptor (CAR)-T cell therapy has achieved significant success in targeted tumor cells eradication. However, data on CAR-T therapies in NSCLC remain limited. This study evaluates the safety and efficacy of CEA CAR-T cell therapy in r/r NSCLC. **Methods:** Adult metastatic NSCLC patients with relapse after ≥2 lines of treatment were enrolled and administered intravenous CEA CAR-T cells at three dose levels (0.75×10^6, 1.5×10^6, and 3×10^6 CEA CAR-T cells/kg).Peripheral blood samples were collected on day 28 post-infusion and analyzed using 10x Genomics single-cell RNA sequencing (scRNA-seq).The primary endpoint was safety , and secondary endpoints including efficacy and pharmacological evaluation. **Results:** From August 1, 2023, to July 15, 2024, a total of 18 patients were screened, and 15 received CAR-T infusion. The median age was 60 years , with a median of 4 prior therapy lines (range 2-10 lines). Among 6 patients receiving the maximum dose (3×10^6 cells/kg), no dose-limiting toxicities, grade 4 cytokine release syndrome or ICANS were observed. No adverse events were observed during a three-month long-term safety evaluation. With a median follow-up of 5.7 months, 7 patients achieved PR, 6 had SD, and 2 experienced PD. The best DCR was 87%, and ORR was 47%. Notably, patients with ≥30% intense and complete CEA staining in tumor cells and no brain metastases showed better PFS (72.7% vs. 25.0%, p=0.03) and OS (90.9% vs. 0%, p=0.003). CEA CAR-T cells reached maximum concentration at a median of 10 days (range 7—60 days) post-infusion. At the third month, all 12/12 patients with available CAR-T cell copy number data maintained high levels of CAR-T cells, with a median of 8,236 gDNA copies/μg , and in the patient with a follow-up of 13 months, CEA CAR-T cells were still detectable at 50,760 gDNA copies/μg. The scRNA-seq was performed in 12 patients. Responders exhibited a higher percentage of NK cells in a less exhausted state, characterized by reduced activity of immunosuppressive pathways and lower expression of stress-associated genes. Further cell-cell communication analysis suggested HLA-DRB1 expression in NK cells might be influenced by interactions with the CD244 in $CD8^+$ T cells. **Conclusions:** A single infusion of hypoxia-responsive CEA CAR-T demonstrated promising efficacy and manageable safety in r/r NSCLC. The findings highlight the potential role of specific NK cell states and immune interactions in the therapeutic effects of CEA CAR-T therapy. Research Sponsor: the National High Technology Research and Development Program of China; 2021YFA1101500; the National Natural Science Foundation of China; 81873427 and 82070217; National Natural Science Foundation of China; 82473220, 81772477; Fundamental Research Program of Shanxi Province; 202303021221192; 2023 COVID-19 Research Project of Shanxi Provincial Health Commission; 2023XG005; Four“batches”innovation project of invigorating medical through science and technology of shanxi province; 2023XM003; Research and Innovation Team Project for Scientific Breakthroughs at Shanxi Bethune Hospital in Shangxi Province; 2024OAXIANG01.

Clinical response at different doses.

	All dose level (n=15)	Dose level 1 (n=3)	Dose level 2 (n=6)	Dose level 3 (n=6)
Disease control	13 (87%)	2 (66%)	6 (100%)	5 (84%)
Overall response	7 (47%)	1 (33%)	4 (67%)	2 (33%)
Partial response	7 (47%)	1 (33%)	4 (67%)	2 (33%)
Disease stable	6 (40%)	1 (33%)	2 (33%)	3 (50%)

Data are n (%).

S1900E: A phase II study examining impact of co-mutations on sotorasib for previously treated stage IV/recurrent *KRAS* G12C mutated (MUT) non-squamous (Non-sq) non-small cell lung cancer (NSCLC) (ECOG-ACRIN led Lung-MAP Sub-study).

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Background: In previously treated *KRAS* G12C MUT NSCLC, the allosteric KRAS G12C inhibitor sotorasib had superior outcomes compared to docetaxel (ORR 28% vs 13%). S1900E was the first to prospectively test sotorasib in *KRAS* G12C MUT NSCLC according to co-mutations (CO-MUT) in tumor suppressor genes such as *TP53*, *STK11*, and *KEAP1*. We report on the results of *TP53* and *STK11* CO-MUT cohorts of S1900E and hypothesized that CO-MUT would not impact the efficacy of sotorasib. **Methods:** Pts with *KRAS* G12C MUT identified by FoundationOne CDx tissue assay in the LUNGMAP screening master protocol were assigned to S1900E. Pts with stage IV/recurrent non-sq NSCLC who had progressed after ≥1 line of systemic therapy, and were ECOG PS 0-1 were eligible. There were 3 biomarker cohorts: 1 (*TP53* CO-MUT & wild type [WT] *STK11*, *KEAP1/NFE2L2/CUL3)*; 2 (*STK11* CO-MUT & WT *TP53*, *KEAP1/NFE2L2/CUL3)*; 3 (all others). The primary objective was to evaluate the confirmed objective response rate (ORR) per RECIST 1.1 in each cohort. Accrual goals for Cohorts 1 and 2 were 40 and 25 evaluable pts, respectively, based on a 1-stage binomial design with 90% power to rule out a 14% ORR (historical second-line docetaxel ORR) at the 1-sided 5% level. **Results:** S1900E completed accrual with 118 total pts and 103 evaluable from Apr 2021-Dec 2024; 59 (57%) were female and 86 (84%) were non-Hispanic white. In the *TP53* CO-MUT (N=48; 40 evaluable) and *STK11* CO-MUT (N=28; 25 evaluable) cohorts, respectively, 48% and 68% received only one prior line of therapy, 70% and 76% received both platinum chemotherapy and PD-(L)1 immunotherapy, 68% and 24% were female, known PD-L1 expression (≥1% / ≥50%) was 95%/45% and 43%/0%, and almost all had smoked. In the *TP53* CO-MUT cohort, confirmed ORR was 35% (CI 23-47). In the *STK11* CO-MUT cohort, confirmed ORR was 16% (CI 4-28). Disease control rate (DCR), duration of response (DOR), investigator progression-free survival (PFS), and overall survival (OS) (Table 1) had numerically higher values in the *TP53* CO-MUT cohort. Adverse event rates ≥ Grade 3 were similar to prior reports of single agent sotorasib. **Conclusions:** *TP53* CO-MUT cohort met its primary endpoint, while the *STK11* CO-MUT cohort did not, suggesting that *STK11* CO-MUT have detrimental effect on sotorasib in *KRAS* G12C NSCLC. S1900E Cohort 3, which may include *KEAP1/NFE2L2* and other CO-MUT, will be reported later, as will resistance patterns identified through ctDNA analysis. Clinical trial information: NCT04625647. Research Sponsor: NIH/NCI/NCTN grants U10CA180888, U10CA180819.

	TP53 CO-MUT (N=40)	*STK11* CO-MUT (N=25)
ORR (90% CI)	**35%** (23-47)	**16%** (4-28)
DCR (90% CI)	**78%** (67-88)	**60%** (44-76)
Follow-Up Median mo	19.5	16.8
DOR [Median mo (95% CI)]	**7.1** (2.7-11.5)	**6.2** (1.6-NA)
PFS [Median mo (95% CI)]	**5.7** (3.0-8.4)	**4.1** (2.6-7.1)
OS [Median mo (95% CI)]	**18.2** (12.2-33.7)	**8.0** (5.1-14.2)

8519 Rapid Oral Abstract Session

Safety and efficacy of olomorasib + immunotherapy in first-line treatment of patients with *KRAS* G12C-mutant advanced NSCLC: Update from the LOXO-RAS-20001 trial.

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Background: Olomorasib, a potent, highly selective second-generation KRAS G12C inhibitor has demonstrated promising activity and a favorable safety profile in *KRAS* G12C-mutant NSCLC when combined with pembrolizumab. Here, we report updated results from LOXO-RAS-20001, a phase 1/2 trial (NCT04956640) of olomorasib, in patients (pts) with *KRAS* G12C-mutant NSCLC receiving olomorasib + pembrolizumab, and focus on pts receiving the combination as first-line (1L) therapy. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC (tissue or plasma) in the 1L metastatic setting were eligible. Any PD-L1 level (0-100%) was permitted. Two dose levels of olomorasib (50 and 100 mg, orally twice daily) + pembrolizumab were evaluated. Adverse events (AE) were assessed across all treated pts; objective response rate (ORR) per RECIST v1.1 was assessed in pts with at least one post-baseline response assessment or who discontinued treatment before the first response assessment. **Results:** As of 13 November 2024, a total of 43 pts received olomorasib + pembrolizumab (50 mg, n=21; 100 mg, n=22) in the 1L setting with a median age of 70 years (range, 58-83); 10 (23%) were PD-L1 negative, 13 (30%) were PD-L1 1-49%, 19 (44%) were PD-L1 ≥50% and 1 (2%) was unknown. Median duration of follow-up was 5.5 months (range, 0.1-24.4). All grade TRAEs in ≥10% of pts (olomorasib- and/or pembrolizumab-related) were ALT/AST increased (33%/30%), diarrhea (28%), fatigue (16%), nausea (14%), pruritus (12%) and decreased appetite (12%); grade 3 TRAEs in ≥10% of pts were ALT/AST increased (26%/16%). Hepatic events were overall manageable with dose adjustments and/or corticosteroids. No pts had co-occurring total bilirubin increased or discontinued both study treatments due to hepatic events. Pneumonitis was reported in 2 pts (grades 2 and 4). The AE profile was generally comparable across doses. TRAEs led to olomorasib dose reduction in 16% of pts and discontinuation of combination treatment in 5% (2) pts. At time of data-cut, 33 pts remain on treatment and 10 discontinued. Among the 40 efficacy-evaluable 1L pts, at a median follow-up of 9 months (95% CI, 6-12), ORR was 70% (28/40; 95% CI, 54-83; 1 CR, 23 PR, 4 unconfirmed PR pending/ongoing) across all PD-L1 expression levels and disease control rate (DCR) was 90% (36/40; 95% CI, 76-97). In pts with PD-L1 ≥50%, ORR was 82% (14/17; 95% CI, 57-96) and DCR was 94% (16/17; 95% CI, 71-99). Median duration of response was not reached and progression free survival rate at 6 months was 80%. **Conclusions:** Olomorasib + pembrolizumab in the 1L metastatic setting demonstrated favorable safety and encouraging antitumor activity in pts with *KRAS* G12C-mutant advanced NSCLC across all PD-L1 expression levels. A global, registrational study investigating this combination in 1L NSCLC is currently enrolling (SUNRAY-01, NCT06119581). Clinical trial information: NCT04956640. Research Sponsor: Eli Lilly and Company.

8520 Rapid Oral Abstract Session

Sosimerasib monotherapy in patients with previously treated KRAS G12C–mutated non-small cell lung cancer: Primary results of a phase 2 study.

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Background: KRAS G12C mutation is a poor prognostic factor for Non-Small Cell Lung Cancer (NSCLC). Sosimerasib is a novel potent and highly selective KRAS G12C inhibitor. Here we report the primary results from a Phase 2 study of sosimerasib in patients with advanced NSCLC harboring the KRAS G12C mutation. **Methods:** In this open-label, multicenter, single-arm, pivotal phase 2 study, patients with locally advanced/metastatic KRAS G12C mutated NSCLC after failure with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitors were enrolled and treated with sosimerasib 500mg orally once daily. The primary endpoint was objective response rate (ORR) assessed by independent review committee (IRC) per RECIST v1.1. The secondary endpoints included duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** A total of 145 patients were enrolled. The median age was 63 years, 85.5% were male, and previous treatment lines ranged from 1 to 3, with 84.1% patients having received both platinum-based chemotherapy and anti-PD-1/PD-L1 inhibitors. By 3 November 2024, the median follow-up duration was 6.8 months (range: 0.4-10.9). IRC-confirmed ORR was 52.4% (95% CI: 44.0-60.8) with median TTR of 1.4 months (range: 1.2-8.4), DCR was 87.6% (95% CI: 81.1-92.5). Median PFS was 7.2 months (95% CI: 5.6-NA). Median DOR and median OS were not reached. At the data cutoff date, Treatment-related adverse events (TRAEs) were reported in 138 (95.2%) patients, grade 3-4 TRAEs occurred in 58 (40.0%) patients. No TRAE was fatal. Most common TRAEs were alanine aminotransferase increased (66.2%), aspartate aminotransferase increased (62.8%), anaemia (31.7%), gamma-glutamyl transferase increased (26.2%) and blood alkaline phosphatase increased (22.1%). TRAEs leading to drug interruption, dose reduction, and permanent discontinuation occurred in 35 (24.1%), 15 (10.3%), and 3 (2.1%) patients, respectively. **Conclusions:** Sosimerasib monotherapy has shown promising anti-tumor activity with manageable safety profile in locally advanced/metastatic NSCLC patients harboring KRAS G12C mutation. This study is still ongoing and longer follow-up will provide more solid evidence. Clinical trial information: ChiCTR2200059986. Research Sponsor: None.

8521 Poster Session

First-line (1L) datopotamab deruxtecan (Dato-DXd) + rilvegostomig in advanced or metastatic non-small cell lung cancer (a/mNSCLC): Results from TROPION-Lung04 (cohort 5).

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Background: 1L anti–PD-(L)1 antibodies ± chemotherapy are standard of care for patients (pts) with a/mNSCLC without actionable genomic alterations (AGAs). However, not all pts experience response to treatment. Dato-DXd, a TROP2-directed antibody-drug conjugate, has shown efficacy in pts with a/mNSCLC alone or combined with PD-(L)1 inhibitors. Rilvegostomig, a bispecific antibody targeting PD-1 and TIGIT, has also shown preliminary efficacy in pts with a/mNSCLC. Consequently, the combination of Dato-DXd and rilvegostomig may have the potential to enhance responses. **Methods:** TROPION-Lung04 (NCT04612751) is a phase 1b, open-label, dose-escalation and expansion study enrolling pts with a/mNSCLC without AGAs. In cohort 5 (C5; C5a, PD-L1 tumor proportion score [TPS] ≥50% and C5b, PD-L1 TPS <50%) treatment-naïve pts received Dato-DXd (6 mg/kg) + rilvegostomig IV Q3W. Pts were treated until disease progression or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) per investigator (RECIST v1.1). **Results:** At data cut-off (DCO; 24 Oct, 2024), 40 pts had received Dato-DXd + rilvegostomig (C5a, n=20; C5b, n=20); 29 (72.5%) had non-squamous histology. Median treatment duration was 5.1 months (range 0.7–18.6); 21 pts discontinued Dato-DXd (adverse events [AEs], n=9; progressive disease [PD], n=9), 20 discontinued rilvegostomig (AEs, n=8; PD, n=9) and 20 (50.0%) pts were still on any study treatment at DCO. All pts (N=40, 100%) had treatment-emergent adverse events (TEAEs); 60.0% (n=24) had grade ≥3 TEAEs and 50.0% (n=20) had serious TEAEs. The most common TEAEs were stomatitis (52.5%; grade 3, 2.5% [n=1]), fatigue (grouped term, 50.0%, all grade 1/2), alopecia (45.0%, all grade 1/2) and nausea (42.5%, all grade 1/2). Ocular surface events occurred in 12 pts (30.0%); grade 4, n=1. Adjudicated drug-related interstitial lung disease/pneumonitis was reported in 5 pts (grade 3, n=2). There were six fatal TEAEs (respiratory failure, general physical health deterioration, death, intestinal perforation, sepsis, cardiac arrest); however, none were related to either study treatment. Confirmed ORR for all pts was 57.5% (95% CI 40.9, 73.0); disease control rate was 95.0% (95% CI 83.1, 99.4). Responses were observed across both squamous (45.5%; 95% CI 16.7, 76.6) and non-squamous histologies (62.1%; 95% CI 42.3, 79.3) and all PD-L1 levels. DoR and PFS were immature at DCO. **Conclusions:** The safety profile for the combination of Dato-DXd + rilvegostomig was consistent with the expected toxicities of each agent and without new safety findings. Dato-DXd + rilvegostomig had encouraging activity as 1L treatment for pts with a/mNSCLC without AGAs, with responses seen in both histologies and across all PD-L1 levels. Clinical trial information: NCT04612751. Research Sponsor: This trial is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

8522 Poster Session

Exploratory ctDNA analyses for the EVOKE-1 study in metastatic non-small cell lung cancer (mNSCLC).

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Background: In NSCLC, ctDNA analysis complements assessment of clinical efficacy and identifies molecular alterations that may be prognostic or predictive of treatment. EVOKE-1 compared sacituzumab govitecan (SG) vs docetaxel in mNSCLC that had progressed on platinum-based and anti–PD-(L)1 therapy. Although statistical significance was not met, SG showed numerical improvement in overall survival (OS) vs docetaxel. Here, we assessed the value of ctDNA as a biomarker in available samples from EVOKE-01. **Methods:** The biomarker evaluable population (BEP) comprised 497 patients (pts), representing 82% of the ITT population. Cell-free DNA was extracted from blood collected at baseline and cycle 2 day 1 (C2D1). Samples were analyzed using the Guardant Infinity assay, a tumor-agnostic platform that measures ctDNA levels and gene variants from a comprehensive gene panel. **Results:** ctDNA was detected at baseline in 449 pts (90.3% of BEP), and higher ctDNA was a negative prognostic for OS, regardless of treatment. mOS was 12.7 vs 10.0 mos (HR 1.58, 95% CI: 1.11–2.26) for $<$ vs $\geq$ median ctDNA level with SG and 10.8 vs 7.2 mos (HR 1.78, 95% CI: 1.28–2.46) with docetaxel. ctDNA was undetectable in 48 pts who had a longer survival (mOS NR in either arm) than those with detected ctDNA. At C2D1, median ctDNA reduction was 59% and 75% with SG and docetaxel (P=.33); $\geq$50% reduction was achieved in 103 (44%) vs 121 pts (51%), respectively. Changes in ctDNA levels at C2D1 were prognostic, with pts achieving $\geq$50% reduction having a longer OS than those with $<$50% reduction of ctDNA. Actionable genomic alterations identified included *KRAS*, *EGFR*, *ALK*, *ROS*, *ERBB2*, *MET*, and *NTRK* alterations. As expected from the required local/central testing for mutations at study entry, only a small number of pts with *EGFR/ALK* alterations were identified. *KRAS* mutations had a negative prognostic effect, whereas the group of pts with *EGFR/ALK/ROS* alterations was too small for conclusive results. Analysis of mutations (*TP53*, *KEAP1*, *STK11*) potentially contributing to anti–PD-(L)1 resistance showed that between SG and docetaxel, 167 (68%) and 171 pts (68%) had *TP53* mutations and 184 (75%) and 194 pts (77%) had $\geq$1 of these 3 mutations. The frequency of these mutations was similar across pts with PD/SD and those with CR/PR as best response to last prior PD-(L)1 therapy. Harboring *TP53* mutations was a negative prognostic factor in both arms: mOS was 11.3 mos vs NA (HR 1.67, 95% CI: 1.11–2.54) with *TP53* mutation vs wildtype with SG and 9.2 vs 13.9 mos (HR 1.71, 95% CI: 1.18–2.47), respectively, with docetaxel. *KEAP1/STK11* mutations were also negative prognostic markers. **Conclusions:** This analysis did not identify differences in ctDNA clearance with SG vs docetaxel. Regardless of treatment and in line with previous reports, high ctDNA was a negative prognostic marker for OS in mNSCLC. Furthermore, alterations of *KRAS*, *TP53*, and *KEAP1/STK11* represent negative prognostic factors. Clinical trial information: NCT05089734. Research Sponsor: Gilead Sciences, Inc.

Whole-genome and transcriptome landscape of actionable driver-negative lung adenocarcinoma.

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Background: Driver-negative lung adenocarcinoma (DN-LUAD) without actionable genomic alterations (AGAs) has a poor prognosis. A deeper understanding of its molecular background, particularly across the entire genome, is crucial for improving risk assessment and therapeutic development. **Methods:** We performed deep whole-genome sequencing (WGS; tumor depth: 100–120x, normal depth: 30x, paired-end reads: 150 bp) and RNA sequencing using fresh-frozen tissues from four institutions. DN-LUAD was defined as LUAD without known actionable mutations or gene fusions. We analyzed somatic mutations, copy number alterations (CNAs), and structural variations (SVs). Tumors were classified as whole-genome doubling (WGD) if more than half of the autosomal tumor genome showed at least two copies in the major copy numbers of somatic cells. HRDetect score ≥0.7 was used to determine the presence of homologous recombination DNA repair deficiency (HRD) (Davies H, et al. Nat Med. 2017). Gene Set Enrichment Analysis (GSEA) was used for pathway analysis. **Results:** Among the 745 patients (pts), 517 were classified as having DN-LUAD. WGS identified AGAs undetected by whole-exome sequencing (WES) in 33 (4.4%) pts (*EGFR* 13, *KRAS* 7, *BRAF* 5, *ERBB2* 4, *MET* 4, and *HRAS* 1). The frequently observed genomic alterations in DN-LUAD are shown in the Table. WGD was observed in 62.1% (n = 321) of DN-LUADs and was significantly associated with higher TMB, CNA, and SV burden. Tumor suppressor gene (TSG) mutations in *TP53*, *STK11*, and *KEAP1*, as well as *CDKN2A* copy number loss and SVs, were significantly more frequent in WGD pts. HRD was identified in 19 DN-LUAD pts (3.7%), with a significantly higher frequency in the WGD group (WGD vs. without WGD; 4.98% vs. 1.5%, p = 0.016). GSEA showed significant ($q < 0.0001$) upregulation of cell cycle pathways (E2F targets, G2M checkpoint, and MYC targets) and downregulation of immune pathways (allograft rejection and interferon-gamma response) in DN-LUADs with WGD. **Conclusions:** This largest-ever WGS study identified AGAs undetectable by WES and uncovered a subgroup of DN-LUAD characterized by increased genomic instability driven by multiple TSG alterations associated with WGD, which was also more likely to exhibit HRD. WGD was associated with the upregulation of cell cycle pathways and the downregulation of immune pathways. These findings highlight the critical role of WGS in elucidating the pathogenesis of DN-LUAD. Research Sponsor: None.

	All N = 517	WGD n = 321	Without WGD n = 196	*p*
Median TMB (Mutations/Mb)	6.6	10.2	3.0	<0.0001
Median No. of CNAs	101	117	77	<0.0001
Median No. of SVs	185	244	103	<0.0001
TP53	381 (74)	277 (86)	104 (53)	<0.0001
SMARCA4	59 (11)	43 (13)	16 (8)	0.094
STK11	56 (11)	42 (13)	14 (7)	0.049
CDKN2A	44 (9)	33 (10)	11 (6)	0.092
KEAP1	40 (8)	34 (11)	6 (3)	0.003
***CDKN2A* loss**	106 (21)	78 (24)	28 (14)	0.009
***MET* amplification**	44 (9)	34 (11)	10 (5)	0.045
CDKN2A	135 (26)	95 (30)	40 (20)	0.028
FHIT	125 (24)	99 (31)	26 (13)	<0.0001

Potential biomarker of PD-L1 expression phenotypes in tumor and immune cells for combined PD-1 and CTLA-4 blockade therapies in advanced NSCLC.

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Background: Pembrolizumab-based chemo-immunotherapies (Pembro) and nivolumab plus ipilimumab-based immunotherapies with or without 2 cycles of chemotherapies (Nivo+Ipi) have improved survival in patients with advanced NSCLC compared to the conventional chemotherapy. However, biomarkers to support appropriate choice in these immunotherapies remain unclear. **Methods:** From 2019 to 2023, this multicenter, observational study retrospectively reviewed advanced NSCLC patients who received first-line Pembro or Nivo+Ipi and had evaluable PD-L1 expression status on tumor cells (tumor proportion score [TPS], 22C3) and immune cells (immune cell [IC] score, SP142). Survival curve comparisons between treatments were conducted using restricted mean survival time (RMST) estimation in place of Log-rank test, when the proportional hazard assumption was not met. Additionally, the genomic and expression profiles associated with TPS and IC score were assessed using whole-exome sequencing and RNA sequencing in available NSCLC samples. **Results:** A total of 198 patients were included (Pembro/Nivo+Ipi: 137/61). In the Pembro cohort, patients with high TPS ($\geq$ 50%) had significantly longer progression-free survival (PFS) than those with low TPS ($<$ 50%) (median PFS [mPFS, months]: 8.1 vs. 7.1, P = 0.02; hazard ratio [HR] = 0.59 [0.38–0.92]), while no significant difference in PFS was observed based on IC score (high vs. low: mPFS 7.4 vs. 6.8, P = 0.11, HR = 0.72 [0.49–1.07]). In the Nivo+Ipi cohort, PFS did not significantly differ by TPS (high vs. low: mPFS 4.0 vs. 4.0, P = 0.26; HR = 0.51 [0.16–1.68]), whereas patients with high IC score ($\geq$ 1) had significantly longer PFS than those with low IC score (= 0) (mPFS: 7.7 vs. 2.8, P = 0.04; HR = 0.53 [0.28–0.98]). A durable PFS benefit of Nivo+Ipi over Pembro was observed only in patients with low TPS/high IC score (mPFS: 12.4 vs. 6.6; Schoenfeld individual test: $P < 0.05$; $RMST_{Nivo+Ipi}/RMST_{Pembro}$ [2 years] = 1.5, P = 0.049, Table). Sequence analyses revealed that tumors with low TPS/high IC score had significantly higher tumor mutational burden (TMB) than other tumors (median TMB: 18.2 vs. 1.9 [/mb]; $P < 0.001$) and showed distinct enrichment in antigen presentation and T-cell receptor signaling pathways. **Conclusions:** Nivolumab plus ipilimumab-based immunotherapies demonstrated superior durable response compared to pembrolizumab-based chemo-immunotherapies in patients with low TPS/high IC score. PD-L1 phenotypes based on TPS and IC score could guide the optimal selection of immunotherapies for advanced NSCLC patients. Research Sponsor: None.

Efficacy comparison in patients with low TPS (< 50%)/high IC score (≥ 1).

Treatments	mPFS (months)	PFS rate at 2 years	RMST at 2 years	$RMST_{Nivo+Ipi}/RMST_{Pembro}$ at 2 years	P value
Pembrolizumab-based chemo-immunotherapies	6.6	6%	8.5	1.5 [1.0–2.3]	0.049
Nivolumab plus ipilimumab-based immunotherapies	12.4	41%	12.9		

8525 Poster Session

Effects of immediate elevation of inflammatory cytokines after platinum, pemetrexed, and pembrolizumab on antitumor efficacy in advanced non-squamous, non-small cell lung cancer.

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Background: Inflammatory cytokines play a crucial role in the tumor microenvironment and may serve as potential biomarkers for the sustained efficacy of PD-1/L1 inhibitors combined with chemotherapy. Numerous studies have been conducted on cytokines to date; however, studies on cytokine fluctuations immediately after administration remain notably limited. **Methods:** A prospective observational study at Wakayama Medical University enrolled 110 patients with thoracic malignancies receiving PD-1/L1 inhibitors as first line therapy from Oct 2019 to Nov 2023. We analyzed 41 patients with advanced or recurrent non-squamous, non-small cell lung cancer treated with platinum, pemetrexed, and pembrolizumab (CPP). Peripheral blood samples were collected at baseline, day 3($\pm$1), day 7($\pm$1), and day 42. 40 serum proteins were quantified using a Luminex 200 analyzer and a Milliplex MAP system. The association between cytokine increase and progression-free survival (PFS) was statistically analyzed. **Results:** Patient characteristics were as follows: median age (range), 71 (46-84) years; male/female, 33/8; adenocarcinoma/other, 36/5; performance status (PS) 0/1, 8/33; stage IV/recurrence, 31/10; cisplatin/carboplatin, 16/25; PD-L1 tumor proportional score (TPS) $<$1/1-49/$\geq$50, 14/12/15. The dose of dexamethasone at the first treatment was 6.6 mg (3.3-9.9 mg). Among the 40 measured cytokines, 10 showed an average increase of $\geq$50% from baseline to Day 3, of which 7 were inflammatory or immune-stimulatory (IL-1α, G-CSF, CXCL10, CXCL13, IL-6, IL-15, MCP-1). Five of them decreased by Day 7. Eight cytokines showed an increase of $\geq$50% from baseline to Day 7, of which 4 were inflammatory, and all of them were among those $\geq$50% elevated at Day 3 (IL-1α, G-CSF, IL-6, MCP-1). A univariate Cox proportional hazard analysis revealed that an increase in IL-6 or MCP-1 at day 3 (Day 3/0 ratio $>$1) was significantly associated with longer PFS [IL-6: HR 0.41 (95%CI 0.17-0.97), p=0.049; MCP-1: HR 0.43 (95% CI 0.19-0.97), p=0.042]. After adjustment for age, PS, and PD-L1 TPS in the multivariate analysis, MCP-1 remained a significant predictive factor (HR 0.36, 95% CI 0.13-0.97, p=0.043). PFS curves were significantly different between MCP-1 increased and decreased cases (median PFS 463 vs. 201 days, p=0.036), with 12-month PFS rates of 60% and 31%, and 25-month PFS rates of 50% and 8%, respectively. **Conclusions:** This study demonstrated that inflammatory cytokines increased immediately after CPP, despite the concomitant use of dexamethasone for antiemesis. Furthermore, the immediate increase in MCP-1 after treatment was associated with prolonged PFS, suggesting its potential as a predictor of treatment efficacy and providing insights into the mechanisms of chemo-immunotherapy. Research Sponsor: Japan Society for the Promotion of Science: JSPS; JP21K07247.

8526 Poster Session

Characterization of histology-dependent immunobiological differences in metastatic NSCLC: Implications for treatment with PD-1 and LAG-3 inhibitors.

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Background: The treatment paradigm for metastatic non-small cell lung cancer (mNSCLC) without actionable genomic alterations does not differentiate between histologic subtypes for the use of checkpoint inhibitors. However, there is growing recognition of differences between squamous (SQ) and non-squamous (NSQ) lung cancer that may impact response to treatment. For example, in the RELATIVITY-104 study, addition of the LAG-3 inhibitor relatlimab to anti-PD-1 + platinum-doublet chemotherapy (PDCT) showed improved clinical benefit among patients with PD-L1 ≥1%, which was further enriched with NSQ histology. There is an unmet need to understand differences in tumor biology between NSQ and SQ histologies in patients with mNSCLC to inform on mechanisms underlying differences in clinical activity of anti-PD-1 + PDCT, alone or in combination with a LAG-3 inhibitor. **Methods:** Data were obtained from molecular profiling of baseline tumor samples of treatment-naive patients enrolled in the phase 3 CheckMate 227 (NCT02477826) study. PD-L1 (N=1739) and LAG-3 expression (N=540) were evaluated using immunohistochemistry. Somatic mutations and copy number alterations were assessed using the FoundationOne panel (N=1368). Gene expression, analyzed through RNA sequencing (N=465), was used to characterize differences in tumor immunobiology, including differential gene expression, pathway enrichment, and calculation of cell type-specific scores representing different immune and stromal cell types. **Results:** Transcriptional and mutational analyses revealed clear differences between NSQ and SQ tumors. NSQ tumors showed enrichment of immune pathways (e.g., antigen presentation and T cells), while SQ tumors exhibited enrichment of pathways consistent with rapid cell growth and numerous oncogenic alterations (e.g., p53 and PIK3CA). Differences in the relationship between tumor PD-L1 expression and the tumor microenvironment by histology were observed; PD-L1 expression was positively correlated with immune infiltration scores in NSQ but not SQ tumors, suggesting that drivers of PD-L1 expression may differ by histology. Consistent with previously published reports for mNSCLC, PD-L1 expression enriched for 1L anti-PD-1 + PDCT benefit in NSQ but not SQ tumors (CheckMate 227 Part 2). Differences in LAG-3 ligand expression by histology and PD-L1 expression were noted. Both canonical LAG-3 ligands, MHC-II and FGL-1, were expressed at higher levels in NSQ tumors. Within NSQ tumors, relative expression of each ligand varied by PD-L1 expression, with high MHC-II expression specifically in NSQ, PD-L1 ≥1% tumors. **Conclusions:** These data provide a supporting mechanistic rationale for the use of tumor histology in addition to PD-L1 expression to identify patients who would benefit from the addition of a LAG-3 inhibitor to PD-1 inhibitor + PDCT. Clinical trial information: NCT02477826. Research Sponsor: Bristol Myers Squibb.

Unraveling relatlimab (RELA)-specific biology: Biomarker analyses in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with 1L nivolumab (NIVO) + RELA high-dose (HD) and platinum-doublet chemotherapy (PDCT).

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Background: The addition of RELA HD, a lymphocyte activation gene-3 (LAG-3) inhibitor, to NIVO + PDCT has improved clinical benefits vs NIVO + PDCT for pts with PD-L1 expression ≥1% and NSQ histology in RELATIVITY-104 study. We report exploratory biomarker analyses from this study to elucidate mechanisms underlying NIVO + RELA HD + PDCT activity. **Methods:** Baseline and on-treatment blood samples were analyzed by flow cytometry for pharmacodynamic (PD) changes in immune cell populations including proliferating LAG-3-expressing CD4+ and CD8+ effector memory (EM) and central memory (CM) T cells. Baseline tumor samples were analyzed by monoplex immunohistochemistry (IHC) for tumor cell PD-L1, LAG-3, and CD8 expression. Associations between biomarkers and overall response rate (ORR) and progression free survival (PFS) were assessed. **Results:** NIVO + RELA HD + PDCT significantly modulated levels of proliferating LAG-3 expressing EM and CM T cells in the periphery on-treatment; no such PD change was observed with NIVO + PDCT. Among pts with NSQ histology, baseline tumor LAG-3 expression ≥1% showed improved ORR and median PFS in both treatment arms compared with LAG-3 <1%. Further, the benefit of RELA HD addition to NIVO + PDCT was also seen in patients with LAG-3 <1%, suggesting that baseline LAG-3 expression at 1%, unlike PD-L1 expression, would not help identify patients who can benefit from LAG-3 inhibition (Table). In contrast to NSQ, the same association trend of PD-L1 and LAG-3 expression with efficacy was not observed in pts with SQ histology, which could be partly attributable to the limited sample size in some SQ subgroups. Interestingly, PD-L1 ≥1% is more strongly correlated with CD8 T cells in NSQ as compared to SQ. **Conclusions:** These data represent the first in-depth biomarker analyses from a randomized phase 2 study to reveal that RELA can expand proliferating LAG-3 expressing T cells in NSCLC. NIVO + RELA HD + PDCT activity might be particularly robust in pts with NSQ histology and PD-L1 expression ≥1%, where CD8 T cells are enriched. The ongoing phase 3 RELATIVITY-1093 study is evaluating 1L NIVO + RELA HD + PDCT vs standard-of-care pembrolizumab + PDCT in mNSCLC. Clinical trial information: NCT04623775. Research Sponsor: Bristol Myers Squibb.

Efficacy of NIVO + RELA HD + PDCT vs NIVO + PDCT in pts with NSCLC by baseline histology, PD-L1 and LAG-3 expression.

NIVO + RELA HD + PDCT vs NIVO + PDCT	NSQ, PD-L1 ≥1% (n = 50 vs 48)	NSQ, PD-L1 <1% (n = 48 vs 46)	NSQ, LAG-3 ≥1% (n = 56 vs 42)	NSQ, LAG-3 <1% (n = 38 vs 42)	SQ, PD-L1 ≥1% (n = 29 vs 23)	SQ, PD-L1 <1% (n = 22 vs 21)	SQ, LAG-3 ≥1% (n = 38 vs 34)	SQ, LAG-3 <1% (n = 13 vs 10)
PFS HR (90% CI)	0.55 (0.36–0.85)	1.24 (0.84, 1.83)	0.81 (0.54, 1.22)	0.79 (0.51, 1.23)	0.78 (0.46, 1.34)	1.25 (0.7, 2.23)	0.97 (0.61, 1.52)	0.98 (0.45, 2.15)
ORR, %	58% vs 39.6%	35.4% vs 34.8%	57.1% vs 45.2%	34.2% vs 26.2%	44.8% vs 43.5%	81.8% vs 66.7%	52.6% vs 55.9%	84.6% vs 50%

Genomic and circulating tumor DNA landscape in young-onset non-small cell lung cancer.

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Background: To explore the underlying biology in young patients (pts) with non-small cell lung cancer (NSCLC), we analyzed the genomic diversity of serial circulating tumor DNA (ctDNA). **Methods:** We analyzed ctDNA data from a national database Guardant Health NGS panel of 83 loci from a population of 5210 NSCLC pts between the ages of 18-50 collected between 1/20-6/2020, with longitudinal samples from 931 pts (2 samples), 286 pts (3 samples), and 166 pts (> 3 samples) with at least 90 days between the first and last sample. We evaluated statistical significance using Spearman correlation, the Mann-Whitney U test, the signed-rank test, or Fisher's exact test. We used Gene Ontology enrichment analysis and Ingenuity for genomics and MetaboAnalyst for metabolomic pathway analysis. **Results:** Out of 5,210 young adult (YA) NSCLC pts, 6,624 liquid NGS tests were conducted, of which 9% of pts were between 18 and 35 years old, defined as very young adults (VYA), and 91% were between 35 and 50 years old, defined as young adults (YA). Overall, mutation frequency increased significantly with age (Spearman r = 0.08, $p = 1.9 \cdot 10\text{-}10$). Most pts were female (2,826, 54%).Mutation frequency was higher in males (Mann-Whitney $p = 1.8 \cdot 10^{-5}$). The rate of targetable alterations was 48% in YA and 46% in VYA-NSCLC patients, with EGFR being the most common alteration (24% in YA, 18.4% in VYA). Of the 13 genes with mutation frequencies of at least 5%, there are 11 genes with more alterations in males and 2 in females. Immune-related pathways were infrequently altered (4.8%), while TP53/DNA damage (50%), EGFR/RAS (30%), PI3K (35%), and β-catenin/APC (28%) pathways were frequently altered. Endocrine resistance pathways altered second most (p=0.03), likely due to distinct biology or treatment effects. Metabolomic analysis identified methylation-related pathways (28.6%), including MAT1A, as the most prominent metabolomic pathways (p = 0.02). Longitudinal analysis revealed increased ctDNA burden with tumor progression. Comparing the first-to-last ctDNA in the same pts, we identified genes with distinct patterns of alteration in YA and VYA pts (Tab-1). TP53 and EGFR remain highly mutated but with stable mutation rates (TP53: 51% to 52%, EGFR: 41% to 41%). **Conclusions:** Targetable alterations are highly prevalent in YA and VYA NSCLC, exhibiting distinct ctDNA mutation frequencies upon serial testing. DNA methylation can potentially regulate gene expression in metabolic pathways, suggesting therapeutic avenues. Research Sponsor: None.

Highest positive and negative changes in mutation frequencies from first to last sample in YA and VYA NSCLC using Guardant serial ctDNA.

Genes in 1st and last sample (Difference range)	Young (35-50 Yo)	Very young (<35 Yo)	Uncorrected Signed Ranked Test P-Value
Rise in mut freq.			
KRAS	0.35	0.25	0.01
MET	0.65	0.16	0.00
BRAF	0.50	0.60	0.08
APC	0.16	0.33	0.33
Decline mut freq. in at least one group	0.56	-0.25	0.01
PIK3CA	0.08	-0.20	0.75
BRCA2	1.0	-0.20	0.08
MYC			

8529 Poster Session

Sacituzumab tirumotecan (sac-TMT) in combination with tagitanlimab (anti-PD-L1) in first-line (1L) advanced non-small-cell lung cancer (NSCLC): Non-squamous cohort from the phase II OptiTROP-Lung01 study.

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Background: Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a novel linker to conjugate a belotecan-derivative topoisomerase I inhibitor. The complementary mechanisms of action of sac-TMT and PD-1/L1 inhibitor may provide more potent antitumor activity. Sac-TMT was safety combined with tagitanlimab (anti-PD-L1, KL-A167) and demonstrated promising activity for the combination in 1L NSCLC (*Fang et al. 2024*). Here, we report updated results by PD-L1 expression with additional enrolled patients (pts) and extended follow-up from non-squamous cohort in the phase II OptiTROP-Lung01 study (NCT05351788). **Methods:** Advanced NSCLC pts with no prior systemic therapy and no actionable genomic alterations were enrolled to receive sac-TMT (5 mg/kg Q3W or Q2W) plus tagitanlimab (1200 mg Q3W or 900 mg Q2W) until disease progression or unacceptable toxicity. Tumor assessments per RECIST 1.1 were performed once every 6 weeks for the first 12 months (mo), and every 12 weeks thereafter. The PD-L1 tumor proportion score (TPS) was detected by IHC 22C3 pharmDx assay. **Results:** As of 30 Dec 2024, 81 pts (median age: 60.0 years; male: 79.0%; ECOG PS 1: 91.4%) with non-squamous histology were enrolled. The majority (66.7%) had PD-L1 TPS$<$ 50% (42.0% for $<$ 1%, 24.7% for 1% - 49% and 33.3% for $\geq$ 50%). After median follow-up of 17.1 mo, the confirmed objective response rate (ORR) was 59.3%; The disease control rate (DCR) was 91.4%; Median duration of response (mDOR) was 16.5 mo (95%CI: 11.7, 22.1); Median progression free survival (mPFS) was 15.0 mo (95%CI: 10.8, 24.8). Among pts with PD-L1 TPS$<$ 1%, the confirmed ORR was 47.1%; mPFS was 12.4 mo (95%CI: 7.6, 15.4); while for pts with PD-L1 TPS$\geq$ 1%, the confirmed ORR was 68.1%; mPFS was 17.8 mo (95%CI: 14.5, NE). Among pts with PD-L1 TPS$\geq$ 50%, the confirmed ORR was 77.8%; mPFS was 17.8 mo (95%CI: 10.8, NE). Most common ($\geq$ 10%) Grade $\geq$ 3 treatment-related adverse events (TRAEs) were neutrophil count decreased (45.7%), anemia (16.0%), white blood cell count decreased (14.8%) and stomatitis (11.1%). No TRAE led to treatment discontinuation or death. **Conclusions:** Sac-TMT in combination with tagitanlimab demonstrated promising antitumor activity in treatment-naive advanced non-squamous NSCLC. The durable clinical activities were observed regardless of PD-L1 expression. This combination therapy showed a tolerable safety profile based on known profiles of the individual agents, with no new safety signals observed. A phase 3 study comparing sac-TMT plus pembrolizumab *vs.* chemotherapy plus pembrolizumab as 1L treatment for PD-L1 negative pts with advanced non-squamous NSCLC is ongoing (NCT06711900). Clinical trial information: NCT05351788. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Clinical, genomic, and pathological features and therapeutic outcomes of non-small cell lung cancer with MTAP-loss.

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Background: MTAP-cooperative PRMT5 inhibitors are under development for MTAP-loss solid tumors. However, clinical, genomic, and pathological features of non-small cell lung cancer (NSCLC) with MTAP-loss are still unclear. **Methods:** Using the large-scale clinical-genomic database of LC-SCRUM-Asia, the clinical, genomic, and pathological features and therapeutic outcomes of patients with NSCLC with MTAP-loss were investigated. MTAP-loss, CDKN2A-loss, targetable genomic alterations, and tumor mutation burden (TMB) were analyzed using FoundationOne CDx. PD-L1 TPS was evaluated using PD-L1 IHC 22C3. **Results:** MTAP status was successfully analyzed in 253 samples from NSCLC patients between February 2017 and May 2018. MTAP loss was detected in 54 of 253 (21%) NSCLCs distributed in 33 of 170 (19%) adenocarcinoma, 15 of 60 (25%) squamous cell carcinoma and 6 of 23 (26%) others. The patients with MTAP-loss NSCLC showed no significant difference in age, sex, smoking history, and ECOG PS compared to the patients with MTAP-intact NSCLC. In the patients with MTAP-loss NSCLC, the median age was 68 years old, 63% were male, 78% were ever smokers, and all had ECOG performance status (PS) 0-1. CDKN2A-loss was detected in 100% of MTAP-loss and 12% of MTAP-intact. The frequency of targetable genomic alterations did not differ significantly between MTAP-loss and MTAP-intact NSCLC (44% vs 38%). The frequencies of EGFR and KRAS mutations in MTAP-loss NSCLC were 20% and 15%, respectively, and those in MTAP-intact NSCLC were 21% and 10%, respectively. TMB was significantly lower in MTAP-loss NSCLC than in MTAP-intact NSCLC (Median 6.3 vs. 7.6 Mut/Mb, P = 0.03). MTAP-loss NSCLC tended to have lower PD-L1 TPS than MTAP-intact NSCLC (TPS ≥1%; 50 % vs 63%, P = 0.08). In the adenocarcinoma without targetable genomic alterations cohort, eight patients with MTAP-loss and 47 patients with MTAP-intact received platinum-based chemotherapies without immune-checkpoint inhibitors (ICIs) as the first-line treatment and six patients with MTAP-loss and 45 patients with MTAP-intact were treated with ICIs alone as any line treatment. There was no significant difference in the progression-free survival (PFS) of platinum-based chemotherapies as the first line between the patients with MTAP-loss and MTAP-intact (median 4.7 vs 4.6 months, HR [95%CI] 0.74 [0.35-1.55], P = 0.42). On the other hand, the patients with MTAP-loss treated with ICIs alone showed significantly shorter PFS compared to the patients with MTAP-intact treated with ICIs alone (median 1.9 vs 6.2 months, HR [95%CI] 3.62 [1.05-12.5], P = 0.04). **Conclusions:** The relatively low TMB and PD-L1 TPS might be involved in shortening the PFS in patients with MTAP-loss treated with ICIs alone. Other than that, NSCLC with MTAP-loss showed no distinct feature in patient characteristics, histopathology, and co-occurring targetable genomic alterations. Research Sponsor: AstraZeneca K.K.; Amgen K.K.; MEDICAL& BIOLOGICAL LABORATORIES CO., LTD.; Eisai Co., Ltd.; MSD K.K.; ONO PHARMACEUTICAL CO., LTD.; Kyowa Kirin Co., Ltd.; DAIICHI SANKYO Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; CHUGAI PHARMACEUTICAL CO., LTD.; Nippon Boehringer Ingelheim Co., Ltd.; Bristol-Myers Squibb K.K.; Janssen Pharmaceutical K.K.; Bayer Yakuhin, Ltd.; AbbVie GK; Nippon Kayaku Co., Ltd.

8531 Poster Session

Tumor-derived ILT5 and suppression of T cell immunity in non-small cell lung cancer.

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Background: Immune checkpoint inhibitors targeting PD-(L)1 pathways have revolutionized the treatment of non-small cell lung cancer (NSCLC) since last decade. However, the efficacy is still limited because the immunosuppressive tumor microenvironment (TME) restricts ICI-primed T cell immunity. Therefore, it is quite crucial to block the potential mechanisms in inducing immunosuppression to improve ICI efficacy. Immunoglobulin-like transcript (ILT) 5 is an important immunosuppressive molecule expressed in a wide range of myeloid cells and predicts tumor progression. Our group was the first to report ILT5 expression in solid tumor cells (colorectal cancer). However, the expression and function of ILT5 in NSCLC are still unknown. **Methods:** ILT5 expression in NSCLC tissues and tumor cell lines was determined by PCR, western blotting and immunofluorescence. The impact of tumor-derived ILT5 on T-cell phenotypes and functions was evaluated using flow cytometry and immunofluorescence. ILT5-regulated downstream signals and molecules were determined by RNA sequencing, PCR, western blotting, and flow cytometry. Tumor transplantation and immunotherapeutic models were established in C57/BL6 and NSG mice to explore the effect of ILT5 on tumor progression and the synergies of ILT5 blockade with ICIs. **Results:** ILT5 is highly expressed in NSCLC cells, predicting poor patient survival. ILT5 induced $CD8^+$ T cell exhaustion rather than senescence and apoptosis in the TME. Mechanistically, ILT5 upregulated PD-L1 through the activation of PI3K-AKT-mTOR signaling pathway, which in turn increased PD-1 expression in $CD8^+$ T cells and induced their exhaustion. PIR-B (ILT5 orthlog in mice) overexpression in mice induced $CD8^+$T cell exhaustion and tumor growth in vivo, while PIR-B knockdown had the opposite effect. More importantly, inhibition of ILT5 synergistically enhanced the tumoricidal effect of PD-1 inhibitor in NSCLC immunotherapeutic models. **Conclusions:** Enriched ILT5 expression in NSCLC cells induces $CD8^+$T cell exhaustion via activation of PI3K-AKT-mTOR-PD-L1 pathway. ILT5 inhibition synergistically enhanced the efficacy of PD-1 inhibitor. Our findings identifies a novel mechanism for tumor immunosuppression and develops a promising strategy for improving ICI efficacy. Research Sponsor: None.

8532 Poster Session

Prognostic value of baseline and dynamic circulating tumor cell monitoring in advanced lung cancer patients receiving immunotherapy.

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Background: Circulating tumor cells (CTCs) and PD-L1 expression on CTCs (bPD-L1) are emerging biomarkers for predicting immunotherapy response. This study assessed the prognostic value of baseline and dynamic CTC monitoring in advanced lung cancer patients receiving immune checkpoint inhibitors. **Methods:** We prospectively enrolled 53 advanced lung cancer patients (stages III-IV) undergoing immune checkpoint therapy from June 2023 to January 2025 at The Fifth Affiliated Hospital of Sun Yat-sen University. Baseline characteristics (age, gender, histology, treatment modality) were recorded. CTCs and bPD-L1 status were assessed at baseline, and treatment responses were evaluated using RECIST 1.1 criteria. Serial blood samples were collected at Day 42 (T1) and subsequent visits (T2, T3, or Tn) for CTC dynamics monitoring. **Results:** Baseline Characteristics and CTC Detection: Of the 53 patients, 47 (84.6%) were male and 8 (15.4%) were female, with a median age of 63 years (range: 32–89). Histological subtypes included adenocarcinoma (62.6%), squamous cell carcinoma (16.1%), and small cell lung cancer (17.2%). Treatments included PD-1/PD-L1 inhibitors and chemotherapy. At baseline, CTCs were detected in 60.9% of patients, with detection rates varying by histology: adenocarcinoma (59.6%), squamous cell carcinoma (60.7%), and small cell lung cancer (50.0%). PD-L1-positive CTCs (bPD-L1+) were found in 44.8% of patients, with subtype-specific positivity rates of 41.3%, 39.3%, and 40.0%, respectively. Among 53 patients who completed at least two cycles of immunotherapy, the bPD-L1-positive group (n=17) had an ORR of 64.7% and a DCR of 100%, while the bPD-L1-negative group (n=36) had an ORR of 13.9% and a DCR of 83.3% ($p<0.001$). Multivariate analysis identified bPD-L1 positivity as an independent predictor of ORR (p=0.04). Serial blood samples from 37 patients at Day 42 (T1) showed that all patients with DCR had stable or decreased CTC counts, while all PD patients showed an increase in CTC count. Extended monitoring in 13 patients revealed consistent patterns: CTC counts increased in PD cases and decreased or remained stable in DCR cases, supporting its role in monitoring treatment efficacy. A linear mixed-effects model showed a significant positive association between PD status and elevated CTC counts ($\beta = 0.821$, $p<0.05$), while non-PD showed a trend towards lower CTC counts ($\beta = -0.370$, p=0.1). This suggests that CTC counts may serve as a biomarker for disease progression, particularly in identifying PD patients. **Conclusions:** Baseline and dynamic CTC monitoring, particularly bPD-L1 status, provides strong predictive and prognostic value in advanced lung cancer patients undergoing immunotherapy. These findings suggest CTCs as a non-invasive liquid biopsy for treatment stratification and real-time monitoring of treatment response. Clinical trial information: ChiCTR2400080132. Research Sponsor: None.

8533 Poster Session

Host immune classifier to predict survival with chemoimmunotherapy in PD-L1 ≥50% metastatic NSCLC.

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Background: In the 1st line treatment of advanced NSCLC with PD-L ≥50%, immune checkpoint inhibitor (ICI) monotherapy and chemoimmunotherapy have demonstrated survival benefits over chemotherapy alone. However, no additional biomarkers are currently available to guide the choice between these options. Here we report an analysis from the INSIGHT study evaluating the Host Immune Classifier (HIC), a clinically validated blood-based test, to determine its potential to stratify patient survival and optimize treatment selection. **Methods:** Pre-treatment plasma samples were collected from 271 IIIB/IV NSCLC, 1st line ICI-treated (PD-L1 ≥50%) patients enrolled in the prospective, multicenter observational INSIGHT study (NCT03289780). Samples were analyzed by the HIC test, which categorizes patients as Hot or Cold based on the expression profile of eight proteins measured by MALDI mass spectrometry. Survival outcomes were compared between patients treated with ICI monotherapy (ICI-M) and chemoimmunotherapy (ICI-C), grouped by HIC result. To ensure comparable cohorts, baseline clinical characteristics were balanced using inverse probability weighting (IPW). Overall survival (OS) was evaluated using Kaplan-Meier estimates (95% CI) and the log-rank test. Hazard ratios were calculated with Cox proportional hazards models. **Results:** Among the analysis cohort, 171 subjects received ICI-M, and 100 received ICI-C. After IPW, baseline characteristics, including age, sex, smoking history, ECOG PS, and histology, were balanced. The distribution of HIC classifications was similar, with 70% Hot and 30% Cold. In HIC-Hot subjects, overall survival (OS) did not differ significantly between treatment groups (log-rank p=0.15, Table 1). In contrast, HIC-Cold subjects had significantly better OS with ICI-C than ICI-M (log-rank p=0.012, Table 1). Multivariate analysis confirmed the HIC test as an independent predictor of OS, adjusting for other prognostic factors. **Conclusions:** The HIC test is a robust, independent predictor of OS, unaffected by common prognostic factors. HIC-Hot patients had similar OS when treated with ICI-M or ICI-C, suggesting the potential for treatment de-escalation. Conversely, HIC-Cold patients experienced significantly poorer OS with ICI-M but showed improved OS with ICI-C, indicating the need for more aggressive treatment. These findings underscore the potential clinical utility of the HIC test in guiding 1st line ICI treatment strategies for NSCLC with PD-L1 ≥50%. Clinical trial information: NCT03289780. Research Sponsor: Biodesix Inc.

HIC Test Classification	Treatment	N	12 Month % OS	p value	24 Month % OS	p value	Median OS (Months)	Hazard Ratio (95% CI)	p value
Hot	ICI-M	114	58% (48%, 67%)	0.273	46% (35%, 56%)	0.448	18 (11, 31)	0.7 (0.5, 1.1)	0.14
	ICI-C	66	66% (52%, 77%)		52% (37%, 65%)		Median Not Reached		
Cold	ICI-M	47	26% (14%, 39%)	0.028	10% (1%, 32%)	0.005	3 (2, 6)	0.5 (0.3, 0.9)	0.014
	ICI-C	28	51% (32%, 67%)		36% (17%, 56%)		13 (4, NR*)		

*Not Reached.

Lipid metabolic gene expression and association with decreased overall survival and immunogenicity in *KRAS-STK11* NSCLC.

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Background: Approximately 30% of patients (pts) with non-small cell lung cancer (NSCLC) have alterations (alt) in *KRAS*. How co-alt such as STK11 affect the tumor microenvironment and survival requires further characterization. Recently, our group found that lower expression of lipid metabolic genes in *KRAS* G12C co-alt tumors was associated with worse overall survival (OS). Here, we seek to confirm these findings utilizing a large real-world (rw) patient de-identified database. **Methods:** Approximately 2,187 pts (61%, stage IV) with *KRAS* G12C alt NSCLC who underwent sequencing via the Tempus xT/xR assay with co-alt in *TP53 (44%)*, *STK11 (17%), or LRP1B (4%)* were selected. The groups are mutually exclusive. Single-sample GSEA (ssGSEA) based on 775 lipid metabolic genes (LMG) was used to calculate enrichment scores (LMG ES) for each pt. Pts were dichotomized into low vs. high groups based on their median LMG ES. Immune cell infiltration predicted from gene expression patterns, TMB, and PD-L1 from IHC was evaluated. Risk-set adjusted rwOS was calculated from sample collection date to death from any cause. Hazard ratios (HR) were calculated using Cox proportional hazards model, and p-values were calculated using the Wald test. **Results:** Among pts with *KRAS* G12C alt, the median age was 68, 58% were female, and 84% were White. Pts with *KRAS* G12C/*STK11* alt had the lowest TMB, neoantigen burden, and PDL-1 positivity compared to other cohorts ($p<0.001$ for all). Importantly, the proportion of total immune cells, M1, M2, NK cells, CD8 T cells and regulatory T cells was lowest in tumors with *KRAS* G12C/*STK11* alt ($p<0.001$ for all). To determine if lipid genes were associated with immunogenic changes, LMG ES was compared to immune infiltration. The ES was associated with immune cell infiltration percentages for M1 macrophages (OR 1.11 (1.03-1.21) p=0.012), M2 macrophages (OR 1.27 (1.15-1.40) $p<0.001$) and neutrophils (OR 1.12 (1.04-1.22) p=0.005), with a trend towards significant association with CD4 T cells (OR 1.08 (1.00-1.17) p=0.062). Pts with *KRAS G12C/STK11* alt and low LMG ES had decreased median rwOS (5.4 vs 18.2 months, p=0.0002) compared to pts with a high ES. Multivariate analysis demonstrated that lower LMG ES correlated with reduced rwOS (HR = 1.75 (1.22-2.51, p = 0.002) compared to pts with high ES. Individual gene analysis showed that low *LPL* (HR = 1.85 (1.147-2.97) p=0.012), *LDLRAD4* (HR = 1.72 (1.082-2.72) p = 0.022) and *LDLR* (HR = 1.58 (1.009-2.46) p=0.045) expression was associated with poorer rwOS. **Conclusions:** Low lipid gene expression in *KRAS-STK11* NSCLC was associated with decreased OS. Lipid gene expression and tumor immune cell infiltration were associated, suggesting that lipid metabolism may regulate tumor immunogenicity. These data suggest that lipid metabolic genes should be further explored as potential therapeutic targets for pts with NSCLC and *KRAS-STK11* alt. Research Sponsor: This work was funded by Tempus AI, Inc.

8535 Poster Session

A large validation study of AI-powered PD-L1 analyzer compared to pathologists' assessment of PD-L1 expression in lung cancer.

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Background: Programmed death ligand 1 (PD-L1) expression is a useful biomarker for immune checkpoint inhibitors in advanced lung cancer. However, pathologists' manual evaluation of PD-L1 expression has practical limitations, including observer bias. The development of artificial intelligence (AI)-powered PD-L1 evaluation models has recently progressed. We evaluated the concordance rate of PD-L1 expression as assessed by pathologists and an AI-powered PD-L1 analyzer in lung cancer patients. **Methods:** This multicenter prospective observational study included patients with stage II to IV or recurrent lung cancer (LC-SCRUM-IBIS). PD-L1 Tumor Proportion Score (TPS) was assessed in lung biopsy specimens, by using a 22C-3 Immunohistochemistry (IHC) assay and scanned at $\times$40 magnification using a whole-slide images scanner (Hamamatsu Photonics). The results of PD-L1 TPS were evaluated independently by three lung pathologists trained in IHC assessment of PD-L1 expression. We examined an AI-powered PD-L1 TPS analyzer, namely Lunit SCOPE PD-L1. **Results:** Between February 2017 and May 2018, 1,017 lung cancer patients were enrolled. Of these, adequate tumor samples allow for PD-L1 IHC assays; 847 non-small cell lung cancer (NSCLC) patients and 102 small cell lung cancer (SCLC) patients. Lunit SCOPE PD-L1 training included annotations of a total of 64,245,935 tumor cells. Regarding patients characteristics, the median age was 66, 31% were female, 75% were ever smokers, and the distribution of stages was as follows: stage II, III, IV, or recurrence in 37, 97, 632, and 183 patients, respectively. The histological subtypes included in NSCLC, non-squamous (666 patients), squamous (181 patients). Additionally, 85% were diagnosed by biopsy specimens. In comparing PD-L1 TPS assessed by AI and pathologists, the overall concordance rate was 70% with a kappa value of 0.56 (95% confidence interval [CI], 0.49–0.61). The concordance rate according to PD-L1 TPS $\geq$50%, 1-49%, and <1% was 84%, 94%, and 44%, respectively. Of the 416 patients whom pathologists determined to be TPS <1%, 231 (55%) were TPS 1-49%, and only one patient was determined to be TPS $\geq$50% by AI analyzer. In SCLC patients' analysis, 84% of patients were determined to be PD-L1 <1% by pathologists, with a low concordance rate of 61% (k = 0.29) between pathologists and AI analyzer. **Conclusions:** PD-L1 TPS demonstrated a high concordance between pathologists and AI analyzers in lung cancer patients with TPS $\geq$50% and 1-49%. However, the concordance rate of TPS <1% was low regardless of histology. We will confirm if the AI analyzer accurately predicts treatment outcome, especially in TPS <1%. Clinical trial information: UMIN000026425. Research Sponsor: Lunit Company.

8536 Poster Session

Artificial intelligence-powered spatial analysis of tumor microenvironment in non-small cell lung cancer patients who acquired resistance after EGFR tyrosine kinase inhibitors.

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Background: We evaluated dynamic changes in the tumor microenvironment (TME) after EGFR tyrosine kinase inhibitor (TKI) treatment using an artificial intelligence (AI)-powered spatial TME analyzer and assessed the predictive efficacy of immune checkpoint inhibitors (ICIs) as monotherapy or in combination therapy. **Methods:** An AI-powered whole-slide image (WSI) analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) segmented cancer area (CA), stromal area (CS), and identified tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), fibroblasts (Fibs), and endothelial cells (ECs) in tumor tissue. We analyzed 143 non-small cell lung cancer (NSCLC) samples post-resistance to EGFR TKIs from two cohorts: 1) patients (pts) treated with ICIs at Samsung Medical Center, Korea (October 2015–July 2022), and 2) pts from the ATTLAS phase 3 trial comparing atezolizumab plus bevacizumab, paclitaxel, and carboplatin (ABCP) versus pemetrexed plus carboplatin (PC). Among these, 89 pts received ICI monotherapy, and 54 were from the ATTLAS trial (ABCP: 36, PC: 18). Paired pre-treatment samples were available for 89 pts (62.8%), and whole transcriptome sequencing was performed on 42 samples. **Results:** In the combined pre- and post-TKI samples, TLS area per CA correlated with the TLS signature (ρ=0.439, P=0.003), Fibs with the cancer-associated fibroblast signature (ρ=0.581, P<0.001), TILs with the interferon-gamma signature (ρ=0.498, P<0.001), and ECs with the angiogenesis signature (ρ=0.315, P=0.042), but not VEGF signatures (ρ=0.183, P=0.71). Post-TKI samples showed reduced TILs in CA (P=0.045) and increased ECs in CA (P=0.005), with no significant changes in Fibs (P=0.819) or TLS area (P=0.884). Changes differed by EGFR mutation subtype: L858R mutations were linked to increased ECs (P=0.009), while T790M mutations and exon 19 deletions (19del) were linked to reduced TILs (P=0.033, P=0.045). Higher TILs in CA were associated with better overall response rate (ORR, 41.7% vs. 9.7%, P=0.003) and progression-free survival (PFS, 4.9 vs. 1.8 months, HR=0.41 [95% CI: 0.21–0.79]). Similarly, higher EC levels in CA correlated with improved ORR (19.3% vs. 3.7%, P<0.01) and PFS (2.0 vs. 1.4 months, HR=0.44 [95% CI: 0.28–0.71]). In the ATTLAS cohort, these factors were associated with clinical benefits from ABCP, with a significant association for TILs (HR=0.42 [95% CI: 0.19–0.91, P=0.027]) and a marginal association for ECs (HR=0.29 [95% CI: 0.07–1.15, P=0.067]). **Conclusions:** EGFR-TKI alters the immune landscape of NSCLC. Higher TILs or ECs in CA were significantly associated with favorable outcomes to ICI or combination treatment. Research Sponsor: None.

8537 Poster Session

Molecular analysis of lung adenocarcinomas from the SAFIR02-Lung trial explores metastasis-associated alterations and potential prognostic markers.

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Background: Lung adenocarcinoma (LUAD) molecular heterogeneity influences diagnosis, prognosis, and treatment. Molecular profiling of advanced lesions remains limited compared to early tumors. We analyzed tumors from the SAFIR02-Lung trial to identify molecular alterations associated with advanced LUAD. **Methods:** We analyzed 366 advanced LUAD tumor samples (250 locoregional [lrmLUAD], 116 distant metastases [dmLUAD]) from metastatic patients in the SAFIR02-Lung trial using targeted sequencing of 45 cancer-related genes and comparative genomic hybridization arrays. Data from The Cancer Genome Atlas (TCGA) and three public datasets—MSK-MET, Jee et al., and the AACR Project GENIE—validated our findings. **Results:** Advanced tumors exhibited greater chromosomal instability than early-stage lesions, (fraction of genome altered: 28.0% in lrmLUAD, 29.1% in dmLUAD and 7.2% in early-stage LUAD, $p < 0.01$). Copy-number alterations implicated *LAMB3*, *TNN/KIAA0040/TNR*, *KRAS*, *DAB2*, *MYC*, *EPHA3*, *VIPR2* in tumor progression and *AREG*, *ZNF503*, *PAX8*, *MMP13*, *JAM3*, *MTURN* and *CDKN2A* in metastasis. *CDKN2A* homozygous deletions correlated with poor outcomes in early-stage LUAD (hazard ratio = 2.17, 95% CI: 1.43–3.28, p = 0.01). *KRAS* mutant allele-specific imbalance (MASI), marked by mutant allele amplification, was enriched in advanced samples (8.4% lrmLUAD, 13% dmLUAD, 2.8% early-stage LUAD). Public cohort validation confirmed higher *KRAS* MASI prevalence in metastatic samples vs. primary tumors (3.17% vs. 1.4%; pooled odds ratio = 2.23, 95% CI: 1.43–3.51, $p < 0.01$). *KRAS* MASI tumors were enriched in *CDKN2A*, *MYC*, *TP53*, *and NKX2-1* alterations, and displayed less *STK11* and *KEAP1* variants. **Conclusions:** Chromosomal instability drives disease progression in LUAD. *CDKN2A* homozygous deletions are a negative prognostic biomarker in early-stage tumors. Metastasis-associated alterations, including *KRAS* MASI and *CDKN2A* deletions, highlight mechanisms of progression and potential prognostic biomarkers, warranting further investigation and therapeutic exploration. Nguyen B, et al. Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. Cell 2022;185:563-575.e11. https://doi.org/10.1016/j.cell.2022.01.003. Jee J, et al. Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. Nat Med 2022;28:2353–63. https://doi.org/10.1038/s41591-022-02047-z. The AACR Project GENIE Consortium, AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discovery 2017;7:818–31. https://doi.org/10.1158/2159-8290.CD-17-0151. Research Sponsor: None.

Clinical outcomes and characterization of HER2 alterations in non-small cell lung cancer (NSCLC).

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Background: Subsets of NSCLC carry alterations in the human epidermal growth factor receptor 2 (HER2) gene such as mutations (mt), amplification (amp), and protein overexpression. These alterations reflect distinct patient (pt) populations and disease biology, translating to variable outcomes with immunotherapy +/- chemotherapy. HER2-directed therapies have shown significant efficacy for HER2 mt and to a lesser extent HER2 3+ NSCLC. We describe the genomic landscape of HER2-altered NSCLC in a large cohort of tumors from the Caris database and explore pt outcomes. **Methods:** Next-generation sequencing of DNA (592-gene or WES) and RNA (WTS) was performed on NSCLC samples (n=52,690, Caris Life Sciences, Phoenix, AZ). IHC was performed on FFPE sections (HER2 staining intensity of 2+, >5%). HER2 amp was defined as copy number > 6. Tumor microenvironment studies were calculated by QuantiSeq. Significance was calculated using chi-square, Fisher's exact, or Mann-Whitney U test, with p-values adjusted for multiple comparisons ($q<0.05$). Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards model to calculate hazard ratio (HR) and log-rank tests to calculate P values. **Results:** 670 tumors were HER2 mt (N=492 within the kinase domain, 133 extracellular domain, 47 transmembrane domain, 16 other, 400 HER2 amp, and 272 HER2 IHC 2+. Treatment (tx) received prior to tumor sample collection is not reported in 64.2% HER2 mt, 68.8% HER2 2+, 56.5% HER2 amp (may reflect tx naive pts). Among female pts, HER2 mt was more common than amp or overexpressed 3+ (59.7% vs. 39.8% vs 36.2% $p<0.01$). HER2 mt correlated with improved OS compared to HER2 amp and a cohort of NSCLC driverless tumors (wild type EGFR, ALK, ROS1, RET, KRAS, and HER2). When compared to ROS1+, ALK+ and EGFR mt, HER2 mt had shorter OS (Table). Higher frequency of co-mts are noted in HER2 amp vs mt, including TP53 (90% vs 57%), EGFR (10% vs 6%), SMARCA4 (12% vs 5%), CDKN2A (16% vs 5%), NKX2-1 (2% vs 0.5%) and TMB-H (47% vs 21%), all $p<0.001$. No differences in PD-L1 expression were observed. Higher frequency of co-mts for HER2 IHC 2+ vs HER2 mt, including KRAS (33% vs 3%), KEAP1 (21% vs 7%), BRAF (5% vs 0.8%), EGFR (13% vs 6%) and SMARCA4 (11% vs 5%), all $p<0.001$. HER2 mt tumors had greater infiltration of NK cells, B cells, M2 macrophages, neutrophils and Tregs (FC 1.2-1.3) vs. HER2 IHC 2+. **Conclusions:** This study highlights the significant differences in OS and co-alterations for HER2 mt vs other HER2 altered and NSCLC driverless tumors. This data confirms the unmet need to further explore these differences to optimize tx and improve OS. Research Sponsor: None.

NSCLC cohorts compared to HER2 mt cohort (22.0 months).

NSCLC Cohort	Survival (months)	HR, 95% CI	p-value
HER2 amp	12.3	0.67 (0.57-0.79)	<0.001
HER2 2+	14.1	0.92 (0.77-1.09)	0.33
Driverless	16.2	0.85 (0.77-0.94)	<0.01
ROS1 fusion	35.3	1.3 (1.0-1.7)	0.02
ALK fusion	47.4	1.9 (1.6-2.3)	<0.001
EGFR mt	30.7	1.3 (1.2-1.5)	<0.001

8539 Poster Session

Spatial transcriptomic profiling of the tumor microenvironment in EGFR and KRAS mutant non-small cell lung cancer.

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Background: Immune checkpoint inhibitors have greatly improved outcomes in advanced non-small cell lung cancer (NSCLC). However, patients with EGFR mutant NSCLC have a poor response to immune checkpoint inhibitor therapy. Emerging evidence suggests that an immunosuppressive tumor microenvironment plays an important role in this setting, however, we still lack fundamental knowledge about tumor endothelial cell biology. We hypothesized that oncogene specific changes in the expression of immune-related genes in tumor endothelial cells account for differences in the tumor microenvironment and efficacy of immune checkpoint inhibitor therapy. **Methods:** We utilized spatial transcriptomics (GeoMx Digital Spatial Profiling) on resected tumor tissue of EGFR mutant (n = 5) and KRAS mutant (n = 5) NSCLC patients to investigate the transcriptional signature of tumor, endothelial and stromal cells. Additionally, we used NicheNet to explore intercellular communication between tumor, endothelial, and stromal cells. Immune gene set enrichment analysis scores were calculated using ESTIMATE. Immune cell type proportions were estimated using CIBERSORT. **Results:** Using spatial transcriptomics, we dissected the tumor microenvironment into tumor, stromal and endothelial compartments. By analyzing predicted cellular communication, we found that tumor and stromal cells primarily affect an interferon-related gene signature in tumor endothelial cells. Notable differentially expressed interferon-related genes, that were significantly up-regulated in KRAS mutant and down-regulated in EGFR mutant NSCLC patients, included CXCL9, STAT1, WARS1, IRF1 and ICAM1. In the stromal compartment, immune gene set enrichment analysis scores were significantly lower in EGFR mutant than KRAS mutant NSCLC (median, 355 vs. 713, P = 0.026) indicating an immunosuppressive tumor microenvironment. We observed substantial heterogeneity while exploring the cellular landscape of the stromal compartment in EGFR mutant and KRAS mutant NSCLC. Notably, we found a significantly decreased proportion of pro-inflammatory macrophages in the stromal compartment of EGFR compared to KRAS mutant NSCLC (P = 0.006). **Conclusions:** We identified distinct interferon-related gene signatures in tumor endothelial cells of patients with EGFR and KRAS mutantNSCLC associated with variations in the cellular composition of the tumor microenvironment. This may provide a better understanding for the development of spatial biomarkers to identify which oncogene-driven NSCLC patients are most likely to benefit from immune checkpoint inhibitor therapy. Research Sponsor: University of Virginia (UVA) NCI-designated Comprehensive Cancer Center.

8540 Poster Session

Immune landscape of liver metastases in advanced lung cancer.

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Background: The liver is a frequent site of metastasis and carries a poor prognosis in patients with non-small cell (NSCLC) and small cell lung cancer (SCLC). Patients with liver metastases (LM) derive limited benefit from immune checkpoint inhibitors (ICI), due to hepatic myeloid derived suppressor cell (MDSC) mediated T cell elimination. Here, we used imaging mass cytometry (IMC) to perform single cell, highly multiplexed, analysis of LM and primary lung tumors to investigate how vascular endothelial growth factor (VEGF) influences T cell depletion within the tumor immune microenvironment (TIME) of LM. **Methods:** We comprehensively characterizedthe TIME in LM and primary lung tumors in 21 patients with NSCLC or SCLC using IMC. A panel of 40 antibodies was assembled to interrogate immune subsets and VEGF pathway markers. Each antibody was conjugated to a unique metal isotope. After validation, the antibody cocktail was used to stain the biopsies. Tissue images were segmented using Mesmer, and hierarchical clustering was applied to single-cell expression data to identify phenotypes. Similar clustering of cell neighbor profiles was applied to obtain spatial motifs. Phenotypic and motif frequencies, together with functional expression across phenotypes, were compiled from all samples and compared across conditions. **Results:** Initial visualization of the raw, unsegmented data revealed higher infiltration of $CD8^+$ and $CD4^+$ T cells in LM compared to the lung TIME. After segmentation, marker expression heatmaps uncovered complex cell-cell interaction ecosystems. The liver samples were enriched with M2 macrophages ($CD163^+$), MDSC ($CD11b^+$), and proliferative endothelial cells ($CD105^+$) whereas the lung samples were enriched in tumor cells ($TTF1^+$ for NSCLC and $INSM1^+$/synaptophysin$^+$ for SCLC) and T cells ($CD4^+$, $CD8^+$). Spatial neighborhood profiling of NSCLC liver tissues identified 12 neighborhood types, showing a general trend of mutual exclusivity between MDSCs and $CD4^+$/$CD8^+$ T cells across neighborhoods. Notably, $CD8^+$ T cells in MDSC-enriched neighborhoods exhibited consistently higher FAS expression, a key apoptotic marker. Heterogenous FAS and VEGF signaling across neighborhoods suggested a mixed immune-suppressive and vascularized response in the liver TIME, supporting VEGF's role in mediating MDSC-driven hepatic $CD8^+$ T cell depletion in patients with LM. **Conclusions:** Our findings highlight significant differences in the TIME between LM and primary lung tumors, with LM demonstrating a more immuno-suppressive and VEGF-enriched milieu. The spatial association of MDSCs with $CD8^+$ T cells, along with elevated FAS expression and VEGF signaling suggests a mechanistic role for VEGF in driving immune evasion within liver tumors. These results underscore the potential of VEGF blockade as a therapeutic strategy to overcome T cell suppression and improve ICI efficacy in patients with lung cancer metastatic to liver (NCT05588388, PI Sankar). Research Sponsor: Conquer Cancer Foundation, ASCO; Cedars-Sinai Medical Center, CSRI.

8541 Poster Session

Biomarker testing of lung cancer in North America versus globally.

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Background: Biomarker testing is essential to optimize lung cancer (LC) care, yet uptake of testing is suboptimal due to lack of access, cost, and long turnaround times (TAT). Recent advances now require biomarker testing in early-stage LC. In 2024, the International Association for the Study of Lung Cancer (IASLC) launched a 2nd global survey to measure improvements and barriers to implementation of testing. We compared results from North America (NA) with global results by high income (HIC) and low or middle income countries (LMIC). **Methods:** A multi-disciplinary committee of oncologists, pathologists, pulmonologists, epidemiologists, and advocacy partners created the survey. We used mixed methods, with focus groups and in-depth interviews informing the quantitative survey with IRB oversite. Chi-square tests were utilized to compare frequencies between NA v Other HIC (OHIC) and HIC v LMIC. **Results:** Of the 1677 responses globally, 1501 were from HIC and 176 from LMIC. HIC included 337 responses from NA (287 United States and 50 Canada). Nearly all NA respondents (99%) believe biomarker testing significantly impacts patient outcomes and 94% report a clear understanding of who should be tested (v 91% OHIC, p=0.09). In NA, 66% and 40% ranked biomarker testing as highly important in late- and early- stage LC, respectively (64% and 28% OHIC, p=0.68 and p<0.01). Only 45% of NA respondents were satisfied with biomarker testing conditions (v 52% OHIC, p=0.03), and 69% estimate at least half of LC patients receive biomarker testing (71% OHIC), an increase from 45% in the 2018 survey (p<0.01). We found 40% of respondents from NA sometimes or often began treatment prior to obtaining biomarker results (41% OHIC). Key barriers identified were cost (23%), time (22%), and sample quality (20%), consistent with global and OHIC trends. Mean TAT in NA was 17.1 days (SD 7.8) v 16.1 days (SD 9.0) in HIC. Insufficient tumor was the primary cause for re-biopsy in late and early-stage patients for NA (58%) and HIC (48%). Lastly, 14% of NA reported no additional training in next-generation sequencing beyond medical education (16% OHIC). Globally, conditions were worse in LMIC v HIC including those who sometimes or often begin treatment prior to obtaining biomarker results (73% v 41%, p<0.01) and those who are confident or extremely confident in the adequacy of testing at their institution (48% v 68%, p<0.01). **Conclusions:** Respondents from NA believe they understand the value of biomarker testing for LC and who should be tested. Testing practices have reportedly improved since 2018, yet less than half of NA respondents are satisfied with biomarker testing practices and many patients are still treated without biomarker information. Responses from NA were similar to OHIC, with some exceptions, but significant disparities were evident in LMIC. We identified key barriers that should be addressed to optimize testing practices and patient outcomes. Research Sponsor: International Association for the Study of Lung Cancer (IASLC), via the IASLC Partners for Thoracic Cancer Care.

8542 Poster Session

Prediction of site-specific immune-related adverse events of PD-L1 blockade in advanced non-small cell lung cancer through baseline organ-metastatic landscape: Pooled post-hoc analyses of two randomized controlled trials.

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Background: The patterns of immune-related adverse events (irAEs) during immunotherapy vary among tumors of different origins. However, it remains unknown whether metastases in different organs confer varying susceptibility to irAEs in a specific tumor type. Herein, we explored the impact of the baseline organ-metastatic landscape on the irAE patterns following PD-L1 blockade in advanced non-small cell lung cancer (NSCLC). **Methods:** We conducted a pooled post-hoc analysis of 708 patients with advanced NSCLC who received atezolizumab from two randomized controlled trials (OAK and POPLAR). The association between the baseline metastatic status and both overall and site-specific irAEs was analyzed using multivariate logistic regression and multivariate Cox regression. The Kaplan-Meier method with the log-rank test was leveraged to compare the cumulative risk of irAEs based on organ-specific metastatic status. **Results:** Patients harboring different organ metastases yielded varying vulnerability of irAEs (p = 0.047). Overall, irAEs were less likely to occur in patients with bone metastases (OR = 0.52, p = 0.039) and pleural effusion metastases (OR = 0.65, p = 0.039), while more frequent in patients with brain metastases (OR = 1.96, p = 0.023). Besides, patients with bone metastases experienced a significant delayed onset of irAEs compared to those with metastases to other organs (HR = 0.65, p = 0.007). In terms of the incidence of site-specific irAEs, hepatitis (OR = 0.55, p = 0.03), hypothyroidism (OR = 0.27, p = 0.008), and rash (OR = 0.63, p = 0.039) were less frequent in patients with bone metastases, whereas pneumonia (OR = 3.25, p = 0.046), adrenal insufficiency (OR = 12.71, p = 0.019) and ocular inflammatory toxic (OR = 21.17, p = 0.017) were more concentrated in patients with brain metastases; adrenal insufficiency was particularly prevalent in patients with adrenal metastases (OR = 15.22, p = 0.023). As for the onset of site-specific irAEs, patients with bone metastases experienced significantly earlier onset of hypothyroidism (HR = 0.27, p = 0.008), while those with metastases to brain (HR = 7.81, p = 0.029) and adrenal glands (HR = 12.54, p = 0.029) developed later onset of adrenal insufficiency; liver metastases were associated with earlier onset of hepatitis (HR = 1.8, p = 0.018) and colitis (HR = 5.49, p = 0.033). **Conclusions:** The baseline organ-metastatic landscape might be a predictive factor for overall and site-specific irAEs in advanced NSCLC patients received PD-L1 blockade. Our findings enhance the understanding of organ-specific immunity in immunotherapy under the metastatic setting of NSCLC and may inform personalized immunotherapy strategies. Research Sponsor: National Natural Science Foundation of China; 82373307; Natural Science Foundation of Guangdong Province; 2024A1515013214; China Postdoctoral Science Foundation; 2024M753780; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

8543 Poster Session

A phase II trial to evaluate the safety and efficacy of SSGJ-707, a bispecific antibody targeting PD-1 and VEGF, as a monotherapy in patients with advanced NSCLC.

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Background: SSGJ-707 is a recombinant humanized bispecific molecule built on IgG4 that targets the human programmed death 1 (PD-1) and vascular endothelial growth factor (VEGF). The increase of SSGJ-707 affinity for PD-1 was 10-fold more than that of Ivonescimab in the presence of VEGF. Here, we report the initial results from a phase II study of SSGJ-707 monotherapy in patients (pts) with advanced NSCLC(SSGJ-707-NSCLC-II-01, NCT06361927). **Methods:** Pts with treatment naive advanced NSCLC (without actionable genomic alterations and PD-L1 expression≥1%) were enrolled to receive SSGJ-707 monotherapy until disease progression or unacceptable toxicity. Tumor assessments based on RECIST 1.1 were performed every 6 weeks by investigators. **Results:** As of Jan 10, 2025, 83 NSCLC pts have received SSGJ-707 at dose of 5mg/kg Q3W (n=31), 10mg/kg Q3W (n=34), 20mg/kg Q3W (n=12), 30mg/kg Q3W(n=6). Overall, the median age was 64 years, 83.1% had ECOG PS of 1, 44.6% of pts with squamous cell carcinoma, 66.3% and 33.7% of pts had PD-L1 expression 1%-49% and ≥50%. Among the 76 pts completed at least one efficacy evaluation, ORR and DCR were 29.6% (8/27)/85.2% (23/27), 61.8%(21/34)97.1% (33/34), 54.5% (6/11)/90.9% (10/11) and 25% (1/4)/75% (3/4) at doses of 5mg/kg Q3W, 10mg/kg Q3W, 20mg/kg Q3W and 30 mg/kg Q3W, respectively. SSGJ-707 10mg/kg Q3W demonstrated promising efficacy results in treatment naive advanced NSCLC. Select subgroups are summarized in SSGJ-707 10mg/kg Q3W. The ORR were 54.5% (12/22) and 75%(9/12) in non-squamous and squamous pts respectively. And the ORR were 57% (12/21) and 69%(9/13) in PD-L1 TPS 1%-49% and ≥ 50% pts respectively. 25 pts completed at least two efficacy evaluation in SSGJ-707 10mg/kg Q3W, the ORR was 72% (18/25), DCR was 100% (25/25). For the 83 pts, 65 pts (78.3%) experienced treatment related adverse events (TRAEs), 20 pts (24.1%) experienced grade≥3 TRAEs. The most common TRAEs included hypercholesterolaemia (18.1%,15/83), hypertriglyceridaemia (18.1%,15/83), alanine aminotransferase increased (15.7%,13/83) and aspartate aminotransferase increased (15.7%,13/83). TRAE leading to discontinuation occurred in 6% of pts. **Conclusions:** SSGJ-707 monotherapy demonstrated promising efficacy results in treatment naive advanced NSCLC with manageable safety profile. Monotherapy and combination trials with chemotherapy for NSCLC are still ongoing. Research Sponsor: 3S BIO.COM. Clinical trial information: NCT06361927. Research Sponsor: Shenyang Sunshine Pharmaceuticals CO., Ltd.

8544 Poster Session

Clinical features associated with an exceptional response to immunotherapy in patients with metastatic non-small cell lung cancer (NSCLC).

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Background: Immunotherapy with PD1 axis inhibitors is approved for metastatic non-small cell lung cancer (NSCLC). Outside of tumor PD-L1 expression, which predicts immunotherapy sensitivity in metastatic NSCLC, no clinicopathologic characteristics have been identified that reliably predict long-term survival after immunotherapy. To identify clinicopathologic predictors of exceptional response, we compared patients with dissimilar outcomes after immunotherapy. **Methods:** Patients with advanced NSCLC treated at Yale Cancer Center with immunotherapy between 2010–2020 were enrolled on an IRB-approved protocol allowing chart review of clinicopathologic data and further archival tumor tissue analysis. Data collection cutoff was January 14, 2025. We defined three subsets of patients who received immunotherapy without concurrent chemotherapy: Exceptional responders (ER) (continued response without progression ≥3 years after first dose), non-exceptional responders (NER) (initial response followed by progression within 3 years), and primary progressors (PP) (best response of progressive disease). **Results:** 50 ER, 45 NER, and 62 PP were identified. At a median follow-up of 7.2 years, 25, 9, and 6 ER had continued response at 5, 7, and 10 years. ER had a lower frequency of baseline lung, bone, and liver metastases, prior chemotherapy (p=0.005), or lymph node/thoracic radiation (p=0.016) than NER and PP. ER had higher pre-treatment absolute lymphocyte count (ALC) and lymphocyte-to-albumin ratio (LAR), with lower platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR). Of 24 evaluable ER patients, 19 had tumor PD-L1 TPS score ≥50%, compared to 13/21 evaluate NER and 14/34 valuable PP. 47/50 ER were nonsquamous, compared to 36/45 NER and 53/62 PP. Compared to NER only, ER were less likely to have bone metastases (p=0.049) or prior lymph node/thoracic radiation (8% vs 24%, p=0.028). Variables associated with primary progression were female sex (OR = 3.73, 95% CI 1.55–8.9), lung metastases (OR 6.46, 95% CI 2.73–15.27), and low albumin (OR 0.29, 95% CI 0.12–0.72). The presence of brain metastases was not different between cohorts. **Conclusions:** Patients with metastatic NSCLC exhibiting exceptionally durable responses to immunotherapy demonstrate distinct baseline features, with higher pre-treatment ALC and LAR, lower PLR and MLR, and lower prevalence of lung, bone, or liver metastases. They were less likely to have had thoracic/lymph node radiation, suggesting lymph node radiation may influence immunotherapy response. Ongoing molecular studies of biospecimens from these patients include genomic/transcriptomic analysis, HLA typing, and tumor microenvironment analysis of archived tissue to further characterize drivers of differential immunotherapy response. Research Sponsor: None.

8545 Poster Session

Breaking barriers for patients with stage IV non-small cell lung cancer with brain metastases: Insight into the impact of immunotherapy on survival and survival disparities.

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Background: Brain metastases (BM) correlate with poor prognosis, occurring in 10% of non-small cell lung cancer (NSCLC) patients (pts) at diagnosis and up to 40% over the disease course. Immunotherapy (IO) with or without chemotherapy has become the new standard of care for stage IV NSCLC. However, the survival benefit of IO in pts with BM remains unclear as most studies are limited to small sample sizes or highly selected pts with asymptomatic or treated BMs. This study represents the largest real-world data analysis evaluating the survival benefits of IO in stage IV NSCLC pts with BM. **Methods:** Demographics, clinical features, and survival were analyzed in stage IV NSCLC pts with BM from the National Cancer Database (NCDB) from 2014-2020. A multivariate Cox proportional hazards modeling assessed factors impacting mortality. **Results:** Of 204,249 pts with stage IV NSCLC, 30% had BM. The mean age was 68 years, with 54% male. Most pts were White (82%), followed by Black (12%) and Asian (3.1%). Government insurance covered 70% of pts, and 26% had private insurance. Adenocarcinoma was the predominant histology (62%), followed by squamous cell carcinoma (SCC) (20%). Liver and bone metastases were observed in 19% and 42% of pts, respectively. Among pts with BM, 18% received immunotherapy, 53% received chemotherapy, 66% received whole-brain radiation, and 18% received limited-brain radiation. Multivariate Cox analysis showed that pts receiving IO had a 46% lower mortality risk compared to not receiving IO (HR: 0.54, 95% CI: 0.51–0.56, $p < 0.001$), demonstrating the independent benefit of IO in pts with BM, regardless of brain radiation or chemotherapy. Females had a lower mortality risk than males (HR: 0.88, 95% CI: 0.85–0.91, $p < 0.001$). Asian (HR: 0.71, 95% CI: 0.64–0.79), Hispanic (HR: 0.76, 95% CI: 0.65–0.89), and Black pts (HR: 0.88, 95% CI: 0.84–0.93) had improved survival as compared to White. Pts with private insurance have lower mortality risk (HR: 0.94, 95% CI: 0.90–0.98), compared to lack of insurance (HR: 1.19, 95% CI: 1.08–1.31). SCC was linked to worse survival (HR: 1.28, 95% CI: 1.22–1.35). **Conclusions:** IO significantly improves survival in pts with NSCLC with BM, regardless of brain radiation therapy or chemotherapy. However, survival disparities based on histology, insurance status, and demographic factors persist, highlighting the need for more equitable treatment strategies. Research Sponsor: None.

8546 Poster Session

Association between pretreatment emotional distress and survival outcomes in patients with advanced non–small-cell lung cancer: An individual patient data meta-analysis of 4632 patients in 7 trials.

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Background: Emotional distress (ED) associated with worse survival outcomes in patients with melanoma and non-small-cell lung cancer treated with immune checkpoint inhibitors (ICIs). However, several preclinical studies suggest the association between stress and cancer treatment extends beyond ICIs alone. Here we used an individual patient data (IPD) meta-analysis of 4632 patients in 7 trials and a Kaplan-Meier analysis to verify broader connection between ED and survival outcomes in NSCLC patients. **Methods:** We searched Vivli data-sharing platform for studies which reported clinical trials of advanced NSCLC patients treated with atezolizumab and used the EORTC QLQ-C30 scale to define ED status of patients. Integrating IPD and grouped them into four groups according to ED status and treatment, Kaplan-Meier analysis was conducted to estimate median overall survival (mOS) and progression-free survival (mPFS) for each group. Next we utilized the Cox proportional hazards model to estimate hazard ratios (HRs) and 95% CIs for OS and PFS of each trials. The IPD meta-analysis was conducted to generate summary estimates of results of aggregated data. **Results:** Among a total of 4632 participants, 2753 (59.43%) received first-line treatment; 3162 (68.26%) received ICIs; 1802 (38.90%) classified as ED and 2830 (61.10%) classified as non-ED. Kaplan-Meier analysis indicate that ED patients associate with worse survival outcomes, regardless of ICIs or chemotherapy (CT) (HROS=1.21, p=0.01; HRPFS=1.19, p=0.01). Compared with non-ED, ED patients had worse OS in both ICIs (ED vs non-ED, mOS, 13.34 m vs 16.07 m; p=0.01; HR, 1.21 [1.09-1.34]) and CT (ED vs non-ED, mOS, 12.02 m vs 13.93 m; p=0.01; HR, 1.19 [1.04-1.37]). IPD meta-analysis indicate that the ED group exhibited worse OS outcome (HR=1.18 [1.07-1.30], p=0.01). Subgroup analysis confirmed this association in both ICIs (HR=1.18 [1.04-1.34], p=0.01) and CT groups (HR=1.18 [1.00-1.39], p=0.05). Excluded clinical trials which PFS not primary outcome, and investigated the association with ED and PFS in first-line clinical trials. Similarly, Kaplan-Meier analysis show ED patients had worse PFS regardless of ICIs (mPFS, 5.52 m vs 5.58 m; p=0.01; HR, 1.19 [1.06-1.33]) or CT (mPFS, 5.55 m vs 5.59 m; p=0.06; HR, 1.17 [0.99-1.37]). IPD meta-analysis of PFS also supported results above (HR=1.15 [1.03-1.28], p=0.02). **Conclusions:** The NSCLC patients with ED are significantly associated with adverse survival outcomes regardless of CT or ICIs. The findings recommend the implementation of ED status assessment in clinical practice for NSCLC patients to improve their survival outcomes. Research Sponsor: None.

8547 Poster Session

First-in-human study of CJRB-101, a live biotherapeutic product in combination with pembrolizumab in selected types of advanced or metastatic cancer.

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Background: CJRB-101 is a live biotherapeutic product containing a novel strain belonging in the species *Leuconostoc mesenteroides*. Preclinical data support the role of CJRB-101 in eliciting anti-tumor response via induction of macrophage and recruitment of $GZMB^+$ CD8 T cell, thereby eliciting synergy with pembrolizumab. **Methods:** This is a multi-national, open label, phase 1/2 study to evaluate the safety and preliminary efficacy of CJRB-101 with pembrolizumab in patients with non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and melanoma who are immune checkpoint inhibitor (ICI)-naïve or have progressed with ICIs. Patients were treated with pembrolizumab 200 mg every 3 weeks with dose level 1 (1 capsule QD) or 2 (2 capsules BID) of CJRB-101 until unacceptable toxicity or progression of disease. Exploratory endpoints included bulk RNA sequencing of baseline and post-treatment (prior to C2D1) FFPE samples. **Results:** As of Jan 17, 2025, a total of 32 patients were enrolled, including 13 ICI-naïve and 19 ICI-refractory patients. No dose limiting toxicity was observed in the lead in part (dose level 1, n=12) or in subsequent patients in level 2 (n=20). At a median follow-up of 59 days, the median number of treatment cycles was 3. Treatment-related adverse events accounted for 21.9% (n=7/32), mostly grade 1 or 2. Only 1 patient (3.2%) experienced grade $>$ 3 TRAE which was anemia related to CJRB-101. Preliminary efficacy outcomes are shown in Table. Of the 20 patients deemed efficacy evaluable with at least 1 on-treatment scan (ICI naïve, n=10; ICI refractory, n=10), the ORR was 44% for ICI naïve, metastatic NSCLC (n=4/9), and DCR was 30% (n=3/10) for ICI-refractory NSCLC. Bulk-RNA sequencing of baseline samples (n=14) showed that patients who derived clinical benefit (CB, PR+SD, n=7) showed enrichment in T cell activation, and upregulation of innate and adaptive immune response compared to those with no-clinical benefit (NCB; PD, n=7). On treatment biopsied sample showed significant decrease in $PD\text{-}1^+Tim\text{-}3^+$ CD4 (P=0.002) and CD8 (P=0.006) T cells in CB group compared to the NCB group. **Conclusions:** CJRB-101 plus pembrolizumab was well tolerated with manageable safety profile. Preliminary efficacy data show anti-tumor activity in metastatic NSCLC, and early biomarker data support the role of immune activation of CJRB-101. Exploratory analysis of PBMCs, multiplex IHC, PD biomarker, and fecal microbiota metagenomics analysis are ongoing. Clinical trial information: NCT05877430. Research Sponsor: None.

Preliminary efficacy outcomes.

	Treatment status		
Confirmed ORR	**ICI naive**	**ICI refractory**	**Total**
Tumor types (n)	10	10	20
NSCLC (n)	9	10	19
ORR (%)	44%	0%	21%
DCR (%)	67%	30%	64%
HNSCC (n)	1	0	1
DCR (%)	100%	0	100%
Dose of CJRB-101 (n)	10	10	20
0 level (n=6)	4	2	6
ORR (%)	50%	0%	33%
DCR (%)	50%	0%	33%
1 level (n=14)	6	8	14
ORR (%)	33%	0%	14%
DCR (%)	83%	38%	57%

8548 Poster Session

Camrelizumab combined with 2 cycles of chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC): A two-arm, single-center, phase 2 study.

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Background: In the treatment of advanced non-small cell lung cancer (NSCLC), the combination of anti-PD1 and chemotherapy has demonstrated an advantage over chemotherapy alone. First-line treatment of advanced NSCLC with camrelizumab in combination with platinum-based chemotherapy shows promising clinical activity. Nonetheless, the impact of varying chemotherapy cycles on efficacy and safety requires investigation through data from prospective studies. **Methods:** This was a two-arm, single-center, phase 2 clinical trial (ChiCTR2200065078) in which we assigned patients with stage IIIb-IV advanced non-small cell lung cancer (NSCLC) to receive 2 or 4 cycles of platinum-based chemotherapy combined with camrelizumab 200 mg, followed by camrelizumab maintenance therapy until 2 years. The primary endpoint was progression-free survival, and secondary endpoints were objective response rate (ORR), overall survival (OS) and safety. **Results:** As of December 1, 2024, 40 patients were enrolled in this study, including 16 patients in the 2-cycle platinum-based chemotherapy combined with camrelizumab groups (Group A), and 24 patients in the 4-cycle platinum-based chemotherapy combined with camrelizumab groups (Group B) with a median follow-up of 17.6 months. The patients in Group A are older than those in Group B (75.50 [72.75, 77.25] vs. 69.00 [63.75, 72.25]). The median progression-free survival (PFS) were 5.4 months (95% CI, 4.9 to 5.9) for the group A and 13.0 months (95% CI, 5.6 to 20.4) for the group B, respectively (P=0.195). The confirmed overall response (ORR) was 6.2%, (95% CI, 0.6% to 26.4%) for the Group A and 41.7%, (95% CI, 20.7% to 65.9%) for the Group B, respectively (P=0.036). The median OS were 11.4 months (95% CI, 8.6 to 14.2) for the group A and 24.1 months (95% CI, 17.4 to 30.8) for the Group B, respectively (P=0.079). Across the overall population, 97.5% of patients reported any grade of treatment-related adverse event (TRAE), with 6.2% experiencing grade ≥3 TRAEs for Group A, and 12.5% for Group B. **Conclusions:** The 2-cycle group did not show superior progression-free survival (PFS) relative to the 4-cycle platinum-based chemotherapy when combined with camrelizumab. However, the 4-cycle platinum-based chemotherapy group may have resulted in a higher probability of developing grade ≥3 treatment-related adverse events. A combination of a 2-cycle chemotherapy and immunotherapy may be more suitable for elderly patients with advanced lung cancer. Clinical trial information: ChiCTR2200065078. Research Sponsor: None.

8549 Poster Session

Evaluation of the combination of regorafenib + avelumab in patients with non-small cell lung cancer without oncogenic addiction: The phase II REGOMUNE study.

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Background: Combining anti-angiogenic agents with immune checkpoint inhibitors (ICI) in NSCLC has a strong biological rational. This strategy may enhance antitumor immunity by downregulating PD-1/PD-L1 expression, increasing TIL infiltration, and reducing immunosuppressive Tregs and MDSCs, potentially resensitizing patients to ICI therapy. **Methods:** This phase II, single-arm, multicentric trial evaluated the combination of regorafenib (160 mg daily, 3 weeks on/1 week off) and avelumab (10 mg/kg Q2W) in advanced/metastatic NSCLC patients without EGFR/ALK/ROS1 alterations. Eligible patients were previously treated with anti-PD(L)1 inhibitors for ≥4 months and had received ≤2 prior systemic lines. The primary endpoint was the 6-month progression-free rate (PFR6) per RECIST 1.1. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Correlative studies analyzed baseline tumor samples to identify biomarkers of response. A Simon's two-stage design was used, requiring ≥13 non-progressions among 43 patients to demonstrate efficacy. **Results:** Between February 2021 and April 2024, 46 patients were enrolled across four centers (median age: 63, range: 41-88). Median follow-up was 13.4 months. Most patients (94%) had prior platinum-based chemotherapy. Dose adjustments for regorafenib were required in 78.3% of patients due to adverse events. Common grade 3/4 toxicities included erythroderma (15.2%) and oral mucositis/palmar-plantar erythrodysesthesia (13% each). No treatment-related deaths occurred. Among 34 evaluable patients, PFR6 was 35.3% (90% CI: 21.8-50.8), with 6 (17.6%) achieving partial responses and 16 (47.1%) having stable disease. The median duration of the response was 20.3 months (95% CI: 5.1-22.0). Median PFS was 3.7 months (95% CI: 1.9-8.7), and median OS was 25.5 months (95% CI: 8.7-NR). **Conclusions:** The combination of avelumab and regorafenib demonstrated the ability to resensitize a subset of anti-PD(L)1-exposed NSCLC patients to immune checkpoint inhibition, leading to durable responses and a promising 6-month PFR. Biomarker analyses will also be presented, providing insights into predictors of response. Clinical trial information: NCT03475953. Research Sponsor: None.

8550 Poster Session

Identification of immunotherapy early treatment failure in non-small cell lung cancer (NSCLC) using a novel cell-free DNA (cfDNA) tissue-agnostic genome-wide methylome enrichment assay.

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Background: Immune checkpoint inhibitor treatment failure constitutes a significant clinical challenge in non-small cell lung cancer (NSCLC). Molecular residual disease (MRD) detection in NSCLC may allow earlier detection of disease recurrence/progression and enable early treatment intensification or clinical trial enrolment. We have developed a novel tissue-agnostic genome-wide methylation enrichment platform based on cell free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq). Here, we present data on its application as an MRD assay to predict early recurrence or progression in patients (pts) with NSCLC receiving immunotherapy. **Methods:** The study population consists of pts with stage III/IV NSCLC at the Princess Margaret Cancer Centre, treated with definitive chemoradiation followed by consolidative durvalumab (stage III) or with PD-1 inhibitors +/- chemotherapy (stage IV). Pts underwent serial blood collection prior to initiation of treatment, 2-4 weeks after treatment initiation and approximately 6-8 weeks thereafter until progression. 5-10 ng of cfDNA was isolated from plasma. A classifier was trained on an independent set of lung and non-cancer samples to quantify relative circulating tumor DNA (ctDNA) content. The analysis considered multiple timepoints. Results were considered "positive" if there was a detected result at any follow-up timepoint. Results were considered "negative" if all follow-up timepoints were reported as not detected. Progression-free survival (PFS) was compared between groups using a log-rank test. Hazard ratio (HR) was estimated using Cox proportional hazards model. **Results:** A total of 187 samples from 63 unique pts (44% stage III and 56% stage IV) were analyzed and correlated with PFS. Pts with a positive MRD test showed significantly worse PFS than those who tested negative (HR 4.8; 95% CI, 2.1-10.8, $P<0.0001$), sensitivity 80%, specificity 91%. The lead time between MRD positivity and progression was up to 12.6 months, with a mean of 5.1 months. Secondary analysis of pts with stage III NSCLC revealed significantly worse PFS in MRD-positive pts compared to MRD-negative pts (HR 8; 95% CI, 1.4-46.7, $P=0.007$). **Conclusions:** MRD detection using genome-wide methylome enrichment correlates strongly with PFS in pts with advanced NSCLC receiving immunotherapy. This tissue agnostic assay shows promise for early identification of treatment failure, enabling timely selection of patients for treatment intensification or clinical trials. Research Sponsor: None.

A phase I trial of intratumoral adenovirus-interleukin-12 (IT-ADV/IL-12) and atezolizumab in metastatic non-small cell lung cancer (NSCLC) progressed on first-line immunotherapy.

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Background: Interleukin-12 (IL-12) is a cytokine that enhances anti-tumor immunity via interferon-gamma release and has demonstrated synergistic effects with immune checkpoint inhibitors (ICIs) in immunoquiescent tumors. We report results of phase I trial of intratumoral adenovirus-interleukin-12(IT-ADV/IL-12)plus atezolizumab in metastatic NSCLC patients who progressed on prior ICI. **Methods:** This institutional single-arm, open-label phase I trial enrolled 13 patients with metastatic NSCLC who progressed on ICI from October 2021 to February 2024. First 2 patients received IT-ADV/IL-12 at 5×10^{11} viral particles (vp), while the remaining 11 patients received a reduced dose of 3×10^{11} vp as per protocol. Atezolizumab (1200 mg) was given every 3 weeks for up to 1 year or till disease progression. Endpoints were safety (as per Common Terminology Criteria for Adverse Events v5.0) and disease control rate (DCR), including complete response (CR), partial response (PR), or stable disease (SD) as defined by RECIST v1.1. **Results:** 12/13 patients were included in analysis (1 patient excluded due to rapid progression before starting atezolizumab). All patients had initial response to prior ICI (4/12 with CR and 8/12 with PR) but later developed resistance. DCR was 50% (6/12), median progression-free survival (PFS) was 2 months, and median overall survival (OS) was 10.5 months. 2/12 (25%) patients were alive at the time of analysis with median follow up time of 22 months. PD-L1 expression did not affect treatment response. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 4 patients, who demonstrated a higher likelihood of treatment response (p = 0.06), with all 4 achieving stable disease (SD). Most common TRAE of any grade was fatigue (4/12, 33%). There were no grade 4 or 5 events, and no treatment discontinuation related to TRAE. Next-generation sequencing results were available in 10/12 patients. The most common mutation was TP53, detected in 9/10 patients. There was no statistically significant association between the presence of TP53 mutation and treatment response. **Conclusions:** IT-ADV/IL-12 plus atezolizumab was safe, tolerable, and showed promising clinical benefit in metastatic NSCLC with acquired resistance to ICI, without new safety concerns. Presence of TP53 mutation did not impact the treatment response. Research Sponsor: Genentech.

Study Characteristics	Results (n=12)
Age (median) years	69 years
Female (n)	5 (41.6%)
PD-L1	
<1%	5 (41.6%)
>1%	7 (58.3%)
Sites of progression after IL-12 therapy	
Local (lung)	9 (75%)
Distant visceral	5 (41.6%)
Brain	1 (8.3%)
Regional Lymph node	6 (50%)
IT ADV/IL-12 related Grade 3 adverse events (n)	
Fever	2
Dyspnea	1
Hyponatremia	1
Anemia/leukopenia	1
Pneumonia	1
Response	
DCR (n)	6 (50%)
Progression (n)	6 (50%)
Median PFS	2 months
Impact of PD-L1 expression on PFS	
<1%	3.6 months
>1%	3.29 months (p= .84)
Median OS	10.5 months

8553 Poster Session

Circulating CD28-KLRG1+CD8+ T cells as prognostic indicators in advanced NSCLC chemoimmunotherapy.

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Background: Chemoimmunotherapy has become the standard first-line treatment for advanced non-small cell lung cancer (NSCLC), but patient responses vary. Consequently, identifying predictive biomarkers is crucial to optimize therapeutic strategies. Circulating T cells are a promising focus due to the convenience of blood sampling and the feasibility of repeated monitoring. Deciphering the specific T-cell subsets that respond to chemoimmunotherapy is critical for personalizing treatment and improving outcomes in advanced NSCLC patients. **Methods:** We conducted unsupervised analysis using multi-color flow cytometry on peripheral blood samples from 30 NSCLC patients enrolled in a phase 2 clinical study (ClinicalTrials.gov NCT04836728) to explore correlations between immune cell subsets with therapeutic outcomes. We integrated single-cell RNA and T cell receptor sequencing data from peripheral blood, tumor, and non-tumor tissues of 8 NSCLC patients to study the transcriptional state of key cell types involved in these correlations. **Results:** Flow cytometry analysis revealed that a higher proportion of CD28-KLRG1+ CD8+ T cells was found in the peripheral blood of patients with durable clinical benefit (DCB) and improved overall survival (OS). Within these T cells, the CD57+ subset was positively correlated with OS at baseline, while the CD57- subset was negatively correlated. However, during treatment, both subsets showed a positive association with OS, highlighting the predictive value of CD28-KLRG1+ CD8+ T for chemoimmunotherapy response. Further phenotypic and functional analyses demonstrated that CD28-KLRG1+ CD8+ T cells are highly proliferative (Ki67) and produce anti-tumor cytokines (IFN-γ, IL-2, and TNF-α) upon TCR stimulation, indicating their immune-responsive role. Although these cells expressed relatively low levels of exhaustion markers such as PD-1 and TIGIT, they exhibited high expression of TCF1 and TOX, pointing to a progenitor exhausted T cell state characterized by reduced exhaustion and enhanced functional potential. Single-cell transcriptomic and TCR profiling revealed that CD28-KLRG1+ CD8+ T cells underwent significant clonal expansion in the peripheral blood during chemoimmunotherapy, evidenced by the higher clonality index and lower Inverse Simpson index, indicating their superior clonal expansion capacity upon activation. Longitudinal analysis showed that these cells had the highest proportion of expanded clones during treatment, primarily distributed in the effector T cell clusters, suggesting their anti-tumor activity during chemoimmunotherapy. **Conclusions:** Circulating CD28-KLRG1+ CD8+ T cells are a valuable biomarker for predicting outcomes in first-line chemoimmunotherapy for patients with advanced NSCLC. These findings highlight their functional activity, clonal expansion, and role in antitumor immunity during treatment. Research Sponsor: National Natural Science Foundation of China; 82273083; National Natural Science Foundation of China; 82272733.

8555 Poster Session

T-cell effector cytokine signature as predictor of survival and toxicity in metastatic NSCLC patients treated with immunotherapy.

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Background: Immune checkpoint inhibitors (ICIs) have led to significant prolongation of survival in patients with advanced non-small cell lung cancer (NSCLC). However, less than 20% have durable long-term survival. Presence of a pre-existing tumor immune response that can subsequently be unleashed by ICIs predicts success to ICI. Specifically, a T- cell effector replete tumor immune microenvironment predicts for improved survival, following ICI. Given intra-tumor heterogeneity, we asked whether baseline and on treatment T cell effector mediated serum cytokines predict benefit from ICI in metastatic NSCLC. We also asked whether cytokines predicted immune related adverse events (iRAEs) from ICI in these patients. **Methods:** To assess whether serologic markers were associated with response and toxicity to immunotherapy, we conducted a multiplex ELISA for a panel of 70 innate and adaptive immune cytokines and chemokines in 100 NSCLC patients treated with PD-1 inhibitors, either as monotherapy or in combination with chemotherapy. Cytokine expression was correlated with outcomes (progression- free and overall survival, PFS/OS) and occurrence of any grade 3 or greater iRAE. Kaplan Meier analyses were performed for survival analyses, with the median value used to stratify cytokines. We then compared the predictive value of this cytokine signature with other predictive signatures for outcomes from ICIs. **Results:** Increased concentrations of baseline TRAIL correlated with improved PFS and OS; conversely, decreased baseline IL-3, IL-6, IL-8, APRIL, IL20, IL33, MCP4, IL-7, and TARC correlated with improved PFS. Increased baseline SDF1 and TRAIL correlated with OS; conversely, decreased baseline IL-6, IL-8, TPO, I-TAC, IL-3, APRIL, IL-20, IL-33, MCP4, MCP2, IL-15, MCSF, PDGFa, VEGFA, and MIP1d correlated with improved OS. Increased concentrations of TRAIL correlated with increased concentrations of SDF1, Perforin, and GzmB (T effector cell, Teff signature). A high Teff signature was associated with a statistically significant improvement in OS, in univariate and multivariate analysis. IL1b and IL-17a were statistically higher in on treatment samples taken from in patients who developed IRAE, whereas Eotaxin3 and MIP1d were lower in on treatment samples taken from in patients who developed IRAE. **Conclusions:** We report that an increase in a Teff cell cytokine signature at baseline predicts long term survival from ICI and may reflect the presence of a pre-existing immune response characterized by increased T-effector cells that are then subsequently unleashed by ICI therapy. Conversely, higher baseline levels of IL-1β and IL-17 indicate the presence of a heightened inflammatory state that predisposes to the occurrence of iRAEs, following ICI therapy. Research Sponsor: Veterans Affairs Merit Award I01CX001560.

Comparative efficacy of osimertinib with and without radiation therapy in EGFR-mutated non-small cell lung cancer with brain metastases.

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Background: Osimertinib has demonstrated efficacy in managing brain metastases in EGFR-mutated non-small cell lung cancer (NSCLC). However, the optimal approach—using CNS-penetrant tyrosine kinase inhibitor (TKI) therapy alone versus combining it with radiation therapy—remains uncertain. This study examines whether Osimertinib combined with radiation provides superior intracranial control and outcomes compared to Osimertinib alone. **Methods:** Patients aged ≥18 years with NSCLC and brain metastases diagnosed between January 2010 and December 2024 were identified via the TriNetX Research Network. Two cohorts were analyzed: those receiving Osimertinib with stereotactic radiation or radiosurgery within six months (cohort 1) and those without radiation (cohort 2). Propensity score matching balanced baseline characteristics. Outcomes included survival, hospitalization rates, CNS complications, and second-line treatment initiation. A Kaplan-Meier analysis evaluated survival and mortality while a Cox proportional hazards model assessed the effects of covariates. **Results:** A total of 76,474 NSCLC patients were identified, 13,377 had brain metastases, and 743 received Osimertinib. Kaplan-Meier analysis indicated lower mortality in cohort 1 at 3 years (HR = 0.674, p = 0.0029), 5 years (HR = 0.719, p = 0.0091), and overall (HR = 0.709, p = 0.0063). CNS complications (risk difference = 20.28%, $p < 0.0001$) were higher in cohort 1, with 11 patients diagnosed with radiation necrosis after treatment, representing a 5.28% risk. Additionally more people in cohort 1 developed interstitial lung disease (risk difference = 9.1%, p=0.0016). Second-line treatment initiation (HR = 1.741, p = 0.0166) was also higher in cohort 1. Key predictors of increased mortality included hypertension (HR = 1.366, p = 0.0047), bone metastases (HR = 1.608, $p < 0.0001$), and liver metastases (HR = 1.319, p = 0.0408). Stereotactic radiosurgery in particular was associated with a lower hazard ratio (HR = 0.487, p = 0.0031). **Conclusions:** Combining Osimertinib with stereotactic radiation or radiosurgery improves survival in NSCLC with brain metastases but may increase CNS complications and second-line treatment rates. These findings highlight the need to balance survival benefits with treatment risks to optimize patient care. Research Sponsor: None.

8557 Poster Session

Updated analysis from NEJ045A study: Safety and efficacy of durvalumab plus carboplatin and etoposide for previously untreated extensive-stage small-cell lung cancer patients with a poor performance status.

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Background: Although the combination of an anti-PD-L1 antibody and platinum-based chemotherapy has become the standard care for extensive-stage small-cell lung cancer (ES-SCLC) patients (pts), its safety and efficacy for those with a poor PS are unclear. In the NEJ045A study, by adjusting the doses of carboplatin (CBDCA) and etoposide (ETP), durvalumab (DUR) plus CBDCA and ETP demonstrated tolerability and efficacy for ES-SCLC pts with a poor PS, meeting the primary endpoint of tolerability. Here, we report the updated data from NEJ045A, including the long-term effects of ICIs. **Methods:** Previously untreated ES-SCLC pts with PS 2–3 were enrolled. Eligible pts received 1500 mg DUR plus CBDCA and ETP every 3 to 4 weeks for up to 4 cycles, followed by DUR maintenance therapy. Initial dosages of CBDCA and ETP were AUC 4 and 80 mg/m^2 in PS 2 and AUC 3 and 60 mg/m^2 in PS 3. The dosages for the subsequent cycles were adaptively determined based on the adverse events (AEs) of the previous cycles. **Results:** From April 2021 to October 2023, 57 pts (43 pts with PS 2 and 14 pts with PS 3) were enrolled. At the data cutoff (Oct 3rd, 2024), the median follow-up period for overall survival among patients with censored data was 23.4 months (12.9-32.7) in the FAS population. The median age was 74 years old (range 55-86). 79% was male. The median number of cycles of induction therapy was 4 (range 1-4), and the median number of cycles of durvalumab maintenance was 3 (range 1-16) in PS 2 and 7 in PS 3 (1-22). A total of 34 patients (64%) completed induction therapy, comprising 28 pts (67%) in PS 2 and 6 pts (50%) in PS 3. Doses of CBDCA and/or ETP were increased during induction therapy in 24% of PS 2, and 18% of PS 3. Updated median PFS in PS 2 and PS 3 were 4.5 months (95% CI, 3.1-5.8) and 4.5 months (95% CI, 1.4-8.2). The 1-year survival rates in PS 2 and PS 3 were 50% (95% CI, 37.0-67.7) and 18% (95% CI, 5.2-63.7). Updated median OS in PS 2 and PS 3 were 11.3 months (95% CI, 6.7- 16.1) and 5.1 months (95% CI, 2.1-8.5). Patients who completed induction therapy demonstrated longer OS compared to those who did not (median OS, 15.0 vs. 3.8 months). Treatment was discontinued in 100% of PS 2 and 93% of PS 3, and the reasons for discontinuation (PD/AE/other) were 79%/12%/9% in PS 2 and 38%/54%/8% in PS 3. **Conclusions:** DUR + CBDCA + ETP therapy was well tolerated for ES-SCLC with poor PS, and completion of induction therapy was associated with an improvement in OS. Clinical trial information: CRB3180025. Research Sponsor: Astra Zeneca.

8558 Poster Session

Avidity engineered multifunctional antibodies for stimulation and orchestration of innate and adaptive immune cells in tumor tissues.

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Background: Antibodies and ADCs are mainstays in the treatment of cancer. However, given difficulties in achieving a deep and sustained response, significant improvements are desirable. We report on first in class "Booster" molecules, based on clinically validated ADCC-competent antibodies, equipped with two immunomodulatory domains that are affinity engineered to be functional only when in contact with a tumor cell. We see strong expansion and increased cytotoxicity of immune cells in the presence of cancer cells *in vitro*, activation of relevant immune cell types *ex vivo*, and reduction of tumor burden *in vivo*, with significantly better activity than adoptive cell therapy or control antibody without these immunomodulatory domains. **Methods:** NRG mice were engrafted with luciferase-expressing SKOV3 cells via intraperitoneal injection 7 days prior to treatment. Mice received 1 million human NK cells isolated from healthy donors. Compounds were administered biweekly, and low dose IL2 thrice weekly. Blood was collected weekly, and tumor burden monitored weekly *via* bioluminescence. *ex vivo*: *in situ* activation of tumor infiltrating immune populations was evaluated by nanostring in freshly isolated tumor tissue. *in vitro*: cytotoxicity was measured by quantifying the number of alive tumor cells using automated microscopy. Expansion was performed by stimulating NK cells weekly with tumor cells that were opsonized with Booster or antibody, NK cells were counted weekly to determine expansion. **Results:** Mice treated with a TROP2 targeting Booster demonstrated superior tumor control than sacituzumab treated mice, with strong tumor remission by day 35. High NK counts were observed in the blood of Booster treated mice, and no NK cells were detected in that of sacituzumab treated mice. In the peritoneal cavity, NK counts were up to 100x higher in Booster treated mice than in sacituzumab treated mice. Our Booster reprograms the immune microenvironment *ex vivo* in freshly isolated tumor tissue, transforming a cold tumor into a hot tumor. It activates multiple cytotoxic and IFN-γ pathways, stimulates CD8+ T cell activation, downregulates pro-tumor pathways in Tregs and induces a phenotypic shift in macrophages from the immunosuppressive M2 to the pro-inflammatory M1 phenotype. In separate *in vitro* assays we saw sustained expansion and enhanced cytotoxicity of NK cells for at least 6 weeks. Cells stimulated with TROP2 Booster showed prolonged tumor control, whereas sacituzumab antibiody stimulated cells failed to sustain tumor control beyond 21 days. **Conclusions:** In correlation with extensive *in vitro* and *ex vivo* data, we observe a prolonged and significant improvement in tumor control in mice treated with Boosters compared to mice treated with control antibody. Work is ongoing to develop these molecules, with the first clinical trial expected to start next year. Research Sponsor: None.

8559 Poster Session

Predictive value of circulating tumor DNA detection for long-term survival in patients with advanced lung cancer undergoing chemoimmunotherapy.

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Background: Chemoimmunotherapy (ChemoIO) has emerged as the first-line standard treatment option for advanced non-small cell lung cancer (NSCLC) without drive gene mutation. However, only a portion of patients experienced long-term survival, even among those who achieved partial or complete response (PR or CR) in early assessments. This study assessed circulating tumor DNA (ctDNA) detection in predicting long-term survival in advanced NSCLC patients using a novel 2365-gene fixed panel integrating mutation, copy number variation (CNV), and fragmentomics (Frag). **Methods:** Based on the SheildingUltra panel developed by Geneseeq, using a discovery cohort composed of over 200 lung cancer and healthy plasma samples, AI-driven models were developed to improve the ctDNA detection sensitivity by incorporating mutations, CNV, and Frag. The enhanced panel was retrospectively validated in a cohort of 107 advanced NSCLC patients using plasma samples collected during PR/CR stages of ChemoIO. Moreover, the fixed panel was prospectively evaluated in an independent cohort of 38 patients who achieved PR/CR in early assessments, with blood samples collected both before treatment and on Day 1 of Cycle 5 (C5D1) of therapy. The value of ctDNA detection results for predicting long-term survival was subsequently evaluated in both cohorts. **Results:** The enhanced fixed panel demonstrated robust performance in the discovery cohort, effectively discriminating lung cancer patients from healthy individuals through the integration of mutations, CNV, and Frag. In the retrospective validation cohort including 107 patients in PR/CR status, ctDNA-negative patients had significantly longer progression-free survival (PFS) (median PFS: not reached [NR] vs. 14.1 months, hazard ratio (HR): 0.36 (95% confidence interval [CI]: 0.18-0.74), P=0.004) and overall survival (OS) (median OS: NR vs. NR, HR: 0.10 (95% CI:0.02-0.43), P≤0.001) compared to ctDNA-positive patients. In the prospective validation cohort, the ctDNA status determined from plasma collected at C5D1 successfully stratified patients into groups with long- and short- PFS and OS. The median PFS was NR for both groups, with a HR (95% CI) of 0.19 (0.04-0.92) and a p-value of 0.021. The median OS was also NR for both groups, with a HR (95% CI) of 4.56e-10 (0-infinity) and a p-value of 0.011. However, the pre-treatment ctDNA status was not significantly associated with survival. **Conclusions:** Using a novel ctDNA detection panel incorporating mutation, CNV, and Frag, we found the ctDNA status during the treatment may serve as a potential biomarker for predicting long-term PFS in advanced NSCLC patients undergoing ChemoIO. Additional prospective studies are needed to confirm these results and guide clinical decisions for optimal immunotherapy in NSCLC patients. Research Sponsor: None.

8560 Poster Session

Phase 2 study of pembrolizumab (pembro) plus plinabulin (plin) and docetaxel (doc) for patients (pts) with metastatic NSCLC after progression on first-line immune checkpoint inhibitor alone or combination therapy: Initial efficacy and safety results on immune re-sensitization.

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Background: Immune checkpoint inhibitor (ICI)-based treatment regimens have become the standard of care for first-line treatment of EGFR/ALK wild-type NSCLC. However, >60% pts inevitably develop progressive disease (PD) from acquired resistance (AR), which could be due to T cell exhaustion and antigen presenting cell (APC) pathway mutation. For patients with PD, the standard of care (SOC) is still doc, while the efficacy is limited with ~10% ORR, median PFS 3.7 months in TROPION-Lung01. Thus, there is a huge unmet need for this setting of patients. Plin is a selective immunomodulating microtubule-binding agent which promotes dendritic cell maturation and enhances anti-tumor T cell response. The mechanism of action has been validated via *in vitro*, *in vivo* models, and human trials, suggesting that plin may have the potential to overcome immunotherapy AR. This phase 2 study was aimed to evaluate the efficacy and safety of pembro combined with plin and doc in pts with metastatic NSCLC who had progressed after ICI. **Methods:** In this single-arm phase 2 trial, metastatic NSCLC pts who developed acquired resistance on immunotherapy alone or in combination with platinum-doublet chemotherapy were enrolled. Participants received pembro 200 mg, plin 30 mg/m^2, and doc 75 mg/m^2 intravenously day 1 every 21days. The primary endpoint is investigator-based ORR per RECIST 1.1. The secondary endpoints included PFS, OS, DoR and safety. The sample size is 47 patients. The ORR and DOR was assessed in the evaluable set. **Results:** At of the 21th Jan, 2025, data cutoff, 47 pts were enrolled, the median follow-up time was 8.7 months, median age of 67.5 (rang 44-83), 80.9%(n=38) were male, 68.1% had smoking history. Histology included 66% with non-squamous, 34% with squamous cell carcinoma. Efficacy and safety were analyzed in the 45 patients, 40 patients were evaluable. The ORR was 20% (confirmed ORR was 17.5%) and the median DoR was 9.4 m; the DCR was 81.6% (defined as PR and SD> 4 months), median PFS was 8.2 m (current 6 m PFS rate was 60.2%, 12 m PFS rate was 29.9%), OS had not been reached (6 death since the first patient enrollment of 02/2023) . G3 or higher treatment-related AEs (TRAEs) were reported by 37.8% of pts, ≥5% TRAEs include diarrhea (6.7%), myelosuppression (8.9%) and hypertension (8.9%). **Conclusions:** Pembro plus plin and doc in pts with metastatic NSCLC who developed PD on ICI shows promising efficacy, with doubling PFS and DCR compared with historical data of doc. The AEs of the triple combination treatment is manageable. Further investigations into which pts would benefit from continued ICI treatment after progression is warranted. Clinical trial information: NCT05599789. Research Sponsor: BeyondSpring and MSD China. Plinabulin was provided by BeyondSpring and pembrolizumab by MSD China.

8561 Poster Session

A phase 2 study of HLX07 plus serplulimab with or without chemotherapy versus serplulimab plus chemotherapy as first-line therapy in advanced squamous non-small cell lung cancer.

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Background: Approved first-line therapies of PD-L1/PD-1 inhibitors plus chemotherapy conferred significant survival benefits for advanced squamous non-small cell lung cancer (sqNSCLC). However, the prognosis remains to be improved. The epidermal growth factor receptor (EGFR) is highly expressed in sqNSCLC and associated with a poor prognosis. This study aimed to compare the efficacy of HLX07, a novel humanized anti-EGFR antibody, plus serplulimab (anti-PD-1 antibody) ± chemo versus serplulimab plus chemo as first-line option for advanced sqNSCLC. **Methods:** This randomized, multicenter phase 2 study consisted of 4 parts that assessed varied combinations of HLX07 (at different doses), serplulimab, and chemotherapy. Part 3 evaluated the preliminary efficacy of the three-drug combination and is presented below. Patients with stage IIIB/IIIC or IV sqNSCLC that was not amenable to surgery or radiation therapy and high tumor expression of epidermal growth factor receptor (H score≥150) and no prior systemic therapy were randomized 1:1 to receive intravenous HLX07 at 800 mg (group A) or 1000 mg (group B), in combination with serplulimab (300 mg) and chemotherapy (carboplatin and nab-paclitaxel), once every three weeks. The primary endpoints were independent radiological review committee (IRRC)-assessed objective response rate (ORR) and progression-free survival (PFS) per RECIST 1.1. **Results:** As of 31 December 2024, 27 patients were enrolled and randomly assigned to group A (n=13) and group B (n=14) in part 3. 15 (55.6%) patients had metastatic disease. With a median follow-up of 16.0 months, IRRC-assessed confirmed ORR per RECIST 1.1 was 69.2% (95% CI 38.6–90.9) in group A and 71.4% (95% CI 41.9–91.6) in group B. Disease control rate was 92.3% (95% CI 64.0–99.8), and 100% (95% CI 76.8–100.0), respectively. Median PFS was 15.1 (95% CI 4.1–not available) months in group A and not reached in group B. The median overall survival and duration of response were not reached in either group as of the data cutoff date. All the patients in both groups reported treatment-emergent adverse events (TEAEs); most common TEAEs of any grade included neutrophil count decreased (92.3% vs. 71.4%), white blood cell count decreased (84.6% vs. 85.7%), anemia (84.6% vs. 78.6%), platelet count decreased (76.9% vs. 71.4%), hypokalemia (53.8% vs. 64.3%), rash (46.2% vs. 57.1%), alopecia and hypocalcemia (46.2% vs. 50.0% for each). 6 (46.2%) patients, and 8 (57.1%) in group A, and B reported immune-related adverse events, respectively. **Conclusions:** First-line HLX07 plus serplulimab and chemotherapy showed encouraging preliminary efficacy with a manageable safety profile in patients with advanced sqNSCLC which warrants further investigation. Clinical trial information: NCT04976647. Research Sponsor: Shanghai Henlius Biotech, Inc.

Differential predictive impact of PD-L1 expression on immunotherapy outcomes and immunophenotype in squamous versus non-squamous NSCLC.

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Background: PD-L1 tumor proportion score (TPS) is a key biomarker for immune checkpoint inhibitors (ICIs) efficacy in non-small cell lung cancer (NSCLC), but its predictive value in patients (pts) with squamous (SQ) histology remains uncertain, highlighting the need for histology-specific studies. **Methods:** Clinicopathologic, genomic, and outcomes data were collected and analyzed from advanced NSCLC pts treated with ICIs ± chemotherapy (CT) at Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. Cox regression tested the association between PD-L1 levels and survival to ICIs by histology, adjusting for potential confounders such as treatment regimen and line. Multiplexed immunofluorescence (mIF) on baseline tissue samples quantified CD8+, PD1+, CD8+/PD1+, and FOXP3+ densities, stratifying by PD-L1 TPS and histology. **Results:** Among 4967 NSCLC pts treated with ICIs ± CT, 727 (14.6%) had SQ histology. Among pts with available PD-L1 TPS, 1359 (37.9%) had TPS <1%, 1061 (29.6%) 1–49%, and 1167 (32.5%) ≥50%. Increasing PD-L1 TPS of <1%, 1–49% and ≥50% correlated with significant stepwise improvements in progression-free (PFS) and overall survival (OS) in pts with NonSQ NSCLC but not in those with SQ (Table 1). In SQ NSCLCs, there was no difference in PFS and OS between pts with PD-L1 TPS of 1–49% vs ≥50%, while only a dichotomized PD-L1 TPS (<1% vs ≥1%) was predictive of longer survival in this histology (PFS adjusted hazard ratio [aHR]: 0.72, p<0.01; OS aHR: 0.76, p=0.02). Comparing histologies, PFS and OS to ICIs ± CT were similar between SQ and NonSQ NSCLCs in PD-L1 TPS subgroups of <1% and 1–49%. However, among pts with a PD-L1 TPS ≥50%, those with NonSQ NSCLC had longer survival compared to SQ (PFS aHR: 1.30, p=0.01; OS aHR: 1.43, p<0.01), indicating stronger predictive value of increasing PD-L1 TPS levels only in NonSQ. mIF analysis (229 samples: 22 SQ, 207 NonSQ) showed lower intratumoral CD8+, PD1+, CD8+/PD1+, and FOXP3+ densities in SQ vs NonSQ. Increasing PD-L1 TPS significantly correlated with higher CD8+ cells in NonSQ NSCLCs (R = 0.25, p<0.01) but not in SQ (R = -0.034, p = 0.89). A similar association was observed for PD1+, CD8+/PD1+, and FOXP3+ cells. **Conclusions:** Increasing PD-L1 levels show stepwise PFS and OS improvements in NonSQ but not in SQ NSCLCs, where TPS acts as a dichotomous (<1% vs ≥1%) rather than continuous predictor. These findings have implications for treatment decision making as well as ICIs trial design and interpretation. Research Sponsor: None.

	PD-L1 TPS <1% vs 1-49%	PD-L1 TPS <1% vs ≥50%	PD-L1 TPS 1-49% vs ≥50%
SQ PFS mo	4.0 vs 6.6	4.0 vs 6.2	6.6 vs 6.2
aHR, p	*0.72, <0.01*	*0.71, 0.01*	*0.99, 0.95*
NonSQ PFS mo	4.6 vs 5.8	4.6 vs 8.2	5.8 vs 8.2
aHR, p	*0.79, <0.01*	*0.56, <0.01*	*0.70, <0.01*
SQ OS mo	13.0 vs 17.0	13.0 vs 17.5	17.0 vs 17.5
aHR, p	*0.77, 0.04*	*0.76, 0.06*	*0.98, 0.92*
NonSQ OS mo	14.7 vs 18.3	14.7 vs 27.7	18.3 vs 27.7
aHR, p	*0.81, <0.01*	*0.59, <0.01*	*0.72, <0.01*

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Clinical outcomes and predictors of response to PD-(L)1 blockade in patients with oncogene-driver negative NSCLC who have never smoked.

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Background: Non-small cell lung cancer (NSCLC) in patients (pts) who have never smoked is associated with poor response to immune checkpoint inhibitors (ICI). However, most studies have focused on pts with actionable oncogenes (e.g., EGFR, ALK, ROS1, RET, MET), and it remains unclear whether specific clinicopathologic and genomic features can predict ICI response in those without these actionable drivers. **Methods:** Clinicopathologic characteristics and outcomes data were collected from pts with metastatic, oncogene driver-negative, NSCLC who received ICI across 5 academic cancer centers in US and EU. Single sample gene set enrichment analysis was performed on NSCLC samples from the Stand Up To Cancer (SU2C) cohort to characterize transcriptomic correlates of response to ICI monotherapy in responders and non-responders. **Results:** Of 5639 pts with metastatic NSCLC analyzed, 708 (12.6%) tested negative for actionable oncogene drivers and had never smoked. Among these, median age was 64 years, 59.5% were women, 65.2% had ECOG PS 0/1, and 83.8% had adenocarcinoma. At a median follow-up of 36.9 months (mo), objective response rate (ORR) was 21.8%, median progression-free survival (mPFS) was 4.5 mo, and median overall survival (mOS) was 16.9 mo in this patient population. Pts with PD-L1 TPS ≥1% had significantly higher ORR (31.1% vs. 16.1%, $p<0.01$), and longer mPFS (HR 0.74, $p<0.01$) compared to those with PD-L1 <1%. Similarly, pts with very high TMB (≥90^{th} percentile) had higher ORR (52.2% vs 22.8%, $p<0.01$), longer mPFS (HR 0.50, $p<0.01$), and mOS (HR 0.40, $p<0.01$) compared to those with a TMB <90^{th} percentile. Pts with positive PD-L1 expression ≥1% and very high TMB had the highest ORR and the longest mPFS and mOS compared to pts with either one of these biomarkers alone. Treatment outcomes also varied by regimen: pts receiving dual PD-(L)1+CTLA-4 blockade or PD-(L)1 blockade + chemotherapy had higher ORR compared to those receiving PD-(L)1 monotherapy (30.0% vs 36.5% vs 10.3%, respectively, $p<0.01$). Dual PD-(L)1+CTLA4 inhibition was also associated with significantly longer mPFS (9.4 vs 6.9 vs 2.9 mo, $p<0.01$) and mOS (47.5 vs 19.7 vs 14.7 mo, $p<0.01$) compared to PD-(L)1 + chemotherapy and PD-(L)1 monotherapy, respectively. These differences were validated in pts receiving these regimens as first-line therapy. In NSCLC samples from pts who had never smoked without oncogenic driver mutations in the SU2C cohort, responders to ICI showed upregulation of innate and adaptive immune responses pathways, including enhanced MHC I/II antigen presentation, as well as increased T-cell activation, proliferation, and chemotaxis. **Conclusions:** These results emphasize how PD-L1≥1%, very high TMB, and use of dual checkpoint blockade are associated with improved outcomes in pts who have never smoked with oncogene-driver negative NSCLC, aiding personalized ICI use in this neglected population. Research Sponsor: None.

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Efficacy and safety of metronomic oral vinorelbine combined with PD-1 inhibitors as first-line therapy in advanced non-small-cell lung cancer in elderly patients.

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Background: Elderly individuals aged over 70 constitute the majority of Non-small cell lung cancer(NSCLC) patients. However, their poor general status, multiple co-morbidities, and limited social support present significant challenges in antitumor treatments, especially standard platinum-based chemotherapy. Metronomic chemotherapy (MCT) involves the regular administration of chemotherapy drugs at low doses, offering improved safety, anti-angiogenic tumor effects, and immune modulation compared to conventional chemotherapy. In light of these considerations, we have designed a phase II trial to evaluate the efficacy and safety of PD-1 inhibitors plus metronomic oral vinorelbine (mOV) as first-line therapy for elderly patients with metastatic NSCLC. **Methods:** Elderly patients(≥70 years) with previously untreated locally advanced or metastatic NSCLC without a sensitising EGFR mutation, ALK fusion or ROS1 fusion and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 were recruited for this study. Patients received PD-1 inhibitors combined with mOV (30mg, TIW1, day 1-3-5 per week) for 6 cycles, followed by PD-1 inhibitors maintenance until disease progression or intolerable toxicities. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety profiles. **Results:** From March 2021 to November 2024, 37 patients were enrolled in the study. The median age was 77 with 31 (83.8%) males. Median follow-up time was 13.5 months (range 1.8 months-44.7 months). The median PFS was 10.9 months (95%Cl: 1.0 months-20.9 months) and the median OS was 26.2 months (95%Cl: (6.7 months-45.7 months). The ORR and DCR were 33.3% (95%C1: 17.3%-47.5%) and 86.1% (95%Cl: 71.9%-95.7%), respectively. Compared to those with low PD-L1 expression (PD-L1 TPS <50%), patients with high PD-L1 expression (PD-L1 TPS ≥50) had significant prolonged PFS [mPFS=6.1 months vs 23.0 months, p=0.01, HR = 0.19 (95%CI 0.05-0.69)] and OS [mOS=6.1 months vs not reached, p=0.02, HR = 0.09 (95%CI 0.01-0.70)]. Adverse events (AEs) of any grade were observed in 29 (78.4%) patients of which immune-related adverse events (irAEs) occurred in 14 (37.8%) patients. Grade 3-4 adverse reactions were reported in 5 (13.5%) patients, 4 of which were irAEs, including immune-associated pneumonia, myocarditis, myositis, enteritis and hepatitis. No grade 5 adverse events were reported. **Conclusions:** The regimen of PD-1 inhibitors plus mOV as first-line therapy showed significant survival benefits and a favorable safety profile in elderly patients with driver-gene-negative metastatic NSCLC, particularly those with high PD-L1 expression. Clinical trial information: ChiCTR2300074586. Research Sponsor: National High Level Hospital Clinical Research Funding of China; BJ-2023-073.

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Analysis of genomic and immune microenvironment differences in Chinese populations: Revealing potential mechanisms of poor immunotherapy outcomes in patients with EGFR mutation and ALK fusion non-small cell lung cancer.

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Background: Non-small cell lung cancer (NSCLC) patients with EGFR mutations or ALK fusions often exhibit suboptimal responses to immunotherapy, yet the genomic and immunological basis for this remains poorly understood. This study aims to elucidate the genomic and immune microenvironment differences in NSCLC patients harboring EGFR mutations or ALK fusions that may contribute to their distinct immunotherapy responses. **Methods:** We analyzed tumor specimens from 12,528 NSCLC patients using a comprehensive next-generation sequencing (NGS) panel targeting 733 genes. Of these, 191 patients also underwent multiplex fluorescence immunohistochemistry (mIHC) analysis to assess the immune microenvironment. Subgroups included patients with EGFR mutations, ALK fusions, both EGFR mutations and ALK fusions, and those wild-type for both EGFR and ALK. We compared these groups for DNA damage response (DDR) gene mutation frequencies, tumor mutational burden (TMB), intratumoral heterogeneity (ITH), and immune microenvironment. **Results:** Among the cohort, 6389 (51%) harbored EGFR mutations and 300 (2.4%) had ALK fusions. Patients with EGFR mutations or ALK fusions exhibited significantly lower DDR mutation frequencies compared to their wild-type counterparts ($P<0.001$). TMB levels showed a gradient: wild-type > EGFR mutation > EGFR mutation with ALK fusion > ALK fusion ($P< 2.2e-16$), with wild-type patients having markedly higher TMB than any other group ($P< 2.22e-16$, $P=0.0047$, $P< 2.22e-16$). Conversely, ITH was lowest in wild-type patients and progressively higher with ALK fusions ($P=0.017$), EGFR mutations ($P< 2.22e-16$), and combined mutations ($P< 2.22e-16$). Lower ITH was associated with higher immunogenic neoantigen production, correlating with improved immunotherapy responses. Immunohistochemical analysis revealed that EGFR-mutant tumors had significantly fewer M1 tumor-associated macrophages (CD68+ HLA-DR+) ($P<0.001$) within the tumor parenchyma and reduced CD4+ T cell ($P=0.013$) infiltration in the tumor stroma compared to wild-type. **Conclusions:** Our findings suggest that low TMB, high ITH, and a suppressed immune microenvironment characterize EGFR-mutant and ALK-fusion NSCLC, potentially undermining their immunotherapy efficacy. These genomic and immunological signatures, particularly ITH and immune cell distribution, might be critical factors affecting the immunotherapy responsiveness of these patient subsets, warranting further investigation into tailored therapeutic strategies. Research Sponsor: None.

A phase II study of durvalumab, doxorubicin, and ifosfamide in recurrent and/or metastatic pulmonary sarcomatoid carcinoma (KCSG LU-19-24).

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Background: Pulmonary sarcomatoid carcinomas (PSCs) are very rare and aggressive tumors with poor prognosis. While conventional cytotoxic agents have limited efficacy in PSC, immune checkpoint inhibitors or doxorubicin showed potential efficacy. We evaluated the efficacy and safety of durvalumab, doxorubicin, and ifosfamide for recurrent and/or metastatic PSC. **Methods:** Patients with recurrent or metastatic PSC received durvalumab (1500 mg, day1), doxorubicin (20 mg/m^2 IV, days 1–3) and ifosfamide (1.5 g/m^2 IV with mesna, days 2–4) every 3 weeks for up to 4 cycles, followed by durvalumab monotherapy until disease progression or unacceptable toxicity, upto 12 months. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR) and toxicity. **Results:** A total of 20 patients (15 male, 5 female) were enrolled, and the median age was 63.5 (range, 44-75). Sixteen (88.9%) of the 18 evaluable cases were PD-L1 positive. Six (30.0%) out of 20 patients had previously received palliative chemotherapy. Among them, 18 patients were evaluable for the primary endpoint. ORR was 35.0% (95% CI, 17.7-55.8%) based on modified RECIST version 1.1. and the median DOR was 5.3 months (95% CI, 1.7-not estimated). After a median follow-up duration of 7.0 months (range, 1.2-37.6), the median PFS and OS were 4.8 months (95% CI, 2.0-6.5 months) and 9.4 months (95% CI, 5.5-26.8 months), respectively. Adverse events (AEs) of any grade were reported in 19 patients with serious AEs in 10 patients. The most common AEs were nausea (9.7%), anemia (7.5%), vomiting (5.4%). No treatment-related deaths were reported. **Conclusions:** Given its rarity and aggressiveness of PSC, the combination of durvalumab, doxorubicin, and ifosfamide demonstrated promising efficacy in recurrent and/or metastatic cases. Further studies are required to validate these findings and optimize treatment strategies for PSC. Clinical trial information: NCT04224337. Research Sponsor: None.

Race-associated clinicogenomic correlates of outcomes to immune checkpoint inhibitors alone or with chemotherapy in non-small cell lung cancer (NSCLC).

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Background: PD-L1 low and STK11 mutations are associated with immune checkpoint inhibitor (ICI) resistance in non-small cell lung cancer (NSCLC). It is unclear whether there are differences in clinicogenomic predictors by race and ethnicity. **Methods:** We retrospectively studied NSCLC patients 18 or older, without targetable EGFR or ALK alterations, treated with frontline combination chemotherapy with ICI (ICI-chemo) or ICI monotherapy (ICI-mono) between January 2014 and February 2020 at MD Anderson Cancer Center. 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:** 1648 patients met inclusion criteria. Poor performance status (PS) frequency was statistically significantly different among groups, highest in African American (AA) (30.7%) and Native Alaskan/Hawaiian or American Indian (NAHAI) (30%) patients (Table). Steroid prescription within one month of ICI start was also more frequent in AA (46.4%) and NAHAI (40%) patients. However, heavy smoking was more frequent in White (62%) patients. Mutation rates were statistically significantly different for KRAS and STK11 but not TP53 (Table). KRAS mutations were most frequent in White (24.7%) and AA patients (24.2%). STK11 mutations were most frequent in AA (14.4%) patients. TP53 mutations were most frequent in HL and Black (43.6%, 41.8%) patients. Median overall survival (OS) was lower (21.3 and 24.5 months) for HL and NAHAI patients and higher (25.4, 26.4, and 30.7 months) for White, Black, and Asian patients, though not statistically significantly different (Table). **Conclusions:** AA and HL patients had lower rates of heavy smoking but higher rates of poor genomic prognostic factors. Asian patients had the lowest rates of heavy smoking, KRAS, TP53, and STK11 mutations, but the highest rates of PD-L1 <1%. Despite several traditional clinicogenomic prognostic factors being poor for minority racial/ethnic groups, OS difference was not statistically significant. Research Sponsor: Philanthropic Contributions to The University of Texas MD Anderson Lung Moon Shot Program; 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=1648, No. (%)	1305 (79.2)	153 (9.3)	101 (6.1)	79 (4.8)	10 (0.6)	
ECOG PS 2-3 at ICI start	265 (20.3)	47 (30.7)	23 (22.8)	20 (25.3)	3 (30)	**0.003**
Steroids within 1 mo of ICI start	480 (36.8)	71 (46.4)	39 (38.6)	29 (36.7)	4 (40)	**0.02**
20+ Pack Years Smoking	652 (62)	63 (50)	26 (46.4)	18 (43.9)	5 (55.6)	**0.001**
PD-L1 <1%	313 (24)	31 (20.3)	16 (15.8)	25 (31.6)	1 (10)	**0.01**
$KRAS_{mut}$	322 (24.7)	37 (24.2)	23 (22.8)	6 (7.6)	4 (40)	**0.001**
$TP53_{mut}$	486 (37.2)	64 (41.8)	44 (43.6)	25 (31.6)	4 (40)	0.1
$STK11_{mut}$	129 (9.9)	22 (14.4)	7 (6.9)	2 (2.5)	1 (10)	**0.005**
Median OS (mo)	25.4	26.4	21.3	30.7	24.5	0.2

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Predictive implications of immune-related adverse events after exposure to VEGF inhibitors on outcomes in patients with advanced NSCLC treated with prior immune check point inhibitor.

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Background: Immune-related adverse events (irAEs) have been associated with enhanced antitumor immune activity, potentially correlating with improved clinical outcomes. Implications of delayed irAE after exposure to VEGF inhibitors on clinical outcomes remain poorly defined. We hypothesize that patients who develop irAEs during or following immune checkpoint inhibitors (ICIs) therapy will demonstrate improved overall survival (OS) and progression-free survival (PFS) compared to those who do not develop irAEs. **Methods:** We conducted a single center retrospective chart review of patients with non-small cell lung cancer (NSCLC) who had received at least one line of immunotherapy and subsequently underwent treatment with ramucirumab upon progression. Patients were categorized based on the presence or absence of irAEs during or after ICIs. 41 patients were identified. Kaplan-Meier estimates and log-rank tests were used for survival analyses, while Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** Of 41 identified subjects, median age was 63, 83% had adenocarcinoma, 56% had metastatic disease at presentation and 93% had received previous chemotherapy. Initial immunotherapy received was pembrolizumab 66%, nivolumab 20% and durvalumab 10%. For second line treatment, 85% received ramucirumab with docetaxel. 37% (n=15) of patients experienced irAE after ICIs. From the start of ramucirumab, the median OS was 8.0 months for patients with irAEs versus 6.0 months for those without, and the median PFS was 7.0 months versus 3.0 months, respectively. HRs suggested a trend favoring longer survival for patients with irAEs (HR for PFS = 0.52; 95% CI: 0.25–1.08; p=0.0072 and HR for OS = 0.62; 95% CI: 0.29–1.27; p=0.0192), though not statistically significant. Patients who developed delayed irAEs (after the start of ramucirumab) (n=4, 9.7%) had significantly prolonged OS, 34.5 months (HR 0.22; 95% CI: 0.05–0.94; p=0.0406) and PFS 33.5 month (HR 0.18; 95% CI: 0.043–0.80; p=0.0234) compared to those without. The most common irAEs were colitis (47%), rash (20%), and pneumonitis (13%). **Conclusions:** Our findings suggest that the occurrence of irAEs during or after immunotherapy may be associated with improved outcomes in patients with advanced NSCLC who receive ramucirumab-based treatment. Although the observed survival benefit for patients with any irAE was not statistically significant, those who developed delayed irAEs after initiating ramucirumab exhibited significant prolongation of OS and PFS. This raises the possibility that delayed irAEs after exposure to VEGF likely suggests a reinvigorated immune response and may serve as a prognostic marker. Further prospective validation in larger patient cohorts is warranted to investigate these findings. Research Sponsor: None.

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Digital pathology–based AI spatial biomarker to predict outcomes for immune checkpoint inhibitors in advanced non-small cell lung cancer.

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Background: Accurate prediction of outcomes with anti-PD-1/PD-L1 immune checkpoint inhibition (ICI) remains a significant challenge in non-small cell lung cancer (NSCLC). In this study, we develop an artificial intelligence (AI) approach for single-cell analysis of H&E-stained whole-slide images (WSIs) to predict objective response and clinical benefit of ICI in two independent cohorts of NSCLC patients. **Methods:** For biomarker discovery, we analyzed WSIs and clinical data from 118 advanced lung cancer patients at Stanford University. Of these, 46 patients (39%) were treated with ICI monotherapy and 72 (61%) patients were treated with ICI and concurrent chemotherapy. For external validation, 233 advanced lung cancer patients treated with ICI monotherapy at MSKCC were used. Deep learning models were deployed for automated tumor area detection and segmentation of cell nuclei in WSIs. We developed a fully automated cell annotation approach that leverages multiplex immunofluorescence and trained a deep learning model to classify nuclei into 10 cell types on H&E images, including tumor cells and major immune and stromal cells such as T cells, B cells, neutrophils, macrophages, fibroblasts, and endothelial cells. A total of 331 features were computed to quantify cell composition and cell-cell spatial interactions in the tumor microenvironment. Treatment outcomes were assessed using progression-free survival (PFS) and best objective response per the Response Evaluation Criteria in Solid Tumors (v1.1), with statistical significance reported at the 95% confidence level. **Results:** Five spatial features were included in the prediction model that characterize the cell-cell interactions between tumor cells, fibroblasts, T cells, and neutrophils. In the validation cohort, the spatial biomarker had a strong association with PFS (hazard ratio=5.46, $P<0.0001$), while the association of PD-L1 expression with PFS was modest (hazard ratio=1.67, $P=0.002$). For patients with high PD-L1 expression (TPS>50%), the spatial biomarker significantly stratified patients for PFS (hazard ratio=5.21, 95% CI 3.21-8.48, $P<0.0001$). For predicting objective response, a multivariate model consisting of the spatial features achieved AUROC=0.76 compared to AUROC=0.66 for PD-L1 TPS, while combining the spatial features with PD-L1 expression led to AUROC=0.78. **Conclusions:** A single-cell computational pathology approachidentifies interpretable spatial biomarkers that predict ICI response and outcomes in advanced lung cancer. The spatial biomarker could help to select patients with high tumor PD-L1 expression who are most suited for ICI monotherapy. Further validation of these findings is warranted. Research Sponsor: None.

8570 Poster Session

SMET12 and toripalimab combined chemotherapy in patients with advanced non-small cell lung cancer who are treatment-naive or have developed resistance to standard therapy.

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Background: SMET12 is a recombinant anti-EGFR and CD3 bispecific antibody independently developed by Zhejiang Shimai Pharmaceutical. This study aims to evaluate the efficacy and safety of SMET12 in combination with toripalimab and chemotherapy in treatment-naïve, post-first-line immune checkpoint inhibitor-resistant, and EGFR mutation-positive advanced non-small cell lung cancer (NSCLC) patients who are resistant to TKI treatment. **Methods:** This is a single-arm, cohort clinical study involving three cohorts. The primary inclusion criteria are histologically confirmed EGFR protein-expressing metastatic NSCLC patients, specifically divided into: (1) Cohort A: treatment-naïve subjects; (2) Cohort B: subjects resistant to first-line immune checkpoint inhibitor therapy; (3) Cohort C: EGFR mutation-positive subjects resistant to TKI treatment. All subjects will receive a combination regimen of SMET12, toripalimab, and chemotherapy after entering the treatment phase, with the chemotherapy cycle being 2-4 cycles. After chemotherapy, subjects with stable or effective results will enter the maintenance therapy phase with SMET12 and toripalimab until disease progression or unacceptable toxicity occurs. The treatment regimen is as follows:SMET12 30μg Q2W + toripalimab 3mg/kg Q2W+ chemotherapy Q3W. Specific chemotherapy regimens are: Cohort A: pemetrexed + carboplatin Q3W for lung adenocarcinoma; nab-paclitaxel + cisplatin Q3W for lung squamous cell carcinoma; Cohort B: docetaxel Q3W; Cohort C: pemetrexed + carboplatin Q3W. The primary endpoints are safety and efficacy indicators, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS). **Results:** From March 7, 2024, to January 21, 2025, a total of 31 patients participated in this study, of which 27 patients were evaluable for efficacy. The results showed: the ORR for Cohort A was 83.3%, DCR was 100%, and the median PFS was 8.3 months (95%CI: 3.79, 12.8); the ORR for Cohort B was 22.2%, DCR was 66.7%, and the median PFS was 4.2 months (95%CI: 3.62, 4.78); the ORR for Cohort C was 41.7%, DCR was 100%, and the median PFS was 7.2 months (95%CI: 5.0, 9.4).Grade ≥3 treatment-related adverse events included leukopenia (19.4%), pneumonia (16.1%), immune-related pneumonitis (13.0%), immune-related hepatitis (3.2%), immune-related myositis (3.2%), and anemia (3.2%). **Conclusions:** SMET12 in combination with toripalimab and chemotherapy shows good tolerability and efficacy in treatment-naïve, post-immune therapy-resistant EGFR protein-expressing, and post-TKI treatment-resistant EGFR mutation-positive advanced NSCLC patients. Clinical trial information: NCT06208033. Research Sponsor: None.

8571 Poster Session

Exploratory study on the impact of intestinal low-dose radiation on the efficacy and prognosis of immunotherapy in metastatic non-small cell lung cancer.

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Background: Radiotherapy (RT) can be a palliative measure for metastases of metastatic non-small cell lung cancer (mNSCLC). However, RT to abdominopelvic metastases can cause additional intestinal radiation, that may lead to microbial imbalance. Recent research have revealed the influence of intestinal microbiota on immunotherapy (IO). Thus, this study aims to explore the impact of intestinal radiation doses on the efficacy and prognosis of IO for mNSCLC. **Methods:** Collect clinical data from patients with mNSCLC who underwent IO combined with abdominopelvic RT for metastases at Shandong Cancer Hospital over the past five years. Use the Varian Eclipse system to outline the contours of the large and small intestines and record the dosimetric parameter. Calculate overall survival (OS) and progression-free survival (PFS) using the Kaplan-Meier method, compare inter-group differences using the log-rank test, and analyze risk factors associated with OS and PFS through Cox regression analysis. **Results:** Exploratively, we set 1 Gy and 3 Gy as the thresholds for the mean intestinal radiation dose. A total of 232 patients were included, with 76 patients (32.8%) having small intestine mean radiation dose (SIMRD) < 1 Gy, and 67 patients (28.9%) having SIMRD between 1-3 Gy. 153 patients (65.9%) received first-line IO, while 79 patients (34.1%) received second-line IO. Compared with the < 1 Gy and ≥ 3 Gy groups, patients with SIMRD between 1-3 Gy not only had the highest objective response rate (ORR) after 3 months (21.1% vs. 43.3% vs. 7.9%), but also significantly prolonged OS (14.8 months vs. 22.6 months vs. 7.7 months, $P < 0.001$) and PFS (7.2 months vs. 10.0 months vs. 4.3 months, $P < 0.001$). Subgroup analysis of first-line and second-line therapy patients yielded similar conclusions. Compared with the < 1 Gy and 1-3 Gy groups, patients with colon mean radiation dose ≥ 3 Gy also exhibit relatively poor OS (14.8 months vs. 12.6 months vs. 10.1 months, $P = 0.036$) and PFS (7.4 months vs. 7.3 months vs. 4.2 months, $P = 0.006$). Multivariate Cox regression analysis showed that SIMRD between 1-3 Gy was an independent predictive factor for OS (HR = 0.41, $P < 0.001$) and PFS (HR = 0.56, $P < 0.001$). We prospectively enrolled 14 patients with mNSCLC who received first-line IO combined with metastasis RT, with 9 patients undergoing efficacy evaluation. The results revealed that the ORR was highest (66.7%) in the group with SIMRD between 1-3 Gy, and both 2 patients with progression were in the group with SIMRD ≥ 3 Gy. **Conclusions:** In patients with mNSCLC receiving IO combined with metastasis RT, low SIMRD may significantly enhance the long-term prognosis of IO, potentially relying on the interaction between host immunity and gut microbiota. To validate this hypothesis, we are prospectively collecting blood and feces from patients before and after RT, with the prospective cohort being enrolled. Research Sponsor: National Natural Science Foundation of China; 82172720; CSCO-Nav HER2-related Solid Tumors Research Foundation; Y-2022HER2AZMS-0291; National Natural Science Foundation of China; 82403791; Natural Science Foundation of Shandong Province; ZR2024QH459; Shandong Province University "Youth Innovation Team Program"; 2024KJJ027.

Artificial intelligence-powered spatial analysis of tumor infiltrating lymphocytes and tertiary lymphoid structures in non-small cell lung cancer patients treated with immune-checkpoint inhibitors±chemotherapy.

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Background: This study evaluates the predictive utility of an artificial intelligence (AI)-powered whole-slide image (WSI) analyzer for assessing Tumor-infiltrating lymphocytes (TILs) and tertiary lymphoid structures (TLSs) in patients (pts) treated with ICIs, either as monotherapy or in combination with chemotherapy. **Methods:** An AI-powered WSI analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) was utilized to segment cancer area (CA) and cancer stroma (CS), and identification of tumor infiltrating cells (TILs) and tertiary lymphoid structure (TLS) on tumor tissues. Pre-treatment H&E-stained WSIs were obtained from Samsung Medical Center (n = 533), and other multi-center cohorts (Shen et al, 2024, n=634). After quality control, 1,144 samples (98.0%) were used included in the final analysis. Pts were stratified into risk groups; good risk (high TILs in CA and high TLS area per CA), poor risk group (low TILs in CA and low TLS area per CA), and intermediate risk group (others). Among them, 988 pts had available PD-L1 expression data, 435 underwent whole transcriptome sequencing, and 292 underwent whole exome sequencing. **Results:** TILs in CA correlated significantly with the interferon gamma pathway (ρ=0.49, P<0.001), and the T-cell inflamed score (ρ=0.56, P<0.001). Similarly, TLS area per CA was significantly correlated with TLS imprinting (ρ=0.48, P<0.001), and B cell receptor signature (ρ=0.42, P<0.001). Among 1,144 pts, 1,044 received ICI monotherapy, and 100 underwent combination therapy with ICI and chemotherapy. ICIs were administered as first-line therapy in 245 pts (24.1%), and second line in 524 (45.8%). The risk groups were distributed as follows: good risk (n=279, 24.4%), intermediate risk (n=437, 38.2%), and poor risk (n=428, 37.4%). Pts with PD-L1 tumor proportion score ≥50% were more frequent in the good-risk group (47.3%) than in intermediate (37.5%) or poor-risk groups (30.6%, P=0.001). Smoking history showed no significant association with risk groups (P=0.958). Pts receiving ICI monotherapy showed significant differences in overall response rate (ORR: 28.9% vs. 19.7% vs. 16.3%, P<0.001), median progression-free survival (mPFS: 6.1 vs. 3.5 vs. 2.4 months, P<0.001), and median overall survival (mOS: 26.4 vs. 14.6 vs. 11.3 months, P<0.001) among the good, intermediate, and poor-risk groups, respectively. Similar trends were observed in pts receiving ICI plus chemotherapy: mPFS (10.3 vs. 8.4 vs. 4.7 months, P=0.005), and mOS (27.9 vs. 22.4 vs. 17.6 months, P=0.047). Notably, *KEAP1* mutations were significantly more frequent in the poor-risk group (17.4% vs. 7.9%, P=0.020). **Conclusions:** AI-powered analysis of TILs and TLSs effectively stratifies NSCLC pts into risk groups, predicting efficacy outcomes of ICIs with or without chemotherapy.
Research Sponsor: None.

8573 Poster Session

First-line envafolimab in combination with recombinant human endostatin and chemotherapy for advanced squamous non-small cell lung cancer: Updated results from a prospective, single-arm, multicenter phase II study.

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Background: Immunotherapy combined with chemotherapy has been established as the standard first-line treatment for patients with advanced squamous NSCLC (sq-NSCLC) without oncogenic driver mutations. Antiangiogenic drugs enhance immunotherapy efficacy by normalizing blood vessels and remodeling the tumor microenvironment. However, they pose a high bleeding risk in sq-NSCLC treatment. Recombinant human endostatin (Rh-endostatin), the only approved agent for sq-NSCLC, can prolong survival without increasing bleeding risk. This trial aimed to investigate the efficacy and safety of Envafolimab, the first approved subcutaneous single-domain anti-PD-L1 antibody, plus Rh-endostatin and chemotherapy as first-line treatment for advanced sq-NSCLC. **Methods:** This prospective, single-arm, multicenter, phase II trial was conducted at 3 research centers in China (NCT05243355). Patients with pathologically confirmed primary advanced or locally advanced unresectable sq-NSCLC. were enrolled. Patients received Envafolimab (300 mg, subcutaneously, day 1) and Rh-endostatin (210 mg, continuous intravenous infusion over 72 hours, day 1-3) combined with paclitaxel (175mg/m^2, day 1) or albumin paclitaxel (260 mg/m^2, day 1), and cisplatin (75 mg/m^2 , day 1-3), or carboplatin (AUC 5, IV, day 1); every 3 weeks for 4-6 cycles, followed by maintenance Envafolimab until disease progression (PD), unacceptable toxicity, or patient refusal. The primary endpoint was the 1-year PFS rate, and the secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and tolerability. **Results:** From December 2021 to December 2024, 33 eligible patients were enrolled, 26 of whom were included in the safety and efficacy analysis. As of December 16, 2024, the median follow-up was 16.5 months (95%CI: 8.1, NA). According to RECIST v1.1, the ORR was 65.4%, and the DCR was 96.2%. The median PFS (mPFS) was 12.4 months (95%CI: 11.4, NA) with a 1-year PFS rate of 59.9% (95%CI: 43.0%, 83.3%). The median OS (mOS) was 24.6 months (95%CI: 12.2, NA) with 1-year OS rate of 70.7% (95%CI: 54.2%, 92.1%) and a 2-year OS rate of 54.7% (95%CI: 36.9%, 81.1%). Overall, adverse events (AEs) of any grade were reported in 84.8% (28/33) of patients. The most common AEs were myelosuppression, alopecia, and nausea, which were more likely to be chemotherapy-related. 33.3% (11/33) of patients experienced immune-related AEs (irAEs). No unexpected AEs were observed. **Conclusions:** Our results demonstrated that Envafolimab in combination with Rh-endostatin and chemotherapy resulted in favorable clinical outcomes with a manageable safety profile, representing a promising treatment modality as first-line therapy for advanced sq-NSCLC. Clinical trial information: NCT05243355. Research Sponsor: None.

First-line immunotherapy with or without chemotherapy versus BRAF plus MEK inhibitors for patients with BRAF^{V600E}-mutated metastatic non-small cell lung cancer: The FRONT-BRAF study.

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Background: Patients (pts) with BRAF^{V600E} mutated non-small cell lung cancer (NSCLC) can be effectively treated with BRAF and MEK inhibitors (BRAFi+MEKi) or with immune checkpoint inhibitors ± chemotherapy (ICI±CT). Which one should be prioritized as initial systemic treatment in this population remains unclear. **Methods:** Clinicopathologic data were collected from pts with metastatic BRAF^{V600E} mutated NSCLC treated with 1st line ICI±CT or BRAFi+MEKi between 2015 and 2024 at 17 centers across the United States, Europe, and Brazil. **Results:** Of 284 patients, 88 received ICI±CT and 196 received BRAFi+MEKi. Compared to pts treated with BRAFi+MEKi, pts receiving ICI±CT were more likely to have a history of smoking (83% vs. 61%, P<0.001) and a higher median PD-L1 tumor proportion score (TPS) (68% vs 30%, P<0.001). ICI±CT, compared to BRAFi+MEKi, was associated with a lower objective response rate (ORR, 49% vs 63%, P=0.03), similar median progression-free survival [mPFS, 9.6 vs.12.2 months (mo.), HR 1.13, P=0.43], but significantly improved median overall survival (mOS, 40.9 vs 25.1 mo., HR 0.69, P=0.039), even after adjusting in a multivariable model (HR 0.66, P=0.02). Consistent results were observed in a propensity score-matched cohort (1:1 ratio, N=75 pts per treatment group), where ICI±CT, compared to BRAFi+MEKi, was associated with improved mOS (40.9 vs 22.7 mo., HR 0.63, P=0.04), but similar ORR and mPFS. In key subgroup analyses, ICI±CT, compared to BRAFi+MEKi, was associated with longer mOS in pts with a history of tobacco smoking (HR 0.60, P=0.01), PD-L1 TPS ≥1% (HR 0.66, P=0.039), and without brain metastases (HR 0.66, P=0.045). A shorter mPFS was noted in pts without tobacco smoking history (HR 1.94, P=0.03). In evaluating genomic correlates of treatment efficacy, pts with *TP53* co-mutations (N=107) had worse outcomes compared to pts with wild-type *TP53* (N=121) when treated with BRAFi+MEKi, including shorter mPFS (HR 1.67, *P*=0.01) and mOS (HR 1.77, *P*=0.01), but not with ICI±CT. Notably, pts with *TP53* co-mutations had longer mOS with ICI±CT compared to BRAFi+MEKi (48.4 vs 18.8 mo., HR 0.46, *P*=0.005). In contrast, pts with *IDH1* co-mutations (N=9) had worse outcomes compared to pts with wild-type *IDH1*(N=188) when treated with ICI±CT, including shorter mPFS (HR 4.04, *P*=0.03) and mOS (HR 6.12, *P*=0.007), as well as shorter mPFS with BRAFi+MEKi (HR 2.73, *P*=0.03). Safety of BRAFi+MEKi was comparable whether administered as 1st line or as 2nd line therapy following ICI±CT, with similar rates of adverse events of any grade (71% vs 76%, P=0.58) and grade ≥3 (22% vs 23%, P=0.92). **Conclusions:** Initial therapy with ICI±CT, compared to BRAFi+MEKi, showed a lower ORR, similar PFS, but superior OS, particularly among specific subgroups of pts. A prospective evaluation of the optimal 1st-line therapy for this population is warranted. Research Sponsor: None.

8575 Poster Session

A meta-analysis of safety and efficacy of datopotamab deruxtecan and sacituzumab govitecan for second line treatment of metastatic non-small cell lung cancer (NSCLC).

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Background: Subsequent line treatment options for metastatic NSCLC remain limited. We sought to analyze the efficacy and safety of two Anti-TROP-2/topoisomerase inhibitor antibody-drug conjugates (ADCs), sacituzumab govitecan (SG) and datopotamab deruxtecan (Dato-DXd), for NSCLC treatment via a meta-analysis. **Methods:** A systematic search in PubMed, Scopus, and Cochrane identified 2348 studies. After excluding duplicates (1263) and screening abstracts (1085), 25 studies underwent full-text review, and 5 RCTs (3 Dato-DXd, 2 SG) were included. All included studies involved patients with advanced NSCLC that progressed on first-line treatment. Binary random effects and pooled proportions were calculated separately for Dato-DXd and SG using OpenMeta. The Mantel-Haenszel method with random effects estimated risk ratios and odds ratios with 95% confidence intervals for ADCs vs. docetaxel. Heterogeneity was assessed using I^2 statistics. **Results:** 616 Dato-DXd and 353 SG patients were included. Pooled proportions (PP) for grade 3 adverse events were 34.0% (Dato-DXd) and 75.4% (SG) while drug discontinuation rates were 7.1% (Dato-DXd) and 7.0% (SG), respectively. Efficacy outcomes included event rate, disease control rate, and overall response rate. For Dato-DXd, these pooled proportions were 52.0%, 76.5%, and 29.4%; for SG, they were 44.8%, 67.6%, and 14.3%. PPs and relevant statistics are included in table 1. When compared to docetaxel, combined ADCs showed no significant risk reduction in progression [RR: 0.96 (0.89 – 1.05), p=0.40, I^2=7%] or mortality [RR: 0.90 (0.58 – 1.38), p=0.63, I^2=43%]. Odds ratios for disease control rate [1.39 (0.76 – 2.54), p=0.29, I^2=83%] and overall response rate [1.33 (0.40 – 4.42), p=0.64, I^2=94%] were also insignificant. **Conclusions:** Direct comparisons between ADC (Dato-Dxd and SG) and docetaxel did not show a significant difference in disease progression or death rate. This study was limited by the small number of participants and heterogeneity of published literature as many clinical trials are still ongoing. Despite this, SG and Dato-DXd had a promising overall response rate of 67.6% and 76.5%, respectively. Research Sponsor: None.

Pooled proportions of Dato-Dxd and SG to docetaxel.

	Datopotamab Deruxtecan				Sacituzumab Govitecan			
	Value	95% CI	P-Value	I^2	Value	95% CI	P-Value	I^2
Event Rate	0.520	(0.258, 0.782)	<0.001	97%	0.448	(0.211, 0.686)	<0.001	90.8%
DCR	0.765	(0.727, 0.803)	<0.001	0%	0.676	(0.627, 0.726)	<0.001	0%
ORR	0.294	(0.230, 0.358)	<0.001	49.6%	0.143	(0.106, 0.180)	<0.001	0%
G3AER	0.340	(0.215, 0.465)	<0.001	86%	0.754	(0.572, 0.937)	<0.001	91.1%
DDR	0.071	(0.026, 0.116)	0.002	69.1%	0.070	(0.011, 0.130)	0.20	74.2%

Abbreviations: DCR, disease control rate; ORR, overall response rate; G3AER, grade 3 adverse events rate; DDR, drug discontinuation rate.

8576 Poster Session

Efficacy of immune checkpoint inhibitors (ICIs) in advanced large cell neuroendocrine carcinoma (LCNEC) of the lung: A systematic review and meta-analysis.

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Background: LCNEC of the lung is a high-grade neuroendocrine carcinoma with characteristics of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Guidelines for optimal treatment for LCNEC are lacking due to the paucity of randomized control trials. Treatment regimens are often extrapolated from SCLC and NSCLC. Immunotherapy has revolutionized the outcomes of solid malignancies, including lung cancers, in the past decade. In this study, we assess the efficacy of ICIs in advanced LCNEC. **Methods:** A systematic literature search was conducted on PubMed, Embase, and Google Scholar for studies assessing the role of ICIs in advanced LCNEC of the lung. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. A random effects model was used to pool the outcomes along with 95% confidence intervals (CI). Statistical analyses were performed using program R version 4.4.1. **Results:** We included 12 studies- 11 retrospective and 1 prospective analysis. The total number of advanced LCNEC patients across all the studies was 470. 241 patients received ICIs in total, either as monotherapy or in combination with chemotherapy or anti-angiogenic agents. The pooled Objective Response Rate (ORR) for patients receiving ICIs was 34.71% (95% CI: 27.75-41.97, I^2: 26.2%), whereas the pooled Disease Control Rate (DCR) was 71.87% (95% CI: 59.57-82.92, I^2: 67.7%). The most common ICIs across the cohort were atezolizumab, camrelizumab, nivolumab, and pembrolizumab. A subgroup analysis of three double-arm studies comparing chemotherapy alone (n=42) versus a combination of chemotherapy and ICIs (n=42) as a first-line treatment was performed. We found a favoring trend of the combination over chemotherapy alone for ORR (RR=1.58, 95% CI: 0.92-2.70; p=0.095), although non-significant, but significant advantage for DCR (RR=1.32, 95% CI: 1.04-1.68; p=0.021). **Conclusions:** ICIs have become the standard of care for treating SCLC and NSCLC in various combinations. ICIs, based on our meta-analysis, have also demonstrated encouraging results in advanced LCNEC. However, tumor factors such as molecular subtypes, genomic profiles, and other predictors influencing the response to ICIs need to be elucidated. Further larger prospective studies are awaited to determine their potential in this rare but aggressive subtype of lung cancer. Research Sponsor: None.

8577 Poster Session

Artificial intelligence for immunotherapy response assessment in lung cancer using PET-CT reports.

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Background: Accurate and timely assessment of immunotherapy response is vital for optimizing lung cancer management. This study evaluates the efficacy of a large language model (LLM), Gemini 1.5 Pro, in automating response assessment using positron emission tomography/computed tomography (PET/CT) reports based on the European Organization for Research and Treatment of Cancer (EORTC) criteria. **Methods:** Google Gemini 1.5 Pro was selected due to its large context window capacity and its free availability via the web interface.The model was utilized with explicit instructions on applying EORTC criteria and fine-tuned using few-shot prompting. Pre- and post-immunotherapy PET-CT reports in text format from 33 lung cancer patients, anonymized in compliance with HIPAA regulations, were independently classified by the LLM and an experienced nuclear medicine specialist. Performance metrics, including precision, recall, F1-score, and support, were calculated for each response category. Inter-rater agreement was assessed using Cohen's Kappa. **Results:** The nuclear medicine specialist classified 5, 21, 6, and 1 cases as complete metabolic response (CMR), progressive metabolic disease (PMD), partial metabolic response (PMR), and stable metabolic disease (SMD), respectively, while Gemini 1.5 Pro classified 5, 20, 7, and 1 cases accordingly. The LLM achieved an overall accuracy of 97% and demonstrated excellent agreement with the expert (overall Cohen's Kappa: 0.945). F1-scores were 1.00 for CMR and SMD, 0.98 for PMD, and 0.92 for PMR, with per-label Kappa scores ranging from 0.904 (PMR) to 1.00 (CMR and SMD) (Table 1). **Conclusions:** Gemini 1.5 Pro exhibits strong potential for automating accurate immunotherapy response assessment in lung cancer using PET-CT reports. Its high concordance with expert evaluations underscores its utility in streamlining clinical workflows and improving efficiency. Validation with larger, more diverse datasets is warranted to support its clinical implementation. Research Sponsor: None.

Performance metrics of Gemini 1.5 Pro for immunotherapy response assessment.

Response	Precision	Recall	F1-score	Support	Cohen's Kappa
CMR	1.00	1.00	1.00	5	1.000
PMD	1.00	0.95	0.98	21	0.936
PMR	0.86	1.00	0.92	6	0.904
SMD	1.00	1.00	1.00	1	1.000

CMR, Complete Metabolic Response; PMD, Progressive Metabolic Disease; PMR, Partial Metabolic Response; SMD, Stable Metabolic Disease.

8578 Poster Session

Multimodal AI using host, tumor, and ghost biomarker for predicting immunotherapy efficacy in NSCLC.

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Background: Almost all NSCLC patients (pts) without driver alterations received a first-line based immunotherapy (IO). It is unclear if pts with very poor (VP) overall survival (OS <6 months) will benefit from IO, advancing the hypothesis that this population might benefit more from next-generation drugs or supportive care. Non-response to IO is often linked to host immune fitness, such as circulating immune profiling (CIP). These "ghost biomarkers" can guide clinicians in making critical decisions, such as sparing IO in VP pts. APOLLO 11 study, aimed to develop an AI multimodal tool combining real-world data (RWD), CT-radiomics (CTRAD), and CIP to identify IO survival prediction VP pts. **Methods:** Data collected at Istituto Nazionale Tumori di Milano included: CTRAD features extracted using both a CT-scan Foundation Model (FM CTRAD) and PyRadiomics (pyRAD) features. The two methods were compared. Fluorescence-Activated Cell Sorting (FACS) analysis focused on identifying circulating low-density neutrophils and myeloid cells. Machine Learning (ML) multimodal pipelines for both classification (using LASSO as feature selector) and survival (using COX-ML) were developed using respectively OS < 6 months as threshold and overall survival as continuous outcome. SHAP explainability was applied to identify the most influential features contributing to model predictions. **Results:** Among 932 screened NSCLC pts treated with IO a (720 retrospective-R, 212 prospective-P), 495 had available baseline CT scans, with 638 lesions in the lung (397), lymph nodes (208), and pleura (29). Baseline FACS analysis was performed on 236 patients (162 R, 74 P). 117 pts had all three modalities. 4000 FM RAD features were extracted and reduced to 52 using PCA, while 107 features with pyRAD. Bimodal models with RWD and FACS achieved better performance (AUC 0.71±0.11) than bimodal models with RWD and CTRAD achieving an AUC 0.66±0.07 with pyRAD and 0.62±0.08 with FMRAD). The multimodal ML model, including all data modalities, achieved AUC 0.76 (±0.12). SHAP showed that high frequency of total myeloid cells (CD11b) and of immature neutrophils (CD10-CD16-), high LDH, high ECOG, low BMI, and two rad features as the most important for predicting VP. The survival multimodal model achieved a c-index of 0.76 ±0.10. **Conclusions:** The multimodal tool including all data modalities demonstrated superior performance in predicting OS. SHAP identified all data modalities as relevant, highlighting key "ghost biomarkers" for predicting OS and identifying VP pts. Given that this biomarker is fast (results within one day) and cheap (approximately €/$300), it can be easily integrated with RWD and RAD, which are readily available in clinical practice. This tool can reduce financial toxicity by guiding pts to the appropriate treatment. Finally, pyRAD features compared to FM features seem to perform better in bimodal models. Clinical trial information: NCT05550961. Research Sponsor: FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI DI MILANO.

8579 Poster Session

Longitudinal plasma proteomic analysis: A monitoring strategy for NSCLC patients treated with immunotherapy.

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Background: Real-time monitoring is critical for tailoring treatments to individual patient responses in clinical oncology. Plasma proteomics offers a comprehensive systemic view of disease progression, tumor activity, immune responses, and various biological processes, making it a powerful tool for clinical decision-making. This study explores the feasibility of three specific plasma proteomic signatures for longitudinal monitoring of treatment responses in patients with non-small cell lung cancer (NSCLC) undergoing therapy with immune checkpoint inhibitors (ICIs). **Methods:** Plasma samples were collected from patients with advanced NSCLC receiving PD-1/PD-L1 inhibitor-based regimens. Cohort-1 (n=225) includes samples collected before treatment (T0) and 4-6 weeks after treatment initiation (T1). Cohort-2 (n=56) included samples collected pre-treatment and every three months, up to 36 months. Aptamer-based proteomic profiling quantified ~7,000 plasma protein analytes per sample. Three proteomic signatures were derived from T0–T1 changes in Cohort-1 and tracked in Cohort-2, then compared with radiologic imaging-based response evaluation. **Results:** Three distinct plasma proteomic signatures were identified. The first, featuring soluble PD-1 and PD-L1, indicates drug presence in circulation. The second reflects T-cell activation (e.g., CD8A, LAG3, IL2R), linked to drug uptake, without confirming a favourable tumor response. The third includes intracellular proteins indicative of lung tissue damage, allowing dynamic disease monitoring. Lung tissue damage signature correlated with radiologic imaging-based response evaluation (PR: n = 79, −4.19 [−12.47, 3.58]; SD: n = 125, 1.03 [−1.87, 5.01]; PD: n = 30, 3.37 [0, 7.27]; KW P-*value* = 0.01). Longitudinal analysis of these signatures facilitated early detection of non-responders in an average of 6.6 months [4 - 9.2 months, n=13] prior to radiologic evaluation. Among progressors, nine cases identified responders who later developed acquired resistance, distinguishing them from patients who did not respond to therapy at all. These findings highlight the potential of proteomic profiling to provide comprehensive systemic insights. A comparative analysis with ctDNA will also be presented to further validate these results. **Conclusions:** Our study demonstrates the feasibility of using plasma proteomic signatures to monitor responses to ICIs in NSCLC. We highlight the potential and emphasize the need to further develop these plasma-based monitoring tools through more extensive prospective studies. Such advancements are essential for establishing proteomic signatures as dependable decision-support tools in NSCLC treatment protocols. Research Sponsor: None.

8580 Poster Session

Phase 2 study of atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed for elderly patients with advanced non-squamous non-small cell lung cancer: CJLSG1902.

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Background: Chemotherapy, including immune checkpoint inhibitors and platinum-containing agents, is a standard of care for patients with advanced non-small cell lung cancer (NSCLC). Pembrolizumab in combination with pemetrexed and cisplatin/carboplatin is approved as first-line treatment for patients with metastatic non-squamous NSCLC based on the results of KEYNOTE-189. However, data on the efficacy and safety of this regimen are limited in patients ≥75 years old. On the other hand, the results of the post hoc integrated analysis of IMpower130 and IMpower132 suggest that the efficacy and safety of atezolizumab in combination with platinum-based chemotherapy is maintained in patients ≥75 years old. **Methods:** This multicenter, open-label, phase 2 trial was conducted at 28 institutions in Japan to evaluate the efficacy and safety of atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed. Eligible patients had metastatic/recurrent non-squamous NSCLC without sensitizing EGFR or ALK mutations, were aged ≥75 years, had received no prior systemic chemotherapy, and had an ECOG performance status of 0 or 1. For induction therapy, patients received atezolizumab (1,200 mg/body), pemetrexed (500 mg/m^2) and carboplatin (area under concentration-time curve 5 mg/mL/min) on day 1 of each 21-day cycle. For maintenance therapy, patients received atezolizumab (1,200 mg/body) and pemetrexed (500 mg/m^2) on day 1 of each 21-day cycle. Treatment continued until radiographic progression or unacceptable toxicity was observed. The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), overall survival (OS), and safety. This trial is registered with the Japan Registry of Clinical Trials (jRCTs041200032). **Results:** From July 2020 to January 2023, 60 patients were enrolled in this study. Median age was 77.0 years (range 75-86), 84.1% of the patients were male, and 25.5% had a PD-L1 TPS ≥50%. The median PFS was 7.49 months (80% CI 5.52-7.75, exceeding the threshold of 5.5 months), and the median OS was 16.82 months (80% CI 14.49-20.93). The ORR was 55.9% (95% CI 42.4-68.8). The most common grade 3 or 4 adverse events were neutropenia (40.7%), leukopenia (35.6%), anemia (35.6%), and thrombocytopenia (30.5%). Serious adverse events were observed in 19 patients (6 with pneumonitis, 6 with febrile neutropenia). No treatment-related deaths were observed. **Conclusions:** This study met the primary endpoint of PFS. Atezolizumab with carboplatin plus pemetrexed followed by maintenance atezolizumab with pemetrexed showed favorable efficacy and the safety profile was manageable. This combination therapy is an encouraging option as a first-line treatment strategy for elderly patients with metastatic non-squamous NSCLC. Clinical trial information: 041200032. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

8581 Poster Session

Radiomic phenotypes of tumor angiogenesis compared with PD-L1 in pre-treatment prediction of outcomes across immunotherapy regimens in NSCLC: An external validation study.

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Background: Tumor angiogenesis is critical to cancer progression and treatment resistance, as evidenced by the success of therapies targeting both immune activation and neoangiogenesis. Conventional biomarkers like PD-L1 unreliably predict long-term patient outcomes such as overall survival (OS). Quantitative Vessel Tortuosity (QVT) isolates tumor-associated vessels and quantifies abnormal vascular architecture from pre-treatment radiography. We developed novel QVT Phenotypes of chaotic tumor angiogenesis and externally validated their use in the pre-treatment prediction of long term survival across multiple immunotherapy treatment strategies. **Methods:** QVT Phenotype is a radiomic AI biomarker developed and validated using a real-world dataset of 639 NSCLC patients from 6 institutions. Pre-treatment CT scans of 375 patients from institutions 1-3 were used for phenotype discovery (Dataset A). Deep learning models automatically extracted lung lesions and adjacent vessels. 910 QVT metrics of vascular abnormalities (e.g. curvature, twistedness, and branching) were computed and used to identify intrinsic vascular phenotypes via an unsupervised clustering agnostic. Two validation cohorts from external institutions 4-6 were used to evaluate association with 3-year OS: ICI monotherapy (Mono-ICI) recipients of mixed PD-L1 status (Dataset B, n=172) and Chemo-ICI recipients with PD-L1 TPS<50% (Dataset C, n=90). **Results:** 38% of patients were QVT High, with twisted and erratic growth patterns on pre-treatment CT scans indicating chaotic angiogenesis. Across validation cohorts (Datasets B+C), QVT-High emerged as a strong marker of poor survival (HR=2.26; p=<1E-5). In Dataset B, QVT-High better predicted poor Mono-ICI outcomes (HR=2.23, p=0.00080) than PD-L1 status (HR=1.99, p=0.032), with a 23.0 month reduction in median OS compared to QVT Low. QVT Phenotype maintained significance within the subset (n=61) of PD-L1 High patients (HR=3.02, p=0.017). In Dataset C, QVT-High stratified Chemo-ICI recipients by OS (HR=2.71, p=0.00060), while PD-L1 status failed to reach significance (HR=1.70, p=0.083). QVT-High Chemo-ICI patients had a 16.3 median OS reduction compared to QVT-Low patients. **Conclusions:** This validation study establishes QVT Phenotype as a non-invasive biomarker using standard-of-care pretreatment radiographic scans. QVT Phenotype of chaotic tumor angiogenesis is both interpretable and treatment-agnostic. QVT Phenotype predicted survival across multiple immunotherapy regimens in NSCLC, outperforming PD-L1. QVT phenotyping can be used to identify patients unlikely to benefit from existing SOC treatments. Future work will explore using QVT Phenotypes to identify patients who may benefit from escalated therapeutic strategies, including those incorporating anti-angiogenic mechanisms. Research Sponsor: None.

8583 Poster Session

Validation of HistoTME-predicted immune subtypes and immunotherapy outcomes using human interpretable features (HIFs) from H&E images in non-small cell lung cancer.

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Background: Tumor microenvironment (TME) plays a critical role in tumor progression and response to treatment, especially in improving the response to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). However, current methods are costly and not feasible for routine clinical use for characterizing the TME. Addressing this, we recently developed Histo-TME, an AI-powered tool that accurately characterizes TME subtypes and ICI responses from routine hematoxylin-eosin (H&E) scanned images. This study aims to validate and interpret HistoTME-predicted subtypes using a series of machine learning (ML) models (PathExplore, PathAI, Boston, MA) that output human interpretable features (HIFs) to quantitatively characterize the TME. **Methods:** We analyzed 1375 H&E images from 689 NSCLC patients using PathExplore algorithm, which yielded 171 HIFs spatially characterizing tumor-immune cell interactions. Unsupervised k-means clustering (UMAP) identified distinct patient subgroups based on these HIFs. We compared these subgroups to Histo-TME classifications from the same cohort and evaluated their association with immunotherapy response using Kaplan-Meier (KM) and Cox proportional hazards analyses. **Results:** Five distinct clusters with varying immune infiltration were identified using the 171 HIFs in UMAP clustering. Three out of five clusters characterized by the abundance of macrophages, plasma cells, lymphocytes and fibroblasts within proximity of tumor cells (i.e. 40μm radius), resembled the "Immune Inflamed" subgroup as predicted by HistoTME. There was no survival difference between HIF- and HistoTME-predicted immune inflamed and immune-desert clusters in KM analysis ($p>0.05$). Both HIF-defined clusters and the HistoTME subtypes had similar median overall survival times (4.33 vs. 4.18 years for "Immune Inflamed", $p>0.05$; 1.84 vs. 2.62 years for "Immune Desert", $p>0.05$) in KM analysis. Multivariate analysis adjusted for AJCC stage, age, smoking, ECOG, and CCI demonstrated that both methods have comparable predictive values for overall survival (HIF clusters; HR: 0.69, CI: 0.58-0.81; $p<0.001$ vs. HistoTME subtypes; HR: 0.80, CI: 0.68-0.94; $p=0.008$). **Conclusions:** This study independently validates our published HistoTME method, confirming its ability to accurately identify patients who are likely to respond to ICI therapy using H&E scanned images. Our findings underscore the importance of incorporating TME characteristics using AI-based approaches in routine histopathology and clinical decision-making workflows. Research Sponsor: None.

8584 Poster Session

Survival and safety of two year-fixed duration vs continuous immune checkpoint inhibitor therapy in advanced or metastatic NSCLC: A systematic review.

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Background: The optimal duration of immune checkpoint inhibitor (ICI) therapy in advanced or metastatic non-small cell lung cancer (NSCLC) is unknown. While multiple randomized clinical trials (RCTs) have shown the benefit of ICI-based regimens over chemotherapy, they were not designed to test optimal duration of ICI. Most trials opted to continue ICI indefinitely or stopping at two years if no progressive disease or treatment limiting immune-related adverse events (irAEs) emerged. There is concern for increased cumulative risk of irAEs with indefinite treatment. **Methods:** A systematic review of randomized controlled trials (RCTs) and real-world evidence (RWE) studies was performed for adult patients with advanced/metastatic NSCLC treated with ICI therapy (alone or in combination) up to August 24, 2024. Studies were included if they specifically reported on patients who completed a minimum of 2 years of therapy. Databases, conference abstracts and clinical trials were queried. Patients were divided into two cohorts: a two year-fixed cohort where ICI therapy was discontinued after 2 years, and a continuous cohort where ICI therapy was continued beyond 2 years. **Results:** The database search identified 8741 records of which 174 articles were screened. The final qualitative analysis included 20 studies (11 RCTs and 9 RWE studies) and 5027 patients. There were 23 cohorts that belonged to the 2 year-fixed group (N=2051) and 7 that belonged to the continuous group (N=2976). Outcomes of patients in the 2 year-fixed arms from RCTs were excellent with 5-year overall survival (OS) rates in the range of 69-83%. This was supported by RWEs which showed similar OS rates. Continuous treatment with ICIs had similar OS rates in both RCTs and RWE and was comparable to the 2 year-fixed arms. Four RWE studies compared hazard ratios (HR) for survival outcomes among 2 year-fixed vs continuous arms and did not find any statistically significant difference. Patients that completed 2 years of therapy in RCTs tended to have greater rates of irAEs compared to the baseline population but lower rates of grade 3 or 4 events. Three out of four RWEs reported higher rates of irAEs in the continuous vs 2 year-fixed arms. These findings were likely associated with longer exposure to immunotherapy. A large proportion of patients that developed progressive disease after the 2 year-mark in both 2 year-fixed and continuous arms was alive at data cut-off. Many of these were re-challenged with ICI therapy. Data from RWEs showed that larger/academic centers tended to favor 2 year-fixed therapy whereas the reverse was true for community centers. **Conclusions:** Survival outcomes after ICI discontinuation at 2 years are comparable to continuous therapy in advanced/metastatic NSCLC. Immune-related adverse events tend to accumulate over time. Progressive disease is often localized and amenable to ICI re-challenge. Research Sponsor: None.

8585 Poster Session

Phase 2 study of telomere-targeting agent THIO sequenced with cemiplimab in third-line immune checkpoint inhibitor–resistant advanced NSCLC: Evaluation of overall survival (OS).

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Background: Despite advancements in third line treatments, long-term survival for advanced non-small cell lung cancer (NSCLC) remains suboptimal, with median survival follow-up of only 5.8 months.[1] Among patients treated with prior platinum chemotherapy and immune checkpoint inhibitors (ICIs), the median survival was reported to be 6.47 months[2]. Treatment options for ICI-resistant patients are limited. THIO, a telomere-targeting agent that modifies telomeres in cancer cells, demonstrates improved overall survival (OS) independent of PD-L1 expression. **Methods:** NCT05208944 is a phase 2, multicenter, open-label study that enrolled 79 patients with advanced NSCLC who relapsed after 1–4 prior treatments, including ICIs. In the third line therapy 22 patients treated with THIO (60, 180, or 360 mg) were evaluated for OS and their prior PD-L1 expression at the time of study enrollment (C1D1). **Results:** In the third line therapy 22 patients have a current median survival follow-up of 13 months which significantly surpassed the benchmark value, and in the 180 mg dose group (n=10) it reached 16.9 months compared to 5.8 months for the benchmark.[1] THIO followed by cemiplimab was generally well tolerated in this difficult-to-treat population. The response to THIO and cemiplimab, demonstrated by partial response (PR) and stable disease (SD) was independent of baseline PD-L1 status. This indicates that THIO can be effective across patients regardless of their PD-L1 status. **Conclusion:** THIO demonstrates clinically meaningful OS improvement in third line patients with advanced NSCLC, independent of PD-L1 status. The improved OS observed in patients treated with THIO in sequential combination with an ICI, compared to standard chemotherapy, supports its potential to expand treatment options for ICI-resistant advanced NSCLC. Clinical trial information: NCT05208944. Research Sponsor: MAIA Biotechnology Inc.

8586 Poster Session

Efficacy profile of pembrolizumab for primary pulmonary NUT carcinoma: A systematic review and meta-analysis.

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Background: Primary pulmonary NUT carcinoma is an exceedingly rare and aggressive malignancy characterized by chromosomal rearrangements involving the NUT gene. With limited therapeutic options and an extremely poor prognosis, treatment strategies have focused on identifying effective targeted and immunotherapeutic approaches. Pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, has shown promise in various malignancies, particularly those with high tumor mutational burden or PD-L1 expression. However, despite its use, its efficacy in NUT carcinoma remains poorly understood due to the rarity of this disease and a paucity of robust clinical data. This systematic review and meta-analysis aim to explore the available evidence on the clinical data of pembrolizumab in treating primary pulmonary NUT carcinoma, focusing on progression-free survival (PFS), and overall survival (OS) by consolidating outcomes from case reports and case series. **Methods:** A systematic review and meta-analysis were conducted to evaluate the effectiveness of pembrolizumab in the treatment of primary pulmonary NUT carcinoma. A comprehensive search of PubMed, Embase, and Cochrane was performed for articles published between January 2014 and December 2024, using the keywords "pembrolizumab," "Pulmonary NUT carcinoma," and "NUT midline carcinoma." Inclusion criteria included reports of patients treated with either pembrolizumab monotherapy or pembrolizumab in conjunction with other therapies for Primary Pulmonary NUT Carcinoma for any duration. Reports that did not mention PFS or OS were excluded. **Results:** A total of 39 reports involving 56 patients with primary pulmonary NUT carcinoma treated with pembrolizumab, either in conjunction with other therapies or monotherapy, were analyzed. The median overall survival (OS) was 7.3 months (95% CI: 5.2–8.8), and the median progression-free survival (PFS) was 4.6 months (95% CI: 3.1–5.7). Among three patients receiving pembrolizumab monotherapy as a second-line or later treatment, the median PFS was 2.9 months. **Conclusions:** Pembrolizumab has been explored as second-line or later therapy for primary pulmonary NUT carcinoma based on its success in treating NSCLC. Our analysis revealed a median progression-free survival of 4.6 months and a median overall survival of 7.3 months for patients with primary pulmonary NUT carcinoma receiving pembrolizumab, illustrating the continuing challenge of treating this rare malignancy. Importantly, there are no randomized controlled trials investigating pembrolizumab in this rare malignancy, highlighting a critical gap in evidence. Prospective clinical trials and further research into biomarkers predictive of treatment response are urgently needed to optimize therapeutic strategies and improve outcomes for patients with this aggressive disease. Research Sponsor: None.

8587 Poster Session

Survival after osimertinib dose-reduction, discontinuation in 1L *EGFR*-mutated metastatic non-small cell lung cancer (mNSCLC).

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Background: Osimertinib (osi) has become standard of care in 1L EGFR mt (+) mNSCLC following the FLAURA trial in patients (pts) with classical sensitizing mutations. However, limited data are available on the effect of osimertinib dose reductions on survival outcomes compared to pts on full dose. **Methods:** We performed a single-institution retrospective analysis of pts with *EGFR*-mutated mNSCLC treated with 1L osi from 2018-2023 Clinical trial pts were excluded. Pts who underwent dose reduction were compared to those maintained on full dose (at least 80mg daily). Baseline demographics, disease characteristics, treatment history, toxicity, and clinical outcomes were abstracted from the electronic medical record (EMR) and compared using independent sample t-tests and chi-square analyses as appropriate. Median progression free survival (mPFS) and overall survival (mOS) were compared via Kaplan-Meier log-rank analysis and Cox regression analysis, with sex, race, age, PS, smoking hx, CNS involvement, and mutation status included *a priori*. **Results:** 171 pts with mNSCLC treated with 1L osi were identified. 26 (15%) required dose reduction. Patient sex (p=0.458), racial distribution (p=0.421), ECOG PS>1 at diagnosis (p=0.730) and smoking history (p=0.485) were comparable between reduced dose and full dose pts (Table 1). 44% vs 34% had CNS metastases at diagnosis (p=0.192). Rates of *TP53* (p=0.712) and atypical *EGFR* mutations (p=0.393) were also comparable. All dose-reduced pts experienced AEs, compared to 48% of full-dose pts (p<0.001). Dose-reduced pts had inferior mPFS (17.0 months [11.5-22.5]) compared to full-dose pts (24.6[19.2-28.8]; p=0.043. PFS with dose-reduction was inferior compared to full dose with (p=0.041) or without CNS metastases (p=0.048). On multivariable analysis, dose-reduction was associated with inferior PFS (p=0.047) regardless of baseline characteristics. OS, however, was comparable in pts with and without dose-reduction (36.7 [28.1-45.4] vs 39.2 [34.8-43.7]; p=0.749)). 14 pts (8%) discontinued osi due to AEs, of whom 9 (64%) were previously dose reduced. mPFS was comparable (p=0.334) between pts who discontinued and those who did not, as was mOS (p=0.910). **Conclusions:** Dose reduction of osimertinib was relatively uncommon and associated with inferior PFS but similar OS in 1L pts with *EGFR*-mutated mNSCLC. Research Sponsor: None.

Baseline characteristics and survival.

Baseline Characteristics	Dose reduced (n=26)	Full dose (n=145)	Sig (p)
Female	59.6%	63.0%	0.458
Race			0.421
White	63.0%	67.0%	
Black	3.7%	12.3%	
Asian	33.3%	19.1%	
ECOG PS>1	0%	6.8%	0.730
Smoking Hx	37.0%	39.7%	0.485
CNS mets	44.4%	33.5%	0.192
Mutation Status			
TP53	55.7%	53.1%	0.712
L858R	35.8%	38.2%	0.675
Exon19del	45.7%	45.0%	0.819
Atypical mutation	18.5%	16.8%	0.393
Adverse Events (AEs)			
Experienced AEs	100%	48.3%	**<0.001**
Discontinued due to AE	34.6%	3.4%	**<0.001**
Survival (months)			
mPFS	17.0[11.5-22.5]	24.6[19.2-28.8]	**0.043**
mOS	36.7 [28.1-45.4]	39.2 [34.8-43.7]	0.910

Significant findings in bold.

Clinical relevance of starting alectinib at a reduced dose in patients with ALK-positive non-small cell lung cancer.

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Background: Alectinib has been approved for Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) at a lower dose (300 mg twice daily: b.i.d.) in Japan than the rest of the world (600 mg b.i.d.). To evaluate the clinical relevance of reducing the starting dose of alectinib, we compared the clinical outcomes of patients treated with one of the two doses. **Methods:** This study included patients with advanced ALK-positive NSCLC who received alectinib at Samsung Medical Center, Korea. The progression-free survival (PFS), overall survival, cumulative incidence of central nervous system (CNS) progression, and safety profiles were retrospectively reviewed and compared. **Results:** Among 306 patients, 32 and 274 received alectinib at either 300 or 600 mg b.i.d., respectively. The 300 mg group showed a slight but not significant advantage in PFS (HR 0.82, 95% CI 0.44-1.51, p=0.51) and overall survival (HR 0.51, 95% CI 0.20-1.21; p=0.13) compared with the 600 mg group. Interestingly, the superior survival outcome in the 300 mg group was remarkable in patients with lower body weight (≤60 kg). However, this advantage diminished at higher body weights (>60~75 kg or >75 kg). In addition, there was a slight tendency toward a higher incidence of CNS failure in the 300 mg group of patients with baseline brain metastasis (HR 1.76, 95% CI 0.53-5.8; p=0.36). Although the safety profiles were mostly mild and manageable in both groups, the 600 mg group showed more frequent adverse events than the 300 mg group and required dose reduction in 137 patients (50%). **Conclusions:** Alectinib at 300 mg b.i.d. seems an acceptable dose in patients with ALK-positive NSCLC even in areas outside Japan. Notably, our data favor 300 mg b.i.d. in patients with lower body weight and no baseline brain metastasis, considering the more tolerable safety profiles and the potential to reduce medical costs. Research Sponsor: None.

8589 Poster Session

Depth of response and progression-free survival in patients with advanced *ALK*-positive non–small-cell lung cancer treated with lorlatinib.

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Background: After 5 years of follow-up in patients with *ALK*-positive non-small cell lung cancer (NSCLC) treated with lorlatinib, median progression-free survival (PFS) was still not reached in the phase 3 CROWN study (NCT03052608). This represents the longest PFS for any single-agent molecular targeted treatment in advanced NSCLC and all metastatic solid tumors. Depth of response (DepOR) is defined as the best percent shrinkage in tumor size compared with baseline. In this post hoc analysis of data from the CROWN study, we assessed the association between DepOR and PFS. **Methods:** The CROWN study is an ongoing, international, open-label, randomized, phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated *ALK*-positive advanced NSCLC. Patients were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily. This analysis examined how DepOR is associated with baseline demographics, tumor characteristics, PFS, and tumor biomarkers. Patients were evaluable for DepOR if they had target lesions at baseline and ≥1 adequate postbaseline assessment up to the time of progressive disease or new anticancer therapy. A genAI tool (12/20/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** In the lorlatinib group, 142 of 149 (95%) randomized patients were evaluable for DepOR; 29 (20%) had 0%-50% DepOR, 65 (46%) had >50%-75%, and 48 (34%) had >75%-100%. Baseline demographics and tumor characteristics were similar between the DepOR groups, although the percentage of patients with baseline brain metastases was higher in the greater DepOR group. PFS improved with increasing DepOR (Table). Key biomarker analyses evaluating *EML4-ALK* long- and short-variant subgroups and circulating tumor DNA dynamics, based on DepOR groups, will be reported. **Conclusions:** Greater DepOR was associated with PFS benefit in patients with advanced *ALK*-positive NSCLC treated with lorlatinib. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

PFS in patients evaluable for DepOR (n=142).

	0%-50% DepOR	>50%-75% DepOR	>75%-100% DepOR
DepOR in the lorlatinib group, n (%)	29 (20)	65 (46)	48 (34)
PFS			
Probability of being event free (95% CI), %			
At 3 years	41.0 (22.6-58.6)	68.2 (55.1-78.2)	77.5 (62.1-87.2)
At 5 years	36.9 (19.3-54.7)	62.3 (48.6-73.3)	74.8 (59.0-85.2)
Median (95% CI), months	12.7 (7.2-NE)	NE (60.0-NE)	NE (NE-NE)
HR (95% CI)[a]		0.39 (0.21-0.73)	0.25 (0.12-0.53)

NE, not evaluable.
[a]Unstratified analysis comparison vs 0%-50% group.

Impact of lorlatinib dose modifications on adverse event outcomes in the phase 3 CROWN study.

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Background: In an updated analysis of the CROWN study (NCT03052608), after 5 years of follow-up, lorlatinib continued to show superior efficacy over crizotinib in patients with previously untreated advanced *ALK*+ non-small cell lung cancer (NSCLC), with median progression-free survival (PFS) still not reached. A post hoc analysis of CROWN found no impact on PFS or time to intracranial progression with lorlatinib dose reductions within the first 16 weeks. These findings underscore the importance of dose modifications to mitigate toxicity and maintain long-term treatment efficacy. The objective of this analysis was to further characterize lorlatinib dose reductions and their impact on safety and adverse event (AE) outcomes. **Methods:** The CROWN study is an ongoing, international, open-label, randomized phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated advanced *ALK*+ NSCLC. Patients were randomized 1:1 to receive lorlatinib 100 mg once daily (QD; n=149) or crizotinib 250 mg twice daily (n=147). This post hoc analysis used data from the 5-year follow-up to assess time to dose reduction, duration of treatment with reduced dose, and its impact on AEs and outcomes associated with lorlatinib. A genAI tool (12/13/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** At 5 years of follow-up, 49 of 149 patients in the lorlatinib arm had ≥1 lorlatinib dose reduction. Treatment is ongoing in 33% of patients who had 1 dose reduction (n=24) and in 20% who had 2 dose reductions (n=25). In patients who had 1 dose reduction to 75 mg QD, median time to dose reduction was 7.1 months (range, 1.7-64.8), and median duration of treatment with the 75-mg dose was 42.2 months (range, 0.2-68.3). In patients who had 2 dose reductions (dose reduced to 75 mg QD and then again to 50 mg QD), median time to second dose reduction was 11.3 months (range, 2.5-56.9), and median duration of treatment with the 50-mg dose was 20.7 months (range, 0.5-61.8). In patients who had 1 or 2 dose reductions, all-cause AEs associated with dose reductions are shown in the table. Of the 30 AEs leading to 1 dose reduction, 27% of events resolved and 13% partially resolved. Of the 59 AEs leading to 2 dose reductions, 46% of events resolved and 5% partially resolved. **Conclusions:** This post hoc analysis of the CROWN study showed that dose reductions were effective in managing AEs associated with lorlatinib. These findings show the importance of dose modifications to mitigate toxicity and continue lorlatinib treatment for prolonged periods of time in patients with advanced *ALK*+ NSCLC. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

AEs associated with dose reductions in >2 patients, n (%)	Any grade	Grade ≥3
1 dose reduction (n=24)		
Any	23 (96)	14 (58)
Peripheral edema	4 (17)	2 (8)
2 dose reductions (n=25)		
Any	24 (96)	11 (44)
Peripheral edema	6 (24)	0
Blood triglycerides increased	3 (12)	2 (8)
Disturbance in attention	3 (12)	0
Generalized edema	3 (12)	1 (4)

8591 Poster Session

Dynamic changes in target protein expression following treatment in NSCLC: Simultaneous evaluation of MET, TROP2, HER2, B7-H4, and MDM2 expression in paired biopsies.

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Background: Antibody-drug conjugates and bispecific antibodies targeting non-small cell lung cancer (NSCLC) tumor surface antigens are under development, but the impact of prior treatments on target protein expression remains unclear. This study evaluates changes in the expression of multiple therapeutic target proteins in the same patient before and after treatments. **Methods:** Patients diagnosed with NSCLC underwent rebiopsy after treatments at the National Cancer Center Hospital between 2014 and 2023 were eligible. Tissues were obtained by surgery, bronchoscopy, or needle biopsy with an interval of at least 100 days of systemic anti-cancer therapy. We investigated clinicopathological features in paired specimens focusing on tumor-associated surface proteins potentially related to novel drug development such as MET, TROP2, HER2, B7-H4, and MDM2. TROP2, B7-H4, and MDM2 were evaluated using the H-score. HER2 was evaluated on a scale from 0 to 3+, as previously reported. For MET, a scoring system was adopted in which overexpression (OE) was defined as IHC 3+ positive cells representing 25% or more of the cells. **Results:** A total of 51 cases were included in this study. The median age was 64 years. Of the patients, 27 (57%) were male, 33 (65%) were smokers, and 45 (88%) had lung adenocarcinoma. EGFR 24 cases (47%)/ALK 8 cases (16%)/BRAF 1 case (2%)/ROS1 1 case (2%) were identified among 34 cases with actionable genetic alterations (AGAs). The proportion of MET OE before and after treatment was 33.3%/45.1% overall. In subgroup analyses, the proportions were 38.2%/47.1% (AGA positive), 23.5%/41.2% (AGA negative), 36.0%/52.0% (PD-L1 positive), and 30.8%/38.5% (PD-L1 negative). For HER2 positive (2+, 3+) cases, the overall proportions were 20.9%/11.6%, while subgroup proportions were 15.2%/12.1%, 40.0%/10.0%, 20.0%/15.0%, and 21.7%/8.7%, respectively. The proportion of patients who experienced change in protein expression after previous treatment was as follows: MET, 31.4%; TROP2, 29.4%; HER2, 27.9%; B7-H4, 0.0%; MDM2, 51.0%. **Conclusions:** MET, TROP2, HER2, and MDM2 showed expression changes before and after treatment in approximately 30% of patients. There were differences in the rate of change depending on whether AGA was present, with a higher rate of change in AGA negative patients. Based on these findings, rebiopsy after treatment is recommended when considering therapies targeting tumor surface protein antigens. Research Sponsor: None.

Percentage change in MET, TROP2, HER2, B7-H4, and MDM2 following previous treatment.

	MET (%)	TROP2 (%)	HER2 (%)	B7-H4 (%)	MDM2 (%)
Proportion changing (n=51)	31.4	29.4	27.9	0.0	51.0
AGA positive (n=34)	32.4	20.6	21.2	0.0	52.9
Elevated	20.6	17.6	9.1	0.0	32.3
Decreased	11.8	3.0	12.1	0.0	20.6
AGA negative (n=17)	29.4	47.1	50.0	0.0	47.1
Elevated	23.5	47.1	10.0	0.0	17.6
Decreased	5.9	0.0	40.0	0.0	29.4

AGA; actionable gene alternation.

8592 Poster Session

RC108 in combination with furmonertinib in patients with locally advanced or metastatic EGFR-mutated non-small-cell lung cancer (NSCLC) with MET over-expression: Results from a phase Ib/II trial.

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Background: Patients (pts) who have progressed on EGFR-TKI treatment have limited treatment choices when accompanied by MET overexpression. RC108 is a MET-directed ADC with the microtubule inhibitor monomethyl auristatin E (MMAE) as the cytotoxin and it may overcome primary/secondary MET-driven resistance to EGFR-TKI. We report the preliminary safety and efficacy results of RC108+furmonertinib (F, a third-generation EGFR-TKI) in pts with MET-overexpressing and EGFR-mutated locally advanced or metastatic (la/m) NSCLC who failed prior EGFR-TKI from a phase 1b/2 trial (NCT05821933). **Methods:** The key eligibility criteria were histologically or cytologically confirmed la/m NSCLC with at least one documented EGFR sensitizing mutation, MET-overexpression (defined as IHC 1+/2+/3+ in ≥10% of tumor cells), and disease progression on prior 1st/2nd/3rd-generation EGFR-TKI treatment. Pts received RC108 (at doses of 1.5 or 2.0 mg/kg, Q3W) + F (80 mg, QD) until disease progression or intolerable toxicity. Radiological tumor assessment was performed every 6 weeks by investigators per RECIST v 1.1. The primary endpoints were safety and objective response rate (ORR). Data cutoff date for this analysis was Sep 12, 2024. **Results:** A total of 31 pts were enrolled and received at least one dose of treatment, including 2 and 29 pts in the 1.5 and 2.0 mg/kg cohorts, respectively. The most frequent treatment-related adverse events (TRAEs) were nausea (51.6%), asthenia (48.4%), decreased appetite (45.2%), vomiting (45.2%), white blood cell count decreased (35.5%), alopecia (35.5%), and hypoesthesia (32.3%). Grade ≥3 TRAEs occurred in 7 (22.6%) pts. TRAEs led to treatment discontinuation in 1 (3.2%) pt. One pt died due to abnormal hepatic function, possibly related to the study treatment per the investigator's assessment. Among the 24 pts with at least one post-baseline tumor assessment in the 2.0 mg/kg cohort (79.2% with ECOG PS 1, 58.3% with exon 19 deletion, 33.3% with exon 21 L858R, and 62.5% with ≥2 prior lines of treatment), the ORR was 37.5% (95% CI: 18.8-59.4) and disease control rate (DCR) was 75.0% (95% CI: 53.3-90.2). In the 18 pts with ≥10% of tumor cells with 1+/2+/3+ membrane staining and ≤20% tumor cells with strong (3+) cytoplasmic staining, ORR was 50.0% (95% CI: 26.0-74.0) and DCR was 83.3% (95% CI: 58.6-96.4). The progression-free survival data were immature and under follow-up. **Conclusions:** RC108+F showed encouraging antitumor activity with manageable safety profile in pts with MET-overexpression. At the same time, this study demonstrated better efficacy in the population with lower MET expression in the cytoplasm. We will continue to explore more beneficial populations in future studies. Clinical trial information: NCT05821933. Research Sponsor: RemeGen Co., Ltd.

8593 Poster Session

Impact of standard vs reduced dosing of sotorasib on efficacy and toxicity in KRAS G12C–mutated advanced non-small cell lung cancer: A systematic review and meta-analysis.

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Background: KRAS is the most common oncogenic driver in lung adenocarcinoma. Advances in targeted therapies such as Sotorasib have improved outcomes, but optimizing dosing strategies is crucial to balance efficacy and tolerability. Sotorasib serves as an illustrative example, as it was the first drug for which the FDA requested a dose optimization strategy. The FDA's decision to maintain 960 mg dose was influenced by CodeBreaK100 and CodeBreaK200 trials. CodeBreaK100, which demonstrated an ORR of 36%, formed the basis for accelerated approval, while CodeBreaK200 confirmed clinical benefit. A post-approval dose randomization study comparing 240 mg and 960 mg doses found no clear exposure-safety relationships, though ORR was numerically higher for 960 mg. However, tolerability remains challenging with 960 mg dose, often requiring dose reductions in clinical practice. This systematic review and meta-analysis evaluates the impact of starting at 960 mg of Sotorasib versus reduced dose on efficacy and toxicity, with implications for optimizing dosing strategies in targeted therapies. **Methods:** We conducted a systematic search of PubMed, EMBASE, SCOPUS, CINAHL, and Web of Science up to Oct 1,2024. Eligible studies included randomized clinical trials, prospective and retrospective studies, reporting efficacy outcomes (ORR, PFS), and treatment-related adverse events. Pooled estimates for efficacy and toxicity outcomes were calculated using random effects model. **Results:** Out of 4510 studies screened, 145 full-text articles were assessed for eligibility, resulting in 14 studies, of which 9 focused on Sotorasib. The pooled ORR was 32% (95%CI 28%-36%) for patients starting at 960 mg (n=889), compared to 26% (95%CI 19%-34%) for those starting at a reduced dose (n=130) with no statistically significant difference (RR 1.26, 95%CI 0.87-1.83). The pooled hazard ratio for PFS did not show a significant benefit for starting at 960 mg compared to at reduced dose (HR 0.77, 95%CI 0.56-1.05). Adverse events leading to dose reduction and discontinuation at 960 mg were 16% (95%CI 10%-23%) and 9% (95%CI 6%-13%), respectively. Limited toxicity data were available for those who started treatment at reduced dose, precluding direct comparison. **Conclusions:** While the standard 960 mg dose of Sotorasib showed a trend toward higher ORR compared to starting at reduced doses, it is associated with significant toxicity, resulting in frequent dose reductions and treatment discontinuation. No significant PFS benefit was observed with starting at 960 mg dose, highlighting the need to optimize dosing strategies that balance efficacy with tolerability.Future studies should include subgroup analyses of efficacy and tolerability for dose reductions to guide optimal dosing regimens, aligning with initiatives like the FDA's Project Optimus to improve patient outcomes. Research Sponsor: None.

8595 Poster Session

Area deprivation index and EGFR-mutated non-small-cell lung cancer.

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Background: Survival outcomes in patients with non-small-cell lung cancer (NSCLC) have improved in recent decades with availability of immunotherapy and targeted therapies such as inhibitors of mutated epidermal growth factor receptor (EGFR). However, significant disparities in lung cancer outcomes exist, with many patients not offered biomarker testing and subsequent underuse of targeted therapies. Because it is not well known how social determinants of health (SDOH) impact the use of targeted therapies, we conducted a study to determine the association between area deprivation index (ADI) and presence of mutated EGFR in a large electronic health record (EHR) database. ADI is a validated measure of neighborhood socioeconomic deprivation, a SDOH metric. **Methods:** This retrospective, observational study used Epic Cosmos, a United States database of deidentified data derived from EHR, to measure the association between ADI and EGFR mutations in patients with stage IV NSCLC treated between January 1, 2015 and December 31, 2022. Receipt of EGFR inhibitors (EGFRIs) was used as a surrogate marker for mutated EGFR, as pathology and molecular data for individual patients were not available from aggregate data. Chi square analysis was used to compare ADI between those who did and did not receive EGFRIs. **Results:** From a total of 6866 patients meeting criteria for inclusion in our analysis, 653 (9.5%) received EGFRIs while 6213 (90.5%) did not. In the EGFR population, 210 (32.2%) were in the top two quintiles of ADI (most deprivation) while 275 (42.1%) were in the bottom two quintiles of ADI (least deprivation). For the non-EGFR population, 3137 (50.5%) were in the top two quintiles while 1373 (22.1%) were in the bottom two quintiles. Patients who received EGFRIs were more likely to be in the bottom two quintiles of ADI compared to those who did not (OR 2.99, 99% CI 2.32-3.84, $p<0.0001$). To control for confounding variables, this analysis was repeated after stratifying by geography, sex, smoking status, insurance, and race. This difference in ADI between the EGFR and non-EGFR groups persisted within strata of similar patients including White females with a smoking history in the Northeast with Medicare (OR 7.28, 99% CI 1.56-34.01, p=0.0009) and White females with a smoking history in the Midwest with Medicare (OR 4.76, 99% CI 1.19-19.10, p=0.0038). **Conclusions:** These data suggest that patients with EGFR mutations, as determined by receipt of EGFRIs, were more likely to reside in neighborhoods with less socioeconomic deprivation. Because of limitations posed by our analytic approach, we were unable to determine if there was a direct association between ADI and the molecular profile of NSCLC, or if these findings are primarily related to differential access to care. Nonetheless, the association persisted within strata of similar demographics, suggesting that it is not entirely explained by confounding related to geography, race, sex, or smoking status. Research Sponsor: None.

8596 Poster Session

Final results of afatinib plus chemotherapy with genomic profiling in osimertinib-refractory EGFR-mutant NSCLC: NEJ025B.

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Background: Osimertinib is commonly used as a first-line treatment for EGFR-mutated advanced NSCLC. However, the optimal treatment following osimertinib failure remains unclear. This study evaluated afatinib plus chemotherapy for EGFR-mutated NSCLC resistant to osimertinib. Initial findings were presented at ASCO2023, and this report provides final data, including blood NGS analysis. **Methods:** Patients (pts) with EGFR mutations (Del19 or L858R) after osimertinib failure were treated with afatinib (20 mg daily) combined with carboplatin (AUC5 mg/mL/min) and pemetrexed (500 mg/m^2 every 3 weeks), followed by maintenance therapy with afatinib plus pemetrexed until progression or unacceptable toxicity. The primary endpoint was the 6-month progression-free survival rate (6M-PFSR). Secondary endpoints included PFS, OS, ORR, DOR, and safety. Blood samples were collected before and during treatment, and at progression, to evaluate biomarkers using CAPP-SEQ. **Results:** Between June 7, 2020, and January 19, 2022, 36 pts were enrolled. One pt met exclusion criteria, leaving 35 pts for efficacy analysis. The mean age was 70 years; 60% were women, and 54.3% were non-smokers. The median observation period was 29.1 months (cutoff date: January 18, 2024). The primary endpoint, 6M-PFSR, was 57.1% (95% CI, 39.3–71.5), exceeding the threshold of 35%. Notably, 28.6% of pts achieved long-term PFS of ≥1 year. ORR was 51.4%, DCR was 88.6%, median PFS was 8.2 months, median DOR was 5.6 months, and median OS was 22.5 months. By mutation type, ORRs were similar for Del19 and L858R (46.7% and 55.0%, respectively), but median PFS was longer for Del19 than for L858R (9.6 vs. 5.2 months). Pts who had responded to prior osimertinib (CR/PR, n=29) had longer median PFS than non-responders (SD/PD/NE, n=6) (8.5 vs. 5.8 months). Adverse events (AEs) from TKI and chemotherapy were common but manageable. The most frequent AEs were diarrhea (52.8%), anorexia (47.2%), fatigue (36.1%), and paronychia (36.1%). Interstitial pneumonia occurred in 3 pts (8.3%), with one treatment-related death. In plasma NGS analysis, clearance of EGFR mutations during treatment was a key predictive factor. Pts without EGFR mutation clearance had shorter PFS and OS compared to those with clearance (PFS: 5.7 vs. 12.0 months; OS: 15.7 vs. 34.4 months). Efficacy was observed even in pts with p53 mutations, a known resistance factor. MET gene amplification was detected in 4 pts upon resistance. **Conclusions:** Afatinib combined with platinum-based chemotherapy demonstrated satisfactory efficacy and manageable toxicity in pts with tumors refractory to osimertinib. EGFR mutation clearance during treatment was predictive of therapeutic outcomes. This regimen may be a promising second-line option after osimertinib failure. Clinical trial information: 021200005. Research Sponsor: Boehringer Ingelheim.

Final results of a phase 1 study of EP0031, a next generation selective RET inhibitor (SRI) in patients with SRI naïve or pretreated advanced RET-altered tumors.

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Background: EP0031 (A400/KL590586), a first in class next gen selective RET inhibitor (SRI) with FDA Fast Track Designation, has broad potency against common RET alterations, including resistance mutations. It has greater potency, antitumor activity, and CNS penetration/activity compared with 1st gen SRIs (Garralda et al. JCO 2024; 42:16; abstr 8556; Zhou et al. JCO 2023; 41:16, abstr 3007). We report final data from the dose finding and optimization Phase 1 trial in the US and Europe. **Methods:** The study recruited pts with RET-altered NSCLC, medullary thyroid cancer (MTC) and other solid tumors and included pts ≥ 18 years, PS 0 or 1, with/without asymptomatic, stable brain mets, who received EP0031 QD in 28 days' cycles. **Results:** A total of 40 pts (23 F, 17 M, median age 59 y), 22 NSCLC (20 SRI pre-treated, 1-6 prior lines), 12 MTC (7 SRI pre-treated, 1-4 prior lines) and 6 pts with other tumors (4 SRI pre-treated) were enrolled across 4 cohorts: 20 (n=3), 60 (n=10), 90 (n=16) and 120 (n=11) mg QD. The 60, 90 and 120mg cohorts were expanded for dose optimization. 9 pts had stable brain mets at baseline. No DLTs were observed. Most frequent G1/2 TEAEs (≥20%) were headache, anemia, ALT/AST increase, constipation, dizziness, hyperphosphatemia, blurred vision, keratitis, blood creatinine increased, dry mouth, dyspnea and fatigue. G3 TEAEs were rare and included (≥5%): hyponatremia, hypertension, anemia, AST/ALT increase, headache, diarrhea and ulcerative keratitis. Interruptions, reductions and discontinuations related to study drug were seen in 16 (40%), 8 (20%) and 1 (2.5%) pt. 25 pts with prior SRI were response evaluable. 5 PRs and 6 SDs reported in 15 NSCLC pts, with complete resolution of brain mets in 3/5 pts. Median DoR was 7.3mo (range 5.4-16.3). In 7 MTC pts, 2 PRs (DoR 6.6 – 9.2mo) and 2 SDs seen. Of 3 pts with other tumors, a pancreatic cancer pt had SD for 3.5 mo, and a pt with papillary thyroid cancer was clinically stable for 9 mo. In pts who were SRI naïve, 1 CR and 1 PR were reported in 2 NSCLC pts; and 5 PRs (1 uPR) were reported in all MTC pts. Baseline on-target RET resistance mutations were detected in 6/31 prior SRI pts (19.4%) with evidence of activity in 3, and sustained reduction and clearance of ctDNA (including RET resistant mutations: G810R solvent front and L730V, L730I roof mutations). Plasma exposures increased proportionately with dose. 90mg QD was selected as RP2D, with plasma levels $>IC_{90}$ for all relevant RET fusions/mutations. **Conclusions:** There is a need for new treatments for pts that progress on 1st gen SRIs. EP0031 was associated with durable responses in advanced RET altered solid tumors previously treated with SRI, including pts with brain mets, with a manageable safety profile. These data confirm that the first in class next gen SRI EP0031 has the potential to address a high unmet need. Phase 2 trials are evaluating EP0031/KL590586 in US, Europe, UAE and China. Clinical trial information: NCT05443126. Research Sponsor: Ellipses Pharma.

Longer follow-up for survival and safety from the EVOKE-01 trial of sacituzumab govitecan (SG) vs docetaxel in patients (pts) with metastatic non-small cell lung cancer (mNSCLC).

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Background: EVOKE-01 (NCT05089734) assessed the efficacy and safety of SG vs docetaxel in pts with mNSCLC that progressed after platinum-based chemotherapy and anti–PD-(L)1 (IO) treatment. The study did not meet statistical significance for overall survival (OS) at final analysis. Here, we report updated survival and safety outcomes after longer follow-up, providing insight into the tolerability of SG over a prolonged period of administration. **Methods:** Pts were randomized 1:1 to receive SG (n = 299; 10 mg/kg IV, days 1 and 8) or docetaxel (n = 304; 75 mg/m^2 IV, day 1) in 21-day cycles until progression or unacceptable toxicity. OS was the primary endpoint, while safety was a key secondary endpoint. **Results:** As of Oct 21, 2024, median follow-up was 23.5 months. Median exposure with SG vs docetaxel was 3.5 vs 2.3 months; 33.4% vs 17.7% of pts, respectively, were exposed to study drug for ≥6 months. The longer follow-up preserved the numerical improvement in OS favoring SG in the intent-to-treat population (HR 0.89, 95% CI: 0.74–1.07; P = .1028) and in subgroups of interest, including nonresponders to prior IO, and across squamous and nonsquamous histologies (**Table**). Most common any-grade treatment-emergent adverse events (TEAEs) with SG vs docetaxel were fatigue (57.8% vs 56.6%), diarrhea (52.7% vs 33.7%), and alopecia (43.6% vs 30.2%). In line with the primary analysis, 68.6% vs 76.0% of pts receiving SG vs docetaxel experienced grade ≥3 TEAEs, mainly neutropenia (25.3% vs 36.8%), fatigue (12.5% vs 9.7%), and diarrhea (10.5% vs 3.8%). Discontinuations due to TRAEs were seen in 7.4% vs 14.2% of pts receiving SG vs docetaxel. There were no additional AEs leading to death reported with longer follow-up (Table). **Conclusions:** Consistent with the final analysis, SG showed a numerical improvement in OS vs docetaxel. Long-term safety showed SG is well tolerated, consistent with minimal increase in AE rates since prior report and an improved safety profile over docetaxel, despite longer treatment exposure. Clinical trial information: NCT05089734. Research Sponsor: Gilead Sciences, Inc.

Median OS, mo (95% CI) HR (95% CI)	SG	Doc
Nonresponsive (SD/PD) to last IO	n = 192 11.8 (9.6–12.8) 0.83 (0.66–1.04)	n = 191 8.3 (6.9–10.2)
Responsive (CR/PR) to last IO	n = 106 9.7 (8.4–14.3) 1.05 (0.78–1.43)	n = 113 10.8 (9.2–12.8)
Squamous	n = 84 10.3 (8.1–13.2) 0.89 (0.63–1.25)	n = 80 9.2 (6.9–11.0)
Nonsquamous	n = 215 11.6 (9.4–12.9) 0.89 (0.72–1.11)	n = 224 9.9 (7.9–11.2)
With prior therapy for AGA	n = 19 12.9 (7.2–23.9) 0.63 (0.31–1.29)	n = 25 7.0 (5.2–11.6)
TEAE, % (safety population)	**n = 296**	**n = 288**
Any grade	99.7	98.3
Grade ≥3	68.6	76.0
Serious TEAEs	47.6	44.4
Leading to dose reduction	29.7	39.2
Leading to discontinuation	10.1	16.7
TRAEs leading to discontinuation	7.4	14.2
Leading to death	3.4	4.2
TRAEs leading to death	1.4	1.0

8600 Poster Session

A retrospective study of anlotinib plus third-generation EGFR-TKIs in advanced non-small cell lung cancer with gradual or oligo progression after EGFR-TKIs treatment (ALTER-L058).

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Background: Despite the significant improvement in progression-free survival (PFS) for non-small cell lung cancer (NSCLC) patients with EGFR mutations, attributed to the advent of third-generation EGFR tyrosine kinase inhibitors (TKIs), the inevitable development of acquired resistance continues to pose a critical challenge that severely affects the long-term efficacy of these treatments. This study aims to evaluate the efficacy and safety of anlotinib in combination with third-generation EGFR-TKIs in advanced NSCLC patients experiencing gradual or oligo progression following EGFR-TKIs. **Methods:** ALTER-L058 was a retrospective study conducted at 16 hospitals in China. Eligible patients aged 18 to 75 years with histologically or cytologically confirmed NSCLC who tested positive for EGFR mutations and exhibited gradual or oligo progression following treatment with third-generation EGFR-TKIs. Patients continued their regimen of EGFR-TKIs with or without anlotinib after gradual or oligo progression. Anlotinib was administered orally at a dose of 8-12 mg per day for two weeks, followed by a one-week break, within a three-week cycle. The primary endpoint was PFS. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety profiles. **Results:** From 1/2020 to 12/2023, a total of 150 patients were enrolled in the study. Among these, 100 patients received third-generation EGFR-TKIs plus anlotinib treatment, while 50 patients only received third-generation EGFR-TKIs. From treatment initiation of EGFR-TKIs, compared with third-generation EGFR-TKIs alone, median PFS was prolonged with third-generation EGFR-TKIs plus anlotinib (23.2 versus 19.5 months; hazard ratio (95% CI): 0.56 (0.36-0.86); P = 0.0008). From gradual or oligo progression after EGFR-TKIs treatment, mPFS was significantly extended with the combination of third-generation EGFR TKIs and anlotinib compared to third-generation EGFR TKIs alone (9.2 versus 5.4 months; hazard ratio (95%CI): 0.40 (0.25-0.65); P < 0.0001). The incidence of grade 3 or higher treatment-related adverse events was 37.0% (third-generation EGFR-TKIs plus anlotinib) and 34.0% (third-generation EGFR-TKIs), respectively. **Conclusions:** Continuous treatment with anlotinib after the emergence of gradual or oligo progression during the third-generation EGFR-TKIs therapy prolonged the clinical benefit of EGFR-TKIs, demonstrating favorable survival outcomes and manageable toxicity. Clinical trial information: ChiCTR2500095741. Research Sponsor: None.

8601 Poster Session

First-in-human phase I/II study of BYS10 in patients (pts) with locally advanced or metastatic RET-altered solid tumors: Preliminary dose escalation results.

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Background: RET alterations occur in non-small cell lung cancer (NSCLC, 2%), thyroid cancer (TC, 10%–20%) and a range of tumor types (<1%). RET inhibitors substantially improved the clinical outcomes of pts with RET-altered solid tumors. BYS10 is a highly potent and RET-specific inhibitor that overcomes RET V804 and G810 mutations, and exhibits high selectivity for RET over KDR. This study is to evaluate safety, tolerability, pharmacokinetics (PK) and efficacy of BYS10 in Chinese pts with RET-altered solid tumors. **Methods:** In phase I, following an accelerated titration and BOIN design, eligible pts were treated with BYS10 at 25 to 600 mg daily dose. Primary endpoints included safety, tolerability, MTD and DLTs. Secondary endpoints included PK and preliminary antitumor activity. **Results:** As of 10 July, 2024, a total of 51 pts were enrolled in dose escalation cohorts at 25/50 mg QD (n = 1/1) and 50/100/200/250/300 mg BID (n = 3/12/12/9/13). The MTD was not reached. Treatment related adverse events (TRAEs) occurred in all subjects, the most common TRAE were elevated AST (64.7%), elevated ALT (58.8%), elevated TBIL (45.1%), decreased WBCs (43.1%), decreased NEUT (33.3%), hyperuricaemia (31.4%), hypertension (29.4%), hypoalbuminemia (25.5%), Elevated SCr (23.5%) and headaches (23.5%). Grade 3 to 4 TRAEs >5% included elevated AST (25.5%), elevated ALT (13.7%) and hypertension (9.8%) reported at 100 to 300 mg BID doses. Serious adverse events were recorded in 7 pts. Exposure of BYS10 increased in a dose-dependent manner from 25 to 600 mg. In 40 evaluable pts, the confirmed overall response rate (ORR) and disease control rate (DCR) by independent review committee per RECIST v1.1 were 62.5% and 85%, In pts with RET-fusion NSCLC (n=30), RET-fusion thyroid cancer (TC, n=6) and RET-mutant medullary thyroid cancer (MTC, n=4), the ORR/DCR were 60%/80%, 83.3%/100% and 50%/100%, respectively. Intracranial antitumor activity was observed by investigators in 4 pts with at least 1 measurable intracranial lesion (one intracranial complete response). The ORR/DCR by IRC in 200 mg and 300 mg BID cohorts were 66.7%/100% and 75%/91.7%, respectively. **Conclusions:** BYS10 was well tolerated and showed dose-dependent exposure. Preliminary antitumor activity was observed in pts with RET-altered NSCLC, TC and MTC. The study is still ongoing. Clinical trial information: ChiCTR2400085264. Research Sponsor: Baiyunshan Pharmceutical Holdings Co., Ltd. Baiyunshan Pharmceutical General Factory.

Dysregulation of DNA damage repair in lung cancer driven by *MTAP* loss: Mechanistic insights and target discovery.

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Background: *MTAP* loss leads to methylthioadenosine (MTA) accumulation, disrupting downstream metabolic pathways. Targeting synthetic lethal interactions with *MTAP* loss offers a promising therapeutic strategy. The DNA damage response (DDR) pathway, essential for genomic stability, is commonly dysregulated in lung cancer, impacting treatment response and prognosis. Emerging evidence has highlighted potential association between *MTAP* loss and mutations in DDR genes, suggesting that investigating their relationship is critical for uncovering disease mechanisms and identifying novel biomarkers and therapeutic targets. **Methods:** Hybridization capture sequencing with StarPanel NGS Assay (1,326 genes) was conducted on 2,258 Chinese lung cancer patients' tumor and matched peripheral blood samples. Then somatic and germline mutations, and TMB values of each sample were obtained. Based on a depth-based algorithm, differences between tissue and control samples in CNVs from the gene level were analyzed. Besides, we utilized shifts in germline heterozygous SNPs within the gene region to assist in determining if the loss was homozygous or heterozygous. **Results:** Homozygous and heterozygous deletions of *MTAP* were detected in 11.07% and 6.95% of all samples. Notably, 61.67% of these samples exhibited co-loss of *MTAP*, *CDKN2A* and *CDKN2B*. The median TMB was significantly higher in samples with *MTAP* loss (3.85 mut/Mb) compared to those with intact *MTAP* (2.56 mut/Mb). In samples with homozygous *MTAP* loss, the top somatically co-altered genes were *EGFR* (76.00%), *TP53* (57.60%) and *CDKN2A* (52.80%). Gain-of-function (GoF) mutations were most prevalent in *EGFR* (56.80%), *KRAS* (12.00%) and *MDM2* (10.00%), while Loss-of-function (LoF) mutations were most common in *TP53* (50.40%), *RBM10* (11.60%) and *PTEN* (7.60%). Notably, LoF mutations in *MTAP*-loss samples showed a higher prevalence of DDR genes compared to *MTAP*-intact samples, including *RAD50* (2.40% vs. 0.00%, $p < .0001$) and *POLQ* (2.40% vs. 0.00%, $p < .0001$). Enrichment analysis further revealed LoF mutations unique to *MTAP*-loss samples were significantly enriched in the DDR pathway ($p < .0001$). For top germline pathogenic mutations, two DDR genes, *RECQL4* (0.80% vs. 0.38%, $p = 0.29$) and *BRCA2* (0.40% vs. 0.43%, $p = 1$), showed no significant differences between *MTAP*-loss and *MTAP*-intact samples. **Conclusions:** Potential association exists between *MTAP* loss and DDR pathway dysregulation, which may impact tumorigenic processes and therapeutic vulnerabilities. The enrichment of DDR-related LoF mutations indicates *MTAP* loss could exacerbate genomic instability by impairing DNA damage repair mechanisms, thereby increasing TMB and driving cancer progression with a distinct molecular profile. These vulnerabilities are primarily driven by somatic mutations, providing a rationale for exploring personalized treatment strategies. Research Sponsor: None.

Real-world treatment patterns and time-to-treatment discontinuation among advanced ALK-positive non-small cell lung cancer patients.

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Background: Advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) is typically treated with ALK tyrosine kinase inhibitors (TKIs) in the first-line (1L) setting. While clinical trials provide efficacy data, real-world evidence on treatment patterns and time-to-treatment discontinuation or death (TTD) remains scarce. Such evidence may better inform modern clinical practice and decision-making regarding long-term treatment planning and sequencing decisions. **Methods:** This retrospective observational cohort study analyzed patients with advanced ALK+ NSCLC in the Optum Clinformatics Data Mart (2016–2021). Eligible patients were ≥18 years of age, with ≥6 months of continuous enrollment prior to the index date, a lung cancer diagnosis identified via ICD-10 codes, and ≥1 prescription fill for an ALK TKI. Outcomes included TTD for 1L and second-line (2L) therapies, assessed using the Kaplan-Meier (KM) method. Treatment patterns, including discontinuation rates and transitions to 2L therapy, were also evaluated. **Results:** Among 680 patients, 1L therapy distribution was as follows: crizotinib (n=366, 53.8%), alectinib (n=267, 39.3%), brigatinib (n=22, 3.2%), and ceritinib (n=25, 3.7%). Lorlatinib (n=16) was excluded from the analysis due to its atypical use in 1L during the study period, potentially reflecting unique clinical scenarios. The median TTD for 1L therapy was 8.3 months overall (95% CI: 6.7–9.7). TTD by therapy was as follows: alectinib, 15.3 months (95% CI: 11.0–21.4); brigatinib, 7.8 months (95% CI: 3.6–18.1); ceritinib, 7.6 months (95% CI: 4.3–23.5); crizotinib, 5.7 months (95% CI: 4.7–6.8). Only 168 (24.7%) patients transitioned to another ALK TKI in 2L, with alectinib being the most common among 1L crizotinib recipients, and lorlatinib being the most common among 1L alectinib and brigatinib recipients. Median TTD for 2L therapies was 8.0 (95% CI: 5.7-11.7) months overall. **Conclusions:** This study provides real-world evidence on TTD and treatment patterns among advanced ALK+ NSCLC patients. Transition rates to 2L ALK TKIs were lower than expected based on clinical trials, with high rates of discontinuation without transition. With alectinib, brigatinib, and lorlatinib equally recommended as 1L options in US clinical guidelines, these findings provide real-world evidence to help clinicians differentiate among therapies and guide treatment sequencing decisions. Research Sponsor: None.

1L ALK TKI (n)	Transition to 2L ALK TKI (%)	Median 1L TTD (Months, 95% CI)
Alectinib (267)	51 (19.1%)	15.3 (11.0–21.4)
Brigatinib (22)	2 (9.1%)	7.8 (3.6–18.1)
Ceritinib (25)	14 (56.0%)	7.6 (4.3–23.5)
Crizotinib (366)	101 (27.6%)	5.7 (4.7–6.8)
Overall (680)	168 (24.7%)	8.3 (6.7–9.7)

1L first-line, *2L* second-line, *ALK* anaplastic lymphoma kinase, *TKI* tyrosine kinase inhibitor, *TTD* time-to-treatment discontinuation or death, *CI* confidence interval.

Osimertinib plus repotrectinib phase I trial in TKI-resistant non-small cell lung cancer (NSCLC) with EGFR mutations.

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Background: NSCLC patients with EGFR mutations develop resistance when treated with EGFR TKI. We previously reported that osimertinib combined with TPX-0005 (repotrectinib) ablated STAT3, paxillin, and YAP1 phosphorylation in a preclinical model. Osimertinib-induced Src and FAK phosphorylation was abrogated with TPX-0005 alone or in combination with osimertinib in H1975 (EGFR L858 and T790M) cell line. TPX-0005 potentiated the effect of osimertinib in PC9 and H1975 tumor xenografts without substantial toxicity (Karachaliou et al. eBioMedicine 2017). The findings prompted us to carry out the current study with osimertinib plus TPX-0005, which inhibit Src/FAK/JAK2, in addition to ALK, ROS1 and NTRKs. **Methods:** TOTEM (NCT04772235) is a phase I, two-part study to assess safety, tolerability, pharmacokinetics, and antitumor activity of repotrectinib plus osimertinib in EGFR-mutant patients resistant to previous lines of treatment. Phase Ia was a dose escalation (3+3). Treatment naïve patients were treated with osimertinib 80mg QD plus: repotrectinib 80mg QD, 160mg QD and 160mg BID. In part Ib, patients should have received osimertinib or osimertinib plus chemotherapy as first line treatment. Results from part Ia are presented in this abstract. **Results:** Phase Ia included 15 patients with a median age of 61 yrs (34-71). Of these patients:10 were female (66.7%), 9 had PS1 (60%), and 7 had brain metastasis (48.7%). At the time of starting treatment, two patients had exon 18 (G719X) mutations (p.E709_T710delinsD and p.G719A), 5 had exon 21 (4 p.L858R, 1 p.L861Q) and 8 had exon 19 deletion. Eight patients had p53 co-mutations, other co-alterations included PIK3CA, RET, FAT1, FGFR3 and MYC mutations, CDK4 and EGFR amplification, and MET, ROS1, EGFR and FGFR3 over-expression. Six patients were treatment-naive, four were osimertinib progressors, and five had received two or more previous lines of treatment. With repotrectinib plus osimertinib, intracranial complete response was attained in 3 of the seven patients with brain metastasis (42.85%). The overall objective response rate (ORR) was noted in 5 patients (33.3%), and stable disease in 8 patients (53.3%). Median PFS was 4.4 mo. (95% CI 2.9-NR). Among the adverse events, transient, manageable dizziness was observed in 76% of the patients, and dysgeusia occurred in 48% of cases. Most side effects were grade 1-2, including anemia, diarrhea, fatigue, and liver enzyme elevation. Pharmacokinetic analysis indicated a favorable profile of the combination. Dose level 3 (160mg BID) was safe, therefore, part Ib continued with repotrectinib 160mg BID plus osimertinib 80mg QD in 15 patients enrolled. **Conclusions:** In Part Ia osimertinib + repotrectinib showed impressive intracranial ORR with a manageable safety profile. Part Ib with repotrectinib 160 mg BID plus osimertinib 80 mg is ongoing. Updated results will be presented. Clinical trial information: NCT04772235. Research Sponsor: None.

MK-1084 for KRAS G12C-mutated (mut) metastatic non–small-cell lung cancer (mNSCLC): Results from KANDLELIT-001.

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Background: MK-1084 is an oral, next-generation, selective KRAS G12C-GDP covalent inhibitor. The phase 1 KANDLELIT-001 study (NCT05067283) showed manageable safety and antitumor activity for MK-1084 monotherapy in *KRAS* G12C-mut solid tumors and MK-1084 + pembrolizumab (pembro) in *KRAS* G12C-mut mNSCLC. We report additional NSCLC and preliminary ctDNA data from this study. **Methods:** Pts had confirmed *KRAS* G12C-mut, RECIST-measurable disease and ECOG PS 0-1. Pts with any advanced solid tumor and ≥1 prior systemic therapy received MK-1084 monotherapy 25-800 mg/d in arms 1 and 3. Pts with previously untreated mNSCLC and PD-L1 TPS ≥1% received MK-1084 25-400 mg/d + pembro 200 mg Q3W in arm 2 dose escalation and expansion cohorts. Pts with previously untreated nonsquamous mNSCLC received MK-1084 50-200 mg/d + pembro 200 mg, carboplatin, and pemetrexed Q3W in arm 4. Dose-limiting toxicities (DLTs), AEs, and AEs leading to discontinuation were the primary endpoints; ORR, DCR, and PFS per RECIST v1.1 by investigator review were secondary. *KRAS* G12C variant allele fraction (VAF) and maximum somatic allele frequency (MSAF) in ctDNA were assessed in serial blood samples collected from 23 pts in arm 1 using the Guardant Health OMNI panel. **Results:** There were 99 pts in arms 1+3 (21 with NSCLC), 34 in arm 2 escalation cohorts, 26 in arm 2 expansion cohorts, and 24 in arm 4 as of the 12 Aug 2024 data cutoff. Median study follow-up was 14.8 mo, 16.2 mo, 2.5 mo, and 4.1 mo, respectively. DLTs occurred in 1 pt in arm 2 (gr 3 ALT and AST increase) and 1 pt in arm 4 (gr 3 diarrhea). Drug-related AEs occurred in 62% of pts in arms 1+3, 88% of pts in arm 2, and 96% of pts in arm 4, were gr ≥3 in 9%, 33%, and 58%, and led to discontinuation of any drug in 1%, 20%, and 17%. There was 1 drug-related death (myelosuppression and platelet count decrease in arm 2). Rates of drug-related ALT increase (any/gr ≥3) were 16%/3% in arm 1, 33%/10% in arm 2, and 33%/4% in arm 4. Rates of drug-related AST increase (any/gr ≥3) were 17%/3%, 30%/8%, and 25%/4%. Efficacy is shown in the Table. Median *KRAS* G12C VAF was 14.0% at baseline and 0.9% at week 6; median MSAF was 26.0% and 2.2%, respectively. **Conclusions:** In pts with *KRAS* G12C-mut mNSCLC, MK-1084 shows manageable safety and antitumor activity as monotherapy for previously treated disease and in combination with pembro ± chemo as first-line (1L) therapy. The >90% decrease from baseline in *KRAS* G12C VAF in ctDNA confirms MK-1084 target engagement. The phase 3 KANDLELIT-004 study is evaluating MK-1084 + pembro as 1L therapy for *KRAS* G12C-mut mNSCLC with PD-L1 TPS ≥50%. Clinical trial information: NCT05067283. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

	ORR		DCR		PFS	
Arm	n[a]	% (95% CI)	n[a]	% (95% CI)	n	Med (95% CI), mo
1+3 NSCLC (MK-1084 alone)	21	38 (18-62)	21	76 (53-92)	21	8 (4-NR)
2 escalation (MK-1084 + pembro)	34	74 (56-87)	34	91 (76-98)	34	25 (9-NR)
2 expansion (MK-1084 + pembro)	20	40 (19-64)	20	80 (56-94)	26	NR (NR-NR)
4 (MK-1084 + pembro + chemo)	22	41 (21-64)	22	82 (60-95)	24	NR (5-NR)

[a]Pts with ≥1 MK-1084 dose ≥5 wk before data cutoff.

8606 Poster Session

Clinicogenomic analysis of *EGFR*-mutant lung cancers for identification of Rb inactivation as a hallmark of squamous transformation.

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Background: Histologic transformation to squamous carcinoma (LUSC) is a recognized mechanism of resistance in *EGFR*-mutant lung adenocarcinoma (EGFR+ LUAD) and can occur in 5-8% of patients treated with osimertinib. While our prior work identified the AKT pathway as a possible mediator of LUSC transformation, comprehensive clinicogenomic assessment of this process remains lacking. **Methods:** We performed genomic characterization of *EGFR*-mutant patient samples undergoing LUSC transformation, including: (1) pre- and post-transformation specimens transformed after TKI treatment, and (2) microdissected distinct LUAD and LUSC components obtained from adenosquamous (LUAS) tumors. Retrospective analysis of clinical outcomes such as time-to-treatment discontinuation (TTD) were evaluated in patients with EGFR+ LUAD on frontline osimertinib who have undergone MSK-IMPACT (n=181). Xenograft models (using PC9 and HCC827) mimicking squamous transformation were treated with osimertinib (5-10 mice/group). Phenotypic markers of LUSC (P40 and CK5/6) were assessed by IHC. **Results:** Among patients with EGFR+ LUAD undergoing LUSC transformation (n=20), 50% and 60% had alterations in the AKT or Rb pathway, respectively. When compared to a cohort of never-transforming EGFR+ LUAD (n=1515), patients with transforming LUAD had a higher frequency of AKT (44% vs 18%) and Rb (56% vs 32%) pathway mutations. Clinically, patients with EGFR+ LUAD on first line osimertinib harboring baseline Rb/AKT pathway mutations (n=70) experienced shorter TTD (median 18 vs 24 months, p=0.0261) compared to a Rb/AKT wild-type cohort (n=111). In xenograft models of squamous transformation, Rb inactivation through CRISPR deletion of *RB1* or upstream regulators *CDKN2A/B* led to greater *in vivo* tumor growth in immunodeficient mice treated with osimertinib compared to controls. Histologic assessment revealed induction of squamous markers P40 and CK5/6 in xenografts with Rb inactivation. **Conclusions:** Genomic alterations in Rb and AKT pathways are detected at higher frequency in patients with EGFR+ LUAD undergoing squamous transformation and are associated with worse clinical outcomes to frontline osimertinib. Rb inactivation in xenograft mouse models led to increased squamous-like phenotype and resistance to osimertinib. Detection of these mutations may help identify patients at high risk of treatment resistance and transformation. Research Sponsor: None.

Shifting landscape of resistance to next-generation ALK inhibitors with evolving treatment paradigm in ALK+ lung cancer.

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Background: Next-generation (gen) ALK tyrosine kinase inhibitors (TKIs) are standard first-line (1L) therapy for patients (pts) with *ALK*-rearranged (ALK+) metastatic non-small cell lung cancer (mNSCLC), having supplanted crizotinib (criz). While past studies uncovered mechanisms of resistance to next-gen ALK TKIs, vast majority of analyzed biopsies (bx) were obtained from pts treated with next-gen TKIs after 1L criz, reflecting the outdated treatment paradigm. Limited knowledge exists on the mechanisms of resistance to second- (2G) and third-gen (3G) ALK TKIs received without 1L criz exposure. **Methods:** This retrospective study included pts with ALK+ mNSCLC who received 2G ALK TKIs (alectinib, brigatinib, ceritinib, ensartinib) or 3G TKI lorlatinib (lorl) and had post-progression tissue (TBx) or liquid bx (LBx) assessed by next-generation sequencing (NGS). Frequency (freq) of *ALK* mutations (mut) (on-target) or *MET* amplification (amp) and histologic transformation (off-target) was compared in pts who had vs had not received prior 1L criz. **Results:** We identified 270 pts (median age, 52; 61.1% women) who received 2G TKI (1L criz, n=116; no 1L criz, n=106) and/or 3G TKI (1L criz, n=69; no 1L criz, n=59) and underwent TKI-resistant bx (116 pts with ≥2 bx). In total, 436 post-next-gen TKI bx (280 post-2G TKI, 156 post-lorl) underwent NGS. Post-2G TKI bx detected lower freq of *ALK* mut in pts without vs with prior criz exposure (TBx: 36.8% vs 64.3%, p<0.001; LBx: 44.4% vs 71.7%, p=0.006). Of pts with post-lorl TBx, 43.8% had ≥1 *ALK* resistance mut detected, of which 23.6% had ≥2 co-occurring *ALK* mut. Post-lorl Tbx detected lower freq of *ALK* mut (29.7% vs 53.8%, p=0.024) and lower freq of ≥2 co-occurring *ALK* mut in pts without vs with prior criz (10.8% vs 32.7%, p=0.036), with consistent findings by LBx. In terms of off-target resistance. *MET* amp was detected by post-2G TKI TBx at higher freq in pts without vs with prior criz (17.2% vs 2.5%, p=0.002), but with no significant difference post-lorl without vs with prior criz (13.9% vs 5.8%, p=0.26). Of note, the two post-1L lorl TBx both had *MET* amp or polysomy, without *ALK* mut. Histologic transformation occurred at similar freq in pts without vs with 1L criz after 2G TKIs (4.3% vs 1.2%, p=0.33) and after lorl (2.7% vs 3.8%, p=0.99). Among pts with post-1L 2G TKI bx, on-target resistance (*ALK* mut) was more common with *EML4::ALK* variant 3a/b vs variant 1 (TBx: 56.3% vs 20.0%, p=0.038; LBx: 75.0% vs 13.3%, p=0.003). **Conclusions:** In this largest analysis of post-2G/3G ALK TKI TBx/LBx to date, on-target resistance was less freq after 2G/3G TKIs in pts treated with the current paradigm (upfront 2G/3G ALK TKIs) than the past approach (2G/3G TKI after 1L criz). These findings crystallize a shifting resistance landscape and indicate an increasing role for off-target resistance with upfront 2G/3G TKIs, highlighting a need to uncover and therapeutically address off-target resistance. Research Sponsor: None.

Real-world comparative outcomes of alectinib and brigatinib in ALK-positive non–small cell lung cancer: A retrospective cohort analysis using HIRA data.

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Background: Alectinib and brigatinib are both recommended as first-line treatments for patients with ALK-positive non–small cell lung cancer (NSCLC). However, direct real-world comparisons of these agents remain limited. **Methods:** We retrospectively reviewed patients diagnosed with ALK-positive NSCLC between 2007 and 2023 who did not undergo surgical resection. Among these, 1,009 patients received either alectinib (n=868) or brigatinib (n=141) as first-line therapy on HIRA data. Baseline characteristics, comorbidities (e.g., diabetes, hypertension), and outcomes—including overall survival (OS) and progression-free survival (PFS)—were collected. Cox proportional hazards models adjusted for age ≥70 years, sex, and comorbidities were used to estimate hazard ratios (HRs) for death and disease progression. **Results:** The mean age was 61.56 years (SD 13.72), and 49.45% of patients were male. Patients receiving alectinib were older on average ($p<0.001$), but no significant differences in major comorbidities were observed between the two groups. In unadjusted analyses, brigatinib was associated with a lower risk of death compared with alectinib (HR 0.60, 95% CI 0.40–0.90; p=0.013), but this association was not significant after multivariable adjustment (HR 0.69, 95% CI 0.46–1.03; p=0.07). Conversely, alectinib was associated with significantly longer first and second PFS compared with brigatinib (1st PFS HR 1.53, p=0.012; 2nd PFS HR 4.02, $p<0.001$). Both alectinib- and brigatinib-treated patients who transitioned to lorlatinib demonstrated notably prolonged survival. **Conclusions:** In this real-world study, both alectinib and brigatinib provided favorable survival outcomes in patients with ALK-positive NSCLC. While brigatinib showed a trend toward reduced mortality in univariable analysis, this was not maintained in adjusted models. Alectinib conferred a longer duration of disease control (PFS) in both first- and second-line settings. Further prospective studies are warranted to clarify the optimal sequencing of ALK inhibitors and to validate these findings. Research Sponsor: None.

8609 Poster Session

High-dose furmonertinib combined with bevacizumab and pemetrexed in non-small cell lung cancer patients with EGFR mutations and leptomeningeal metastasis: A prospective real-world study.

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Background: Leptomeningeal metastasis (LM) in lung cancer is always associated with poor prognosis. Our previous study has demonstrated that high-dose furmonertinib offers promising efficacy in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor(EGFR) mutations and LM. In this study, we aim to further evaluate the efficacy and safety of high-dose furmonertinib combined with bevacizumab and pemetrexed in NSCLC patients with EGFR mutations and LM in the real world. **Methods:** Eligible patients had histologically or cytologically confirmed NSCLC harboring an EGFR mutation. Patients were diagnosed as LM according to the EANO-ESMO criteria. They were treated with high-dose furmonertinib (240 mg, daily), bevacizumab (15 mg/kg, every 3 weeks), and pemetrexed (50 mg, intrathecal chemotherapy or 500 mg/m^2, intravenous chemotherapy, every 3 weeks). The primary endpoint was overall survival (OS). Secondary endpoints included time to treatment failure (TTF), ORR-LM (objective response rate in leptomeningeal metastasis) according to the RANO-LM radiologic criteria, clinical response rate (assessed with improvement of neurologic symptoms or signs and changes in the performance status), and adverse events (AEs) (graded according to CTCAE v5.0). **Results:** Between March 10, 2023 and December 31, 2024, 33 patients were enrolled at Henan Cancer Hospital. 10 patients (30.3%) had EGFR exon 19 deletions, 18 patients (54.5%)had exon 21 L858R mutations, and the other 5 patients (15.2%) had non-classical mutations. 20 (60.6%) had an ECOG score of 1-2, while 13 (39.4%) had an ECOG score of 3. Additionally, 22 patients (66.7%) had received at least two prior lines of treatment, and 23 patients(69.7%) had previously been treated with third-generation EGFR-TKIs. 6 patients (18.2%) received pemetrexed via intravenous administration, while 27 patients (81.8%) received intrathecal chemotherapy of pemetrexed. The clinical response rate was 72.7%, the ORR-LM and disease control rate (DCR) assessed by investigator according to RANO-LM radiologic criteria were 64.7% and 94.1%.At the data cut off point of December 31, 2024, 7 (21.2%) patients had died. The median follow-up was 7.8 months. The median OS was not reached. 25 (75.8%) patients experienced treatment-related adverse events (TRAEs) of any grade. Grade 3 adverse events included: diarrhea (6.1%), leukopenia/neutropenia (9.1%), anemia (6.1%), and thrombocytopenia (3%). One patient experienced grade 4 leukopenia and thrombocytopenia. The dose of furmonertinib was reduced to 160mg in 4 patients and intrathecal chemotherapy was discontinued in one patient. **Conclusions:** High-dose furmonertinib combined with bevacizumab and pemetrexed demonstrates remarkable clinical efficacy and tolerable safety in NSCLC patients with EGFR mutations and LM. Clinical trial information: NCT06643000. Research Sponsor: None.

8610 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. **Methods:** Patients with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02122913, NCT02576431) were included. Larotrectinib was administered at 100 mg twice daily. Responses were independent review committee-assessed per Response Evaluation Criteria in Solid Tumours version 1.1. The data cutoff was July 20, 2024. **Results:** At data cutoff, 32 patients were enrolled; 12 patients had known CNS metastases at baseline. The median age was 56 years (range 25–81). One patient (3%) was systemic treatment-naïve in the metastatic/unresectable setting, and 19 (59%) patients received 2 or more prior therapies. All *NTRK* gene fusions were identified by next-generation sequencing (NGS). The overall response rate 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. Median time to response was 1.8 months (range 1.5–7.3). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 34 months (95% CI 13–not estimable [NE]), 22 months (95% CI 10–39), and 41 months (95% CI 17–NE), respectively, at median follow-ups of 37, 38, and 46 months. The 4-year rates for DoR, PFS, and OS were 33% (95% CI 7–60), 26% (95% CI 6–45), and 48% (95% CI 29–68), respectively. The median duration of treatment was 20 months (range 2–75). At data cutoff, 8 (25%) patients remained on treatment: 7 had responded and 1 was not evaluable for response. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 10 (31%) patients. One (3%) patient discontinued treatment due to TRAEs (increased alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase). **Conclusions:** Larotrectinib demonstrates rapid and durable responses, extended survival, 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 targeted treatment. Clinical trial information: NCT02122913, NCT02576431. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

8611 Poster Session

Interim results of PDL1V (PF-08046054), a vedotin-based ADC targeting PD-L1, in patients with NSCLC in a phase 1 trial.

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Background: PDL1V is an investigational antibody-drug conjugate that delivers the cytotoxic agent monomethyl auristatin E to cells expressing programmed cell death ligand 1 (PD-L1). In addition to cytotoxicity, PDL1V elicits antitumor activity via the bystander effect and immunogenic cell death. Here we present the safety profile and preliminary efficacy in patients with metastatic, relapsed/refractory non-small cell lung cancer (NSCLC) enrolled in the phase 1 trial. **Methods:** C5851001 (NCT05208762) is a phase 1 study enrolling patients with relapsed or refractory solid tumors, including NSCLC, whose disease has progressed on standard-of-care therapies. Patients received the PDL1V recommended expansion dose of 1.5 mg/kg on days 1 and 8 of a 21-day cycle using adjusted ideal body weight, and were required to have measurable disease per RECIST v1.1 and ECOG PS ≤1. Patients with genomic alterations were not excluded. The primary objectives of this study are safety, tolerability, and pharmacokinetics, with antitumor activity as a secondary objective. **Results:** As of December 20, 2024, 30 patients with NSCLC have been treated at the recommended expansion dose. The median age was 60 years (range 44-73); 43.3% were male, 66.7% had ECOG PS 1, 23.3% had squamous histology, and 83.3% were PD-L1 positive. The median number of prior lines of therapy was 2.0 (1, 8); 96.7% and 66.7% of patients were previously exposed to anti-PD-1/PD-L1 antibodies and taxanes, respectively. There have been no dose-limiting toxicities at the recommended expansion dose. Peripheral sensory neuropathy (27.2%), nausea (25.0%), diarrhea (23.9%), and fatigue (21.7%) were the most common treatment-related adverse events (TRAEs) for all patients treated in the Phase 1 trial at the recommended expansion dose (N=92); the majority of TRAEs were grade 1-2 in severity, and 5.4% of patients discontinued therapy due to TRAEs. The most common grade ≥3 TRAE was anemia (5.4%). The incidence of treatment-related immune-mediated AEs by investigator assessment was 14.1%; 5.4% for grade 3, with no grades 4 or 5. The investigator-assessed confirmed objective response rate (cORR) for patients with NSCLC was 26.7%, while the cORR was 32.0% for those with PD-L1 expressing tumors. The median duration of confirmed response was 7.8 months (95% CI 4.8, –), and the median follow-up was 10.0 months (95% CI 4.9, 13.1). Objective responses were observed in patients with PD-L1 expressing squamous (n=6) and non-squamous (n=19) tumors (33.3% and 31.6% cORR, respectively). **Conclusions:** PDL1V monotherapy at the recommended expansion dose was generally well tolerated with a manageable safety profile. Encouraging preliminary efficacy in NSCLC was observed, independent of histology. Based on these results, further development of PDL1V in NSCLC is ongoing. Clinical trial information: NCT05208762. Research Sponsor: Pfizer Inc.

8612 Poster Session

Exploring decisional needs of patients considering first line treatment of advanced EGFR+ lung cancer: An interpretive descriptive study.

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Background: With expanding treatment options for EGFR+ metastatic non-small cell lung cancer (mNSCLC), shared decision-making is important in aligning treatment plans with patient values. Targeted therapies like osimertinib offer convenience and independence. New studies like FLAURA2 and MARIPOSA explore therapeutic combinations with intravenous drugs, demonstrating potentially superior efficacy but more side effects, highlighting the need for unbiased and patient-centered approaches. This study explores the decisional needs of patients considering first-line treatments. **Methods:** We conducted an interpretive descriptive qualitative study guided by the Ottawa Decision Support Framework to explore the experiences and perspectives of EGFR+ mNSCLC patients. Interviews were conducted via Microsoft Teams. Inclusion criteria: 18+ years; mEGFR+ NSCLC; current/prior osimertinib therapy; proficient in English. Interviews were conducted using a standardized interview guide with inductive thematic analysis. A sample size of 10-12 was considered sufficient to saturate ideas from participant responses, with additional 3 recruited to ensure saturation. Themes were mapped onto the Ottawa Decision Support Framework. **Results:** Sixteen participants were interviewed from Sep-Nov 2024: age 48-83 (median 62 years); 11 female; 13 currently taking osimertinib; 10 diagnosed >1 year. Many patients reported relying on oncologist recommendation without participation in decision making. Patients with young children had an increased desire to be actively involved in treatment decisions. Key themes from preliminary analysis identified: patients overwhelmingly *trusted their oncologist*, felt *pressure to start treatment quickly*, were *overwhelmed with the diagnosis*, had *inadequate knowledge of the treatment* and potential side effects, and felt *highly responsible to ensure proper drug administration*. Patients valued e*ase and convenience of* [osimertinib] *treatment, few severe side effects, being alive, continuing day to day living*, and *remaining independent for family and travel.* When asked about combination therapy, patients valued *quality of life*, *avoiding increased hospital trips and side effects*, but indicated a *willingness to try.* **Conclusions:** Key themes from preliminary analysis identify crucial components at initial diagnosis, with patients feeling overwhelmed and having inadequate knowledge, thus relying on their trusted oncologists' recommendation. While patients highly valued independence, fewer visits and quality of life, they were willing to try combination therapy, highlighting the importance of oncologists understanding their patient's individual needs and goals of treatment. Treatment choices should reflect the patient's values. These results will be used to create a decision aid that we can pilot in our oncology clinics. Research Sponsor: None.

8613 Poster Session

MYTX-011, a cMET-targeting antibody-drug conjugate (ADC), in patients with previously treated, advanced NSCLC: Updated dose escalation results in the phase 1 KisMET-01 study.

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Background: MYTX-011 is a novel cMET-targeting vcMMAE ADC engineered for pH-dependent binding. This results in more efficient payload delivery, which drives efficacy in tumors over a wide range of cMET expression, including potentially >50% of NSCLC patients (pts). Here we report safety and preliminary efficacy from dose escalation pts who received ≥4.0 mg/kg (mpk), the clinically active dose range, in the Phase 1 KisMET-01 study. **Methods:** KisMET-01 (NCT05652868) is a multicenter, first-in-human study of MYTX-011 in pts with previously treated, locally advanced or metastatic NSCLC. The study comprises dose escalation in pts with NSCLC of any histology or cMET expression, followed by dose expansion in cMET-positive (cMET+) pts selected by immunohistochemistry (Ventana SP44). In dose escalation, cMET expression is analyzed whenever tumor tissue is available. **Results:** As of 7 Jan 2025, 85 pts received ≥1 dose of MYTX-011 (1.0–8.3 mpk Q3W), and 59 pts received doses ≥4.0 mpk. PK showed near dose proportional exposure and low unconjugated MMAE across dose levels. In pts who received ≥4.0 mpk, median age was 67 yr (43–83) and median prior lines of therapy was 3 (1–10); median follow-up was 4.2 mo (0.1–10.4). TRAEs of any grade (Gr)/Gr ≥3 occurred in 90%/48% of pts; the most common (any Gr TRAE ≥20% of pts) were blurred vision (49%), keratopathy (44%), nausea (29%), fatigue (20%), AST increased (20%), and keratitis (20%). Gr 3 or higher TRAEs that occurred in ≥5% of pts were keratopathy (15%), blurred vision (12%), and neutropenia (10%). Ocular events led to treatment discontinuation in 5 (8%) pts, with 3 of 5 treated at doses higher than 5.0 mpk. Unadjudicated pneumonitis/ILD was reported in 2 (3%) pts, both Gr 1 or 2 with 1 leading to treatment discontinuation. Peripheral neuropathy was reported in 15%; all were Gr 1 or 2 and did not lead to dose reduction or discontinuation. No treatment-related death was reported. 35 of 59 pts who received ≥4.0 mpk were cMET+ (2+ at ≥25% tumor cells) with a median follow-up of 3.7 mo (0.7–10.3). ORR was 38% in cMET+ pts with ≥1 post-baseline disease assessment (n=29). DCR at 6 wk/12 wk/24 wk was 97%/83%/53%. ORR was 44% in cMET+ Non-squamous (NSQ) EGFR wild-type (n=16), 38% in NSQ EGFR-mutant (n=8), and 25% in squamous cell carcinoma (n=4). Antitumor activity was similar in cMET+ pts across expression levels and known cutoffs, and no clear dose-response relationship was observed in doses ≥4.0mpk. Doses of 5.0 mpk Q3W with dose-break (2-on 1-off) and 4.0 mpk Q3W were selected for further evaluation in dose expansion. **Conclusions:** MYTX-011 is well tolerated with low rates and severity of AEs commonly associated with cytotoxic and cMET-targeting agents. Preliminary anti-tumor activity suggests MYTX-011 can potentially benefit a wide range of cMET-expressing NSCLC pts. Dose expansion is currently ongoing as of January 2025. Clinical trial information: NCT05652868. Research Sponsor: Mythic Therapeutics.

8614 Poster Session

GBC-11004: An AI-driven novel kinase target with potential to overcome osimertinib resistance in NSCLC.

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Background: Osimertinib resistance poses a significant clinical challenge in the treatment of non-small cell lung cancer (NSCLC), with diverse mechanisms complicating patient outcomes. Conventional next-generation sequencing (NGS) analysis methods often fall short in identifying effective therapeutic targets due to the complexity and heterogeneity of resistance mechanisms. **Methods:** To address this issue, we have developed an artificial intelligence (AI)-driven target discovery platform designed to identify novel and effective drug target genes capable of overcoming Osimertinib resistance in NSCLC, thereby surpassing the capabilities of traditional NGS analysis. Our platform integrates three key components: deep learning (G-TAC), statistical significance testing (G-SET), and a large language model (G-LAT). G-TAC and G-SET evaluate and rank genes according to their responsiveness to Osimertinib and tumor-specific expression. G-LAT assesses these genes based on publications and clinical trials to ensure novelty and efficacy of the identified targets. **Results:** We identified a novel kinase target named GBC-11004, as one of the top-ranked target genes that were found to be overexpressed in patient-derived organoids (PDOs) resistant to Osimertinib. To ascertain the functional impact of GBC-11004, target validation was conducted using PDOs and CRISPR/Cas9-based gene editing. Gene editing in Osimertinib resistant PDOs resulted in a significant decrease in cell viability corresponding to increased indel frequency. Furthermore, we have initiated lead compound optimization by preliminary IC50 analyses using compounds targeting GBC-11004 and observed significantly enhanced sensitivity in the combination therapy group (Osimertinib + GBC-11004 inhibitor) compared to the Osimertinib monotherapy group in resistant PDO models. **Conclusions:** Our results demonstrate the potential of GBC-11004 as a novel therapeutic target for overcoming Osimertinib resistance in NSCLC treatment and emphasize the capability of our PDO-based AI-driven target discovery platform in identifying high-priority novel targets. Research Sponsor: None.

8615 Poster Session

Sacituzumab tirumotecan (sac-TMT) in patients (pts) with previously treated locally advanced or metastatic (LA/M) non-small cell lung cancer (NSCLC) harboring uncommon EGFR mutations: Preliminary results from a phase 2 study.

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Background: Pts with NSCLC harboring uncommon *EGFR* mutations generally have limited treatment options compared to those with the more common *EGFR* mutations. Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a hydrolytically cleavable linker to conjugate a belotecan-derivative topoisomerase I inhibitor. Sac-TMT has shown encouraging antitumor activity in NSCLC pts with the more common *EGFR* mutations (Fang *et al*. AACR 2024). Here we present the preliminary efficacy and safety of sac-TMT in treating uncommon *EGFR*-mutated advanced NSCLC from the Phase 2, open-label, multiple-cohort study (NCT05631262). **Methods:** Advanced NSCLC pts harboring uncommon *EGFR* mutations, including G719X in exon 18, S768I in exon 20, L861Q in exon 21 and exon 20 insertions (ex20ins), who had progressed on or after standard systemic therapy were enrolled. Pts received sac-TMT 5 mg/kg Q2W until disease progression or unacceptable toxicity. Tumor response was assessed per RECIST v1.1 by investigator. **Results:** As of 01 Dec 2024, 42 pts (median age 61 years; 33.3% male; 85.7% ECOG PS 1) were enrolled, including 23 pts with *EGFR* G719X in exon 18, S768I in exon 20, or L861Q in exon 21 and 19 pts with *EGFR* ex20ins. Median number of prior treatment regimens for advanced disease was 2 with 35.7% of pts having ≥3. After a median follow-up of 9.2 months, the objective response rate (ORR) was 35.7% (15/42, 3 pending confirmation). The disease control rate (DCR) was 85.7%. Responses were durable with the median duration of response (mDoR) not yet reached, and the 6-month DoR rate was 90.9%. The median progression-free survival (mPFS) was 9.5 months (95% CI: 5.6, 10.9). In the subset of pts with uncommon non-ex20ins, the ORR was 34.8% (8/23, 1 pending confirmation); the mPFS was 10.9 months (95% CI: 5.6, NE). In the subset of pts with ex20ins, the ORR was 36.8% (7/19, 2 pending confirmation); the mPFS was 9.0 months (95% CI: 2.4, NE). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 52.4% of pts. The most frequent grade ≥3 TRAEs (≥5%) were neutrophil count decreased (45.2%), WBC count decreased (21.4%), anemia (14.3%), and stomatitis (9.5%). No TRAE led to treatment discontinuation or death. No cases of interstitial lung disease/pneumonitis were reported. **Conclusions:** Sac-TMT monotherapy demonstrated promising clinical activity with a manageable safety profile in previously treated advanced NSCLC pts with uncommon *EGFR* mutations. These findings warrant further investigation of sac-TMT as a potential therapy for this population. Clinical trial information: NCT05631262. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Phase I/II study of DZD6008, a 4th-generation EGFR TKI with full BBB penetration, in EGFR-mutant NSCLC.

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Background: NSCLC patients whose disease progressed after 3rd generation EGFR TKI treatment often have CNS metastasis and acquired EGFR resistance mutations, such as C797S mutation. DZD6008 is a 4th generation EGFR TKI, designed to target EGFR sensitizing mutations (L858R/del19), resistant double (T790M and L858R/del19) and triple mutations (C797X, T790M and L858R/del19). Preclinical data shows that DZD6008 has high selectivity against wildtype EGFR and other kinases and is fully blood-brain-barrier (BBB) penetrant. Here we report results from the ongoing phase 1/2 studies in advanced EGFR mutation positive (EGFRm) NSCLC. **Methods:** TIAN-SHAN2 (CTR20241790) is a multi-center, first-in-human phase 1/2 study with expansion designed to evaluate the safety, tolerability, and anti-tumor activity of DZD6008 in EGFRm NSCLC patients who failed prior EGFR TKI treatment. DZD6008's BBB penetration capability was evaluated by measuring the ratio of free drug concentrations in CSF and blood, as well as tumor response of brain lesions. **Results:** Preclinically, DZD6008 showed equal potencies against multiple variants of single, double or triple EGFR mutations, with >50-fold selectivity over wild-type EGFR. In osimertinib-resistant CDX and PDX models carrying EGFR triple mutations, DZD6008 induced profound tumor shrinkage in a dose-dependent manner. As of December 24, 2024, 12 patients with EGFRm NSCLC had been enrolled into dose escalation cohorts of TIAN-SHAN2 study, and treated with DZD6008 at 20 mg to 90 mg once daily (QD). The median age was 61 years, 67% were female, and 50% had an ECOG PS of 1. All patients had adenocarcinoma and carried various types of single, double or triple EGFR mutations. The median lines of prior therapies was 5 (range 2 - 8). All patients had been treated with EGFR TKIs and chemotherapy, and 11 had received prior third-generation EGFR TKI treatment. DZD6008 was well tolerated across the doses investigated, and no dose limiting toxicities were reported. The maximum tolerated dose was not reached. DZD6008 exhibited dose-proportional and linear pharmacokinetic characteristics, with excellent blood-brain-barrier penetration (CSF to free plasma ratio >1) in patients with baseline brain metastasis. Ten out of 12 patients (83.3%) showed target lesion tumor shrinkage following DZD6008 treatment. Partial response was observed at ≥ 20 mg in patients with various EGFR mutations. Anti-tumor activity was observed in patients with brain metastasis. The longest duration on treatment was >6 months (treatment ongoing). **Conclusions:** DZD6008 is a novel, highly selective, full-BBB penetrant EGFR TKI with broad-spectrum of activity against different EGFR mutations. In heavily pre-treated EGFRm NSCLC patients, DZD6008 monotherapy was well-tolerated and showed encouraging anti-tumor activity. TIAN-SHAN2 study is ongoing and updated data will be presented at the meeting. Clinical trial information: CTR20241790. Research Sponsor: None.

Patient and caregiver treatment preferences for ALK+ non-small cell lung cancer in the United States.

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Background: Treatment options for non-small cell lung cancer (NSCLC) with ALK rearrangement (ALK+) have distinct benefits and risks. As patients often use ALK inhibitors for years, balancing these considerations is crucial. This study quantified how benefits and risks drive treatment preference and trade-offs between them from patients' and caregivers' perspectives. **Methods:** A discrete choice experiment (DCE) was completed online by Stage 4 ALK+ NSCLC patients and caregivers, recruited via physicians and the ALK Positive advocacy group. The DCE (developed based on literature review, phase 3 trial data and qualitative interviews) repeatedly asked participants to choose between 2 hypothetical treatments described by 7 benefit/risk attributes, each with a plausible clinical level. A mixed logit model estimated the relative impact of each attribute on preferences as relative attribute importance (RAI) and maximum acceptable loss (MAL) of 3-year progression-free survival (PFS) for reduced treatment risks. **Results:** 205 patients (mean age 61.9 years old; mean time since diagnosis: 2.7 years; 34.1% with brain metastasis) and 125 caregivers participated. 29.8% patients and 33.6% caregivers chose treatments based solely on PFS. Treatment preferences were mainly driven by 3-year PFS with less importance placed on adverse events (RAI: patients 4.0-11.0%; caregivers 3.7-13.3%) (Table). Patients were willing to forgo 3.9-8.7% of 3-year PFS to reduce risks of any grade cognitive/mood effects, grade ≥3 abnormal lab results, grade ≥3 lung complications, grade ≥3 weight gain, and any grade myalgia; caregivers were willing to trade 3.7-7.2% of 3-year PFS to reduce any grade cognitive/mood effects, grade ≥3 abnormal lab results, and grade ≥3 lung complications, but not any grade myalgia or grade ≥3 weight gain. **Conclusions:** Patients and caregivers highly prioritized achieving a higher chance of 3-year PFS when choosing treatments. Most were willing to trade PFS benefit for reduced risks, although there was a subset of caregivers who were unwilling to trade any benefit for reduced risks. The extent varied between patients and caregivers. Shared treatment decision making between physicians and patients/caregivers should consider the balance between benefits and risks. Research Sponsor: Takeda Development Center Americas, Inc.

RAI and MAL.

	RAI		MAL of 3-year PFS	
Attributes (Levels)	**Patients (n=205)**	**Caregivers (n=125)**	**Patients (n=205)**	**Caregivers (n=125)**
3-year PFS (30-65%)	50.8%	51.6%	NA	NA
Any grade cognitive/mood effects (0-25%)	11.0%	13.2%	8.7%	7.2%
Grade ≥3 lung complications (0-6%)	9.3%	6.7%	5.4%	3.7%
Grade ≥3 abnormal lab results (0-30%)	8.7%	13.3%	6.8%	5.5%
Grade ≥3 weight gain (0-20%)	8.5%	4.5%	4.7%	NS
Any grade myalgia (0-20%)	7.6%	7.2%	3.9%	NS
Tumor progression in the brain within 3 years (10-55%)	4.0%	3.7%	6.1%	NS

NS: not statistically different to zero (p≥0.05), indicating unwillingness to forgo 3-year PFS to reduce these risks.

LUMINOSITY, a phase 2 study of telisotuzumab vedotin in patients with c-Met protein–overexpressing non-squamous *EGFR*-wildtype advanced NSCLC: Efficacy outcomes by prior therapy.

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Background: Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate comprising the mAb telisotuzumab and the microtubule polymerization inhibitor monomethyl auristatin E. In the phase 2 LUMINOSITY trial (NCT03539536), Teliso-V monotherapy 1.9 mg/kg showed durable responses and a generally manageable safety profile in patients (pts) with c-Met protein–overexpressing (OE) non-squamous (NSQ) *EGFR*-wildtype (WT) non-small cell lung cancer (NSCLC). Herein we present an analysis of efficacy outcomes according to prior platinum or prior platinum and immune checkpoint inhibitor (ICI)-based therapies. **Methods:** Pts (≥18 years) with locally advanced/metastatic c-Met protein–OE NSQ *EGFR*-WT NSCLC who had ≤2 prior lines of therapy, including ≤1 line of chemotherapy, were treated with 1.9 mg/kg Teliso-V Q2W. c-Met protein overexpression (by immunohistochemistry clinical trial assay for MET [SP44] [Roche]) was defined as ≥25% tumor cells with 3+ staining intensity (high: ≥50% 3+; intermediate [int]: 25 to <50% 3+). The primary endpoint was overall response rate (ORR) by independent central review per RECIST v1.1. **Results:** As of 21 Feb 2024, 172 pts received ≥1 dose of Teliso-V and 168 pts were included in efficacy analyses (c-Met high, n=84; c-Met int, n=84). In the c-Met OE total population, 97.6% of pts received prior platinum and 78.6% received prior platinum + ICI. Efficacy data for pts with prior platinum and platinum + ICI therapies are shown in the Table. Among the 172 dosed pts, the most common any-grade treatment-related adverse events (TRAEs) were peripheral sensory neuropathy (31%), peripheral edema (16%), and fatigue (14%). The most common grade ≥3 TRAE was peripheral sensory neuropathy (7%). **Conclusions:** This analysis demonstrated that Teliso-V elicited durable responses in pts with c-Met protein–OE NSQ *EGFR*-WT NSCLC regardless of whether they had received prior platinum or platinum + ICI therapies; the efficacy outcomes in these subgroups were consistent with those in the overall pt population. Clinical trial information: NCT03539536. Research Sponsor: AbbVie, Inc.; n/a

	Platinum	Platinum + ICI	Overall
ORR,[a] n/N (%) [95% CI]			
c-Met OE total	48/164 (29.3) [22.4, 36.9]	38/132 (28.8) [21.2, 37.3]	49/168 (29.2) [22.4, 36.7]
c-Met high	28/81 (34.6) [24.3, 46.0]	22/67 (32.8) [21.8, 45.4]	29/84 (34.5) [24.5, 45.7]
c-Met int	20/83 (24.1) [15.4, 34.7]	16/65 (24.6) [14.8, 36.9]	20/84 (23.8) [15.2, 34.3]
Median DOR,[a] mo [95% CI]			
c-Met OE total	7.2 [5.5, 11.3]	7.2 [5.5, 11.0]	7.2 [5.5, 11.0]
c-Met high	9.0 [3.8, 12.0]	9.0 [3.8, 11.3]	7.2 [4.2, 12.0]
c-Met int	7.2 [4.7, 11.5]	7.2 [5.3, 11.5]	7.2 [4.7, 11.5]

[a]Per independent central review. DOR, duration of response.

EATON: A phase I trial of nazartinib (EGF816) and trametinib in EGFR-mutant (EGFRmut) non-small cell lung cancer (NSCLC).

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Background: EGFR inhibitors (EGFRi) are highly effective in EGFRmut NSCLC, but resistance inevitably emerges. Among the mechanisms of acquired resistance, RAS/MEK pathway activation has been identified in both cell models and patients. Preclinical and clinical data support efficacy of dual MEK and EGFR inhibition in this setting. In the EATON trial we investigated the combination of the MEK inhibitor (MEKi) trametinib (TMT) and the third-generation (3gen) EGFRi nazartinib (NAZ) in patients with EGFRmut NSCLC. **Methods:** EATON (NCT03516214, AIO-TRK-0216) is an academic multicenter, phase I, dose-escalation trial conducted in Spain and Germany. Primary endpoint: maximal tolerated dose (MTD)/recommended phase 2 dose (RP2D); secondary endpoints: pharmacokinetics (PK), safety, preliminary efficacy. Key eligibility criteria: Advanced/metastatic EGFRmut NSCLC, EGFR p.T790M-positive/-negative, no MET amplification, any treatment line. Dose escalation was based on a modified 3+3 up-and-down design in up to 18 patients [Storer, 1989]. TMT and NAZ were dosed once daily (qd) at predefined dose levels (DL) of 0.5 mg/100 mg (DL -1), 1.0 mg/100 mg (DL 1), 1.5 mg/100 mg (DL 2), 1.5 mg/150 mg (DL 3), 2 mg/150 mg (DL 4). The dose-limiting toxicities (DLT) period comprised the first 28 treatment days. **Results:** In total, 19 patients were dosed (mean age, 62 years (range, 44-81); 14 female (73.7%)). Prior EGFRi and 3gen EGFRi use were noted in 17 (89.5%) and 14 (73.7%), respectively. Patients were treated at DL -1 (N=4), DL 1 (N=13), and DL 2 (N=3), with 18 (94.7%) eligible for dose-escalation decisions. DLTs were observed in 4 (22.2%) patients (Grade 3 creatinine phosphokinase elevation, N=3; Grade 3 hypertension, N=1). The MTD was determined to be TMT 1.0 mg qd and NAZ 100 mg qd. After repeated dosing (C1D15) at the MTD, geo-mean C_{max} of NAZ was 336 ng/ml (N=14, CV% 44.8) and of TMT 19.5 ng/ml (N=7, CV% 22.6). Geo-mean AUC_{tau} of NAZ was 3950 ng/ml*h (N=14, CV% 48.7) and of TMT 301 ng/ml*h (N=7, CV% 27.3). Treatment-related adverse events (TRAEs) of any grade were observed in all patients (N=19; 100%) and of Grade ≥3 in nine (47.4%). Discontinuation rates were 26.3% (N=5) and 21.1% (N=4), for TMT and NAZ. Sixteen (84.2%) patients were evaluable for RECIST 1.1 response assessment and 19 (100%) for time-to-event outcomes. One patient had a partial response (ORR, 6.3%; 95% CI, 1.6-30.2) and six had stable disease (37.5%). Median progression-free survival was 2 months (95% CI, 1.7-2.2). Molecular determinants of response and resistance were investigated by 3' RNA and DNA sequencing. **Conclusions:** At the MTD, treatment was safe and moderately tolerable. Preliminary efficacy in this unselected and heavily pre-treated population was limited. A comprehensive biomarker-driven approach may help identify patients more likely to derive clinical benefit. Clinical trial information: NCT03516214.
Research Sponsor: German Federal Ministry of Education and Research (BMBF); Novartis.

8620 Poster Session

Patient-reported outcomes (PRO) evaluating physical functioning and symptoms in patients with pretreated HER2-mutant advanced non-small cell lung cancer (NSCLC): Results from the Beamion LUNG-1 trial.

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Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. Beamion LUNG-1 (NCT04886804) is a Phase Ia/Ib first-in-human study evaluating safety and efficacy of zongertinib in patients with HER2-mutant advanced NSCLC (Phase Ib). Here, we report PRO data on NSCLC-related symptoms, physical functioning, symptomatic adverse events (AEs) and their burden from Phase Ib Cohort 1. The PRO analysis included patients with previously treated HER2-mutant NSCLC who received 120mg QD zongertinib. **Methods:** EORTC QLQ-C30 physical functioning scale, NSCLC-SAQ (cough, dyspnea, pain, fatigue and poor appetite), EORTC IL46/Q168 (side effect burden) and nine PRO-CTCAE items (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. Change from baseline (CFB) to cycle 5 in EORTC QLQ-C30 physical functioning (0-100, higher=better) and NSCLC-SAQ total score (0-20, lower=fewer symptoms) were analyzed using mixed model repeated measures. EORTC IL46 (1 = 'Not at all', 4 = 'Very much') and PRO-CTCAE (0 Never/None to 4 Almost Constant/Very Severe) were analyzed descriptively; maximum baseline-adjusted proportions of patients were calculated. Post-hoc analysis includes contextualizing results based on clinically meaningful thresholds and exploring associations between PRO and clinical endpoints such as objective response. **Results:** The PRO analysis set comprised of 30 patients. High completion rates were observed, over 86%, across PROs and visits. Longitudinal MMRM analysis showed improvements for EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score, with rapid improvement which was maintained to cycle 9; CFB to cycle 5: LS means 9.6 (95% CI: 6.3, 12.9), and -3.9 (95% CI: -4.8, -2.9) respectively. Patients reported low overall side effect burden (EORTC IL46); patients reporting side effect burden on treatment as 'Quite a bit'/'Very much' was equal to baseline reporting (6.7%), with the exception only at cycle 1 day 15 (10%). Patient reported adverse event frequency/severity (PRO-CTCAE items) reflected expected toxicity profiles; diarrhea was reported at the highest frequency (maximum baseline adjusted: 'Frequent'/'Almost constant'=30%), low percentages of patients reported high levels of severity or interference for any adverse event. **Conclusions:** Zongertinib-treated patients reported a rapid improvement followed by stability in physical functioning and NSCLC-SAQ total score. The frequency and severity of patient-reported symptomatic AEs and the overall side effect burden demonstrated favorable tolerability of zongertinib. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

8621 Poster Session

Advancing evidence-based NSCLC testing and treatment across academic and community-based settings.

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Background: Comprehensive testing for guideline-recommended driver mutations in advanced non-small cell lung cancer (aNSCLC) remains underutilized. **Methods:** From Feb to Mar 2024, 20 healthcare professionals (HCPs) were surveyed from one academic and one community-based oncology system in the same region and retrospective chart audits (N=100) were performed to assess current practices, challenges/barriers, and areas for improvement in biomarker testing and use of targeted therapies in aNSCLC. Based on these baseline findings, an expert steering committee, including an oncologist, pathologist, surgeon, and site representatives, developed a NSCLC biomarker toolkit to support evidence-based testing. Clinical teams reviewed the data in audit feedback sessions and developed and implemented action plans to address identified gaps. **Results:** Both academic and community HCPs (aHCPs, cHCPs; 60%) cited *determining the appropriate molecular tests to order for treatment decisions* as their top challenge in integrating targeted therapies into practice. Significant variation was reported in which team member checks insurance authorization for molecular testing and submits the order, and how the medical oncologist is notified when test results are available. Most HCPs (93%) said molecular test results are not consistently scanned into the same chart locations. Compared to aHCPs, cHCPs were more likely to start NSCLC treatment before receiving molecular test results and reported significantly lower confidence in shared decision-making with pts. Top challenges in adverse event (AE) management were *patient communication about recognizing AEs* for aHCPS (80%), and *staying updated on AEs from targeted therapies* (50%) for cHCPs. Chart audits revealed greater variability in frontline therapies prescribed to pts treated in a community setting. Molecular testing was ordered for 86% of pts overall, including 100% in academic settings and 72% in community settings; 81% of pts had a documented mutation. As a result of this initiative, systems developed action plans to integrate the biomarker testing tool into practice, improve workflows for reflex testing, standardize molecular test documentation in EMRs, and utilize AI dashboards and dedicated phone lines to streamline communication with NSCLC patients about treatments and side effects. Additional follow-up data will be presented. **Conclusions:** This project uncovered real-world gaps in biomarker testing and evidence-based integration of targeted therapy for aNSCLC and revealed unique differences between academic and community settings, driving action plans to improve clinical workflows and communication. The biomarker testing toolkit and sustainable process changes implemented in this QI initiative represent key opportunities for improvement that can be implemented in clinics across the country to improve NSCLC care. Research Sponsor: Janssen Biotech, Inc.

Novel potent and selective fourth-generation inhibitors targeting EGFR for NSCLC therapy.

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Background: Epidermal growth factor receptor (EGFR)-activating mutations (Del19 or L858R) are oncogenic drivers of non-small cell lung cancer (NSCLC). Most patients treated with tyrosine kinase inhibitors (TKIs) will eventually develop resistance mutations including the T790M gatekeeper mutation. Osimertinib, a third-generation covalent TKI, is efficacious against the T790M resistance mutation and prevents its onset. However, treatment with Osimertinib inevitably induces additional mutations, especially the C797S mutation, as well as various off-target resistance mechanisms. To date, there are no approved therapies capable of overcoming mutational or non-mutational resistance to third-generation EGFR TKIs. **Methods:** We have characterized the efficacy of two novel fourth-generation EGFR inhibitors, CCM-205 and CCM-308, which are potent against both mutational and non-mutational tumor resistance to Osimertinib. Enzymatic binding affinities were determined by KdELECT assay. Cell-Titer-Glo (CTG) assay was used to assess cytotoxicity (cellular IC_{50}) of CCM-205 and CCM-308 *in vitro* on EGFR triple mutant and other Osimertinib-resistant cell lines, with comparison to both Osimertinib and fourth-generation EGFR inhibitor BLU-945. *In vivo* tumor growth inhibition (TGI) was determined in Osimertinib-resistant xenografts including the triple mutant PC9-DTC (Del19/T790M/C797S) model. **Results:** In Ba/F3 EGFR DTC and LTC cells, CCM-205 / CCM-308 inhibit proliferation with IC_{50}s of 137 nM / 40 nM and 198 nM / 61 nM respectively, while Osimertinib antiproliferation is limited to 1.225 μM and 1.562 μM respectively. Moreover, CCM-205 / CCM-308 spare Ba/F3 EGFR WT better than Osimertinib with IC_{50}s of 577 nM / 294 nM (182 nM for Osimertinib). CCM-205 / CCM-308 also bind tightly to double mutants targeted by Osimertinib with K_ds for EGFR LT (L858R/T790M) of 4.9 nM / 1.2 nM. CCM-205 and CCM-308 are more potent against PC9 DTC cells (IC_{50}s: 1.02 μM and 220 nM, respectively) than Osimertinib (4.10 μM) and are comparable to BLU-945 (559 nM). In addition, CCM-205 / CCM-308 are highly potent against Osimertinib-resistant PC9 (IC_{50}s: 728 nM / 321 nM) and H1975 (IC_{50}s: 1.716 μM / 684 nM) cell lines generated through 8-week treatment with 1 μM Osimertinib (Osimertinib IC_{50} = 3.81 μM and 4.70 μM, respectively), while EGFR-specific fourth-generation inhibitors targeting C797S such as BLU-945 lose potency (IC_{50}s: 7.96 μM and $>$ 10 μM, respectively). In the PC9-DTC xenograft, CCM-205 completely inhibited tumor growth and induced tumor regression ($>$ 100% TGI) exceeding that of BLU-945, while the tumor was resistant to Osimertinib ($<$ 20% TGI), when agents were delivered orally at similar fractions of their maximum tolerated doses (MTDs). **Conclusions:** Novel fourth-generation EGFR inhibitors have been developed that can potentially overcome both on-target and off-target resistance in NSCLC and have potential clinical applications. Research Sponsor: CCM Biosciences.

Final overall survival analysis for a phase 3 randomized trial comparing afatinib to chemotherapy in treatment-naïve non-small cell lung cancer with a sensitizing uncommon epidermal growth factor receptor mutation (ACHILLES/TORG1834).

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Background: The phase 3 randomized trial comparing afatinib to chemotherapy in treatment-naïve non-small cell lung cancer (NSCLC) with a sensitizing uncommon epidermal growth factor receptor mutation (*EGFR*) (ACHILLES) met its primary endpoint at the interim analysis. This trial demonstrated statistically significant improvement in progression-free survival (PFS)with hazard ratio 0.421; 95% confidence interval (CI), 0.251–0.706; p = 0.0010). Here, we report the final updated survival data. **Methods:** In this open-label phase 3 study, treatment-naïve patients (n=109) with sensitizing uncommon *EGFR* mutant NSCLC were randomized 2:1 to receive oral afatinib (30 mg or 40 mg daily) or a combination of platinum (cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6) and pemetrexed (500 mg/m^2), followed by pemetrexed maintenance therapy every 3 weeks. The primary endpoint was PFS according to RECIST 1.1 criteria. Overall survival (OS) was a secondary endpoint. Post-protocol treatment was administered at the physician's discretion. **Results:** As of the 2 December 2024 database lock, the median follow-up time was 33.6 months. Afatinib continued to improve PFS compared with chemotherapy (median, 10.8 months vs 7.0 months; HR [95% CI], 0.528 [0.338–0.827], p = 0.0052). The updated OS HR for afatinib compared to chemotherapy was 0.645 (95% CI, 0.359–1.160; p = 0.1433; 49/109 events, 44.9% maturity). The median OS was 45.0 months (range, 27.0–not estimated) in the afatinib group and 27.0 months (range, 15.9–50.4) in the chemotherapy group. The crossover rate to EGFR-TKI was 90.6% in the chemotherapy arm. Notably, the subgroup receiving a starting dose of 40mg afatinib and the subgroup of younger patients (< 75 years) showed a favorable OS HR (HR 0.371, 95%CI, 0.140–0.986; HR 0.422, 95% CI, 0.201–0.886). No new safety signals were observed in this update analysis. **Conclusions:** This final survival analysis confirmed the superiority of afatinib compared to chemotherapy for uncommon or compound *EGFR* mutation-positive advanced NSCLC. Clinical trial information: jRCTs 031180175. Research Sponsor: None.

Treatment arm	n	Median PFS, mo [95%CI]	PFS HR [95%CI]	Median OS, mo [95%CI]	OS HR [95%CI]
Afatinib					
All	73	10.8 [8.6–13.2]	0.528 [0.338–0.827]	45.0 [27.0–NE]	0.645 [0.359–1.160]
Major uncommon (G719X, L861X, S768I/V)	44	10.0 [7.2–11.4]	0.630 [0.385–1.030]	42.0 [17.8–NE]	0.878 [0.470–1.639]
Other uncommon	5	8.6 [6.1–NR]	1.006 [0.384–2.635]	37.8 [27.0–NE]	0.814 [0.237–2.794]
Compound	24	15.5 [9.1–21.0]	0.414 [0.230–0.748]	NR [30.2–NE]	0.358 [0.132–0.972]
Chemotherapy					
Platinum+Pemetrexed	36	7.0 [4.7–8.3]	-	27.0 [15.9–50.4]	-

8624 Poster Session

Epigenetic and transcriptional consequences of MTAP-loss in lung adenocarcinoma.

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Background: Lung adenocarcinoma (LUAD), the most common lung cancer subtype, has poor survival rates and limited treatment options. Among its molecular drivers, loss of methylthioadenosine phosphorylase (MTAP) is linked to aggressive development and poor outcomes, yet its downstream effects remain unclear. MTAP is essential for purine biosynthesis and S-adenosyl methionine (SAM) production, a key methyl donor for epigenetic regulation. MTAP-loss leads to methylthioadenosine (MTA) accumulation, which inhibits methyltransferase activity and disrupts epigenetic control. However, the impact of MTAP deficiency on transcriptional and metabolic programming in LUAD is still largely unknown, highlighting a critical gap for targeted therapy. This study examines these molecular consequences to identify potential therapeutic vulnerabilities in MTAP-deficient LUAD. **Methods:** RNA-sequencing data for 510 LUAD samples were obtained from The Cancer Genome Atlas (TCGA) via cBioPortal. Samples were classified as MTAP-loss (n=64) or MTAP-normal (n=446) based on mutational data. Differential gene expression was performed using the DESeq2 package for R and the Benjamini-Hochberg procedure was used to control for false discovery rate. DNA methylation (Illumina Human Methylation 450k) was compared between MTAP-loss (n=46) and MTAP-normal (n=404) cohorts. Significantly altered probes were mapped to differentially expressed genes (DEGs). Pathway and gene ontology (GO) analyses were conducted using KEGG, GO, and EnrichR to identify dysregulated pathways. **Results:** DNA methylation analysis revealed 581 hypomethylated and only 51 hypermethylated probes in MTAP-loss samples, underscoring a global hypomethylation phenotype likely driven by MTA accumulation. We identified 343 differentially expressed, hypomethylated genes in MTAP-loss LUAD samples. Of these, upregulated genes were highly enriched in mitochondrial function and stress response pathways, whereas downregulated genes were linked to cell differentiation and developmental processes, suggesting an epigenetically driven metabolic reprogramming. Notably, these alterations may confer heightened cellular survival and adaptability under stress, while curtailing normal differentiation programs. **Conclusions:** Our findings indicate that MTAP loss in LUAD leads to a coordinated shift in DNA methylation and gene expression, promoting survival-focused metabolic and stress responses at the expense of normal regulatory pathways. These results highlight novel vulnerabilities in MTAP-deficient tumors and suggest potential targets for precision therapies. Research Sponsor: None.

8625 Poster Session

Rare ALK: Clinical characteristics and efficacy of targeted therapy in NSCLC with ALK fusions other than EML4::ALK.

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Background: More than 90% of ALK rearrangements in NSCLC lead to recurrent fusions with EML4. The remainder is a heterogeneous group involving more than twenty different fusion partners. Data on prognosis and management of these patients is limited to case reports. **Methods:** This is an international, multicenter, retrospective analysis of advanced NSCLC patients with a non-EML4::ALK-fusion (*rare ALK*) compared to a control cohort of patients harboring typical EML4::ALK-translocations. **Results:** Out of 26,152 NSCLC patients tested by NGS 0.2% showed *rare ALK* with 21 distinct fusion partners identified. The prevalence of typical EML4::ALK fusions in the cohort was within the expected range (1.9%). Sufficient clinical data was available for a total of 51 *rare ALK* and 277 EML4::ALK patients. Median age within the *rare ALK* cohort was 66 years. 59% were male. The majority (88%) presented with adenocarcinoma, 10% had squamous-cell carcinoma. The choice of first-line TKI in *rare ALK* patients was similar to the EML4::ALK control cohort and with alectinib used predominantly (around 50%). Compared to EML4::ALK, patients with *rare ALK* were significantly older, more likely to have ever smoked (59% vs 35%) and, among smokers, had more pack years (15 vs 7 pack years). Objective response rate (ORR) to firstline ALK inhibitor treatment across all treatment lines in patients with *rare ALK* was 68% (95% confidence interval [CI] 53%-80%), while EML4::ALK patients had an ORR of 85% (CI 80%-89%; p=0.01). ALK inhibitors in first-line palliative treatment led to similar PFS in the *rare ALK* (23 months [mo]; CI 7.1-38.9) and the EML4::ALK cohort (25 mo; CI 19.9-30.1; HR 0.92; CI 0.6-1.5; p=0.7). Median overall survival (OS) was 40 mo (CI censored) for *rare ALK* compared to 57 mo (CI 50.7-63.3) for EML4::ALK (HR 0.9; CI 0.5-1.6; p=0.6). Within the *rare ALK* cohort, first-line treatment with platinum-doublet chemotherapy was associated with shorter PFS as compared to ALK inhibitors (5 mo vs 23 mo; HR 3.1; CI 1.2-8.0; p = 0.021) and trended towards shorter OS (24 mo vs 40 mo; HR 2; CI 0.7-5.9; p=0.2). **Conclusions:** Acknowledging the limitations of a retrospective analysis, our data suggest that, compared to EML4::ALK, patients with *rare ALK* fusions derive similar benefit from treatment with ALK inhibitors, which should be preferred over platinum-based therapies as first-line palliative treatment. Research Sponsor: None.

Clinico-genomic characteristics of clinical trial participation and its impact on clinical outcome in metastatic NSCLC: A nationwide database analysis in Japan.

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Background: The clinico-genomic factors influencing clinical trial participation and their impact on clinical outcomes remain unclear. We investigated which clinico-genomic characteristics predict clinical trial participation in patients with metastatic NSCLC and whether trial participation improves clinical outcomes compared to nonparticipation, using a nationwide database. **Methods:** We retrospectively analyzed 2,966 patients with metastatic NSCLC who underwent comprehensive genomic profiling (CGP) testing from March 2019 to December 2023 in the Center for Cancer Genomics and Advanced Therapeutics, a nationwide database. Multivariable logistic regression identified clinico-genomic factors associated with trial participation. Multivariable Cox model compared OS between trial participants and non-trial participants, adjusting for age, sex, smoking status, performance status, liver/brain metastases, FDA-approved/potentially druggable genes, PD-L1 tumor proportion score (TPS). Overall response rate (ORR) by the line of therapy was evaluated. **Results:** Of 2,966 patients, 167 (6%) participated in clinical trials. In the multivariable analysis, *EGFR* mutation (mut), non-squamous (sq) histology, and male sex were associated with a higher likelihood of trial participation, whereas *STK11* mut was associated with a lower likelihood of trial participation. After stepwise selection, biomarker factors (*EGFR* mut, *KRAS* G12C mut, *RET* fusion, *MET* exon 14 skipping mut, PD-L1 TPS $\geq$ 50%) explained 72% of the increased trial participation odds, while clinical factors (age $<$ 65, male sex, non-sq histology) accounted for 28%. Among patients with lung adenocarcinoma (LUAD), *KRAS* G12C and male sex predicted higher trial participation; among those with lung sq cell carcinoma (LUSC), *KRAS* G12C predicted higher trial participation. Participation did not confer an OS benefit in the overall NSCLC cohort (HR, 0.94; 95% CI, 0.74–1.19), in LUAD (HR, 1.03; 95% CI, 0.78–1.37), or in *EGFR*-mut patients (HR, 0.99; 95% CI, 0.52–1.88), but was significantly associated with improved OS in LUSC (HR, 0.29; 95% CI, 0.10–0.78). ORR was not significantly different between trial participants and non-trial participants in 1L (49% vs. 57%, P=0.25), 2L (30% vs. 34%, P=0.75), and 4L (25% vs. 19%, P=0.56) therapy lines, but was significantly higher among trial participants in 3L (46% vs. 23%, P=0.002) and $\geq$5L (48% vs. 18%, P=0.0001). **Conclusions:** Biomarker factors contributed to 72% of the likelihood of trial participation in patients with metastatic NSCLC, underscoring the importance of CGP. Clinical trial participants exhibited survival outcomes comparable to those of nonparticipants. Their higher ORR in later lines of therapy suggests that clinical trial participation may be a potent therapeutic option, particularly after standard treatment. Research Sponsor: None.

Osimertinib plus anlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer with concurrent gene alterations: A single-arm, prospective, multicenter phase II study.

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Background: The standard first-line treatment for advanced EGFR-mutated non-small cell lung cancer (NSCLC) is EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, co-existing mutations can reduce the efficacy of EGFR-TKIs, and combination treatments may offer superior outcomes. Some studies suggest that the combination of Osimertinib and Anlotinib may enhance anti-tumor activity. This study explores the efficacy and safety of this combination as a first-line treatment for advanced NSCLC with EGFR co-existing mutations. **Methods:** This prospective, multicenter phase II trial enrolled patients (pts) with untreated, advanced NSCLC carrying EGFR exon 19 deletions or L858R mutations plus at least one additional mutation in TP53, PI3KCA, or RB1. pts received oral Osimertinib (80 mg daily) and Anlotinib (10 mg daily for 2 weeks, followed by 1 week off), repeated every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint was the 1-year progression-free survival (PFS) rate. Secondary endpoints included median overall survival (mOS), median PFS (mPFS), objective response rate (ORR), disease control rate (DCR), and safety. Exploratory analyses evaluated changes in circulating tumor DNA (ctDNA) and their correlation with clinical outcomes. **Results:** As of June 24, 2024, 38 pts (median age 65 years; 39.5% male; 78.9% ECOG PS 1) were enrolled. EGFR mutations included exon 19 deletions (47.4%) and L858R (52.6%), with co-existing mutations in TP53 (78.9%), PI3KCA (28.9%), and RB1 (2.6%). At baseline, 47.4% of pts had brain metastases. With a median follow-up of 14.5 months, the 1-year PFS rate was 85% (95% CI: 70%-95%), and median PFS was 29.0 months (95% CI: 22.5-NA). The ORR was 76.7%, and DCR was 97.4%. Among the 18 pts with brain metastases, the ORR was 83.3%, and median PFS was 22.3 months (95% CI: 14.6-30.4). All pts experienced treatment-related adverse events (TRAEs), with 18.3% having Grade 3 or higher TRAEs. Common TRAEs included rash (81.6%), hand-foot syndrome (71.1%), oral mucositis (50.0%), hypertension (60.5%), liver function impairment (47.4%), decreased appetite (44.7%), and diarrhea (36.8%). In the 11 pts monitored via next-generation sequencing (NGS), ctDNA clearance post-treatment correlated significantly with improved PFS (median PFS: NR vs. 17.8 months, P=0.015). **Conclusions:** The combination of Osimertinib and Anlotinib shows promising efficacy and manageable toxicity as a first-line treatment for advanced NSCLC with EGFR co-existing mutations, particularly in pts with brain metastases. Post-treatment ctDNA clearance appears to be a potential biomarker for predicting therapeutic response and prognosis. Further investigation is warranted to confirm these findings and explore personalized treatment strategies in NSCLC. Clinical trial information: ChiCTR2300070023. Research Sponsor: None.

Association of circulating tumor DNA (ctDNA) variant allelic frequency (VAF) with outcomes on matched targeted therapies (TT) in advanced non-small cell lung cancer (aNSCLC).

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Background: There is a critical gap in our understanding of the correlation between ctDNA driver VAF and outcomes in patients (pts) with aNSCLC treated with TT. We explore the landscape of driver alterations (alts) in aNSCLC by ctDNA VAF and assess the association with outcomes in pts treated with matched TT. **Methods:** We analyzed 3,146 pts with aNSCLC with a driver positive liquid biopsy (LBx) (FoundationOneLiquid CDx) Targetable driver altswere defined as alts listed in NCCN guidelines and were stratified by VAF. Clinical outcomes were assessed for pts included in the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine aNSCLC clinico-genomic database (FH-FMI CGDB) originating from approximately 280 US cancer clinics (~800 sites of care). For 224 pts receiving matched TT within 60 days of LBx collection, multivariate Cox proportional hazard models were employed to evaluate the association of VAF on real-world progression-free (rwPFS) and overall (rwOS) survival adjusting for clinical and demographic factors. **Results:** Among 3,146 pts with targetable alts detected in LBx, the frequency of drivers with VAF <1% in ctDNA was 36% (1,185/3,262 alts). Distribution of drivers by VAF is shown in the table. For pts in the FH-FMI CGDB treated with matched TT following driver positive LBx, clinical and demographic characteristics were balanced between pts with driver VAF <1% (n = 75) and those with VAF ≥1% (n = 147), except for the presence of liver metastases, which were more common in pts with VAF <1% (12% v 26%; p = 0.0002). There was no significant difference in the median rwPFS for pts with driver VAF <1% vs those with VAF ≥1% (10.8 vs 8.7 months; HR = 1.40 [0.92-2.00]; p=0.12). Similarly, there was no significant difference in median rwOS (32.4 vs 23.2 months; HR 1.20 [0.74-2.00]; p=0.45). To account for potential bias due to varying effectiveness of TT by driver, we limited the analysis to pts treated with EGFR inhibitors: VAF of the *EGFR* mutation did not affect rwPFS (10.8 vs 9.8 months; HR 1.14 [0.69-1.90]; p=0.61) or rwOS (18.3 vs 23.2 months; HR 1.1 [0.61-2.00]; p=0.74). **Conclusions:** Outcomes in pts with aNSCLC receiving matched TT after LBx were comparable between pts with driver VAF <1% and those with VAF ≥1%. Our findings highlight that the presence of a detectable targetable driver alt in aNSCLC is actionable, regardless of ctDNA VAF. Research Sponsor: Foundation Medicine, Inc.

Alteration	VAF <1% (n = 1,185)	VAF ≥1% (n = 2,077)	Percentage <1% VAF [95% Confidence interval]	VAF Range
***KRAS* G12C**	288	566	34 [31-37]	0.1% - 78%
EGFR	457	1,065	30 [28-32]	0.09% - 98%
ALK	129	126	51 [44-57]	0.04% - 49%
RET	47	32	59 [48-70]	0.04% - 36%
ROS1	41	22	65 [52-76]	0.05% - 47%
***MET* exon 14**	75	94	44 [37-52]	0.09% - 80%
NTRK1/2/3	13	7	65 [41-84]	0.11% - 17%
***BRAF* V600E**	71	59	55 [46-63]	0.09% - 35%
ERBB2	64	106	38 [30-45]	0.09% - 77%

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Safety and efficacy of ifebemtinib (IN10018) combined with garsorasib (D-1553) in KRAS G12C mutant solid tumors from a phase Ib/II study: Results from single-arm of non-small-cell lung cancer (NSCLC) and randomized part of colorectal cancer (CRC).

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Background: RAS inhibitors (RASi) need to be combined with optimal partner(s) to maximize their efficacy. Ifebemtinib (ifebe) is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK) demonstrating synergies with RASi both preclinically and clinically. D-1553 is a novel KRAS G12Ci approved in China for KRAS G12C mutant NSCLC. We previously reported a promising ORR of 90.3% in KRAS G12C mutant NSCLC receiving ifebe + D-1553 with pending durability of efficacy. Here we are updating the follow-up (FU) results in NSCLC and also reporting preliminary results of ifebe + D-1553 vs D-1553 in KRAS G12C mutant CRC from a randomized part to decipher the relative contribution of ifebe. **Methods:** Locally advanced or metastatic KRAS G12C mutant NSCLC patients (pts) without any prior systemic anticancer therapy were enrolled in a single arm and received ifebe (100mg QD) + D-1553 (600mg BID). Metastatic KRAS G12C mutant CRC pts with at least 1 prior line of systemic anticancer therapy were enrolled in a randomized part and randomized 1:1 to ifebe (100mg QD) + D-1553 (600mg BID) or D-1553 (600mg BID) alone. **Results:** As of 22-Jan-25, 33 front-line NSCLC pts (81.8% stage IV) were enrolled and received ifebe + D-1553, and 36 previously-treated metastatic CRC pts were enrolled and randomized 1:1 to receive ifebe + D-1553 or D-1553 alone. In NSCLC with a median FU of 13.8 months (range: 1.1, 20.9), 12-month PFS rate is 67.9%, and Kaplan-Meier curve of PFS flattens as treatment continues, predicting durable efficacy. The mDOR, mPFS and mOS are not reached by the cut-off date. In the randomized part of CRC, all 36 pts are radiologically evaluable. The ORR is 33.3% (95%CI: 13.3, 59.0) vs 16.7% (95%CI: 3.6, 41.4) and DCR is 100.0% (95%CI: 81.5, 100.0) vs 77.8% (95%CI: 52.4, 93.6) in ifebe + D-1553 vs D-1553 alone, respectively. The mDOR, mPFS and mOS has not matured yet. The safety profiles of ifebe + D-1553 in both NSCLC and CRC pts are comparable to each single agent. No ifebe- or D-1553-related death or AEs leading to drug withdrawal were reported. The incidence of SAEs and ≥Grd.3 AEs are listed in Table 1. **Conclusions:** Combination of ifebe and D-1553, as a dual-oral regimen, is safe and highly efficacious against KRAS G12C mutant NSCLC with ORR over 90% and durable efficacy. Preliminary results from the randomized part of CRC demonstrated ORR doubling with the combo, validating the add-on benefits of ifebe. Our data suggest that ifebe could be an ideal partner of RASi. Clinical trial information: NCT06166836; NCT05379946. Research Sponsor: None.

Incidence of SAEs and ≥Grd.3 AEs.

	NSCLC	CRC	
	Ifebe + D-1553 N=33 n(%)	Ifebe + D-1553 N=18 n(%)	D-1553 N=18 n(%)
Pts with SAE	**8 (24.2)**	**2 (11.1)**	**4 (22.2)**
ifebe-related	5 (15.2)	2 (11.1)	-
D-1553-related	5 (15.2)	2 (11.1)	1 (5.6)
Pts with ≥ Grd. 3 AE	**11 (33.3)**	**4 (22.2)**	**4 (22.2)**
ifebe-related	7 (21.2)	4 (22.2)	-
D-1553-related	7 (21.2)	4 (22.2)	2 (11.1)

Clinical outcomes of tepotinib and immune checkpoint inhibitor therapy for MET exon 14 skipping NSCLC: A multicentric retrospective analysis.

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Background: The VISION study demonstrated that tepotinib, a MET inhibitor, is effective against MET exon 14 (METex14) skipping NSCLC, but the clinical data on the efficacy and safety of this drug are scarce, and the utility of immune checkpoint inhibitors (ICIs) in patients with METex14 requires further investigation. The present, multicentric, retrospective study evaluated the clinical efficacy and safety of tepotinib and ICIs in patients with METex14 skipping NSCLC. **Methods:** Data on the patient characteristics, treatment details, efficacy, and safety of tepotinib and ICIs in patients with METex14 skipping NSCLC diagnosed at any of six Japanese hospitals between August 2020 and December 2024 were extracted from electronic medical records and retrospectively analyzed. **Results:** Of the 98 patients enrolled, 57 (58.2%) and 41 (41.8%) were male and female, respectively. 60 patients (61.2%) had a smoking history. Histological data indicated adenocarcinoma in most of the patients (68.4%). There were 50 patients (51.0%) with PD-L1 $>$ 50%. Tepotinib was administered to 79 patients with a median age of 75 years (range: 55–90 years). Most of these patients had advanced-stage cancer. Tepotinib was administered as the first-line therapy in 62 patients (78.5%), with 19.0, 55.7, 17.7, 6.3, and 1.3% of this subgroup having ECOG PS 0, 1, 2, 3, and 4, respectively. The median observation period was 29.1 months (range: 1.5–51.5 months). First-line tepotinib therapy achieved a 61.4% overall response rate (ORR; 95% confidence interval [CI]: 48.8–74.0), median progression-free survival (PFS) of 8.2 months (95% CI: 6.3–10.1), and median overall survival (OS) of 24.4 months (95% CI: 9.5–39.2). The most common adverse event (AE) was edema (71.0%), with Grade 3 or higher edema occurring in 12.9% of the patients. Notably, these patients had significantly longer PFS than those without edema (10.8 months [95% CI: 8.0–13.6] vs. 4.2 months [95% CI: 2.8–5.5]; hazard ratio: 0.31; 95% CI: 0.16 to 0.60; P $<$ 0.001). Treatment-related AEs led to tepotinib discontinuation in 15.0% of the cohort, and dose interruption and dose reduction were required in 59.5% and 62.0% of the cohort, respectively. ICI therapy, which was administered to 34 patients at various times, achieved a median PFS of 28.8 months (95% CI: 9.3–52.5) and a median OS of 45.2 months (95% CI: 20.9–77.0). **Conclusions:** The present, real-world analysis corroborated the findings of the VISION study demonstrating the efficacy and safety of tepotinib therapy against METex14 skipping NSCLC. The association between tepotinib-related edema and longer PFS warrants further investigation. Importantly, ICIs appear to be a promising treatment option for this population and deserve further study. Research Sponsor: None.

Vebreltinib plus PLB1004 in EGFR-mutated NSCLC with acquired MET amplification or overexpression after failure on EGFR-TKI treatment: A phase Ib/II study.

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Background: MET amplification (METamp) or overexpression (METov) is the most common "off-target" mechanism that drives resistance to EGFR-TKIs. Vebreltinib is a potent and selective c-Met inhibitor, while PLB1004 is an oral, potent, irreversible, and selective EGFR-TKI with potent blood-brain barrier penetration and broad tyrosine kinase activity. **Methods:** This open-label, multicenter phase Ib/II study evaluated vebreltinib and PLB1004 in Chinese patients (pts) with EGFR-mutated NSCLC with METamp or METov after EGFR-TKI failure. Patients were eligible if they were METamp positive by NGS or FISH, or METov by IHC (3+). Phase Ib part established vebreltinib 150 mg BID and PLB1004 80 mg QD as the RP2D. Phase II further investigated the efficacy and safety of RP2D in four cohorts, stratified by MET gene status and previous EGFR-TKIs: 1: Progression after 1st-/2nd-generation EGFR-TKIs, T790M (-), with METamp (GCN $\geq$ 5 and/or MET/CEP7 $\geq$ 2 by FISH). 2: Progression after 3rd-generation EGFR-TKIs with METamp (GCN $\geq$ 5 and/or MET/CEP7 $\geq$ 2 by FISH). 3: Progression after EGFR-TKIs, T790M (-) for 1st-/2nd-generation TKIs, with METamp (GCN $<$ 5 and MET/CEP7 $<$ 2 by FISH, but positive by NGS). 4: Progression after EGFR-TKIs (1st-/2nd-/3rd-generation), T790M (-) for 1st-/2nd-generation TKIs, with METov (IHC 3+), and without METamp (GCN $<$ 5 and MET/CEP7 $<$ 2 by FISH, and negative by NGS). **Results:** There were 56 pts enrolled, with 13 in phase Ib and 43 in phase II (2/35/1/5 in four cohorts). The mean age was 58.8 $\pm$ 8.9 years, and 53.6% were male with the majority of patients having stage IV disease (98.2%). Prior EGFR-TKIs included 1st- (7.1%), 2nd- (5.4%), and 3rd-generation (87.5%) TKIs. Confirmed overall response rate (ORR) was 50.0%, and all cases (n=28) were partial response (PR). Disease control rate (DCR) was 89.3% (50/56). The median progression-free survival (mPFS) was 9.9 months. In 19 pts with brain metastases, ORR was 42.1% and mPFS was 9.5 months. There were 47 METamp-positive pts as detected by NGS (regardless of FISH), and these pts had an ORR of 53.2% and mPFS of 9.6 months. All pts (100%) reported treatment-related adverse events (TRAEs), with grade $\geq$ 3 TRAEs in 11 pts (19.6%). Serious adverse events were observed in 5 pts (8.9%), all of which were treatment-related. None discontinued treatment or died due to TRAE. The most common TRAEs were rash (64.3%), oedema peripheral (60.7%) and paronychia (48.2%). **Conclusions:** Vebreltinib and PLB1004 at RP2D demonstrates notable efficacy and manageable safety in EGFR-mutated NSCLC with METamp or METov after EGFR-TKIs failure. Findings from our phase Ib+II data suggest that NGS reported METamp+ could be utilized to identify target patients to receive combination of PLB1004 + Vebreltinib. Further studies are warranted to confirm these findings. Clinical trial information: NCT06343064. Research Sponsor: None.

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Hypothesis generative head-to-head study comparing efficacy of afatinib and osimertinib based on immunological biomarkers in Japanese NSCLC patients with *EGFR* mutations: Heat on Beat randomized phase II study.

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Background: Osimertinib (Osi) has been established as a standard of care for patients (pts) with *EGFR*-mutant advanced non-small-cell lung cancer (NSCLC). However, in the FLAURA study, survival superiority of Osi over first-generation EGFR-TKIs was not demonstrated especially in Japanese pts (hazard ratio [HR], 1.39; 95% confidence interval [CI], 0.83 to 2.34; P = 0.22). This is presumably due to the different impact of adverse events or tumor antigen-specific cytotoxicity of T cells on subsequent therapy between both EGFR-TKIs in Japanese pts. On the other hand, there has been no clinical trial comparing second- with third-generation EGFR-TKIs. Therefore, optimal first-line EGFR-TKI may not have been identified in Japanese pts. **Methods:** This was a randomized, open-label, multicenter, phase II study to compare overall survival (OS) between initial treatment with afatinib (Afa) (n = 50) and Osi (n = 50) in pts with advanced or recurrent *EGFR*-mutant NSCLC. Exploration of immunomonitoring through peripheral blood mononuclear cells (PBMC) was also performed, before, during, and after treatment. The co-primary endpoints were the superiority of Afa over Osi at 3-year survival rate and the exploration of immunological biomarkers for treatment outcomes. Enrollment started in May 2020 at 28 sites in Japan with a minimum follow-up of 3 years. **Results:** Overall, 95 eligible pts were analyzed (47 to Afa and 48 to Osi). Objective response rates were 63.8% for Afa vs. 62.5% for Osi. Median progression-free survival (PFS) was 16.7 months (mos) for Afa vs. 14.5 mos for Osi (HR, 1.17; 95% CI, 0.72 to 1.90; P = 0.52). Median OS was 38.8 mos for Afa and not reached for Osi (HR, 1.15; 95% CI, 0.64 to 2.05; P = 0.64), resulting in 54.7% (95% CI, 39.4 to 67.7) for Afa vs. 57.5% (95% CI, 42.2 to 70.1) for Osi at 3-year survival rate. Predominant adverse events with Afa or Osi were diarrhea (92% vs. 31%) and pneumonitis (11% vs. 21%; Grade 5, 0% vs. 6%). Treatment discontinuation rates due to adverse events were 21% with Afa vs. 29% with Osi. The efficacy of Osi varied significantly dependent on the immunological biomarkers, Th7R (stem cell-like CD4 T cells) and Th2. Pts with high Th7R (7.83% or more) had promising PFS (31.0 mos [n = 28] vs. 6.6 mos [n = 20]; HR, 0.38; P = 0.006) and OS (not reached vs. 35.5 mos; HR, 0.56; P = 0.18). In contrast, pts with high Th2 (7.20% or more) had poor PFS (6.6 mos [n = 27] vs. 31.0 mos [n = 21]; HR, 1.78; P = 0.11) and OS (35.5 mos vs. not reached; HR, 2.77; P = 0.03). On the other hand, no immunological biomarkers affected PFS and OS of Afa. **Conclusions:** Afa and Osi both demonstrated favorable clinical activity as first-line treatment in Japanese NSCLC patients with *EGFR* mutations. Although their outcomes are comparable, immunological biomarkers (Th7R/Th2) may refine treatment decisions and warrant further prospective validation. Clinical trial information: jRCTs031190221. Research Sponsor: Boehringer Ingelheim Foundation.

Therapeutic responses in 555 advanced NSCLC patients enrolled in phase I studies at MD Anderson Cancer Center.

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Background: Lung cancer remains the deadliest solid tumor, with non-small cell lung cancer (NSCLC) accounting for 80–85% of cases. Patients enrolling in Phase I studies are often heavily pretreated and face limited treatment options. Understanding their demographics and therapeutic responses is crucial to improving patient outcomes. This study aimed to analyze therapeutic responses in NSCLC patients enrolled in Phase I studies. **Methods:** Data on NSCLC patients treated at the Investigational Cancer Therapeutics (ICT) department, a dedicated Phase I unit at The University of Texas MD Anderson Cancer Center (MDACC), were reviewed from January 2016 to December 2024, using MDACC CHIMERA platform. Collected data included age, gender, histologic type, Eastern Cooperative Oncology Group (ECOG) performance status, prior lines of treatment, treatment regimen, trial details and best response to treatment. **Results:** A total of 555 NSCLC patients were identified, of whom 267 (48.1%) were female. The median age was 64 years. The number of prior chemotherapy lines included: one line (50.3%), two lines (16%), and three lines or more (11.0%). The most frequent histologic type was adenocarcinoma (80.0%), followed by squamous cell carcinoma (15.7%) and NSCLC not otherwise specified (3.1%). The median number of treatment cycles was three, and the median duration of treatment was 2.0 months. The best response was evaluable in 449 cases (80.9%). The overall objective response rate (ORR) was 21.2%, and the disease control rate (DCR) was 71.3%. Clinical trial enrollment were categorized into seven groups: Targeted Monotherapy (TM), 227 cases (40.9%); Targeted Combination (TC), 49 cases (8.8%); Immunotherapy Monotherapy (IM), 81 cases (14.6%); Immunotherapy Combination, 57 cases (IC) (10.3%); Targeted + Immunotherapy (TI), 70 cases (12.6%); Antibody-Drug Conjugates (ADC) Monotherapy, 64 cases (11.5%); and Others (O), 7 cases (1.3%). When the ORR was compared among these groups, the TM group demonstrated the highest ORR at 32.6%, followed by the O group at 28.6% and the TC group at 28.2%. **Conclusions:** Phase I studies, especially those involving regimens containing targeted therapy, may serve as a promising treatment option for pretreated patients with advanced NSCLC. Research Sponsor: None.

Comparison of best response and objective response rates between different regimen groups.

	Targeted Therapy (Monotherapy)	Combination with Targeted Agent	Immunotherapy (Monotherapy)	Combination with Immunotherapy	Targeted Therapy Combined with Immunotherapy	Antibody-Drug Conjugate (Monotherapy)	Others	P
CR	1.6%	0%	0%	0%	0%	0%	0%	<0.001
PR	31.1%	28.2%	4.7%	11.6%	10.5%	12.2%	28.6%	
SD	43.2%	59.0%	57.8%	44.2%	57.9%	65.3%	0%	
PD	24.2%	12.8%	37.5%	44.2%	31.6%	22.4%	71.4%	
ORR	32.6%	28.2%	4.7%	11.6%	10.5%	12.2%	28.6%	<0.001

Abbreviations: CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective Response Rate.

Artificial intelligence-powered real-time model for predicting survival in advanced *EGFR*-mutant NSCLC.

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Background: Novel targeted therapies have led to improved survival in *EGFR*-mutant NSCLC. However, survival outcomes and cancer progression vary. Accurate and practical prediction of progression, survival, and T790M status in advanced *EGFR*-mutant NSCLC is crucial for optimizing patient outcomes and personalizing treatment strategies. This study developed and validated an AI model for predicting survival, and the T790M mutation, integrating clinical, pathological, laboratory, and radiologic data. **Methods:** The model was developed and internally validated using data from Samsung Medical Center (SMC) collected baseline data (at the time of starting EGFR-TKI) and longitudinal laboratory data (during the EGFR-TKI treatment and follow-up) of patients with *EGFR* (deletion 19 or L858R) mutant NSCLC who received EGFR-TKI between 2008 and 2023. The primary outcome was the prediction of progression-free survival (PFS) event within 3, 6, and 12 months from each monitoring point during EGFR-TKI treatment. Secondary outcomes included predicting overall survival (OS) within 3, 6, and 12 months from each monitoring points and the detection of the T790M mutation. **Results:** A total of 3,095 patients participated in the study, with a median follow-up period of 41.5 months. At the time of data lock, 2,713 (87.7%) patients had experienced disease progression, 311 (10.0%) patients continued on first-line EGFR TKI treatment, and 71 (2.3%) patients were lost to follow-up. Among the patients who progressed on first-line EGFR-TKI, 1,083 (39.9%) patients acquired the T790M mutation, and 815 patients received third-generation EGFR-TKI as second-line treatment. Of the 1,630 patients without T790M or with an unknown T790M status, 174 received third-generation EGFR-TKI (117 for leptomeningeal seeding and 57 in a clinical trial), 865 were treated with cytotoxic chemotherapy or other therapies, and 591 were lost to follow-up. A total of 2,985 patients were included in the AI model. Median PFS in total population was 24.0 months (95% CI, 22.5-25.0). and medial overall OS was 50.7 months (95% CI, 48.7-52.9). The training set consisted of 1,910 patients, the validation set had 478 patients, and the test set included 597 patients. The AUC for predicting PFS events at 3, 6, and 12 months from the monitoring point was 0.780, 0.755, and 0.698, respectively. The AUC for predicting OS events at 3, 6, and 12 months from the monitoring point was 0.924, 0.886, and 0.812, respectively. The AUC for predicting T790M detection from the monitoring point at 3, 6, and 12 months was 0.768, 0.737, and 0.666, respectively. **Conclusions:** This study demonstrates a real-time AI-powered model to predict survival outcomes and T790M mutation status in advanced EGFR-mutant NSCLC during EGFR-TKI treatment. The model's ability to accurately forecast PFS, OS, and T790M acquisition offers valuable insights for personalized treatment strategies. Research Sponsor: None.

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Efficacy and omics-based insights of TROP2 ADC in non–small cell lung cancer with or without actionable genomic alterations (AGAs).

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Background: TROP2 antibody–drug conjugate (ADC) has emerged as a promising strategy for advanced non-small cell lung cancer (NSCLC). A trend of enhanced efficacy has been observed in patients with actionable genomic alterations (AGAs), but the validity of AGA status for patient selection remains controversial. Current evidence suggests that endocytosis is a key factor in TROP2 ADC activity. However, systematic analyses of clinicopathological and genetic associations with endocytosis are lacking. This study combined a meta-analysis and omics analyses to identify potential NSCLC populations that respond or are resistant to TROP2 ADC. **Methods:** For the meta-analysis, we searched for trials of TROP2 ADC in advanced or metastatic NSCLC. Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were pooled in the overall population and AGA subgroups. For the omics analysis, given that STK11/KEAP1 mutations are generally mutually exclusive with AGAs and define special subsets, we assessed TROP2 expression and endocytosis activity in three NSCLC categories: AGA-positive (AGA+), AGA–negative/STK11 or KEAP1-mutated (AGA–/SK+), and AGA-negative/STK11 and KEAP1-wild-type (AGA–/SK–). Each NSCLC AGA and key tumor suppressor driver mutation was also evaluated independently. **Results:** A total of 1,387 NSCLC patients from two randomized clinical trials (TROPION-Lung01 and EVOKE-01) and two single-arm trials (TROPION-Lung05 and KL264-01) were meta-analyzed. TROP2 ADC did not significantly improve OS (HR = 0.89, P = 0.12), PFS (HR = 0.90, P = 0.25), or ORR (OR = 1.68, P = 0.39) compared to docetaxel. The pooled ORR for the TROP2 ADC arm was 30% [18%-42%], with higher rates in AGA+ (43% [35–50%]) and EGFR-mutant subsets (45% [37–54%]). However, there was no significant difference in the advantage of TROP2 ADC over docetaxel between patients with and without AGAs ($P_{interaction}$=0.11, 0.51, and 0.79 for OS, PFS, and ORR, respectively). AGA+ tumors exhibited significantly higher TROP2 expression (FDR=0.01) and endocytosis activity (FDR=0.001) than AGA–/SK+ tumors, but no differences were observed between AGA+ and AGA–/SK– tumors. Within AGA– populations, SK– tumors had evidently higher TROP2 expression (FDR=0.0001) and endocytosis activity (FDR=0.01) than SK+ tumors. Among common NSCLC mutations, STK11 mutations showed the lowest levels of both TROP2 expression and endocytosis activity. **Conclusions:** AGA+ NSCLC tends to be more responsive to TROP2 ADC, but AGA status is not a reliable predictive biomarker for patient selection, likely due to heterogeneity within AGA– population. AGA–/SK+ defines a subgroup with the low TROP2 expression and endocytosis activity that may confer primary resistance to TROP2 ADC. We'll present in vitro experiments and clinical data regarding the primary resistance to TROP2 ADC in SK+ NSCLC at ASCO. Research Sponsor: None.

Real-world data on the efficacy and safety of iruplinalkib (WX-0593) in ALK-positive advanced lung adenocarcinoma patients previously treated with lorlatinib.

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Background: Iruplinalkib (WX-0593) is a novel anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI). Here we report the results from a retrospective observational study on efficacy and safety of iruplinalkib in ALK-positive lung adenocarcinoma (LUAD) patients who had previous treatment with lorlatinib. **Methods:** Patients with ALK-positive advanced LUAD who either experienced disease progression on or were intolerant to lorlatinib were evaluated for clinical outcomes including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profiles. **Results:** A total of 11 patients were enrolled in this study, of which five (45%) were male, eight (73%) experienced treatment failure with lorlatinib, and seven (64%) received prior two or more second-generation TKIs. The median age was 49-years old. All patients received 180 mg of iruplinalkib orally daily. The median treatment line with iruplinalkib was six. Brain metastasis and prior treatment were summarized in the table. As of the data cut-off date on December 31, 2024, the median follow-up was 8.1 months. The ORR was 27%, and the DCR was 91%. The 12-month PFS rate was 53.0%, while the median PFS and OS were not reached. Eight (73%) and one (9%) patient experienced any grade and grade $\geq$ 3 treatment-related adverse event (TRAE), respectively. **Conclusions:** Iruplinalkib exhibited promising efficacy and acceptable toxicity in patients with ALK-positive advanced LUAD patients who were previously treated with lorlatinib. Research Sponsor: None.

Parameters	Results (n=11)
Baseline brain metastasis	9 (82%)
Prior ALK TKIs	
Crizotinib + second-generation + lorlatinib	10 (91%)
Second-generation + lorlatinib	1 (9%)
Detailed second-generation ALK TKI	
Aletinib	8 (73%)
Ceritinib	6 (55%)
Brigatinib	3 (27%)
Ensartinib	3 (27%)
Prior chemotherapy	5 (45%)
Prior anti-angiogenesis	8 (73%)
Prior immune checkpoint inhibitor	2 (18%)
Best objective response	
Partial response	3 (27%)
Stable disease	7 (64%)
Progressive disease	1 (9%)
Objective response	3 (27%)
Disease control	10 (91%)
PFS event	3 (27%)
12m PFS rate	53.0%
Median PFS, months	NR
Any grade TRAE	8 (73%)
Grade ≥ 3 TRAE	1 (9%)
TRAE leading to dose interruption/reduction/discontinuation	1 (9%) /0/0

Amivantamab plus chemotherapy vs chemotherapy in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: Outcomes by osimertinib resistance mechanisms in MARIPOSA-2.

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Background: Amivantamab (ami), an EGFR-MET bispecific antibody with immune cell–directing activity, combined with chemotherapy (chemo) is approved for patients with *EGFR*-mutant advanced NSCLC after disease progression on an EGFR TKI. In the phase 3 MARIPOSA-2 study (NCT04988295), ami-chemo significantly improved progression-free survival (PFS) vs chemo after disease progression on osimertinib (osi; HR, 0.48; $P<0.001$). Nearly all patients develop resistance after osi, most commonly *MET* amplifications (*MET*amp) and *EGFR* resistance mutations (Chmielecki *Nat Commun* 2023; Besse *Ann Oncol* 2024; Yang *JTO* 2024). We evaluated outcomes by baseline osi resistance mechanisms in MARIPOSA-2. **Methods:** MARIPOSA-2 enrolled participants (pts) with *EGFR*-mutant (Ex19del or L858R) advanced NSCLC whose disease progressed on osi; ~1/3 received osi as 2L therapy. This analysis included pts randomized to ami-chemo (n=131) or chemo (n=263). Pathogenic alterations were identified by next-generation sequencing (NGS) of blood circulating tumor DNA (ctDNA) with Guardant360 CDx or PredicineCARE assay. **Results:** Baseline ctDNA for NGS analysis of pathogenic alterations was available for 341 pts (87%; ami-chemo, n=120; chemo, n=221). Characteristic of post-osi resistance, the most commonly detected baseline alterations for ami-chemo vs chemo were *MET*amp (10% vs 14%) and secondary *EGFR* (C797X, L718X, G724X, L792X, G796X) resistance mutations (13% vs 18%). Ami-chemo improved median PFS (mPFS) vs chemo among pts with *MET*amp (HR, 0.51; $P=0.078$) and secondary *EGFR* mutations (HR, 0.55; $P=0.125$; Table). Furthermore, ami-chemo significantly prolonged mPFS vs chemo for pts with *EGFR*/*MET* independent (HR, 0.54; $P=0.025$) and unknown (HR, 0.31; $P<0.001$) resistance mechanisms. **Conclusions:** Ami-chemo improved mPFS vs chemo across baseline resistance subgroups, including *EGFR/MET* dependent, independent, and unknown resistance. Ami-chemo is an important treatment option, regardless of baseline osi resistance mechanism, for pts with *EGFR*-mutant advanced NSCLC after progression on an EGFR TKI. Clinical trial information: NCT04988295. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

	Ami-chemo, chemo (n)	Ami-chemo vs chemo, mPFS (mo)	HR (95% CI); *P* value
Detectable baseline ctDNA	104, 195	5.9 vs 4.2	0.49 (0.36–0.68); <0.001
***TP53* co-mutation**	59, 127	5.6 vs 4.1	0.63 (0.44–0.92); 0.014
***MET*amp present**	12, 30	4.4 vs 3.1	0.51 (0.24–1.11); 0.078
Secondary *EGFR* resistance mutations present	15, 39	5.7 vs 5.0	0.55 (0.26–1.19); 0.125
Secondary *EGFR* resistance mutations absent	89, 156	6.2 vs 4.2	0.47 (0.34–0.67); <0.001
***EGFR/MET* dependent**	27, 62	5.5 vs 4.1	0.57 (0.33-0.99); 0.042
***EGFR/MET* independent**	39, 41	5.6 vs 3.9	0.54 (0.31–0.94); 0.025
Unknown	38, 92	9.7 vs 4.2	0.31 (0.17–0.56); <0.001
Independent + unknown	77, 133	7.0 vs 4.2	0.47 (0.32–0.68); <0.001

Vabametkib in MET exon 14 skipping non-small-cell lung cancer: Efficacy and safety from the open-label, phase 2, cohort-1 trial.

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Background: Vabametkib (ABN401) is a tyrosine kinase inhibitor (TKI) targeting MET. It has previously demonstrated preliminary efficacy in patients(pts) with MET genomic aberrations including MET exon 14 skipping mutation (METex14) in lung cancer. Here, we present the efficacy and safety data from cohort 1 (TKI-naïve, METex14 non-small cell lung cancer [NSCLC]) **Methods:** Phase 2 Cohort 1 trial (NCT05541822) is an open-label, global, multicenter study designed to evaluate the safety and efficacy of vabametkib in pts with NSCLC harboring METex14. METex14 status is confirmed via NGS testing and the status is further validated centrally using digital droplet PCR (ddPCR). Pts receive oral vabametkib at a dose of 800 mg once daily (QD) until disease progression or the occurrence of unacceptable toxicity. The primary endpoint is the objective response rate (ORR). Additional outcomes being evaluated include pharmacokinetics (PK), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** This study was conducted across 24 centers in three countries (US, South Korea, and Taiwan). A total of 40 pts with METex14 NSCLC were enrolled and treated, including 24 males (60%) and 16 females (40%), between January 17, 2023, and June 14, 2024. Pts were aged 43-86 years, with 35 Asians and 5 Caucasians. Twenty-one pts were treatment-naive, while 19 had received prior treatment. As of December 24, 2024, the objective response rate (ORR) in the evaluable population (n=37) was 43.2% (95% CI: 27.10–60.51), with 16 out of 37 patients achieving a response. The median PFS was 15.9 months (95% CI:10.9, NA) for treatment-naive pts and 6.2 months (95% CI:5.9, NA) for previously treated pts. The median follow-up for the efficacy population was 7.7 months. Vabametkib's safety was assessed in all 40 treated pts, the most common treatment-related adverse events were nausea (n=28; 70%), diarrhea (n=14; 35%), and vomiting (n=8; 20%) and peripheral oedema (n=5; 12.5%). Grade 3 or higher adverse events occurred in 5 (12.5%) pts, no grade 3 edema were reported in the study population (0%). No grade 5 events in this cohort. **Conclusions:** Vabametkib demonstrates good antitumor activity in pts with METex14 NSCLC, and better toxicity profile with excellent tolerability, compared to FDA-approved MET inhibitors, supporting vabametkib continued clinical development for METex14 NSCLC pts. Clinical trial information: NCT05541822. Research Sponsor: None.

8641 Poster Session

Dermatologic prophylaxis and impact on patient-reported outcomes in first-line *EGFR*-mutant advanced NSCLC treated with amivantamab plus lazertinib: Results from the phase 2 COCOON trial.

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Background: The phase 2 COCOONtrial (NCT06120140) is evaluating the impact of enhanced dermatologic management (DM) in combination with amivantamab (ami) + lazertinib (laz) on reduction of skin and nail adverse events (AEs). At the interim analysis, enhanced DM (COCOON DM) significantly reduced the incidence of grade ≥2 dermatologic AEs by Wk 12 vs standard of care dermatologic management (SoC DM). We assessed patient-reported outcomes (PROs) from COCOON to determine if reducing dermatologic AEs impacts the quality of life (QoL) of patients with *EGFR*-mutant advanced NSCLC. **Methods:** Participants (pts) with previously untreated *EGFR*-mutant (Ex19del/L858R) advanced NSCLC were randomized 1:1 to receive COCOON DM or SoC DM per site practice. Pts received the approved doses of IV ami + oral laz. COCOON DM included oral doxycycline/minocycline (100 mg BID Wks 1–12), clindamycin 1% lotion on scalp (QD Wks 13–52), chlorhexidine 4% to wash hands and feet QD, and non-comedogenic ceramide-based moisturizer to body and face QD. The COCOON DM arm received a digital health tool with training on dermatologic AEs and reminders to increase adherence to the DM regimen. Dermatologic symptoms and impact on pts' health-related QoL were measured with PRO instruments every 2 weeks. The Skindex-16 questionnaire assesses the impact of skin conditions on QoL using 3 subscales (functioning, emotional, symptoms) and an average score (0 – no effect to 100 – effect experienced all the time). Patient's Global Impression of Severity (PGI-S) is a self-reported 4-point rating scale (no symptoms, mild, moderate, severe) assessing severity of nail infection, skin condition, and rash over time. All *P* values reported are nominal. **Results:** As of 13 Nov 2024, 138 pts received COCOON DM (n=70) or SoC DM (n=68) and had ≥12 wks of follow-up (median, 4.2 mo). This analysis focuses on PROs through 12 wks of follow-up (three 28-day ami+laz treatment cycles). Substantial and consistent separation favoring COCOON DM was observed in all post-baseline Skindex subscales indicating lower severity of dermatologic AEs and reduced impact of those AEs on QoL. More specifically, at Cycle 3 Day 15 (~10 wks), a lower average Skindex total score was observed with COCOON DM vs SoC DM (*P*=0.02). More pts in the COCOON DM arm vs SoC DM reported mild or no PGI-S rash, skin condition, or nail infection across the first 3 cycles. At Cycle 3 Day 15, there was a meaningful 3-fold difference for COCOON DM vs SoC DM in pts reporting no symptoms for PGI-S rash (21% vs 7%; *P*=0.04) and skin condition (23% vs 7%; *P*=0.02). There was also a numeric improvement in pts reporting no symptoms for nail infections (27% vs 16%; *P*=0.13). **Conclusions:** Among pts with *EGFR*-mutant advanced NSCLC, COCOON DM reduced the severity of dermatologic AEs and reduced the impact of those AEs on QoL compared to SoC DM. Clinical trial information: NCT06120140. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

Use of targeted therapy, healthcare costs, and survival with large panel testing, narrow testing, or no molecular testing in patients with metastatic non-small cell lung cancer (mNSCLC).

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Background: Treatment guidelines recommend broad molecular profiling for patients with mNSCLC. With the availability of molecular tests with different genes, panel sizes, and specimen types, the testing landscape has become complex. This study aimed to evaluate use of biomarker-targeted therapy, healthcare costs, and overall survival with large panel, narrow, or no molecular testing for mNSCLC. **Methods:** This retrospective analysis used de-identified administrative claims from the Optum Labs Data Warehouse from 01/01/2016 to 03/31/2023. Commercial and Medicare Advantage enrollees with claims evidence of newly diagnosed mNSCLC between 08/01/2020 and 12/31/2022 were identified (index date = first diagnosis code for metastatic disease). Using procedure codes and laboratories on claims around the index date, patients were grouped by use of molecular testing as: 1) large panel ($\geq$51 genes) testing; 2) narrow (individual gene or $\leq$50 gene panel) testing, or 3) no observed molecular testing. Outcomes evaluated in the variable follow-up period were targeted therapy use, healthcare costs (2022 adjusted) per patient per month (PPPM) in the first 180 days of follow-up, and overall survival. **Results:** Of 8,783 patients, 3,634 (41%) had large panel testing, 2,660 (30%) had narrow testing, and 2,057 (23%) had no observed testing; the remaining 5% of patients had molecular testing of unknown size. Use of targeted therapy was higher with large panel testing than narrow testing (12% vs. 8%, $p<0.001$) or no observed testing (3%, $p<0.001$). For commercial patients, mean $\pm$ SD total healthcare costs PPPM were higher for patients with large panel vs. narrow testing ($43,629 $\pm$ 33,097 vs. $38,642 $\pm$ 33,948, $p=0.02$) and were driven by higher pharmacy costs, but total healthcare costs PPPM were similar for patients with large panel vs. patients with no observed testing ($37,545 $\pm$ 50,329, $p=0.11$). For Medicare Advantage patients, mean total healthcare costs PPPM were similar ($p>0.10$) for patients with large panel ($18,321 $\pm$ 18,073), narrow ($18,462 $\pm$ 25,555), or no observed testing ($17,130 $\pm$ 31,955). Patients with large panel testing had higher median overall survival than patients with narrow testing (10.6 vs. 8.5 months, $p<0.001$) or no observed testing (10.6 vs. 5.9 months, $p<0.001$). **Conclusions:** Patients with large panel testing received targeted treatment at higher rates and had better overall survival than patients with narrow testing or patients with no observed testing. Total healthcare costs were similar with large panel testing vs. no testing and similar or higher (but driven by higher pharmacy costs) with large panel vs. narrow testing. Research is ongoing to assess outcomes among patient subgroups with treatment after adjusting for baseline differences between cohorts. Research Sponsor: None.

8643 Poster Session

Comparable efficacy and safety of taletrectinib for advanced ROS1+ non–small cell lung cancer across pivotal studies and between races and world regions.

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Background: Taletrectinib is a highly potent, next-generation, central nervous system–active, selective ROS1 tyrosine kinase inhibitor (TKI) that was evaluated in 2 pivotal ROS1+ non–small cell lung cancer (NSCLC) phase 2 trials: the regional TRUST-I (NCT04395677) and global TRUST-II (NCT04919811) studies. While earlier trials suggest its safety and efficacy data are consistent across racial and geographic factors, further analysis is required to confirm the consistency of outcomes and applicability of results across regions. Here, we compare the efficacy and safety of taletrectinib within and between the pivotal regional TRUST-I and global TRUST-II studies through predefined subgroup analyses. **Methods:** The pivotal cohorts of TRUST-I (N=173) and TRUST-II (N=159) had similar study designs, which included the same primary endpoint (confirmed objective response rate [cORR] by independent review committee per RECIST v1.1) and secondary endpoints, as well as similar inclusion/exclusion criteria and safety evaluation methods. Key efficacy and safety profiles were compared in 3 ways: (a) between TRUST-I and TRUST-II, (b) across Western (North America and Europe) and Asian regions, and racial subgroups, in the pooled study population of TRUST-I and TRUST-II, and (c) between Western and Asian regions and other subgroups in the global TRUST-II study. Relative risk (RR) and associated 95% confidence intervals (CIs) via the Wald method were used to compare data (data cutoff June 2024). **Results:** When comparing TRUST-I and TRUST-II, cORRs were consistent for TKI-naive (91% vs 85%; RR: 0.94 [95% CI: 0.83, 1.07]) and TKI-pretreated pts (52% vs 62%; RR: 1.20 [95% CI: 0.87, 1.66]). Rates of grade ≥3 treatment-emergent adverse events (TEAEs) were consistent across both studies (51% vs 51%, RR: 1.0 [95% CI: 0.81, 1.24]). TEAEs leading to dose interruptions (41% vs 40%) and discontinuations (6% vs 8%) were similar. In subgroup analyses of the pooled patient population by race, Asian and non-Asian patients had similar cORRs in both TKI-naive (89% vs 84%; RR: 0.94 [95% CI: 0.77, 1.15]) and TKI-pretreated (52% vs 68%; RR: 1.30 [95% CI: 0.93, 1.82]) groups. Comparison of different efficacy and safety profiles among subgroups in the pooled data set also showed consistency among races and regions. Within the multiregional TRUST-II study, cORRs were high in TKI-naive patients regardless of region (Western: 81%; Asia: 88%), prior chemotherapy (yes: 90%; no: 84%), and race (White: 83%; Asian: 86%; other: 86%). Similarly, major safety profiles were comparable between Asian and Western patients and between races within TRUST-II. **Conclusions:** Taletrectinib showed comparable efficacy and safety that were not impacted by geographic and racial factors. Therefore, the clinical benefit of taletrectinib is broadly applicable to ROS1+ NSCLC patients globally. Clinical trial information: NCT04395677, NCT04919811. Research Sponsor: Nuvation Bio Inc.

Efficacy and safety of pralsetinib in patients with advanced *RET*-fusion-positive NSCLC: Final data from the phase 1/2 ARROW study.

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Background: *RET* fusions are targetable oncogenic drivers in 1-2% of non-small cell lung cancers (NSCLC). ARROW (NCT03037385) study results (final data lock May 20, 2024) supported the US FDA approval of pralsetinib, a highly potent, oral, selective RET inhibitor for metastatic *RET*-altered NSCLC. Here, we present final study results. **Methods:** ARROW was a phase 1/2 open-label study conducted at 84 sites in 13 countries. Phase 2 included patients with *RET*-fusion-positive NSCLC who received 400 mg pralsetinib once daily (QD). Initially, treatment-naïve patients were not candidates for platinum-based therapy and presented with several unfavorable prognostic factors; this requirement was removed by protocol amendment in July 2019. Primary objectives were overall response rate (ORR, per RECIST v1.1) and safety. Progression-free survival (PFS) and overall survival (OS) are reported in the full efficacy population; the measurable disease population (MDP) was the primary analysis population for ORR and duration of response (DOR). **Results:** 281 patients with *RET*-fusion-positive NSCLC received pralsetinib 400 mg QD, with a median duration of treatment of 14.95 months (mos). Median age was 60 years; 46% were male. In the MDP (n=259), ORR was 70.3% (95% confidence intervals [CI]: 64.3, 75.8) and median DOR was 19.1 mos (95% CI: 14.5, 27.9; Table). In the efficacy population (N=281), median OS was 44.3 mos (95% CI: 30.9, 53.1) with median follow up of 47.6 mos (95% CI: 44.8, 49.2), and median PFS was 13.1 mos (95% CI: 11.4, 16.8). ORR (Table) and median PFS were markedly higher in the US (25.9 mos, n=64) vs. Asia (12.6 mos, n=122) or Europe (12.9 mos, n=95). In the safety population, 95% of patients experienced treatment-related adverse events (TRAEs); 66% experienced ≥grade 3. Common TRAEs included increased AST (n=128 [46%]), anemia (n=121 [43%]), increased ALT (n=98 [35%]), and hypertension (n=77 [27%]). 3 patients died due to TRAEs (pneumonia, n=2; interstitial lung disease and rhabdomyolysis, n=1 each). No new safety signals were identified with this update. **Conclusions:** Pralsetinib produced clinically meaningful and durable responses in patients with *RET*-fusion-positive NSCLC (regardless of prior therapies) with a manageable safety profile, confirming with this longer follow up previously published results. Clinical trial information: NCT03037385. Research Sponsor: Rigel Pharmaceuticals, Inc.; Blueprint Medicines; Genentech/Roche.

	All MDP (n=259)	Prior Platinum (n=130)	Treatment-naive (n=106)
ORR, % (95% CI)			
Overall	70.3 (64.3, 75.8)	63.1 (54.2, 71.4)	78.3 (69.2, 85.7)
US	(n=58) 77.6 (64.7, 87.5)	(n=31) 64.5 (45.4, 80.8)	(n=19) 100 (82.4, 100)
Europe	(n=89) 65.2 (54.3, 75)	(n=36) 63.9 (46.2, 79.2)	(n=43) 65.1 (49.1, 79)
Asia	(n=112) 70.5 (61.2, 78.8)	(n=63) 61.9 (48.8, 73.9)	(n=44) 81.8 (67.3, 91.8)
Median DOR, mos (95% CI)[a]	(n=182) 19.1 (14.5, 27.9)	(n=82) 31.8 (15.1, 40.4)	(n=83) 13.4 (9.4, 21.7)
Median DOR follow up, mos (95% CI)	46.8 (42.3, 50.2)	50.3 (46.9, 56.8)	42.3 (37.4, 44.2)

[a]Per FDA censoring rule.

8645 Poster Session

Final results of a phase II study of cabozantinib in patients with *MET*-altered lung cancers.

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Background: *MET* alterations define a subgroup of non-small cell lung cancers (NSCLC) sensitive to MET tyrosine kinase inhibitors (TKIs). Currently, only type I MET TKIs are approved for treating these patients. We evaluated the activity of cabozantinib, a type II multikinase inhibitor, in MET-altered lung cancers. **Methods:** This is a single-arm, phase 2 trial in which patients with metastatic MET-altered lung cancers received cabozantinib (60 mg daily) until disease progression or intolerable toxicity. A Simon two-stage minimax design was used, with a null hypothesis (H0) of a 10% response rate and an alternative hypothesis (H1) of 30%. With a type I error of 10% and a power of 90%, 16 patients were enrolled in the first stage, with at least two responses required to advance to the second stage, enrolling an additional nine patients. The primary endpoint was objective response rate (ORR) and would be considered met if five or more patients provided an objective response among the 25 evaluable patients treated. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Twenty-eight patients were treated. The median age was 68 (range 38–85) years. Most patients (82%; 23/28) had MET exon 14 alterations; 7% (2/28) had MET amplification only, and 12% (3/28) had concurrent MET exon 14 alteration and amplification. The median number of prior systemic therapies was two (range 1–6), and 86% had previously received a MET TKI. Among the 25 evaluable patients, the ORR was 20% (95% CI, 8.9–39.1). Four out of five patients who achieved a partial response had received prior MET TKI: two with crizotinib, one with tepotinib, and one with capmatinib. The median PFS and OS were 4.5 (95% CI, 3.3-5.7) months and 7.2 (95% CI, 2.9-11.5) months, respectively. Treatment-related adverse events were primarily grade 1 or 2, with the most common being fatigue (39%), diarrhea (39%), palmar-plantar erythrodysesthesia (36%), and anorexia (36%). Grade 3 or higher events included hypophosphatemia (14%), hypertension (11%), and elevated lipase (11%). No treatment-related deaths occurred. **Conclusions:** This trial met its primary endpoint. Cabozantinib demonstrated activity in MET-altered NSCLC, and prospective clinical proof-of-concept that type II MET TKI switching can rescue type I MET TKI progression was established. Clinical trial information: NCT01639508. Research Sponsor: Exelixis.

8646 Poster Session

Rechallenge with first-generation RET inhibitors in *RET*-rearranged NSCLC pre-treated with selpercatinib or pralsetinib: Results from the RET MAP registry.

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Background: *RET* fusions occur in 1-2% of patients with advanced non-small cell lung cancer (aNSCLC). First-generation RET inhibitors (RETi, selpercatinib and pralsetinib), have improved outcomes across treatment lines. Options at progression remain limited, especially in the absence of novel generation RETi. In real-world settings, rechallenge with the same class RETi is sometimes attempted, though efficacy and safety data are lacking. **Methods:** This multicenter retrospective analysis of the RET MAP registry included patients with *RET*-rearranged aNSCLC initially treated with selpercatinib or pralsetinib, followed by rechallenge with the same or a different first-generation RETi, as a single agent or in combination therapy. Clinical features, reasons for initial RETi discontinuation, treatment outcomes, and toxicity were assessed for both treatment courses. **Results:** Among 354 patients treated with first-generation RETi, same class RETi were re-administered in later lines in 33 (9.3 %) patients. At first RETi administration vs rechallenge, median prior lines were 2 (IQR 2–3) vs 4 (IQR 3–5), ECOG PS 0–1 was observed in 26 (78%) vs 25 (76%) patients, and brain metastases in 9 (27%) vs 13 (39%). Reasons for discontinuation of the first RETi were disease progression in 25 (76%) patients and toxicity in 8 (24%). RETi re-administration involved a change of first-generation RETi in 14 (42%) patients, monotherapy in 22 (67%), combination therapy in 11 (33%) (8 with other targeted agents for by-pass resistance, 3 with chemotherapy). It was given immediately after a prior RETi in 13 (39%) patients. At subsequent RETi treatment after progression on a prior RETi, ORR and median PFS were 18% and 2.17 months (95% CI 1.63–NR), respectively, with single-agent RETi (N=17), and 20% and 4 months (95% CI 3.55–NR), respectively, with RETi combined with other targeted agents (N=8). Patients who previously discontinued RETi due to toxicity (N=8) received a different RETi, with ORR and median PFS of 57% and 9.89 months (95% CI 5.33–NR), respectively. In this subgroup, 3 (37.5%) experienced serious side effects at re-administration of a different first-generation RETi. **Conclusions:** Rechallenge a different RETi of the same class is effective after initial discontinuation due to toxicity, though recurrent toxicity may occur in one-third of patients. In contrast, RETi rechallenge after progression demonstrates limited efficacy, primarily in selected cases treated with combination therapies. Research Sponsor: None.

TPS8647 **Poster Session**

TROPION-Lung14: A phase 3 study of osimertinib ± datopotamab deruxtecan (Dato-DXd) as first-line (1L) treatment for patients with *EGFR*-mutated locally advanced or metastatic (LA/M) non-small cell lung cancer (NSCLC).

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Background: Despite the benefit observed with osimertinib, most patients with LA/M *EGFR*-mutated NSCLC develop resistance and treatment options on or after disease progression are limited. Phase 3 clinical trial data, using agents with broad antitumor activity, have demonstrated the potential to extend the clinical benefit of 1L osimertinib and delay the onset of resistance. Dato-DXd, an antibody-drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor, has demonstrated efficacy as monotherapy in NSCLC in TROPION-Lung01, including in patients with *EGFR*-mutated advanced NSCLC. TROPION-Lung14 is evaluating the efficacy and safety of osimertinib ± Dato-DXd as 1L therapy in patients with *EGFR*-mutated LA/M NSCLC. **Methods:** TROPION-Lung14 (NCT06350097) is an ongoing phase 3, open-label, multicentre, randomized study. The study is enrolling patients (aged ≥18 years) with histologically or cytologically confirmed stage IIIB/IIIC or IV non-squamous, *EGFR*-mutated (exon 19 deletion or L858R) NSCLC, no prior EGFR tyrosine kinase inhibitor or other systemic therapy for stage IIIB/IIIC or IV disease, at least one measurable lesion per RECIST 1.1, and WHO performance status (PS) of 0 or 1. Prior to the randomized study period, ~20 patients will receive osimertinib + Dato-DXd in a non-randomized single-arm safety run-in . Following safety run-in, ~562 patients will be randomized 1:1 to osimertinib (80 mg orally [PO] QD) or osimertinib (80 mg PO QD) + Dato-DXd (6 mg/kg IV Q3W). Patients will be stratified by *EGFR* mutation type (Ex19Del vs L858R), WHO PS (0 vs 1) and central nervous system (CNS) metastasis status (yes vs no). Treatment will continue until RECIST v1.1-defined progression or unacceptable toxicity. The primary study endpoint is progression-free survival (PFS) assessed by blinded independent central review. Overall survival is a key secondary endpoint; other secondary endpoints include PFS by investigator, objective response rate, duration of response, PFS2, safety, pharmacokinetics and immunogenicity. Enrollment is ongoing. Clinical trial information: NCT06350097. Research Sponsor: AstraZeneca. This trial is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

TPS8648 **Poster Session**

SOHO-02: Phase III trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations.

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Background: Approximately 2-4% of non-small cell lung cancer (NSCLC) harbor activating human epidermal growth factor receptor 2 (*HER2*) mutations. This represents a major area of unmet medical need as no first-line HER2-targeted therapies are currently approved for patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations. BAY 2927088 is an oral, reversible tyrosine kinase inhibitor that potently targets HER2 and mutant epidermal growth factor receptor. Preliminary evidence from the Phase I/II SOHO-01 trial has demonstrated anti-tumor activity and a manageable safety profile in previously treated patients with NSCLC with *HER2*-activating mutations (PL04.03 presented at IASLC 2024 World Conference on Lung Cancer). Here we introduce the SOHO-02 trial evaluating the efficacy and safety of BAY 2927088 as first-line therapy in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations. **Methods:** SOHO-02 is an ongoing Phase III, open-label, randomized, multicenter trial of BAY 2927088 in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations (NCT06452277). Eligibility criteria include patients aged ≥18 years with: documented histologically or cytologically confirmed, locally advanced or metastatic non-squamous NSCLC; documented activating mutation in the tyrosine kinase domain of HER2; measurable disease per RECIST v1.1; no previous systemic therapy for locally advanced or metastatic disease; and eligibility to receive treatment with the selected platinum-based doublet-chemotherapy and pembrolizumab. Overall, 278 eligible patients will be randomized to BAY 2927088 p.o. 20 mg twice daily or standard of care (SoC; pembrolizumab in combination with cisplatin/pemetrexed or carboplatin/pemetrexed) in 21-day cycles. The primary endpoint is BAY 2927088 efficacy vs. SoC on progression-free survival per RECIST v1.1 as assessed by blinded independent central review (BICR). Key secondary endpoints include BAY 2927088 efficacy vs. SoC on overall survival, overall response rate, disease control rate, and duration of response per RECIST v1.1 by BICR, and BAY 2927088 safety and tolerability vs. SoC. Impact of BAY 2927088 on patient health-related quality of life and symptom severity will be evaluated using EORTC QLQ-C30 and NSCLC-SAQ. Enrollment is ongoing. Clinical trial information: NCT06452277. Research Sponsor: Bayer AG.

TPS8649 Poster Session

Onkoras-101: A phase 1a/1b open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of BBO-8520 in subjects with advanced KRAS^{G12C} mutant non-small-cell lung cancer.

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Background: BBO-8520 is a first-in-class, potent, selective, directly binding, orally bioavailable, covalent inhibitor of KRAS^{G12C}. It is effective against both the active GTP-bound (ON) state and the inactive GDP-bound (OFF) state of KRAS^{G12C}. BBO-8520 is being developed to treat patients with advanced cancer harboring the KRAS^{G12C} mutation. The oncogenic KRAS^{G12C} mutation results in an increased abundance of KRAS^{G12C} in the active GTP-bound (ON) state. While recent approvals of KRAS^{G12C}-targeted therapies provide a new treatment option for patients with KRAS^{G12C}-driven cancers, these agents exclusively target the GDP-bound (OFF) state of the protein, enabling the emergence of heterogeneous adaptive resistance. Thus, there is an urgent need for agents that can provide durable treatment benefit. **Methods:** This first-in-human, multicenter, open-label, Phase 1a/1b study evaluates the safety, tolerability, pharmacokinetics and preliminary antitumor activity of BBO-8520 as monotherapy and in combination with pembrolizumab in subjects with advanced non-small-cell lung cancer (NSCLC) with a KRAS^{G12C} mutation. BBO-8520 is administered orally once daily, in a 21-day treatment cycle. Patients enrolled in the trial must have histologically documented locally advanced or metastatic NSCLC with a KRAS^{G12C} mutation. Patients with treated or stable brain metastases are allowed to participate in the study. During Phase 1a dose escalation, BBO-8520 will be evaluated at escalating doses as monotherapy and in combination with pembrolizumab. The primary objective of Phase 1a is to evaluate the safety and tolerability of BBO-8520 monotherapy or in combination with pembrolizumab and determine the optimal dose(s) for Phase 1b dose expansion. Patients with KRAS^{G12C} -mutant NSCLC who have received prior treatment with KRAS^{G12C} (OFF) inhibitors are allowed to participate in Phase 1a. During Phase 1b dose expansion, BBO-8520 will be evaluated as monotherapy in expansion cohorts of: (1) patients with advanced NSCLC and prior treatment with KRAS^{G12C} (OFF) inhibitors; and (2) patients with advanced NSCLC and no prior treatment with KRAS^{G12C} inhibitors. BBO-8520 will also be evaluated in combination with pembrolizumab in an expansion cohort of patients with advanced NSCLC and no prior treatment with immune checkpoint or KRAS^{G12C} inhibitors. The primary objective of Phase 1b is to verify safety and tolerability of BBO-8520 monotherapy and in combination with pembrolizumab and evaluate antitumor activity (objective response rate evaluation). Clinical trial information: NCT06343402. Research Sponsor: BridgeBio Oncology Therapeutics.

TPS8650 **Poster Session**

Phase 1/2 clinical trial of JIN-A02, a 4th generation EGFR-TKI in EGFR-mutated advanced/metastatic non-small cell lung cancer.

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Background: Epidermal growth factor receptor (*EGFR*) mutations are the predominant drivers of NSCLC. While EGFR tyrosine kinase inhibitors (TKIs) are the primary treatment for *EGFR*-mutant NSCLC patients, resistance inevitably develops, leading to disease progression. JIN-A02, a novel 4th generation EGFR-TKI, intended for oral administration, selectively and reversibly binds to *EGFR* mutations, including the C797S and/or T790M mutation that causes resistance to 3rd generation of EGFR-TKIs. Preclinical studies with *EGFR* C797S and/or T790M mutated cell lines and C797S+ xenograft mice model showed that JIN-A02 inhibits cell and tumor growth in a dose dependent manner and exhibits high selectivity over wild-type *EGFR*. Moreover, JIN-A02 has been shown to penetrate the blood-brain barrier and exhibit anti-tumor activity in an intracranial tumor model. This phase 1/2 study is designed to evaluate the safety and anti-tumor activity of JIN-A02 in *EGFR*-mutant NSCLC patients. **Methods:** JIN-A02 is under evaluation in Phase 1/2, multicenter, an open-label trial (NCT05394831) for subjects with advanced NSCLC harboring C797S and/or T790M mutation as a monotherapy. The primary objective is to assess safety, tolerability, pharmacokinetics, and anti-tumor effect for determining the recommended phase 2 dose (RP2D) of JIN-A02. Inclusion criteria are that the subject ($\geq$ 18 years) must have advanced or metastatic NSCLC showing progressive disease post-treatment with approved standard EGFR-TKIs and/or platinum-based anticancer chemotherapy, with ECOG status 0 or 1. The study consists of 3 parts: dose escalation (Part A), dose exploration (Part B), and dose expansion (Part C). In Part A, JIN-A02 is administered orally once daily from 12.5 mg, and at least 3 subjects are recruited per cohort conducted over 28 days cycles to evaluate the maximum tolerated dose. Dose escalation between cohorts is made at up to twice the prior dose level. Dose-limiting toxicities (DLTs) are assessed over 21 days. Part B aims to further evaluate JIN-A02 safety to determine the RP2D using two preliminary effective dose levels from Part A. In Part C, subjects are divided into 5 cohorts based on the EGFR mutation status (both or single positive for C797S and T790M), and the anti-tumor activity of JIN-A02 is evaluated according to RECIST v1.1 at the RP2D. Clinical trial information: NCT05394831. Research Sponsor: None.

TPS8651 Poster Session

Phase 3 trial of the therapeutic cancer vaccine OSE2101 versus docetaxel in patients with metastatic non-small cell lung cancer and secondary resistance to immunotherapy.

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Background: OSE2101 (TEDOPI) is a therapeutic cancer vaccine composed of multiple peptides restricted to HLA-A2 phenotype targeting tumor-associated antigens (CEA, HER-2, MAGE-2, MAGE-3, P53) frequently expressed in non-small cell lung cancer (NSCLC). In prior studies, OSE2101 strongly induced T cell immune responses, with higher immune responses associated with longer survival (OS). In the randomized ATALANTE-1 study, OSE2101 significantly improved OS with a better safety profile and quality of life (QoL) compared to third-line chemotherapy (CT) in patients with NSCLC with progressive disease (PD) after at least 12-weeks of second line anti-PD(L)1 monotherapy. The aim of the phase III ARTEMIA study is to confirm the benefit of OSE2101 versus CT in second-line treatment of patients with NSCLC and secondary resistance to immune checkpoint inhibitor (ICI) given in the first line setting. **Methods:** HLA-A2 positive patients with metastatic NSCLC without known EGFR, ALK, ROS1 actionable gene alterations, no brain metastases, ECOG PS 0 or 1, who had PD $\geq$ 24 weeks after first line CT-ICI including at least 12 weeks of maintenance ICI without cytotoxic therapy, will be randomized 2:1 to receive either OSE2101 or docetaxel. Randomization will be stratified by histology (squamous vs non-squamous), and ECOG PS (0 or 1). Patients will receive subcutaneous OSE2101 every 3 weeks for 6 injections, then every 8 to 12 weeks up to end of year 2. In the control group, patients will receive docetaxel at 75 mg/m2 per standard of care. Primary endpoint is OS defined as time from randomization to death of any cause. Secondary endpoints include QoL Physical, Role, and Global Health Score by EORTC QLQ-C30 questionnaire, and time to ECOG PS deterioration. Other endpoints are safety, tumor assessments by RECIST 1.1 and Net Treatment Benefit. For patients who agree, biomarkers in tumor biopsies and blood are planned. The primary estimand is OS in all randomized and treated patients using treatment policy approach for intercurrent events and the hazard ratio (HR) as population-level summary.Assuming a HR of 0.70 with a power of 80% using a 2-sided log-rank test, 363 patients will be enrolled to reach 269 events. An interim analysis is planned. The ARTEMIA phase 3 study aims to confirm the benefit on survival and quality of life of the therapeutic cancer vaccine OSE2101 compared to docetaxel in second-line treatment of HLA-A2 positive patients with NSCLC and secondary resistance to immune checkpoint inhibitor. Recruitment is ongoing in North America and Europe. Clinical trial information: NCT06472245. Research Sponsor: OSE Immunotherapeutics.

TPS8652 **Poster Session**

KEYMAKER-U01 substudy 01A: Phase 1/2 study of pembrolizumab plus ifinatamab deruxtecan (I-DXd) or patritumab deruxtecan (HER3-DXd) with or without chemotherapy in untreated stage IV non–small-cell lung cancer.

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Background: A standard-of-care option for metastatic non–small-cell lung cancer (NSCLC) with no targetable genetic alterations includes pembrolizumab plus chemotherapy. However, there remains an unmet need for patients who do not respond to standard treatment. Ifinatamab deruxtecan (I-DXd) and patritumab deruxtecan (HER3-DXd) are investigational antibody-drug conjugates (ADCs) against B7 homologue 3 and human epidermal growth factor receptor 3, respectively, two proteins that are highly expressed in NSCLC tumors. Both I-DXd and HER3-DXd are conjugated with a topoisomerase 1 inhibitor payload, resulting in apoptosis of target cells. Preclinical and preliminary clinical data suggest that combining an immune checkpoint inhibitor with an ADC may provide robust antitumor activity. KEYMAKER-U01 substudy 01A (NCT04165070) is a phase 1/2, two-part, rolling arm, open-label study assessing the efficacy and safety of pembrolizumab plus an investigational agent (part A: vibostolimab, boserolimab, MK-4830, and MK-0482; part B: I-DXd and HER3-DXd), with or without chemotherapy in untreated stage IV NSCLC. We present the study design for KEYMAKER-U01 substudy 01A part B. **Methods:** Eligible participants for KEYMAKER-U01 substudy 01A part B are aged ≥18 years with previously untreated histologically or cytologically confirmed stage IV (per American Joint Committee on Cancer v8) squamous or nonsquamous NSCLC and measurable disease per RECIST v1.1 as assessed by investigator and verified by blinded independent central review (BICR). Additional eligibility criteria include ECOG PS of 0 or 1, provision of an archival tumor sample or newly obtained biopsy of a nonirradiated tumor for biomarker analysis, and no *EGFR, ALK, or ROS1* mutations for which first-line targeted therapy is indicated. In part B, 10–30 participants will be allocated to treatment arms 5–7. In Arms 5 and 6, participants will receive I-DXd plus pembrolizumab 200 mg Q3W (Arm 5) or I-DXd plus pembrolizumab with 4 cycles of carboplatin area under the curve 5 or 6 mg/ml/min (Arm 6); I-DXd dose will be at 8mg/kg. In Arm 7, participants will receive HER3-DXd 3.2, 4.8, or 5.6 mg/kg plus pembrolizumab and carboplatin. Participants can receive I-DXd and HER3-DXd until disease progression or unacceptable toxicity and pembrolizumab up to 35 cycles. The primary endpoint is incidence of dose-limiting toxicities until the start of cycle 2, and AEs and treatment discontinuations due to AEs until 40 days after last treatment (90 days for serious AEs); secondary endpoints include ORR and DOR, both per RECIST v1.1 by BICR, and pharmacokinetic parameters, including maximum concentration (C_{max}) and maximum trough concentration (C_{trough}) of I-DXd and HER3-DXd. Enrollment will be ongoing globally. Clinical trial information: NCT04165070. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8653 **Poster Session**

ARTEMIDE-Lung03: A phase 3, randomized, double-blind, multicenter, global study of rilvegostomig or pembrolizumab in combination with platinum-based chemotherapy as first-line treatment for patients with metastatic non-squamous non-small-cell lung cancer whose tumors express PD-L1.

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Background: In the United States, non-squamous histology accounts for approximately 70% of all non-small-cell lung cancers (NSCLCs), and stage IV disease with no targetable alterations is associated with poor prognosis, with a median overall survival of around 2 years. Immunotherapy targeting programmed cell death (ligand)-1 (PD-1/PD-L1) with or without platinum-based chemotherapy (PBC) is a standard of care first-line (1L) chemotherapy for patients with advanced non-squamous NSCLC. Despite the efficacy of this approach, not all patients respond to PD-1/PD-L1 immunotherapy and more effective therapeutic strategies are needed. Inhibition of the co-inhibitory T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) pathway in combination with PD-1/PD-L1 blockade to increase immunotherapy efficacy is being investigated in NSCLC, as well as other cancer types. Preliminary results (Hiltermann TJN, et al. *J Thorac Oncol [WCLC]* 2024; abstract OA11.03) show that rilvegostomig, a monovalent, bispecific, humanized IgG1 monoclonal antibody targeting both PD-1 and TIGIT receptors, achieved encouraging antitumor response rates and durable responses with a manageable safety profile in NSCLC. The phase 3, randomized, double-blind, multicenter ARTEMIDE-Lung03 study (NCT06627647) will assess the efficacy and safety of rilvegostomig versus pembrolizumab, in combination with platinum-based doublet chemotherapy, as 1L treatment for participants (pts) with non-squamous metastatic NSCLC (mNSCLC). **Methods:** Approximately 878 pts will be randomized 1:1 to either Arm A: rilvegostomig + PBC (pemetrexed + cisplatin or carboplatin) intravenous (IV) every three weeks (Q3W) for 4 cycles followed by rilvegostomig + pemetrexed maintenance treatment IV Q3W, or Arm B: pembrolizumab + chemotherapy IV Q3W for 4 cycles followed by pembrolizumab + pemetrexed maintenance IV Q3W. Eligibility criteria include histologically or cytologically confirmed non-squamous mNSCLC not amenable to curative treatment, tumors expressing PD-L1 (TC $\geq$1%), an Eastern Cooperative Oncology Group performance status of 0 or 1, no sensitizing *EGFR* mutations, *ALK* or *ROS1* rearrangements, or mutations in other oncogenes with approved 1L therapies available. Dual primary endpoints are progression-free survival (Response Evaluation Criteria in Solid Tumors v1.1 by blinded independent central review) and overall survival. Safety/tolerability and biomarkers will also be assessed. The study will be conducted across approximately 350 sites in 25–30 countries. Clinical trial information: NCT06627647. Research Sponsor: AstraZeneca.

TPS8655 Poster Session

Phase 1b/2 study evaluating telisotuzumab adizutecan (ABBV-400; Temab-A) in combination with budigalimab in patients (pts) with advanced non-squamous (NSQ) non-small cell lung cancer (NSCLC) with no prior treatment for advanced disease and no actionable genomic alterations.

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Background: c-Met (MET) protein expression is frequently increased in NSCLC and is associated with poor prognosis. 24% of pts with NSQ *EGFR* wildtype (WT) NSCLC exhibit increased c-Met protein expression, ie, ≥25% 3+ via IHC. Addition of programmed cell death (ligand) 1 (PD-[L]1) inhibitors to chemotherapy (CT) has improved treatment of NSCLC regardless of PD-(L)1 expression. However, more-effective therapies are needed, particularly for pts with no known actionable genomic alterations. Temab-A is an antibody-drug conjugate comprising the c-Met protein–targeting antibody telisotuzumab and the potent topoisomerase 1 inhibitor adizutecan payload attached via a stable cleavable linker. In an ongoing phase 1 study (NCT05029882), Temab-A monotherapy demonstrated manageable safety and promising efficacy in pts with advanced/metastatic (a/m) NSQ *EGFR* WT NSCLC in second line and later, with an objective response rate (ORR) of 48% (23/48) across all c-Met expression levels and clinical benefit rate of 85% (41/48) (De Miguel et al. *Ann Oncol*. 2024;35:S805-S806). Herein, we describe a study evaluating Temab-A in combination with the PD-1 inhibitor budigalimab. **Methods:** This multicenter, global,open-label, phase 1b/2, randomized (in part 2) study (NCT06772623) will enroll ~172 pts (≥18 yr) with a/m NSQ NSCLC. Eligible pts have ECOG 0 or 1, measurable disease per RECIST v1.1, and documented *EGFR* WT and PD-L1 status. Primary objectives are to evaluate safety and tolerability, assess efficacy as measured by ORR by blinded independent central review, and select the recommended phase 3 dose of Temab-A combined with budigalimab. Secondary objectives include assessment of efficacy outcomes (PFS, DOR, OS, and disease control rate), characterization of PK and immunogenicity, and evaluation of PD and potential predictive biomarkers. The study has 2 parts: a safety dose-escalation part 1 and a dose-optimization part 2. Part 1 enrolls ~12 pts who have received ≤1 prior systemic therapy for a/m NSCLC, including platinum-based CT, an immune checkpoint inhibitor, or targeted therapy. Pts receive escalating doses of Temab-A IV Q3W guided by BOIN design in combination with a fixed dose of budigalimab IV Q3W. Dose-limiting toxicities are evaluated during cycle 1. Part 2 enrolls ~160 pts who have not received prior systemic therapy for a/m NSCLC. Pts are randomized 1:1:1:1 to Temab-A at 1 of 2 doses determined in part 1 + budigalimab, to budigalimab + CT, or to SOC (pembrolizumab + CT) arms. Randomization is stratified by PD-L1 expression and history of brain metastases. Treatment continues until disease progression, intolerable toxicity, or other discontinuation criteria are met. The first dosing of the first patient enrolled is planned in March 2025. Clinical trial information: NCT06772623. Research Sponsor: AbbVie Inc.; n/a

TPS8656 **Poster Session**

Krascendo 2: A phase III study of divarasib and pembrolizumab vs pembrolizumab and chemotherapy in patients with previously untreated, advanced or metastatic, *KRAS* G12C-mutated non-small cell lung cancer (NSCLC).

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Background: *KRAS G12C* mutations are found in ~12% of NSCLC cases. The recommended first-line treatment for patients (pts) with advanced or metastatic non-squamous *KRAS G12C*-mutated (*G12C*+) NSCLC is immunotherapy (most commonly pembrolizumab [pembro]) ± chemotherapy (chemo); however, there is an unmet need in this pt population for more efficacious therapies with tolerable and manageable safety profiles. Divarasib is a potent KRAS G12C inhibitor that has shown efficacy and safety as a monotherapy in pts with previously treated, advanced or metastatic *KRAS G12C*+ NSCLC. Previous reports suggest that combinations of KRAS G12C inhibitors and pembro have promising anti-tumor activities with manageable safety profiles. We hypothesize that divarasib plus pembro may be an effective and well tolerated first-line chemo-free treatment option in pts with advanced or metastatic *KRAS G12C*+ NSCLC. **Methods:** Krascendo 2 (CO45042; NCT06793215) is a randomized, open-label, multicenter, global, phase III study, evaluating the efficacy and safety of first-line treatment with divarasib and pembro vs pembro and chemo (pemetrexed + carboplatin/cisplatin), in pts with advanced or metastatic *KRAS G12C*+ NSCLC. Eligible pts (≥18 years old) must have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, measurable disease per RECIST version 1.1, and histologically/cytologically confirmed advanced or metastatic, non-squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy and is previously untreated. Pts must also have known programmed death-ligand 1 (PD-L1) expression status and *KRAS G12C*+ status. Asymptomatic individuals with stable and treated central nervous system (CNS) metastases are eligible. Pts will be randomized 1:1 to receive either oral divarasib daily and intravenous (IV) pembro (in 21-day cycles), or IV pembro, pemetrexed and four cycles of platinum-based chemo (in 21-day cycles), until disease progression, or unacceptable toxicity. Pts will be stratified by PD-L1 expression status (tumor proportion score or tumor cell <1% vs 1–49% vs ≥50%), ECOG PS (0 vs 1), and history of CNS metastases (yes vs no). Pts who show clinical benefit per investigator judgment may continue study treatment after disease progression at the investigator's discretion. Primary endpoints are progression-free survival by blinded independent central review (BICR) and overall survival. Secondary endpoints include confirmed objective response rate and duration of response by BICR, changes in patient-reported symptoms and functioning from baseline to Cycle 5 assessed via questionnaires, and safety. Tumor assessments will occur at screening, every 6 weeks (±7 days) for the first 72 weeks after randomization, and then every 9 weeks (±7 days). Clinical trial information: NCT06793215. 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, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

TPS8657 Poster Session

FIRST-NEC (GFPC 01-2022): A multicenter phase II study evaluating the efficacy and safety of the combination of durvalumab with etoposide and platinum as first line treatment in patients with advanced large-cell neuroendocrine lung carcinomas (LCNECs).

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Background: LCNECs of the lung are rare lung tumors (2%) with difficult histopathological diagnosis (70-80% confirmation rate after centralized review). Platinum–based regimen is currently the recommended first-line treatment for advanced LCNECs. However it results in poor median progression-free survival (PFS) and overall survival (OS) of 5 months and 7.7 months, respectively. Retrospective studies have suggested efficacy of immune checkpoint inhibitors against LCNECs with significantly prolonged OS. In addition, the CASPIAN trial demonstrated the superiority of durvalumab plus platinum-etoposide over chemotherapy alone in patients with extensive-stage neuroendocrine small cell lung cancer, with an acceptable toxicity profile. **Methods:** This ongoing single-arm phase II trial is designed to evaluate the efficacy and safety of durvalumab in combination with platinum-etoposide as first line treatment in pts with locally diagnosed advanced LCNEC. Key selection criteria are age $\geq$ 18 years, ECOG PS 0-1, measurable disease (RECIST 1.1) and locally advanced (Stage III) ineligible for loco-regional therapy or metastatic (Stage IV). Central confirmation of the histopathological diagnosis will be performed for all pts at the start of treatment. All pts will receive 4 cycles of induction with durvalumab 1500mg, platinum (either carboplatin AUC5 or cisplatin 80mg/m^2 at D1) and etoposide 100mg/m^2 (D1-D3), repeated every 3 weeks. Durvalumab 1500mg will be continued alone every 4 weeks for a maximum of 24 additional cycles or until disease progression or unacceptable toxicity. The primary endpoint is to determine, in pts with confirmed diagnosis, 12-month progression-free rate (12M-PFR) as per central radiological review. Secondary endpoints include PFS, OS and safety. Radiological criteria will be described using the RECIST 1.1 both as per investigator's assessment and as per central radiological review. Biomarkers will be studied as predictive and prognostic factors of efficacy. Efficacy will be assessed sequentially every ten pts using a Bayesian approach. Analogous to a frequentist approach from an A'Hern-Fleming single-stage design, 51 evaluable pts will be enrolled. A futility stopping rule will stop the trial if there is a high probability (>80%) that the 12M-PFR is less than or equal to P0 (15%). Finally, a trial emulation will be performed as an exploratory analysis to assess PFS and OS compared to an external control arm by using real-world data from the ESME database. Since the start of recruitment (June 2024), 13 patients with a confirmed diagnosis have been included. Clinical trial information: NCT06393816. Research Sponsor: French ministry of health / French National Cancer Institute (INCa); PHRC-K23-033; Astrazeneca; Not applicable (drug supply).

TPS8658 Poster Session

TeliMET NSCLC-04: A phase 2, open-label, randomized, global study of 2 telisotuzumab vedotin regimens in patients with previously treated c-Met protein–overexpressing, locally advanced/metastatic non-squamous *EGFR* wildtype non-small cell lung cancer.

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Background: c-Met protein (also known as MET protein) overexpression is observed in ~25% of patients with non-squamous *EGFR* wildtype (WT) non-small cell lung cancer (NSCLC) and is associated with poor prognosis. Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate consisting of the monoclonal antibody telisotuzumab and the cytotoxic payload monomethyl auristatin E. The primary analysis of the phase 2 LUMINOSTY trial (NCT03539536) demonstrated that Teliso-V at 1.9 mg/kg once every 2 weeks (Q2W) was associated with durable responses in patients with previously treated c-Met protein–overexpressing (OE) advanced/metastatic (a/m) non-squamous *EGFR* WT NSCLC, and adverse events (AEs) were generally manageable. The overall response rate was 28.6% among all patients with c-Met protein overexpression and 34.6% among those with c-Met high protein overexpression (Camidge et al. *JCO* 2024;42:3000-11). **Methods:** This global, multicenter, open-label, randomized phase 2 study (NCT06568939) evaluates the safety and efficacy of Teliso-V monotherapy at 1.6 mg/kg Q2W and 1.9 mg/kg Q2W in patients with previously treated c-Met protein OE, a/m non-squamous *EGFR* WT NSCLC. Eligible patients are ≥18 years old with c-Met protein OE (≥25% tumor cells at 3+ intensity by immunohistochemistry assay [investigational use only assay for MET (SP44) (Roche)]), a/m non-squamous *EGFR* WT NSCLC. Patients must have measurable disease according to RECIST v1.1, ECOG PS 0–1, and documented disease progression on ≥1 prior lines of therapy (≤1 line of prior chemotherapy) in the a/m setting. Approximately 100 patients will be randomized 1:1 to receive Teliso-V monotherapy at either 1.6 mg/kg or 1.9 mg/kg Q2W until disease progression or other protocol-specified discontinuation criteria are met. The primary safety endpoints are treatment-emergent AEs (TEAEs; any grade and grade ≥2), interstitial lung disease (any grade and grade ≥2), peripheral neuropathy (any grade and grade ≥2), ocular surface disorders (any grade and grade ≥2), TEAEs leading to discontinuation, and grade 5 TEAEs. The primary efficacy endpoint is objective response based on RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are pharmacokinetics, patient-reported outcomes, duration of response by BICR, progression-free survival by BICR, and overall survival. Clinical trial information: NCT06568939. Research Sponsor: AbbVie, Inc.; n/a.

TPS8659 Poster Session

Phase 2, multicenter study of frontline maintenance therapy with lifileucel plus pembrolizumab in advanced non-small cell lung cancer.

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Background: Tumor-infiltrating lymphocyte (TIL) therapy with lifileucel plus pembrolizumab (pembro) demonstrated durable and deepening responses with an objective response rate (ORR) of 64.3% in patients (pts) with anti–PD-1/PD-L1–naive, *EGFR* wild-type, locally advanced or metastatic non-small cell lung cancer (mNSCLC) in cohort 3A of the IOV-COM-202 phase 2 open-label study (NCT03645928), with 4 of 5 ongoing responses lasting >20 months from start of therapy and no new safety signals. We added two new cohorts within this basket study, 3D and 3E, which evaluate if adding lifileucel to pembro ± pemetrexed in the maintenance phase of standard-of-care (SOC) therapy (from tumors procured in treatment-naive pts [3D] versus those who had already started receiving SOC chemotherapy [3E]) is feasible and provides added benefit with an acceptable safety profile. Incorporating TIL with current SOC has the potential to address a major unmet need by improving outcomes that are not durable or adequate for many pts with NSCLC. **Methods:** Pts have tumor resection before cycle 1 (3D) or between cycles 1 and 4 (3E) of frontline platinum-doublet chemotherapy plus pembro. After completion of SOC chemotherapy, a dose of pembrolizumab will be given followed by nonmyeloablative lymphodepletion (NMA-LD) (day −5 to day −3: cyclophosphamide 20 mg/kg/day; day −5 to day −2: fludarabine 25 mg/m2/day). Lifileucel is administered on day 0, followed by IL-2 continuous infusion on days 1–4. Following lifileucel and IL-2, pembro (plus pemetrexed if nonsquamous histology) will be continued for up to 2 years or until disease progression or unacceptable toxicity. Eligible adults have histologically confirmed mNSCLC, no actionable mutations with effective targeted therapy, no prior systemic therapy for metastatic NSCLC, ECOG performance status 0–1, estimated life expectancy ≥6 mo, and ≥1 resectable lesion >1.5 cm in diameter to generate lifileucel. Prior organ allograft or cell transfer therapy, symptomatic brain metastases, current systemic steroid therapy >10 mg/day of prednisone or other steroid equivalent, and active illnesses or autoimmune disorders are not permitted. Endpoints include ORR, complete response rate, disease control rate, and PFS by investigator-assessed RECIST v.1.1, OS, percentage of manufactured lifileucel drug products that meets release specification, and incidence of grade ≥3 treatment-emergent adverse events. Selected exploratory endpoints include in vivo T-cell persistence, correlative biomarkers, and circulating tumor DNA. Enrollment of approximately 20 pts per cohort will take place in Europe and North America. Clinical trial information: NCT03645928. Research Sponsor: Iovance Biotherapeutics, Inc.

TPS8660 **Poster Session**

NAPISTAR 1-01: An international phase I/II trial of the novel ADC TUB-040 in platinum-resistant ovarian cancer (PROC) and relapsed/refractory adenocarcinoma non-small cell lung cancer (NSCLC).

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Background: NaPi2b, encoded by SLC34A2, is a sodium-dependent phosphate transporter overexpressed in various cancers, particularly high levels in high-grade ovarian cancer (HGSOC) and non-small cell lung cancer (NSCLC) adenocarcinomas. This tumor-selective expression pattern makes NaPi2b a compelling target for therapeutic development. TUB-040 is an innovative antibody-drug conjugate (ADC) combining a NaPi2b-specific Fc-silenced monoclonal antibody with the cytotoxic payload exatecan, a potent topoisomerase-I inhibitor exhibiting a robust bystander effect. This ADC utilizes a cleavable dipeptide linker (P5) to achieve a uniform drug-to-antibody ratio of 8, optimizing its potency against heterogeneous tumors. **Methods:** NAPISTAR 1-01 (NCT06303505) is an open-label, multicenter, Phase I/IIa study investigating TUB-040 in platinum-resistant ovarian cancer (PROC) and advanced NSCLC adenocarcinoma . Phase I employs a stepwise dose escalation strategy using adaptive titration design (ATD), followed by a Bayesian Optimal Interval (BOIN) model. The dose escalation framework includes initial double-dosing steps, transitioning to modified Fibonacci increments with intra-patient escalation permissible at low exposure levels. An independent Dose Escalation Board manages safety oversight. Phase IIa involves randomized dose optimization at multiple dosing levels to identify the optimal therapeutic window. Enrollment of approximately 100 patients across the US, EU and UK is planned, with dose escalation currently underway. Clinical trial information: NCT06303505. Research Sponsor: None.

TPS8661 Poster Session

A multicenter, open-label, single-arm phase I/II study to assess the efficacy and safety of WSD0922-FU in patients with EGFR C797Sm+ advanced non-small cell lung cancer (NSCLC) in China (NCT06631989).

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Background: Although 3rd-generation EGFR TKIs, such as Osimertinib, Almonertinib, Furmonertinib, Befotertinib etc. are highly effective in front-line metastatic *EGFR*-mutated (*EGFR*m) NSCLC, treatment resistance ultimately occurs, including the emergence of the on-target C797S mutation for which there are no approved TKIs. WSD0922-FU is an oral, central nervous system (CNS)-penetrant, wildtype-sparing, ATP non-competitive, reversible EGFR inhibitor targeting EGFR aberrations in NSCLC and High-Grade Astrocytoma. It has shown promising preclinical and clinical data, including antitumor CNS activity that may improve patient outcomes. Additionally, combining WSD0922-FU with standard therapies may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with *EGFR*m+ NSCLC. WSD0922-102 (NCT06631989) is an ongoing phase 1/2, open-label, multicenter trial evaluating the efficacy and safety of WSD0922-FU in patients with EGFR C797Sm+ NSCLC in China. **Methods:** Adult patients with EGFR C797Sm+ NSCLC were initially treated with oral WSD0922-FU, with three doses selected from phase I dose escalation (MC1914, NCT04197934) as a bridging PK study in China. After DLT evaluation, expansion was initiated for each dose followed by extension for the dose selected as the recommended phase 2 dose (RP2D). Key inclusion criteria include patients ≥18 years of age with metastatic *EGFR* C797Sm+ NSCLC; Eastern Cooperative Oncology Group performance status 0–1; and failed in the previous 3rd generation EGFR-targeted TKI treatment for bridging PK study, with only one 3rd generation EGFR TKI for expansion and with only one first-line 3rd generation EGFR TKI for extension. All patients must harbor an EGFR C797S resistance mutation (locally assessed for tissue/liquid samples). Key exclusion criteria are tumors harboring EGFR T790M mutations, EGFR exon 20 insertions, or MET aberrations. Dose escalation primary endpoints are maximum tolerated dose, RP2D and safety. The expansion and extension primary endpoints are overall response rate (ORR) by RECIST 1.1. Secondary endpoints include ORR (dose escalation), duration of response, disease control rate, progression-free survival, overall survival, antitumor CNS activity (iORR) by RANO-BM, and safety (dose expansion and extension). The phase 1 dose escalation adopts a 3+3 design. Patients will be enrolled into 3 treatment cohorts: dose escalation (n≈12-15), dose expansion (n≈20), and dose extension (n≈70). Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Enrollment in this study for dose expansion cohorts is ongoing and 15 sites are open across China. Clinical trial information: NCT06631989. Research Sponsor: None.

TPS8662 Poster Session

Phase 2 cohort-2 trial in progress: Vabametkib plus lazertinib for patients with EGFR-mutant NSCLC who developed resistance to 1st-line, 3rd-gen-EGFR TKIs via C-Met dysregulation.

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Background: Third-generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) have emerged as a promising first-line treatment for Non-Small-Cell Lung Cancer (NSCLC) patients with EGFR T790M mutations, as well as EGFR exon 19 deletions and exon 21 L858R mutations. Recently, lazertinib, combined with amivantamab, has been approved as a potential first-line therapy for NSCLC. Despite these advancements, there remains a significant unmet medical need for patients who develop resistance to first-line third-generation EGFR TKIs. ABN401 (vabametkib), a selective oral c-MET inhibitor, has shown anti-tumor activity in preclinical studies, both as monotherapy and in combination with other treatments. Currently in a phase 2 clinical trial, this study aims to evaluate the combination of vabametkib and lazertinib in patients who have developed resistance to 3rd generation EGFR TKIs. **Methods:** ABN401-003 phase 2 cohort-2 is a multicenter, open-label trial that evaluates the dose escalation, safety and efficacy of the combination therapy of vabametkib and lazertinib in patients resistant to first-line EGFR TKIs. Enrollment criteria include MET amplification (GCN >10 by NGS or FISH) or c-MET overexpression (IHC score ≥90). The study consists of three parts: Part 1 (safety run-in), a traditional 3+3 dose-escalation study assesses the safety of vabametkib combined with lazertinib. Up to 18 patients will be evaluated in safety run-in, with dose adjustments based on dose-limiting toxicities (DLTs). Part 2: Randomized Dose Optimization – Two combination dose levels, determined from Part 1, will be tested in 40 patients to identify the optimal dose. Part-2 may be skipped if the maximum tolerated dose (MTD) is established in Part 1. Part 3 [randomized clinical trial – The optimal dose combination will be compared to the standard of care (SOC) in 80 patients. Key secondary endpoints include objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and duration of response (DOR). Additionally, safety and patient-reported outcome will be evaluated. Clinical trial information: NCT05541822. Research Sponsor: None.

TPS8663 **Poster Session**

A phase 1/2 open-label, multicenter, first-in-human study of the safety, tolerability, pharmacokinetics, and antitumor activity of BH-30643 in adult subjects with locally advanced or metastatic NSCLC harboring EGFR and/or HER2 mutations (SOLARA).

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Background: Clinical outcomes for patients with metastatic *EGFR*-mutant NSCLC have steadily improved with successive generations of EGFR tyrosine kinase inhibitors (TKIs). However, there remains significant need for further advancement in progression-free survival (PFS) and overall survival (OS), as these outcomes still fall short when compared to the remarkable benefits observed with newer TKIs in *ALK* and *ROS1* driven NSCLC. BH-30643 is a first-in-class EGFR TKI with a novel macrocyclic structure offering potent, reversible, mutant selective inhibition of classical and atypical *EGFR* activating mutations without vulnerability to common on-target resistance mutations. Cellular activity of BH-30643 was recently described (AACR 2025) demonstrating sub-nanomolar potency for EGFR exon 19del and L858R classical mutations which are maintained in the presence of T790M +/- C797S. High potency was also observed against atypical *EGFR* mutations (e.g., G719X, L861Q, S768I) and exon 20 insertions, as well as mutant *HER2*. Such an OMNI-EGFR inhibitor may have the potential to overcome some of the limitations of earlier agents. **Methods:** SOLARA (NCT06706076, BH-30643-01) is a Phase 1/2, multicenter, open-label, dose escalation, first-in-human study to determine the safety, tolerability, pharmacokinetics, and antitumor activity of BH-30643, in adult subjects with locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations. Enrollment based on local molecular testing and/or liquid biopsy is permitted. Asymptomatic brain metastases (treated or untreated) are eligible. BH-30643 is administered orally twice daily until disease progression or intolerable toxicity. The study consists of an initial dose escalation part using a Bayesian optimal interval design to identify Recommended Dose(s) for Evaluation (RDE). Dose-limiting toxicities (DLTs) are evaluated for the first 21 days of treatment. A subsequent expansion part will further evaluate the RDE(s) to identify a Recommended Phase 2 Dose (RP2D), studying cohorts with or without prior systemic therapy across a range of *EGFR*/*HER2* driver mutations. Efficacy will be evaluated by RECIST 1.1 criteria and toxicity by CTCAE V5.0. Plasma is collected for circulating tumor DNA (ctDNA) analysis at baseline and on treatment. Enrollment is underway, with planned enrollment across ~35 sites in multiple continents. Clinical trial information: NCT06706076. Research Sponsor: BlossomHill Therapeutics, Inc.

TPS8664 **Poster Session**

A randomized phase 3 study of ivonescimab plus chemotherapy versus pembrolizumab plus chemotherapy for the first-line treatment of metastatic non–small cell lung cancer: HARMONi-3.

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Background: The additionof antiangiogenic agents to standard first-line treatment with a programmed cell death protein 1 (PD-1) inhibitor and platinum doublet chemotherapy has shown efficacy in patients with metastatic non–small cell lung cancer (NSCLC). Ivonescimab is a novel tetravalent bispecific antibody that targets PD-1 and vascular endothelial growth factor. In a phase 2 trial, ivonescimab plus chemotherapy showed objective response rates (ORRs) of 71.4% and 54.2% and median progression-free survival (PFS) of 11.1 and 13.3 months in patients with metastatic squamous (SQ) and nonsquamous (NSQ) NSCLC, respectively (1). **Methods:** The multiregional, randomized, double-blind, phase 3 HARMONi-3 trial (NCT05899608) will compare the efficacy and tolerability of ivonescimab plus chemotherapy with pembrolizumab plus chemotherapy as first-line treatment in patients with metastatic SQ or NSQ NSCLC who have not previously received systemic treatment for metastatic disease and whose tumors have no known actionable mutations for which approved first-line therapies are available. Patients will be randomly assigned (1:1) to receive ivonescimab 20 mg/kg every 3 weeks (Q3W) or pembrolizumab 200 mg Q3W combined with chemotherapy (paclitaxel or nab-paclitaxel plus carboplatin for SQ or pemetrexed plus carboplatin for NSQ) for up to 4 cycles, followed by maintenance with ivonescimab or pembrolizumab alone for SQ or in combination with pemetrexed for NSQ for up to 24 months. Randomization will be done in blocks by histology (SQ and NSQ) and stratified by sex (female vs male), age ($<$65 vs $\geq$65 y), geographic region (East Asia vs rest of world), presence or absence of liver or brain metastases at baseline, previous PD-1 or programmed death ligand 1 (PD-L1) inhibitor treatment $>$6 months before the development of metastatic disease (yes vs no), and PD-L1 tumor proportion score ($\geq$1% or $<$1%). The dual primary end points are overall survival and PFS (assessed by investigators per RECIST v1.1). The secondary end points are ORR, disease control rate, duration of response, safety, pharmacokinetics, and immunogenicity. Patients are being recruited in Asia, Europe, and North America, with a target enrollment of 1080 patients (45-50% SQ and 50-55% NSQ). 1. Zhang L et al, ELCC 2024, FPN: 68P. Clinical trial information: NCT05899608. Research Sponsor: Summit Therapeutics, Inc.

TPS8665 **Poster Session**

NVL-330, a selective HER2 tyrosine kinase inhibitor, in patients with advanced or metastatic HER2-altered non-small cell lung cancer: The phase 1 HEROEX-1 study.

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Background: Oncogenic mutations and gene amplifications in the HER2 receptor tyrosine kinase are detected in approximately 2-4% and 1-5% of non-small cell lung cancers (NSCLC) in the US, respectively. Exon 20 insertion mutations (exon20ins) are the predominant *HER2* mutations in NSCLC, and ~50% of patients with *HER2*-mutant metastatic NSCLC develop brain metastases. The antibody drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) has received FDA accelerated approval for *HER2*-mutant NSCLC, but no tyrosine kinase inhibitors (TKIs) are currently approved for this indication. NVL-330 is a novel, brain-penetrant, HER2-selective investigational TKI, designed to address the medical need of targeting *HER2*-mutant tumors, and treating brain metastases, while minimizing treatment related adverse events due to off-target inhibition of wild-type EGFR. **Methods:** HEROEX-1 (NCT06521554) is a first-in-human, Phase 1a/1b trial. The Phase 1a dose escalation portion employs a Bayesian optimal interval design with a 3+3 run-in, followed by a Phase 1b dose expansion. The study population includes adult patients with advanced or metastatic NSCLC with a *HER2* oncogenic mutation (Phase 1a/1b) or amplification (Phase 1a only) determined by local testing. Eligible patients must have received at least one prior systemic therapy including platinum-based chemotherapy with or without immunotherapy, or are unsuitable candidates for available therapies. Prior HER2-directed antibodies and HER2-directed ADCs are allowed. Prior HER2 TKIs are allowed in Phase 1a only. Patients will receive NVL-330 by oral administration once or twice daily. The primary objectives are to evaluate safety and tolerability, determine the recommended Phase 2 dose, and, if applicable, the maximum tolerated dose of NVL-330. Additional objectives include assessment of preliminary activity and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-330. Analyses will be performed to evaluate tumor and blood-based biomarkers of response and other relevant biomarkers. The study is open to accrual. Clinical trial information: NCT06521554. Research Sponsor: Nuvalent.

TPS8666 **Poster Session**

Neladalkib (NVL-655), a highly selective anaplastic lymphoma kinase (ALK) inhibitor, compared to alectinib in first-line treatment of patients with ALK-positive advanced non-small cell lung cancer: The phase 3 ALKAZAR study.

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Background: Oncogenic *ALK* gene fusions are detected in ~5% of advanced non-small cell lung cancer (NSCLC) cases. Among these patients, the incidence of brain metastases at diagnosis is ~40%. Prior generations of ALK tyrosine kinase inhibitors (TKIs) present limitations that may influence efficacy and tolerability, such as inadequate control of brain metastases, treatment-emergent drug-resistant *ALK* mutations, or off-target adverse events, particularly neurological events associated with inhibition of the structurally related TRK kinases. Neladalkib is a potent, brain-penetrant, ALK-selective TKI with preclinical activity against diverse *ALK* fusions and resistance mutations (Lin et al., Cancer Discovery 2024). In the Phase 1/2 ALKOVE-1 study, neladalkib showed encouraging preliminary efficacy in patients with heavily pretreated *ALK+* NSCLC, including in those with *ALK* single or compound resistance mutations and brain metastases (Drilon et al., ESMO 2024). It also exhibited a favorable safety profile consistent with its ALK-selective, TRK-sparing design. The Phase 3 ALKAZAR study aims to demonstrate the superiority of neladalkib over a current standard of care, alectinib, in TKI-naïve patients with advanced *ALK+* NSCLC. **Methods:** ALKAZAR (NCT06765109) is a global, Phase 3, randomized, controlled, open-label study in adult patients with locally advanced or metastatic NSCLC harboring an *ALK* rearrangement per local testing of tissue or blood. Prior systemic anticancer treatment for metastatic disease is not allowed. Patients who received prior alectinib in the adjuvant setting are not eligible. Patients are required to have measurable disease by RECIST. Patients with untreated central nervous system (CNS) disease without progressive neurological symptoms or increasing corticosteroid doses are eligible. Patients with non-ALK oncogenic driver alterations are excluded. Approximately 450 patients will be randomized in a 1:1 ratio to receive either oral neladalkib (150 mg once daily) or oral alectinib (600 mg twice daily), stratified by brain metastases, ethnic origin (Asian vs. non-Asian), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 vs.1 vs. 2). The primary endpoint is progression-free survival by blinded independent central review. Secondary endpoints include intracranial activity, objective response rate, duration of response, overall survival, safety and tolerability, and patient-reported outcomes. Additional analyses will be conducted to investigate candidate biomarkers and molecular mechanisms of response and resistance to neladalkib and alectinib. The study is open to accrual. Clinical trial information: NCT06765109. Research Sponsor: Nuvalent.

TPS8667 **Poster Session**

A phase 2 safety and efficacy study of PRT3789 in combination with pembrolizumab in patients with advanced or metastatic solid tumors and a *SMARCA4* mutation.

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Background: Genes encoding subunits of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex are often mutated in cancer (~20% of all human cancers). The SWI/SNF complex contains either SMARCA2 or SMARCA4 enzymatic subunits for ATP-dependent chromatin remodeling. Since SMARCA2 and SMARCA4 function as mutually exclusive catalytic subunits of the SWI/SNF complex, cells exhibiting SMARCA4 loss rely on its paralog, SMARCA2, making SMARCA2 an attractive therapeutic target. In NSCLC, *SMARCA4* mutations are associated with aggressive and invasive disease. PRT3789 has been shown to increase antigen processing and presentation of unique MHC class I peptides, and increase T-cell activity and IFN-γ production in *SMARCA4*-mutated cancer cells. SMARCA2 degradation by PRT3789 promoted the effects of anti-PD1 therapy in SMARCA4-deficient mouse models, and PRT3789 combined with pembrolizumab (pembro), a humanized immunoglobulin G4 monoclonal antibody, promoted cell death of SMARCA4-deficient NSCLC cells. While inhibitors targeting the PD-1/PD-L1 axis have shown remarkable clinical activity across a broad range of tumor types, some patients demonstrate an inadequate response and disease progression consistent with the natural disease course that may be tied to innate resistance mechanisms. Other patients progressed after a period of disease control, which may be associated with acquired resistance mechanisms. PRT3789 + pembro may re-sensitize resistant cancers to subsequent anti–PD(L)-1 therapy. **Methods:** This is an open-label, 2-part, multicenter study to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of PRT3789 + pembro in patients who are resistant to prior anti–PD(L)-1 therapy. Adults with any advanced, recurrent, or metastatic solid tumor and any *SMARCA4* mutation are eligible to enroll into part 1, a safety run-in to establish the initial safety of PRT3789 376 mg intravenous (IV) once weekly + pembro 200 mg IV every 3 weeks. Part 2 will target adults with advanced, recurrent, metastatic NSCLC or upper gastrointestinal cancer with a *SMARCA4* loss-of-function mutation. Other key eligibility criteria include documented prior or acquired resistance to anti–PD(L)-1 therapy, or received prior standard-of-care therapy, but naive to anti–PD(L)-1 therapy due to PD-L1 negative expression. A safety review committee will evaluate dose-limiting toxicities (DLTs) in part 1 and advise on opening part 2 and regularly review accumulated safety data during the study. The primary endpoints are safety, tolerability, and incidence of DLTs in part 1, and overall response rate and duration of response in part 2. Secondary endpoints include progression-free survival, clinical benefit rate, PK, and PD of PRT3789. This study is actively recruiting. Clinical trial information: NCT06682806. Research Sponsor: Prelude Therapeutics Incorporated.

TPS8668 **Poster Session**

TACTI-004: A double-blinded, randomized phase 3 trial in patients with advanced/metastatic non-small cell lung cancer receiving eftilagimod alfa (MHC class II agonist) in combination with pembrolizumab (P) and chemotherapy (C) versus placebo + P + C.

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Background: Eftilagimod alfa (E), an antigen presenting cell activator, binds to a subset of MHC class II molecules to mediate T cell (CD4/CD8) recruitment/activation.Prior studies in first line (1L) non-small cell lung cancer (NSCLC) (TACTI-002 [NCT03625323]: combining E + pembrolizumab (P); INSIGHT-003 [NCT03252938] combining E with chemotherapy + P [SoC]) showed encouraging efficacy results across all PD-L1 strata & excellent safety profiles. TACTI-004 is a double-blinded, randomized, placebo-controlled phase 3 study testing E + SoC vs. placebo + SoC in 1L NSCLC patients (pts). **Methods:** Approximately 756 pts with 1L NSCLC will be enrolled, irrespective of PD-L1 status, & randomized 1:1 to receive either E + SoC or placebo + SoC. The dual primary endpoint (EP) is overall survival & progression-free survival (RECIST 1.1). Secondary EPs include ORR, disease control rate, duration of response, quality of life, safety & biomarkers. Pts will receive 30 mg E SC q2w for 24 weeks, then q3w and P IV at 200 mg (30 min) q3w; both treatments for up to 2 yrs. Chemotherapy choice will be histology-dependent: non-squamous NSCLC pts will receive IV cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6) + pemetrexed (500 mg/m^2) q3w for 3 mo, then maintenance pemetrexed q3w. Squamous NSCLC pts will receive carboplatin (AUC 5 or 6) + paclitaxel (175 or 200 mg/m^2) q3w for 3 mo. Imaging will be performed q6w until week 18, q9w until week 54 & q12w thereafter. Testing for PD-L1 (22C3) & genetic alterations will be prospectively assessed. Key inclusion criteria: Adults diagnosed with measurable advanced/metastatic (A/M) NSCLC (squamous or non-squamous), not amenable to curative treatment nor locally available oncogenic driver mutation-based 1L therapy. Treatment-naïve for systemic therapy (previous palliative radiotherapy for A/M disease acceptable). Expected survival >3 months & ECOG 0 or 1. Tumour tissue must be available for PD-L1 central testing. Pts may not have tumours with EGFR mutations nor ALK or ROS1 translocations. Stable brain metastasis is acceptable. Clinical trial information: NCT06726265. Research Sponsor: None.

TPS8669 **Poster Session**

A biomarker-directed, multi-center phase II/III study of ctDNA molecular response adaptive immuno-chemotherapy in patients with non-small cell lung cancer (BR.36).

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Background: Minimally invasive analyses of circulating cell-free tumor DNA (ctDNA) have shown clinical value as an early endpoint of immunotherapy response, allowing patients with primary resistance to be rapidly and accurately identified. In the first of two independent stages, the BR.36 trial demonstrated a sensitivity of ctDNA response for radiographic RECIST response of 82% and a specificity of 75%, with a median time to ctDNA response of 2.1 months. **Methods:** BR.36 is a multi-center, open-label, biomarker-directed, phase II/III clinical trial of ctDNA molecular response adaptive immuno-chemotherapy in patients with treatment-naïve metastatic NSCLC. The main objective is to evaluate if adding chemotherapy to pembrolizumab for patients who have persistent ctDNA on liquid biopsy after 6 weeks of pembrolizumab, will result in better PFS and OS compared to patients who remain on pembrolizumab until radiographic clinical progression. Key eligibility criteria include: age ≥18 years, ECOG performance status 0-2, metastatic NSCLC, EGFR and ALK mutation negative and PD-L1 Tumor Proportion Score (TPS) ≥ 50%, at least and not more than 2 cycles of the 200 mg or 2 mg/kg IV Q3W dose/schedule of pembrolizumab as first line systemic immunotherapy at the time of screening and RECIST non-PD or clinically stable PD documented prior to enrolment that can continue on immunotherapy if randomized to that arm. The phase II primary endpoint is PFS and has secondary endpoints of feasibility, overall response rate and safety/tolerability. Sex, RECIST response and ECOG status represent stratification criteria. With 110 randomized patients evaluable for progression (55 patients per arm and 71 PFS events observed in this phase of the clinical trial), we would be able to detect a hazard ratio difference of 0.67 with a 1-sided alpha of 0.2 and power of 0.80 using a phase II screening design. The trial will not stop accrual for the phase II analysis of PFS if feasibility endpoints are achieved. In the phase III portion, a total of 210 randomized patients recruited over 3 years and followed for an additional 24 months are required to detect an OS hazard ratio difference of 0.67 with 1-sided alpha of 0.05 and power of 0.8. The total number of events for the final analysis is expected to be 156, and assuming 10% of patients are lost to follow-up, we are targeting 230 patients to be included overall. The primary endpoint of the phase III portion is overall survival, with secondary endpoints of best overall response, response duration, progression-free survival and safety/tolerability. Exploratory endpoints include longitudinal ctDNA analyses by targeted next-generation sequencing and whole genome sequencing approaches. The BR.36 clinical trial is open to enrollment and to date 2 patients have been registered (ClinicalTrials.gov ID: NCT04093167). Clinical trial information: NCT04093167. Research Sponsor: Cancer Research Institute; The Mark Foundation for Cancer Research; LabCorp.

TPS8670 **Poster Session**

A global phase 2/3, randomized, open-label trial of BNT327/PM8002 in combination with chemotherapy (chemo) in first-line (1L) non-small cell lung cancer (NSCLC).

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Background: The introduction of immune checkpoint inhibition for the treatment of 1L NSCLC has improved survival, however long-term outcomes remain suboptimal, highlighting the need for more efficacious treatments. BNT327 is an investigational bispecific antibody, targeting both PD-L1 and VEGF-A in the tumor and tumor microenvironment (TME). By binding to PD-L1 on tumor cells it is designed to restore effector T-cell function and by binding to VEGF-A within the TME it also reverses the negative impact of VEGF signaling on immune cell infiltration and activation. In addition, via VEGF-A neutralization, it normalizes tumor vasculature. This dual targeting of PD-L1 and VEGF-A aims to deliver better efficacy and safety. Data published on BNT327 has indicated a tolerable safety profile and encouraging anti-tumor activity in patients (pts) with NSCLC (ASCO 2023, ASCO and ESMO 2024). This global Phase 2/3 trial will further assess safety and efficacy of BNT327 plus chemo (Phase 2) and BNT327 plus chemo versus pembrolizumab plus chemo (Phase 3) in pts with advanced NSCLC. **Methods:** This Phase 2/3, multisite, randomized, open-label trial will enroll ~982 pts with stage IIIB/C and stage IV non-squamous cell (NSQ) NSCLC (Substudy A) and squamous (SQ) NSCLC (Substudy B) without actionable EGFR mutations or ALK rearrangements. Each substudy consists of a Phase 2 and a Phase 3 part. During the Phase 2 part, pts will be randomized 1:1 to receive BNT327 at either 1400 mg (Arm 1) or 2000 mg (Arm 2) plus chemo (carboplatin + pemetrexed for Substudy A, carboplatin + paclitaxel for Substudy B) Q3W IV for four cycles, followed by Q3W IV maintenance BNT327 at previously administered doses (with maintenance pemetrexed for Substudy A). In the Phase 3 part, pts will be randomized 1:1 to receive BNT327 at the selected dose (based on the Phase 2 part) plus chemo (carboplatin + pemetrexed for Substudy A, carboplatin + paclitaxel for Substudy B) or pembrolizumab 200 mg plus chemo Q3W IV, followed by Q3W IV maintenance BNT327 or pembrolizumab (both with maintenance pemetrexed for Substudy A). Chemo will be administered at approved doses. Primary endpoints include occurrence of adverse events (AE) and serious AEs, rates of dose interruption, reduction and discontinuation due to treatment-emergent (TE) AEs, objective response rate (ORR) and best percentage change from baseline in tumor size (Phase 2), and both progression free survival (PFS) per blinded independent central review and overall survival (OS) (Phase 3). Secondary endpoints include duration of response, disease control rate (Phase 2), PFS per investigator, ORR, landmark PFS and OS, patient reported outcomes and occurrence of AEs, and rates of dose interruption, reduction and discontinuation due to TEAEs (Phase 3); with efficacy endpoints per RECIST 1.1; safety per CTCAE v5.0. The trial is enrolling. Clinical trial information: NCT06712316. Research Sponsor: BioNTech SE.